California HIV/AIDS Research

Communities Working Together to Meet Today's Challenges

Universitywide AIDS Research Program

20th AIDS Investigators' Meeting
6th Conference on AIDS Research in California

February 20, 2004 • Los Angeles, California

Universitywide AIDS Research Program
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7:00 am	**Registration** Poster Set-Up Continental Breakfast	*Foyer, 2nd Floor*
8:00 am	**Welcome** John Rossi, Ph.D., Beckman Research Institute-City of Hope *Chair, Universitywide Task Force on AIDS* George Lemp, Dr.P.H., Universitywide AIDS Research Program *Director, UARP* Ronald Mitsuyasu, M.D., University of California-Los Angeles *Chair, Conference Local Advisory Committee*	*Pacific*
8:30 – 9:30 am	**Plenary 1: Challenges in Prevention** *Moderator:* Cynthia Gomez, Ph.D., University of California-San Francisco *Speakers:* George Ayala, Psy.D., AIDS Project Los Angeles Kathie Ferbas, Ph.D., University of California-Los Angeles	*Pacific*
9:45 – 11:00 am	**Poster Viewing** Basic Sciences 1 Clinical Sciences 1 Prevention, Health Services & Contexts of Health 1	 *Pacific* *Los Angeles* *Garden East/West*
11:00 – 12:00 pm	**Plenary 2: Health Care Financing** *Moderator:* Michael Montgomery, CA Dept. of Health Services, Office of AIDS *Speakers:* Jeffrey Levi, Ph.D., George Washington University Dana Goldman, Ph.D., RAND Corporation	*Pacific*
12:00 – 1:30 pm	**Lunch & Award Ceremony**	*Golden Gate*

(over)

1:30 – 2:45 pm **Poster Viewing**

Basic Sciences 2	*Pacific*
Clinical Sciences 2	*Los Angeles*
Prevention, Health Services & Contexts of Health 2	*Garden East/West & Verdugo/Del Mar*

Concurrent Afternoon Plenary Sessions

3:00 – 4:15 pm **Plenary 3: Translational Research and Technology Transfer in Biomedicine** *Golden Gate*

Moderator: John Rossi, Ph.D, Beckman Research Institute-City of Hope

Speakers: Richard Ogden, Ph.D., Pfizer
Sarah Adriano, J.D., Mandel & Adriano
John Shih, Ph.D., University of California-Office of the President

3:00 – 4:00 pm **Plenary 4: Disparities in Access and Treatment** *Pacific*

Moderator: Gail Wyatt, Ph.D, University of California-Los Angeles

Speakers: Eric Bing, M.D., Charles R. Drew University
Hector Carillo, Dr.P.H., University of California-San Francisco

4:00 – 5:00 pm **UARP Grant Application Q&A Session** *Pacific*

Basic Sciences

HIV & Chemokines

HIV Host Cell Interactions

Molecular Biology & Transcription

Centers and Institutional Support

Clinical Sciences

Clinical & Vaccine Trials

Prevention, Health Services & Contexts of Health

Adherence

Community Collaborative

Youth

Noteworthy abstracts are of particular relevance to the conference theme or address a topic of special interest.

Basic Sciences

Altered Chemokine Networks and T Lymphocyte Migratory Circuits in Acute SIV Infection

Noteworthy Abstract

Presenter: Ursula Esser, UC-Davis

Authors: Ursula Esser, Denise S. Rodrigues, Candice C. Clay, Christian M. Leutenegger

Principal Investigator: Ursula Esser

UARP Award Number: ID01-D-130

The goal of this study was to examine T lymphocyte homing characteristics during acute simian immunodeficiency virus (SIV) infection in vivo and to define critical parameters of anti-viral immunity and immune surveillance in lymphoid and nonlymphoid compartments in the nonhuman primate model for AIDS.

Three rhesus macaques were intravenously infected with pathogenic strain SIV_{mac251}. In all 3 animals, maximal plasma viral RNA levels were reached at Day 11 post infection (p.i.). Plasma protein levels of proinflammatory chemokine CXCL9/MIG peaked at day 8 or Day 11 p.i., following or coinciding with maximal IFN-?amma production. To investigate the homing potential of peripheral T lymphocytes during this acute infection phase, lymphocytes were isolated at Day 12 p.i., fluorescein dye-labeled in vitro and autologously transferred the same day. T lymphocyte homing to secondary lymphoid organs and distal effector sites was defined in a 2-day time course, and trafficking parameters assessed. Dye-labeled T lymphocytes were identified in all tissues examined, however, the relative distribution of dye-labeled populations was distinct from that observed in 3 healthy, SIV-uninfected macaques. Furthermore, chemokine receptor profiles of peripheral T lymphocytes in the SIV-infected animals revealed increased expression of inflammatory receptors CXCR3 and CCR5 as well as CCR9, associated with homing to the gut mucosa. Altered transcript levels of both homeostatic and inflammatory chemokines were observed in SIV-infected animals, suggesting an important role for both chemokine networks in the acute infection phase.

Our experimental results elucidate circuitry of T lymphocytes in nonhuman primates in both health and disease, and delineate molecular requirements for tissue homing in vivo. Establishment of this trafficking model may reveal critical mechanisms for immune dysfunction in the nonhuman primate model for AIDS, and help define functional parameters of anti-viral immunity in SIV and HIV pathogenesis. Future experiments will be directed towards defining immune system failure or protection in simian AIDS, based on disrupted T lymphocyte homing characteristics and associated functions.

Basic Sciences

Kinetic Difference in R5 and X4 HIV-1 Fusion in Dendritic Cells: Implication for Selective Transmission of R5 Strains

Presenter: Marielle Cavrois, UC-San Francisco, Gladstone Institute of Virology and Immunology

Principal Investigator: Marielle Cavrois

UARP Award Number: F03-GI-2065

Background: Immature dendritic cells (DCs) function as key cellular sentinels at mucosal surfaces. Thus, immature DCs including epithelial Langerhans cells, are likely among the first immune cells to encounter HIV during rectal or vaginal transmission. The ability of these cells to migrate rapidly to lymph nodes may also facilitate spread of HIV infection. When exposed to HIV, DCs can either be productively infected or endocytose intact HIV virions via C-type lectin receptors and subsequently deliver these virions to T cells following migration into lymph nodes (trans-infection) We have recently developed a virion-based fusion assay that can distinguish between viral entry occurring by fusion or endocytosis. Using this assay, we have investigated the capacity of immature or mature monocyte-derived DCs (mo-DCs) to support fusion of R5 or X4 HIV-1 strains and to mediate trans-infection of T-cells.

Methods: $CD14^+$ monocytes were isolated from peripheral blood and differentiated into DCs by culturing for 6 days in the presence of IL-4 and GM-CSF. Maturation of DCs was induced by stimulation with TNF-a and polyIC. Fusion of isogenic HIV-1 viruses with X4 or R5 envelopes, NL4-3 or 81A respectively, was analyzed using a virion-based fusion assay employing mo-DCs or peripheral blood lymphocytes as cellular targets.

Results: At the same viral input, R5-tropic HIV fused to immature DCs at much higher levels than X4-tropic viruses. In contrast, mature DCs supported higher levels of X4-tropic virus fusion and R5 virus fusion was diminished. Interestingly, R5-virion fusion to immature DCs occurred quickly while X4-virion fusion in mature DCs fusion was much slower. Finally, trans-infection of autologous T-cells was weakly supported by immature mo-DCs exposed to R5 viruses while mature DCs were highly efficient in mediating trans-infection with both R5 and X4 tropic viruses.

Conclusions: The rapid and efficient fusion of R5 HIV-1 virions to immature DCs likely explains why these cells only poorly support trans-infection with R5 viruses. This finding strongly suggests that the transfer of R5-tropic HIV from the mucosa to lymph nodes involves the migration of productive infected DCs infection. The highly efficient fusion of R5 strains to immature DCs, relative to X4 viruses, coupled with the viral amplification that occurs during productive infection, could explain why R5-tropic HIV strains are preferentially transmitted.

Basic Sciences

Toll-like Receptor (TLR)-Mediated Macrophage Tolerance Inhibits HIV-LTR Transactivation and HIV Replication

Presenter: Ozlem Equls, UC-Los Angeles

Collaborators: Ken Salehi, Katherine Whittaker, Daning Lu

Principal Investigator: Gayle Cocita Baldwin

UARP Award Number: CC02-LA-001

Repetitive exposure of macrophages to microbial antigens induces a refractory state to further stimulation with microbial antigens. This phenomenon is called macrophage-tolerance or macrophage reprogramming, and it appears to be mediated by innate immune system receptors, toll-like receptors (TLR). We have previously shown that Gram (-) bacterial lipopolysaccharide (LPS)-induced HIV replication is mediated via TLR4 and that costimulation of TLRs induces HIV replication additively. Thus, in AIDS, frequent infections with opportunistic and pathologic bacteria may play a role in macrophage tolerance ultimately affeting HIV replication, HIV pathogenesis and HIV latency. We assessed the impact of (LPS) priming on HIV-LTR transactivation in an HIV-LTR expressing human monocytic cell line THP-1 (THP-LTR-Luc) as well as HIV replication in primary macrophages infected *in vitro* with HIV_{BaL}. HIV-LTR transactivation (as measured by luciferase activity) and HIV replication (as measured by p24 ELISA) were inhibited in LPS primed THP-LTR-Luc and HIV(BAL) infected primary macrophages respectively. In THP-LTR-Luc cells priming with LPS also resulted in decreased TNF-alpha release upon restimulation with LPS. While in LPS-primed HIV-1 infected macrophages, TNF-alpha release was augmented following re-exposure to LPS. Priming of THP-LTR-Luc with substimulatory doses of LPS for 3 hours led to their hypersensitization with increased LPS-induced TNF-alpha release; however LPS-induced HIV-LTR transactivation was still suppressed in these hypersensitized cells. Our results indicate that exposure of HIV-infected macrophages to microbial antigens results in tolerance as manifested by modulated cytokine production and inhibition of HIV-1 replication. Elucidating the effect of macrophage tolerance/reprogramming on cytokine release and HIV replication has important implications in understanding the pathogenesis of HIV in the context of opportuntistic bacterial infections. Moreover, our current findings have established the basis for more mechanistic studies, potentially leading to the development of novel therapeutic interventions to control HIV replication.

Basic Sciences

Expression and Crystallization of AIDS-Related Chemokine Receptors

Presenter: Tracy Handel, UC-Berkeley

Principal Investigator: Tracy Handel

UARP Award Number: ID03-B-005

Chemokines are well recognized as the traffic signals for cell migration in inflammation, routine immune surveillance and lymphocyte development and homing. They function by binding to seven transmembrane G-protein coupled receptors (GPCRs), inducing conformational changes that trigger a cascade of signaling pathways. In turn, these signaling events produce cytoskeletal rearrangements, increased adhesiveness, and cell migration along gradients of chemokines, which provide the directional cues. In addition to chemotaxis, some chemokines stimulate cellular processes such as T-cell activation, protease and cytokine production, the respiratory burst, degranulation, and other defense mechanisms that cause cell damage. Thus, despite the importance of chemokines in the immune response, improper regulation of the chemokine system and unchecked recruitment of cells can lead to a variety of pathologies, including asthma, rheumatoid arthritis, multiple sclerosis, atherosclerosis and cancer. However, the most pandemic disease involving chemokine receptors is AIDs. In this case, HIV-1 uses chemokine receptors, primarily CXCR4 and CCR5, to gain entry into macrophages and T-cells, which ultimately devastates the human immune system. Thus inhibitors of cell entry would be a valuable addition to current therapies that target viral enzymes required for replication (HIV-1 protease and reverse transcriptase), and these two chemokine receptors will be our main targets because of their role as gatekeepers of the cell.

To this end, structures of these chemokine receptors with and without their ligands, and especially in complex with small molecule drug leads would substantially aid the development of anti-AIDS therapeutics. Unfortunately, although a large number of high-resolution structures of chemokines have been solved, much less is known about the chemokine receptors, despite the estimation that greater than 60% of the drugs on the market are directly or indirectly targeted at GPCRs. Whereas ~15,000 structures of soluble molecules have been deposited in the protein databank, the number of high resolutions structures of membrane proteins is less than 30. This lack of knowledge regarding membrane proteins is not surprising, because of the challenges associated with their expression, functional reconstitution, and formation of well-ordered crystals. Fortunately, a number of technical innovations have increased the feasibility of overcoming these barriers. Therefore, the aim of this research supported by UARP is to develop methods to express, purify, natively reconstitute and crystallize chemokine receptors and complexes for structure determination to facilitate drug discovery efforts. As a first step we are exploring several strategies to maximize the expression of these receptors in mammalian cells.

Basic Sciences

R5 HIV-1 Replicates More Efficiently in Primary CD4+ T Cell Cultures Than X4 HIV-1

Presenter: Becky Schweighardt, UC-San Francisco, Gladstone Institute of Virology and Immunology

Collaborators: Becky Schweighardt, Duncan A. Meiklejohn, Edward J. Grace II, Douglas F. Nixon

Principal Investigator: Douglas F. Nixon

UARP Award Number: F02-GI-212

Human Immunodeficiency Virus type 1 (HIV-1) infects cells by binding to the CD4 receptor and one of several coreceptors expressed on the surface of target cells. The chemokine receptors, CCR5 and CXCR4, serve as the major coreceptors for HIV-1. Viral strains that utilize CCR5 as a coreceptor to gain entry into target cells are referred to as R5 strains, and often represent the dominant viral population detected during the early stages of clinical HIV-1 infection. Viral strains that utilize CXCR4 as a coreceptor are referred to as X4 strains, and are often detected in the later stages of disease when $CD4^+$ T cell counts are declining. Despite the link between X4 emergence and disease progression, approximately half of all individuals with AIDS continue to harbor predominantly R5 viruses. Several mechanisms have been suggested to play a role in R5 dominance, including selective transmission and preferential spread of R5 strains. We have found that R5-infected $CD4^+$ T cells produce more progeny virus over time than X4-infected $CD4^+$ T cells, and suggest that this replicative advantage may contribute to spread of R5 strains in vivo.

In this report, we present evidence that R5 HIV-1 replicates more efficiently in CD3/CD28 costimulated $CD4^+$ T cell cultures than X4 HIV-1. We performed careful experimentation to optimize the CD3/CD28 costimulation protocol, and found that stimulation with plate-bound CD3 antibody and soluble CD28 antibody induces high levels of activation in primary $CD4^+$ T cell cultures and renders cells permissible to both X4 and R5 HIV-1 infection. We demonstrate that X4 HIV-1 infects a large percentage of costimulated $CD4^+$ T cells, and that large amounts of progeny virus are produced at the early time points post-infection. However, the viability of X4-infected cultures decrease rapidly, and viral production is no longer detectable by 7 days post-infection. In contrast, R5 HIV-1 only infects a small percentage of cells, and the infected cultures remain viable for extended periods of time post-infection. Despite the paucity of R5-infected cells, high levels of viral production are detected for up to 14 days post-infection. This data demonstrate that R5-infected $CD4^+$ T cells produce more progeny virus over time than X4-infected $CD4^+$ T cells.

We propose that the increased replication capacity of R5 strains may contribute to the R5 dominance of early HIV-1 infection. Our data demonstrate that X4 viruses are able to infect a larger percentage of target cells, but that viral production is restricted by widespread virus-induced cell death of infected and uninfected cells. In contrast, R5 viruses do not induce extensive cell death, and therefore do not deplete the target cell pool. Consequently, R5 replication increases over time, while X4 replication rapidly decreases. We suspect that the variation in viral production may be due to a differential in the life span of infected cells. We hypothesize that R5-infected $CD4^+$ T cells live longer than X4-infected cells, and are therefore able to produce more progeny virus over time. We are currently performing experiments to address this hypothesis. The results of these experiments will provide useful information regarding the mechanism by which R5 HIV-1 strains persist in vivo. In summary, we have found that R5 HIV-1 replicates more efficiently in costimulated $CD4^+$ T cells than X4 HIV-1, and suggest that this replicative advantage may contribute to the preferential spread of R5 strains *in vivo.*

Basic Sciences

Noteworthy Abstract

HIV Vif and the "Knockdown-Dragout" of the Innate Antiviral Factor, APOBEC3G

Presenter: Warner C. Greene, UC-San Francisco

Collaborators: Kim Stopak, Carlos de Noronha, Wes Yonemoto, Ya-Lin Chiu,

Principal Investigator: Warner C. Greene

UARP Award Number: CC02-SF-002

HIV-1 Vif specifically defeats the powerful innate antiviral activity of the cytidine deaminase, APOBEC3G. APOBEC3G is incorporated into virions, which enables it to cause massive hypermutation (G->A) in the nascent retroviral DNA formed during reverse transcription in the subsequently infected cell. Our studies have focused on how Vif impairs the antiviral activity of APOBEC3G (see Stopak et al *Mol. Cell* 12:591-601, 2003). Using an APOBEC3G-specific rabbit antiserum to study the endogenous APOBEC3G protein, we have shown that Vif prevents virion incorporation of the native APOBEC3G enzyme. Vif prevents APOBEC3G encapsidation by depleting the intracellular stores of this enzyme in HIV-1 infected T cells. Pulse-chase radiolabeling, immunoblotting and *in vitro* translation studies indicate that Vif both inhibits APOBEC3G mRNA translation (40-50% decline) and shortens the intracellular survival of the enzyme (2 hours versus >8 hours). These latter effects involve Vif targeting of APOBEC3G for destruction by the 26S proteasome. In terms of potential APOBEC3G cofactors, we find that APOBEC3G assembles into a high molecular weight ribonucleoprotein complex (>700 kD) and that Vif appears to induce disassembly of this complex. These studies coupled with the biological effects of APOBEC3G suggest that the Vif-APOBEC3G axis represents an attractive new target for anti-HIV drug development. Small molecules that either block Vif assembly with APOBEC3G or Vif induced depletion of APOBEC3G could preserve the intracellular expression levels of this antiviral enzyme required for its effective incorporation into virions. APOBEC3G could then execute its potent DNA mutator function leading to a marked decline in HIV infectivity and spread.

Basic Sciences

HIV Vif and APOBEC3G: a Crucial Fight between a Human and a Viral Protein

Noteworthy Abstract

Presenter: Roberto Mariani, The Salk Institute for Biological Studies

Collaborators: Roberto Mariani, Darlene Chen, Barbel Schrofelbauer, Francisco Navarro, Renate Koenig, Brooke Ballman, Henrietta Nymark-McMahon, Carsten Muenk, Nathaniel R. Landau

Principal Investigator: Nathaniel Landau

UARP Award Number: IS02-SI-704

HIV Vif is required for HIV replication in primary human T cells and monocytes. Vif is necessary in these cells to overcome the inhibitory activity of the cellular protein ABOBEC3G/CEM15, a protein that belongs to a family of RNA editing enzymes and deaminates minus strand DNA cytosines to uracils. In the studies presented here we report how HIV Vif counteracts APOBE3G antiviral function and the mechanism of action. We also report analysis of APOBEC3G cloned from other species like rodent and primates. We found that HIV-1 Vif forms a complex with human APOBEC3G that prevents APOBEC3G virion encapsidation. Interestingly, HIV-1 Vif is not able to form a complex with the murine APOBEC3G. Vif excludes human APOBEC3G from being encapsidated in virions but is not able to prevent encapsidation of mouse or AGM APOBEC3G. Once encapsidated in virions mouse or AGM APOBEC3G deaminate the minus strand of the newly synthesized viral reverse transcripts in the target cells determining degradation of such transcripts. As a result, the mouse and AGM enzymes are potent inhibitors of wild-type HIV-1 replication. The antiviral activity of the different APOBEC3G is widely conserved among them, but the species-specificity of Vif:APOBEC3G interaction could explain why HIV-1 replication is restricted to humans.

These findings elucidate a very important intereaction between host factors and HIV. These findings also provide a molecular mechanism for Vif function that can be used for therapeutical purposes and lead to better understanding of disease progression.

Basic Sciences

In Vivo Trafficking Pathways of B and T Lymphocytes in Health Rhesus Macaques

Presenter: Candice Clay, UC-Davis

Authors: Candice C. Clay, Denise S. Rodrigues, Laurie L. Brignolo, Abbie Spinner, Ross P. Tarara, Charles G. Plopper, Christian M. Leutenegger, Ursula Esser

Principal Investigator: Ursula Esser

UARP Award Number: ID01-D-130

Lymphocyte migratory circuits in human and nonhuman primates remain largely unexplored, due to the difficulty to define cell trafficking in vivo. However, this knowledge may reveal critical aspects of immunity and lymphocyte homeostasis in health and disease. Furthermore, in vivo lymphocyte trafficking studies may facilitate defining mechanism(s) of immune dysfunction in the nonhuman primate model for AIDS.

Here, we developed a model for in vivo lymphocyte trafficking in nonhuman primates, and delineated homing characteristics of unstimulated peripheral blood mononuclear cells (PBMC) to lymphoid and nonlymphoid compartments in healthy rhesus macaques. Lymphocyte homing of autologous, carboxyfluorescein diacetate, succinimidyl ester (CFSE)-labeled PBMC was defined within 48 hours of intravenous transfer. The highest relative frequency of CFSE+ lymphocytes was observed in peripheral blood and spleen. Expression of chemokine receptor CCR7 and its ligands CCL19/MIP-3 beta and CCL21/6Ckine correlated with naïve T lymphocyte homing to paracortical regions of lymph nodes, and predominant exclusion from the follicular zone. The highest proportion of B lymphocytes migrated to the spleen. Low levels of lymphocyte trafficking were detected to liver, thymus and bone marrow. Homeostatic proliferation was observed in peripheral blood and spleen.

In this study, we established novel techniques to study in vivo lymphocyte trafficking in nonhuman primates. Importantly, we defined phenotypic and functional parameters that delineate lymphocyte migratory circuits in rhesus macaques in vivo. Our data suggest that lymphoid and nonlymphoid organs are under continuous immunosurveillance in healthy macaques, and that this model may serve to investigate aberrant patterns in disease.

Basic Sciences

Analysis of Toxoplasma Bradyzoite (tissue cyst) Development

Presenter: Mike Cleary, Stanford University

Principal Investigator: John Boothroyd

UARP Award Number: D02-ST-405

During Toxoplasma gondii infection, rapidly dividing tachyzoites develop into slowly growing, encysted bradyzoites. In most cases of Toxoplasma infection, bradyzoite cysts remain dormant in brain and muscle tissues and cause no overt disease. Occasionally, such cysts rupture and the released parasites are easily destroyed by an intact immune system. AIDS patients, however, are unable to control the bradyzoite stage of the infection and often develop serious symptoms, During Toxoplasma gondii infection, rapidly dividing tachyzoites develop into slowly growing, encysted bradyzoites. In most cases of Toxoplasma infection, bradyzoite cysts remain dormant in brain and muscle tissues and cause no overt disease. Occasionally, such cysts rupture and the released parasites are easily destroyed by an intact immune system. AIDS patients, however, are unable to control the bradyzoite stage of the infection and often develop serious symptoms, including potentially fatal encephalitis. Little is known about bradyzoite physiology or the molecular mechanisms that regulate the development of tachyzoites into bradyzoites. The primary goals of this project are to expand the known set of developmentally regulated genes and to identify the mechanisms that control bradyzoite development. The specific aims and progress towards those aims are outlined below:

Aim 1. Identify genes that are differentially expressed during bradyzoite development

We have also developed a novel method of measuring mRNA synthesis and decay using microarrays. By taking advantage of a parasite enzyme that can incorporate a RNA precursor added to the culture media, we can label mRNA during a short time period then enrich for this labeled RNA. This method will facilitate the goal of identifying early changes in gene expression and has already proven useful in detecting both increased and decreased transcription at 48hrs after bradyzoite induction when traditional methods detect no significant changes. We are also able to use this method to perform pulse-chase analysis of mRNA half-lives for all genes on the microarray. The pulse-chase can identify genes with different stabilities in tachyzoites versus bradyzoites. Measurements of both synthesis and mRNA half-life have been used to study changes in gene expression at 48 hours of bradyzoite development and will be used to analyze early timepoints (t= 1, 3, 6, 8 and 12 hours) following exposure to bradyzoite-inducing factors.

Aim 2. Identify factors that regulate bradyzoite development

Based on our initial microarray analysis, we chose one gene for targeted deletion. This gene is Methionine Aminopeptidase 2 (Met-AP 2). Cloning and sequence analysis show that this gene has high homology to Met-AP2 of humans and yeast. Met-APs are known to regulate protein translation and protein stability by selectively cleaving the initial methionine from proteins. T. gondii Met-AP2 is up-regulated in developing bradyzoites as early as 48hrs after induction and is likely to regulate bradyzoite-specific protein expression. Met-AP2 transcripts can be detected in tachyzoites but are rapidly turned over (as determined by pulse-chase analysis), thus meeting another criterion for potential regulators of bradyzoite development. A targeted gene-deletion vector was designed for Met-AP2 and introduced into T. gondii. Initial screening for "knock-out" parasites, based on a PCR assay, has shown that the gene has been knocked out within a population of

parasites. We are curently working to clone out the Met-AP2 knockout. Once this strain has been cloned its ability to form bradyzoites both in vitro and during infection of mice will be assayed.

The most significant impact of these results is the development of a novel method for measuring mRNA synthesis and turnover. This technique will allow us to more sensitively analyze changes in gene expression during bradyzoite development. Identification of a bradyzoite-specific Met-AP2 also has potential therapeutic impact, and the analysis of Met-AP2 knockout parasites will demonstrate the validity of this enzyme as a drug target.

Basic Sciences

Identification of Host Factors Mediating Hematopoietic Abnormalities in HIV Infection

Presenter: Zoran Galic, UC-Los Angeles

Principal Investigator: Zoran Galic

UARP Award Number: F02-LA-213

Severe and multiple hematopoietic abnormalities have been reported in HIV-infected individuals. These defects have been shown to be independent of direct infection and killing of the hematopoietic progenitor cells and are thus mediated by poorly understood indirect mechanisms. The goal of our research is to better define those mechanisms. SCID-hu mice transplanted with human fetal thymus and liver tissues (Thy/Liv implants), exhibit alterations in human hematopoiesis following HIV infection similar to those seen in humans. We used this model in combination with microarray analysis to identify HIV-induced alterations in host gene expression *in vivo*. The expression of IP-10 and MIG, two known myelosupressive factors not previously implicated in HIV-induced suppression of hematopoietic activity, was found to be strongly induced. To test whether these factors could directly cause inhibition of hematopoiesis in the SCID-hu model we will overexpress IP-10 and MIG in Thy/Liv implants using lentiviral vectors. These vectors are currently being constructed in our lab. Concurrently, to test the potential inhibitory effects of IP-10 and MIG in the context of HIV infection, SCID-hu mice will be infected with different strains of HIV and blocking antibodies to IP-10, MIG or both proteins will be administered to the animals according to the protocol described in our proposal.

Since, it is possible that inhibitory factors other than IP-10 and MIG contribute to the suppression of hematopoietic progenitors we will also attempt to purify and characterize the colony forming suppressive activity detected in the supernatant of HIV-infected thymocytes. Taken together, these studies may help identify host factors that contribute to the defect in hematopoiesis seen following HIV infection in humans, which in turn may point the way toward novel therapies and treatments for this aspect of HIV pathogenesis.

Basic Sciences

HIV directly impairs cytotoxic T cell function

Presenter: Scott Kitchen, UC-Los Angeles

Collaborators: Scott G. Kitchen, Nicole R. Jones, Stuart LaForge, Jason K. Whitmire, Bien-Aimee Vu, Zoran Galic, David G. Brooks, Stephen J. Brown, Christina M. Kitchen, Jerome A. Zack

During the course of HIV infection, $CD8^+$ cytotoxic T lymphocyte (CTL) responses are unable to fully suppress viral replication. It is not clear how this occurs or whether HIV has a direct effect on CTL function. HIV proviral DNA is present in $CD8^+$ T cells in vivo, however the consequences of HIV infection in this cell type are unknown. Infection of $CD8^+$ cells occurs via the CD4 molecule, which is induced following costimulation of antigen-naïve $CD8^+$ T cells. We investigated how the CD4 molecule on human $CD8^+$ T cells contributes to $CD8^+$ cell functions and the effects of HIV infection on these responses. In the current study we show that ligation of the CD4 molecule expressed on $CD8^+$ T cells results in increased expression of Interferon-gamma (IFN-g) and Fas-ligand (FasL), two important effector molecules. Further, HIV infection down-regulates CD4 cell surface expression and perturbs the IFN-g, FasL, and cytotoxic responses of CD8 cells. This provides a mechanism by which HIV can directly impair $CD8^+$ T cell function and could help explain the defects in the naïve CTL response in HIV infected individuals.

Basic Sciences

Identification of novel HIV gp120 Binding Proteins

Presenter: Oscar A. Negrete, UC-Los Angeles

Principal Investigator: Benhur Lee

UARP Award Number: ID02-LA-073

DC-SIGN is a C-type lectin that can bind HIV envelope gp120 with high affinity and transfer the virus from monocyte-derived dendritic cells to permissive T-cells. Although viral attachment to dendritic cells is considered to be the crucial step in the establishment of a primary viral infection, and DC-SIGN clearly plays a role in this initial attachment step, it is unclear that DC-SIGN binding to gp120 can account for all the HIV binding activity exhibited by dendritic cells. Therefore, we are developing a method for screening cDNA libriaries using a dimeric gp120-Fc fusion protein that re-capitulates gp120's properties to bind CD4 and DC-SIGN to search for other gp120 binding proteins. In addition, we will use similar screening methods to search for endogenous ligands to DC-SIGN, other than the established ICAM-2 and ICAM-3 ligands, in order to further understand the how these endogenous ligands affect HIV binding and transfer.

Currently, we have chosen K562 as our target cells for our retroviral cDNA screen. K562 express little or no endogenous ligands to gp120 and DC-SIGN and we have shown MMLV-based retroviral GFP reporter virus was able to efficiently transduce K562 cells. We have devised a strategy to pre-enrich for gp120-Fc binding cells by panning with magnetic beads (Miltenyi) coupled with anti-PE antibodies. Our studies show that we were able to achieve a 24-fold and 70-fold enrichment when starting out with 0.5% or 0.01% DC-SIGN positive cells, respectively. Additionally, we are able to obtained milligram amounts of properly re-folded soluble DC-SIGN that binds to gp120 in a reproducible and specific fashion to use in the cDNA library screen.

We will plan to use this pre-enrichment strategy to pan our retroviral cDNA library transduced K562 target cells until at least 5-10% of cells are gp120-Fc positive. We will then subject this pre-enriched cell population to traditional FACS sorting. The discovery of the full complement of gp120 binding receptors on dendritic cells, in addition to additional endogenous ligands to DC-SIGN will aid efforts to understand the biology of dendritic cell mediated viral transfer.

Basic Sciences

The N-terminal Region of SIV but not HIV-1 Nef Associates with a Novel PAK-related Kinase Activity

Presenter: Erwin Antonio, UC-Davis

Collaborators: Erwin Antonio, Scott Wong, Michael Ye, Sarah Goodell, Earl T. Sawai

Principal Investigator: Earl T. Sawai

HIV/SIV nef encodes a membrane-targeted accessory protein (~27-34 kDa) that is important for the unperturbed development of AIDS. Multiple intracellular functions have been described for Nef, including CD4 and MHC I downregulation, cellular activation through the modulation of signaling pathways, and the enhancement of virion infectivity. The recruitment of cellular serine/threonine, p21-activated kinase (PAK) by Nef is a conserved property of HIV and SIV. This interaction leads to the activation of PAK (i.e. autophosphorylation of p62), a phenotype that correlates with disease progression in SIV-infected rhesus monkeys.

Our previous studies map the central core region of both HIV and SIV Nef as a determinant of PAK binding and activation. In this study, we demonstrate that a region of the N-terminus of SIVmac239 Nef also associates with a kinase activity that phosphorylates an ~49 kDa protein (p49). This kinase activity appears to be different from that associated with the central core region of Nef as autophosphorylation of PAK (p62) is not observed in immunoprecipitates of Nef mutants that only contain the N-terminus. Moreover, we have found that the N-terminus of SIV Nef co-immunoprecipitates with PAK using an anti-PAK antibody. We observed that the first 108 amino acids of SIV Nef are sufficient for this interaction in co-immunoprecipitation analyses of CD8-Nef fusion proteins. Furthermore, the N-terminal kinase activity is found only for Nef molecules containing the N-terminal segment of SIV Nef but not of HIV Nef, as characterized for CD8-HIV/SIV Nef chimeras that exchange N-termini. Further analyses suggest that the N-terminal p49 signal is not a derivative of p62 but instead an unrelated protein that serves as a substrate for PAK.

In conclusion, we have identified two independent binding domains of SIV Nef that are important for interacting with PAK. The kinase activities associated with each domain appear to be distinct: the N-terminus mediates p49 phosphorylation whereas the core region is responsible for p62 autophosphorylation. The N-terminal kinase activity does not associate with HIV-1 Nef, which retains the ability to induce autophosphorylation of p62. We speculate that these distinct phosphorylation profiles represent a fundamental difference in the mechanism of Nef-mediated PAK activation by HIV and SIV. Taken together, these results indicate that Nef-PAK interaction is highly conserved for HIV and SIV and may represent an important target for the development of HIV therapeutics.

Basic Sciences

Mechanism of Enhancement of Virus Production by HIV-2 Env

Presenter: Paula Cannon, Children's Hospital Los Angeles

Authors: Beth Noble, Paolo B. Abada, Paula M. Cannon

Principal Investigator: Paula Cannon

UARP Award Number: ID03-CHLA-036

The ability of HIV to cause disease is dependent on continuous and high-level production of virus in the body over a number of years. We are interested in events that govern the efficiency with which infected cells produce virus, including those determined by two different HIV proteins – the Vpu accessory protein in HIV-1 and its counterpart in HIV-2, the Env glycoprotein. Although several studies have addressed how the Vpu protein acts to increase virus production, the mechanism by which the HIV-2 Env mediates this process has received limited attention and is relatively unknown.

Our studies of HIV-2 Env have determined that two separate domains in the protein are involved. First, a tyrosine-based motif in the cytoplasmic tail (YRPV) is absolutely required. Interestingly, the HIV-2 tail can be functionally replaced by the HIV-1 tail, which also contains this motif, despite the fact that the HIV-1 Env does not itself stimulate budding. Using chimeric HIV-1/HIV-2 Envs, we have mapped this second, HIV-2-specific functional domain to the ectodomain of the protein. We have further demonstrated that both functional domains are required to be present in *cis* on the same molecule, suggesting an interaction.

The mechanism underlying the enhancement of budding is at present completely unknown. Using a combination of molecular and cell biology approaches, we are investigating the cellular machinery involved in this process. Increased understanding of both the viral and host cell factors involved in these events may lead to the identification of novel anti-HIV targets for drug development.

Basic Sciences

Use of Artificial Transcription Factors to Inhibit HIV-1 Transcription

Presenter: Scott R. Eberhardy, The Scripps Research Institute

Collaborators: David J. Segal, Joao Goncalves

Principal Investigator: Carlos F. Barbas, III

UARP Award Number: F03-SR-214

Despite impressive advances in the treatment of AIDS, many obstacles remain in the goal of long-term control of HIV replication in infected patients. Inhibition of HIV-1 transcription is a potential point of control for inhibition of viral replication. Our laboratory has developed the ablility to target a specific DNA sequence through the use of polydactyl zinc finger proteins (ZFP). By appending an activation or repression domain to a given ZFP, specific upregulation or downregulation of a gene may be achieved. With this study we hope to synthesize ZFPs that could repress HIV-1 gene expression.

For this study, a number of ZFPs that bind to unique 18 bp sequences of the HIV-1 LTR were designed and the KRAB repression domain was fused to these proteins to repress transcription of HIV-1. Sequences were targeted around the HIV-1 promoter region both upstream and downstream of the transcription start site. In addition, ZFPs were constructed that would bind to the highly conserved $tRNA^{lys}$ primer binding site. The ZFPs were tested for their ability to inhibit transcription of a luciferase reporter driven by the HIV-LTR. Of the constructs tested, two ZFPs were found that showed a 10-20 fold inhibition of the luciferase construct. One of these, KRAB-HLTR3, binds near an Sp1 binding site upstream of the transcription start site, while the other ZFP, KRAB-PBS2, binds to the primer binding site. Subsequent experiments have shown that these proteins are also able to inhibit replication of several strains of HIV-1 in a primary cell line following stable lentiviral delivery.

Future studies in our lab will try to determine the identity of human genes needed for HIV-1 infection using combinatorial libraries of polydactyl ZFPs. By combining zinc finger domains with known sequence specificity, we have generated libraries of ZFPs that have the potential to regulate every gene in the human genome. The library will be introduced into cells that will be infected with HIV-1, then a population of cells that is more resistant (or more susceptible, depending upon the selection strategy) will be isolated and single clones will be amplified to determine the sequence of the ZFP responsible for the effect and find the gene that it regulates. Using these methods we hope to find ZFPs that can be used to treat AIDS and also to discover novel genes that provide druggable targets.

Basic Sciences

Structural and Functional Studies of the AAA ATPase Vps4

Presenter: Timothy D. Fenn, Stanford University

Collaborators: Steven Chu, Nikolaus Grigorie

Principal Investigator: Timothy D. Fenn

UARP Award Number: F03-ST-216

Tracking of cellular cargo requires a number of targeting and processing enzymes. During viral infection, parts of the cellular transport machinery are utilized in order to process and export viral components, and thus permit virus propagation. One such component is Vps4, a cellular sorting protein exploited by HIV-1 during viral budding. However, the exact mechanism and utility of Vps4 is not currently well known or understood. Through X-ray crystallographic analysis and single molecule (a technique by which discrete kinetic and single enzyme properties can be elucidated) experiments, we are studying the Vps4 mechanism such that its role in HIV-1 budding, and cellular transport in general, can be better understood.

Basic Sciences

Nuclear factor kappaB (NF-κB) Regulation by Inhibitor kappaB (IκB) Proteins

Presenter: Gourisankar Ghosh, UC-San Diego

Principal Investigator: Gourisankar Ghosh

UARP Award Number: ID03-SD-051

IκB proteins regulate transcriptional activities of NF-κB dimers primarily by modulating the nucleo-cytoplasmic partitioning of NF-κB. Using x-ray crystallography and biochemistry, we have elucidated the mechanism of inactivation of NF-κB by the prototypical IκB proteins, IκBκ and IκBβ, at a molecular level. Unprocessed p105 and p100, the precursors of p50 and p52, respectively, also function as inhibitors of NF-κB. Our understanding of why these precursor molecules are processed in a limited manner and how these unprocessed atypical IκB proteins non-specifically inhibit NF-κB is limited. Our current work focuses on how NF-κB inhibition by various IκB proteins provides specificity in gene regulation.

Basic Sciences

NF-κB p50 biogenesis involves proteasome-mediated endoproteolytic cleavage and asymmetric processing of the p105 homodimer

Presenter: Anu Krishnamoorthy, UC-San Diego

Principal Investigator: Anu Krishnamoorthy

UARP Award Number: F02-SD-203

As a member of the inflammation, cell growth, and apoptosis regulating NF-κB transcription factor family, the protein p50 plays critical roles in the regulation of gene expression by forming potent transactivating dimers with other members of the family, including RelA, c-Rel, and RelB., NF-κB remains in the cytoplasm in an inactivated form, complexed to inhibitory proteins belonging to the IκB family. In response to various stimuli, active NF-κB migrates to the nucleus. Nuclear NF-κB then specifically binds a ten base pair DNA motif in the promoters of many response factor genes activating their transcription. The most abundant form of NF-κB is the p50•p65 heterodimer. The biogenesis of p50 from its precursor, the transcriptional inhibitor p105, is still poorly understood.

X-ray structures of IκB/NF-κB complexes allow us to propose and test a new model for p50 biogenesis. We propose that the p105 homodimer is asymmetric in which one C-terminal IκB-like Region (CIR) associates with the N-terminal p50 dimer while the other CIR remains unbound. We show that the 20S proteasome endoproteolytically cleaves the latter and selectively degrades it moving towards the C-terminus, thereby forming the p105/p50 complex. Degradation of the N-terminus is inhibited by a glycine rich region.

It is now known that several viruses, including the human immunodeficiency virus (HIV-1), use NF-κB for their own transcriptional activation. This has been made possible by the incorporation of NF-κB binding sites in the enhancer region of the viral genome. Constitutive NF-κB activity in cells infected with virus enhances viral infectivity. Advances in our understanding of cellular regulation of p50 would help in the determination of the role of this crucial transcription factor in the regulation of HIV persistence.

Basic Sciences

Cyclin T1 Polymorphisma Implications for HIV Replication

Presenter: Xin Lin, UC-San Francisco

Principal Investigator: Xin Lin

UARP Award Number: F02-SF-200

Human cyclin T1 is the critical host cellular factor that supports HIV Tat transactivation. Only the human but not the cyclin T1 from mouse supports HIV replication due to a single amino acid change. We have recently found four different splicing and two point mutation polymorphisms in cyclin T1 present in humans or primates. We have studied the functional consequences of such polymorphisms in support HIV Tat transactivation by examining them in NIH3T3 cells for the rescue of the Tat phenotype. Our studies indicate that these different cyclin T1 mutants have distinct functional consequences in supporting HIV Tat transactivation. Some of these mutant forms of cyclin T1 can also have dominant negative effect in blocking Tat transactivation. We have also performed quantitative RT-PCR to measure the ratios of different splicing mutant of cyclin T1 in resting and activated lymphocytes. These studies might lead to gene therapy and predict the future course of HIV infection

Basic Sciences

Three-dimensional Structure of HIV Integrase-DNA Complexes by Electron Microscopy and Single Particle Image Analysis

Presenter: Gang Ren, The Scripps Research Institute

Collaborators: Gang Ren, Kui Gao, Rick Bushman, Mark Yeager

Principal Investigator: Gang Ren

UARP Award Number: F02-SRI-211

A critical early event in HIV infection is reverse transcription of the viral RNA genome and integration of the resulting cDNA into the host chromosome. The latter step is accomplished by the virally-encoded integrase enzyme, a potential therapeutic drug target. Integrase is the only one of the three HIV enzymes for which clinically useful inhibitors are not available. Integrase is nevertheless an attractive target for antiretroviral drugs, since it is clear that integration is required for viral replication. In addition, there are no known cellular enzymes that resemble integrase in sequence or function, so inhibitors of integrase have the potential to be relatively nontoxic.

We are using electron microscopy and single particle image analysis to examine structure/function relationships of HIV integrase/DNA complexes. In this approach each particle image represents a particular two-dimensional projection view of the three-dimensional (3D) object, and computational analysis sorts the various views into groups that can be averaged. Merging of these class averages yields a three-dimensional density map.

Recombinant, His-tagged HIV integrase was purified by nickel chelation chromatography. Images of negatively stained integrase- DNA complexes were recorded using a Philips/FEI electron microscope operating at 100 kV. Thus far, ~2,000 individual particle images have been processed, and we have derived a 3D density map at ~27 Å resolution. The complex has a triangular base with an edge measuring ~85 Å and a thickness of ~38 Å. There are two ~45 Å arms that extend from the base, one with a diameter of ~28 Å and the second with a diameter of ~35 Å. The arms and base form a distinctive "horseshoe" shape that may serve to bind DNA. The 3D map provides a molecular envelope into which we now plan to dock the atomic resolution X-ray structures of integrase domains. The resulting pseudo-atomic model will allow us to test various models that have been proposed for the complex.

Basic Sciences

Inhibition of Tat-Mediated Transactivation of the HIV Promoter By SDF-1γ, a Novel Splice Variant of the SDF-1 Gene

Presenter: Eric Verdin, UC-San Francisco

Principal Investigators: Christian Callebaut, Eric Verdin

UARP Award Number: CC02-SF-002

We have isolated a cDNA for a third splice variant of the human SDF1 gene. This novel cDNA encodes a novel protein, SDF-1γ, with the primary sequence identical to SDF-1α and an additional 30 amino acids at the C-terminus. Part of this C-terminal extension shares strong sequence homology with the RNA binding domain of the HIV-1 Tat protein. To test the possibility that SDF-1γ might compete with Tat for TAR binding, we co-transfected expression vectors for Tat and SDF-1γ with a luciferase reporter gene driven by the HIV promoter. SDF-1γ, but not the closely related SDF-1α, inhibited Tat-dependent transactivation of the HIV promoter in a dose-dependent manner. No significant inhibition of HIV transcription occurred when Tat-independent transcription was assayed. Immunofluorescence microscopy analysis of tagged SDF-1γ showed a subcellular localization both in the cytoplasm and in the nucleolus. In vitro binding experiment demonstrated that SDF-1g binds TAR RNA. Finally, overexpressed SDF-1γ inhibited the replication of both X4 and R5 HIV strains in several cell lines. These results indicate that SDF-1γ can inhibit Tat-dependent HIV transcription and suggest a role for SDF-1γ in modulating HIV replication *in vivo.*

Basic Sciences

Identification of a Novel Carboxy-terminal Domain of the SIV_{mac239} gp41 Intracytoplasmic Tail Important for Inhibiting Nef-Mediated PAK Activation

Presenter: Michael Ye, UC-Davis

Collaborators: Michael Ye, Gary Rhodes, Earl T. Sawai

Principal Investigator: Earl T. Sawai

UARP Award Number: R00-D-136

The envelope (env) gene of HIV and SIV encodes a glycosylated protein (gp160) that is cleaved proteolytically to generate the surface (SU, gp120) and transmembrane (TM, gp41) subunits. The gp120 subdomain of the envelope glycoprotein mediates virus-cell interaction, while gp41 facilitates virus-cell fusion. Interestingly, among the retroviruses, HIV and SIV encode an unusually long gp41 intracytoplasmic domain (ICD; 150-170 amino acids) whose function is not well understood. Unlike the gp41 ICD, Nef function has been well characterized. Nef is a 27-34 kDa myristylated protein that is important for pathogenesis. Nef down-regulates CD4 and MHC-I from the cell surface, activates cellular kinases including PAK and the Src family of kinases, and is critical for virion infectivity and high titer virus replication. Importantly, our lab demonstrated that PAK activation is closely linked to high virus loads and progression to AIDS.

Previously, we reported that the gp41 ICD specifically inhibits Nef-mediated PAK activation in in vitro kinase assays. Using amino- and carboxy-terminus deletion mutations of the ICD, we demonstrated that the ^{839}RSATET^{844} motif, located within an intervening region between the lentiviral lytic peptides (LLP-1 and LLP-2), was important for inhibiting PAK activation. This gp41 ICD-mediated inhibition of PAK activation was dose-dependent. Additionally, both HIV and SIV envelope proteins inhibited PAK activation. Presently, our analysis of the SIV_{mac239} gp41 ICD reveals that the RSATET motif is encompassed by a putative tryptophan-rich domain. This novel domain is comprised of three WxxxxE repeats (where W represents tryptophan, E represents glutamate, and x represents any amino acid) that are separated by five amino acids and is located between LLP-1 and LLP-2. Our deletion mapping studies suggest that either LLP-1 or LLP-2, in conjunction with the RSATET motif, is necessary and sufficient for inhibiting PAK activation. Lastly, point mutations of the ICD reveal that two highly conserved residues within the RSATET motif, are important for inhibiting PAK activation.

In conclusion, we have identified a novel, tryptophan-rich domain of the SIV_{mac239} gp41 ICD. The putative WxxxxE domain, which encompasses the RSATET motif, appears to be important for inhibiting Nef-mediated PAK activation. This is the first demonstration that a viral structural protein, gp41 ICD, is capable of modulating the activity of a viral regulatory protein, Nef. More importantly, the ICD might inhibit Nef-mediated PAK activation to regulate virus replication and, therefore, the pathogenic potential of HIV and SIV. Thus, the ICD of envelope might represent a novel therapeutic target.

Basic Sciences

Potential Role of the Protein Kinase CDC2L5 in Regulating HIV Transcription

Presenter: Jasper Yik, UC-Berkeley

Collaborators: Jasper H. N. Yik, Zhiyuan Yang, Qiang Zhou

Principal Investigator: Jasper Yik

UARP Award Number: F03-B-204

Replication of HIV in its host requires the participation of the host's co-factor P-TEFb (Positive Transcriptional Elongation Factor b), which is composed of cyclin-dependent kinase 9 (CDK9) and its regulatory subunit cyclin T1 (CycT1). A related protein kinase, called CDC2L5, shares extensive sequence homology with CDK9, and thus may have functions related to those of CDK9. Here, we report that similar to CDK9, CDC2L5 is also associated with CycT1 and thus should be reclassified as a new member of the cyclin-dependent kinase family. Moreover, CDC2L5 can also bind to the 7SK RNA, which is involved in the inhibition of CDK9's activity and suppression of HIV transcription. These results suggest that the activity of CDC2L5 is under similar regulation as that of CDK9. Future studies are required to determine the functions of CDC2L5, in relation to CDK9's ability to activate general and HIV gene transcription. The information gains from this study could be useful for developing new methods for AIDS therapy by specifically targeting these HIV-related cellular events that involve CDK9 and CDC2L5.

Basic Sciences

Regulation of transcriptional elongation of HIV-1 LTR

Presenter: Sunnie Yoh, The Salk Institute for Biological Studies

Principal Investigator: Sunnie Myeung-sun Yoh

UARP Award Number: F02-SIBS-215

HIV-1 transcription is characteristically attenuated at the level of initiation and elongation in the absence of the Tat transactivator. The molecular basis of attenuation is not well defined. Although nascent HIV-1 transcripts form a hairpin structure and are capable of pausing RNA polymerease II (RNAPII), removal of the TAR region fails to release the block to elongation. Attenuation may therefore arise from the basic structure of the HIV-1 core promoter. Recently, various celluar factors have been identified that regulate transcriptional elongation. Negative elongation factors are required for the block at the early step of the elongation where as other positive factors have been shown to be required for the efficient elongation by RNAPII. Thus, the transcriptional attenuation might also result from either the presence of the negative elongation factors at promoters or absence of postive elongation factors or both. The goal of this projet is to characterize the mechanisms that govern transcriptional elongation of HIV-1 LTR both in the absence and presence of Tat. My specific aims are to identify the elements in the HIV-1 core promoter that attenuate transcription elongation in the absence of Tat, to analyze the role of a cellular elongation factor Spt6 in the HIV-1 transcription and to develop a chromatin-based cell free transcription system that recapitulates elongation control by a cellular enhancer and Tat as well as Spt6.

To dissect the core promoter contribution to transcription attenuation, the elements in the HIV-1 core promoter structures are systematically replaced with mammalian counterparts and assayed for the alleviation of the transcriptional attenuation in the absence of Tat. When the HIV-1 initiatior(INR) in the core promoter is replaced with a canonical INR element, the transcriptional activity is slightly enhanced both in the in vitro transcription and in vivo transfection assays. Secondly, I have identified that a positive elongation factor spt6 can alleviate the the early elongation block in HIV-1 transcription significantly. The positive effect of Spt6 on elongation was evident not only on non-chromatin HIV-1 templates but also on the templates that are assembled into chromatin. Lastly, I develped a chromatin-based in vitro transcription system that recapitulates elongation control by the cellular enhancers and Tat as well as Spt6.

My current hypothesis is that spt6 is a general positive elongation factor for RNAPII transcription whose association with RNAPII is required for a processive transcriptional elongation. Data from both my lab and others suggest that in vivo, Spt6 is recruited to the RNAPII complex shortly after gene activation and migrates with the elongating RNAPII along the gene. Thus, the transcriptional attenuation by HIV-1 LTR might due to the inability to recruit Spt6 by RNAPII complex assembled on HIv-1 core promoter where as ones assembled at other cellular genes can. Although transcription of many cellular genes is processive in vitro, in vivo it is marked by a frequent pausing. The pausing and restart of transcription are achieved by recruiting different transcription factors to RNAPII at each step. Currently, only HIV-1 LTR transcription can be efficiently stalled in vitro which enables one to dissect the mechanisms of elongation control and ultimately elucidate how cellular gene transcription is regulated at the elongation level.

Basic Sciences

Target site preferences of APOBEC3G on HIV-1 reverse transcripts

Presenter: Qin Yu, The Salk Institute for Biological Studies

Collaborators: Q. Yu, R. König, S. Pillai, M. Kearney, S. Palmer, D. Richman, J. Coffin, N. R. Landau

Principal Investigator: Qin Yu

UARP Award Number: F03-SIBS-215

HIV-1 Vif blocks the antiviral activity of human APOBEC3G, a cellular cytosine deaminase. APOBEC3G encapsidated into the Vif-deleted virions deaminates cytosines of the viral reverse transcripts to uracil on the next round of infection. HIV-1 Vif does not block the antiviral activity of primate and mouse APOBEC3G. Here, we present a detailed study of the mechanism of deamination and the target site specificity of human, mouse and African green monkey (AGM) APOBEC3G.

Wild type and Dvif HIV-1 produced in the presence or absence of APOBEC3G was used to infect cells. The newly synthesized and integrated viral DNA from the infected cells was amplified. Nucleotide sequences of LTR, gag, pol, env, and nef were determined. The sequence data showed that APOBEC3G deaminated the HIV-1 reverse transcripts over the entire genome. Deamination occurred in a graded frequency over the genome in a direction corresponding to the predicted length of time during reverse transcription that each region is not double-stranded DNA. Mutations were most frequent in env and least frequent in U3. Although mutations are almost exclusively G→A changes in the plus-strand, C→T changes were found in regions where the plus-strand transiently becomes single stranded during reverse transcription. The consensus target sites for human APOBEC3G deamination in di-, tri-, and quadruple-nucleotide context were determined. AGM APOBEC3G had a consensus target sequence similar to the human enzyme, whereas mouse APOBEC3G was less stringent. A small number of integrated proviruses was generated from Vif- virions containing human APOBEC3G. The integrated proviruses were heavily mutated and unable to encode functional proteins. Interestingly, most of the integrated proviruses contained mismatched DNA strands, with less mutations in the minus strand compared to the plus strand.

In summary, our results demonstrated that 1) the hypermutation rate is related to the length of time that a region is not in a double-stranded DNA form; 2) Human APOBEC3G preferentially introduces mutations at consensus target sites; 3) APOBEC3G induced mutations were maintained in the integrated provirus plus-strand.

Basic Sciences

In Vitro Study of the Efficacy of ImmunoPro Rx and Ganciclovir in Inhibiting the Growth of CMV

Presenter: Mitchell Abrahams, BioMolecular Sciences, Inc.

Authors: Mitchell Abrahams, Louise G. Chatlynne, Roger Mazlen, Dharam V. Ablashi

Principal Investigator: Mitchell Abrahams

Human Cytomegalovirus (CMV) is a β-herpesvirus that is known to cause disease and complications in transplant patients and other immunocompromised people. ImmunoPro Rx (IP) is a biologically active whey protein, from cows that have not been treated with hormones. It contains undenatured milk proteins, lactoferrin, immunoglobins, and active peptides. IP can be viewed as a delivery system of both cysteine and lactoferrin. Ganciclovir is a nucleoside analog with know efficacy against CMV. The current study was undertaken to see if a synergistic antiviral effect would occur if Ganciclovir and IP were used in concert. Cultures of primary human foreskin fibroblasts were infected with CMV, strain AD 169 at 10X $TCID_{50}$. These cultures were then treated with IP at 1,000, 500, 250, 125, and 62.5 μg/mL. Ganciclovir was tested at 12, 4, 1.33, 0.44, and 0.147 μM. These same dosages of Ganciclovir were also combined with either 1,000 or 125 μg/mL IP. Uninfected cells were also dosed at the same combinations to test for cytotoxicity. The cultures were incubated for 7 days and then a cytoproliferation assay was run on the cultures. The cytoproliferation assay uses a fluorescent dye that measures reduction/oxidation, and therefore measures actively metabolizing cells. CMV infection causes cell death. Therefore fluorometric values of infected cultures with drugs that are higher than those without drugs would indicate drug efficacy. The values for replicate cultures at the same experimental condition were averaged. The negative control, uninfected cells with no experimental reagent, was fixed at 100%, and all other experimental conditions were calculated as a percentage of the negative control. No cytotoxicity was seen for the two drugs, either alone or in combination. Most concentrations of IP by itself had a negligible effect on the growth of the virus, except for the lowest dosage used 62.5 μg/mL, which showed some inhibition of viral growth, i.e. more growth of healthy cells. Most dosages of Ganciclovir alone showed some inhibition of viral growth; 4 μM gave the most inhibition. When Ganciclovir was combined with IP at 1000 μg/mL, little or no effect on the virus was seen. However, when Ganciclovir was combined with IP at 125 μg/mL, a marked synergy was seen was seen between the two drugs at all concentrations of Ganciclovir except 12 μM, where little change was seen over Ganciclovir by itself. The greatest viral inhibition was seen with 4 μM G and 125 μg/mL IP; those cultures grew nearly as well as the uninfected control.

Basic Sciences

In Vitro Study of the Efficacy of ImmunoPro Rx and Foscarnet in Eliminating the Infectivity of HHV-6A

Presenter: Mitchell Abrahams, BioMolecular Sciences, Inc.

Authors: Mitchell Abrahams, Louise G. Chatlynne, Roger Mazlen, Dharam V. Ablashi

Principal Investigator: Mitchell Abrahams

HHV-6A is the most common strain of the virus found in cases of multiple sclerosis (MS) and chronic fatigue syndrome (CFS). Thus far Foscarnet is the drug that has been found to be the most effective against HHV-6 infection, but physicians are reluctant to use it because of its toxicity. Here we demonstrate that ImmunoPro Rx, biologically active whey protein, is effective against HHV-6 either alone or in combination with Foscarnet. Cultures of HSB-2 cells, a T-lymphoblastoid cell line derived from a patient with acute lymphoblastic leukemia, were infected with HHV-6A, GS strain at a multiplicity of infection (MOI) that caused 42% of the cells to die in 10 days (assay 1). These cultures were then treated with ImmunoPro Rx (IP) at 1,000, 100, 10, 1, 0.1, or 0 μg/mL. Uninfected cells were also dosed at the same concentrations to test for cytotoxicity. The same test system was used to test combinations of ImmunoPro Rx and Foscarnet. In this assay a higher HHV-6 MOI was used so that only 12% of the cells were left alive after 7 days (assay 2). In this assay, Foscarnet was tested at 300, 200, 30, 15, and 7.5 μg/mL alone, and these same dosages of Foscarnet were also combined with either 1,000 or 125 μg/mL IP. A cytotoxicity control without virus was run for both assays. After assay 1 was cultured for 10 days and assay 2 was cultured for 7 days, a cytoproliferation assay was run on the cultures. The cytoproliferation assay uses a fluorescent dye (Alamar Blue) that measures reduction/oxidation. The values for replicate cultures at the same experimental condition were averaged. The negative control, uninfected cells with no experimental reagent, was fixed at 100%, and all other experimental conditions were calculated as a percentage of the negative control. IP demonstrated virtually no cytotoxicity at any concentration used. When used alone Foscarnet demonstrated severe cytotoxicity at 300 μg/mL and mild cytotoxicity at all other concentrations used. When used in combination with IP at 1,000 μg/mL Foscarnet had only mild cytotoxicity at 300 and 200 μg/mL, and none at lower concentrations. With 125 μg/mL IP the cytotoxicity of Foscarnet was also reduced, but not as dramatically. In assay 1 (IP alone, lower viral MOI) with 1,000 μg/mL of ImmunoPro Rx no viral activity was evident (99.5% of negative control), at 100 μg/mL partial inhibition of the virus was noted (79.7% of negative control). In assay 2 (drug combination, higher viral MOI), neither IP nor Foscarnet alone was efficient at maintaining healthy cells in the presence of virus, but in combination both concentrations of IP were able to eliminate all (100% with 1,000 μg/mL IP) or nearly all (94.3% of negative control with 125 μg/mL IP) the HHV-6 with only 7.5 μg/mL of Foscarnet present. At levels of Foscarnet above 30 μg/mL the efficacy of the combinations fell off due to the cytotoxicity of the Foscarnet. IP is able to eliminate lower levels of HHV-6 infectivity by itself, and in combination with low levels of Foscarnet it can eliminate very high levels of HHV-6. IP can counter the cytotoxic effects of Foscarnet.

Basic Sciences

Ubiquitin Targeting to Enhance Immune Response to HIV Antigens

Presenter: Don J. Diamond, Beckman Research Institute of the City of Hope

Collaborators: Pirouz Daftarian, Rahul Sharan, Saima Ali, Wahajul Haq, Jeff Longmate

Principal Investigator: Don J. Diamond

UARP Award Number: ID02-BRI-054

Introduction: The goal of developing a vaccine strategy for HIV infection remains elusive. Past initiatives that focused exclusively on the humoral response have been disappointing, when clinical trials of these concepts have been tested in humans. Newer approaches that focus on the cellular arm of the immune system have taken hold as the principal means by which HIV infection may be controlled in human populations. Since the HIV genome is relatively small, and the major antigens have been defined, we concentrated on investigating the immune response to these major antigens in mouse models as well as in laboratory bench studies of these antigens. Two antigens that have been a major focus of our studies are pol and gag. We have focused on the reverse transcriptase (RT) portion of the pol gene in our current strategies.

Topic Addressed: The purpose of this grant is to investigate the influence of a genetic modification of HIV genes that are known to be the target of the human immune response. This modification is referred to as ubiquitination, or the addition of the ubiquitin gene to the HIV gene being evaluated. This process often results in a protein that has increased rates of degradation, which has been associated with increased immune recognition in animal model systems. We have undertaken the task of evaluating whether the ubiquitin modifications of the HIV-pol and gag genes will render them better recognized by the immune system of mice that are engineered with a human immune response transplantation antigen, HLA A2. These mice are serving as the recipients of HIV genes engineered with the ubiquitin modification into attenuated poxvirus vectors. This model will allow us to test both the immunogenicity and the capacity for protection against these antigens by HIV vaccines either in the form of peptides or the genes expressed in poxviruses. We also have the opportunity to evaluate the recognition capability of these recombinant poxviruses towards a human HIV infected T cell line that was obtained from the NIH AIDS Reference and Reagent Collection. We have made substantial progress in constructing poxviruses that express the HIV genes discussed in the original application. These include native sequences or codon-optimized genes prepared by Dr. Gary Nabel's group at the NIH Vaccine Research Center. We have also made progress in evaluating whether more virulent poxviruses (Western Reserve Strain) that express the HIV genes *gag* and *pol* can be used as a challenge virus in a vaccine model in which a peptide vaccine is administered to the mice prophylactically. We have made significant progress in this area, and recently published a report in the Journal of Immunlogy that substantiates the validity of the protection model after vaccination with the peptide vaccine. We have been able to develop a powerful analysis tool more informative than in vitro studies that we originally proposed. The modified forms of the HIV antigens have been evaluated by Western Blot, as well as a challenge study in transgenic mice. More recently, we have been evaluating the use of CpG DNA as an adjuvant for the peptide vaccines. A variety of peptides that are fusions that are CTL and T-help epitopes have been evaluated in the

transgenic mouse model with and without CpG DNA. Our conclusion is that the vaccines benefit from the inclusion of CpG DNA, and they are relatively ineffective without it. This effectiveness has been translated into protection from vaccinia virus challenge using both native and ubiquitinated forms of the HIV pol gene. We also evaluated the HIV-gag gene using epitopes that were predicted to be immunogenic several years ago. These vaccines are also potent in the presence of CpG DNA that is a phosphorothioate-substituted molecule. Finally we have also conjugated the DNA to the fusion peptide to obtain a more sensitive model for use in either prophylactic or therapeutic vaccination models. This concept will be discussed, and examples of its successful use will be illustrated.

Impact: The challenge study refinement which provides guidance in choosing which vectors will be most efficacious in the human studies is an improvement that has been instituted since submission of this proposal. This refinement in experimental design should lead to a more interpretable study, since it has been established that immunogenicity is not inexorably connected to the protective capacity of a vaccine. These studies will improve on our original proposal to follow individual vector forms of HIV antigens for further analysis in larger scale studies as vaccine candidates for prevention of HIV infection. We will also discuss the impact of CpG DNA as an adjuvant in this model system.

Basic Sciences

Toward an Animal Model of RNA Interference against Retroviral Pathogenesis

Presenter: Wen-Yuan Hu, The Salk Institute for Biological Studies

Principal Investigator: Frederic D. Bushman

UARP Award Number: F03-SIBS-213

Acquired immunodeficiency syndrome (AIDS) induced by HIV-1 has been a major global health problem. The current treatment of HIV-1 infection with reverse transcriptase and protease inhibitors in combination therapy represents a major breakthrough in the battle against AIDS. Although these inhibitors have dramatically reduced the rate of HIV and AIDS-related mortality, they can not eradicate virus and also have shown problems with side effects, toxicity, and emerging drug-resistant strains. Also, the difficulty in producing a highly effective vaccine has revealed the need to develop new drugs and new therapeutic strategies to slow the spread of the virus. In the past year, several independent groups including ours have demonstrated that RNAi can be engineered to target HIV genomic RNA. The data suggest that RNAi might become an alternative therapeutic approach to inhibit HIV replication.

RNA interference (RNAi) is evolutionarily conserved in plants and animals, and is thought to protect cells against viruses and transposons. The RNAi pathway knocks down gene expression by degrading the target mRNA using short (19-23 bp) interfering RNA (siRNAs) complementary to the target gene sequence for recognition. This then directs a bound nuclease to cleave the targeted mRNA. In this study, I focus on investigating approaches to inhibiting HIV replication in tissue culture cells, and to develop a mouse model that will allow inhibitory strategies to be tested in vivo.

I have begun experiments designed to establish a mouse model to study whether RNAi can be stably triggered to protect mice from retroviral infection in vivo. Friend virus (FV) has been selected as our model. The Friend virus is a complex of a replication-defective spleen focus-forming virus (SFFV) and a replication-competent murine leukemia virus (MLV) helper. Friend virus causes a multistage erythroleukemia when the FV envelope protein (gp55) binds to the erythropoietin receptor (EpoR) on the cell surface. It induces massive splenic proliferation of erythroid precursor cells. Infected mice develop heptosplenomegaly and eventually die due to malignant tumor progression. I have constructed a series of oligonucleotides encoding short hairpin sequences complementary to the FV gp55 gene and also MLV env gene. A tissue specific polII (EpoR) promoter and a polIII (U6) promoter were used to express these shDNAs. The inhibitory effect of the RNAi constructs against SFFV and MLV replication was primarily examined in the tissue culture before introducing into the transgenic mice. My preliminary data have shown that the ICR mice infected by Friend virus developed heptosplenomegaly, and the production of Friend virus was reduced by our engineered constructs in tissue culture. Those DNA constructs that are active in in vito experiments have been delivered into mice to generate RNAi mouse lines. Progress in this study will be described. I believe that this study will contribute to developing RNA-based therapeutic strategies to prolong infected patient's lives beyond the limits of current therapies.

Basic Sciences

New Agents for the Treatment of HIV

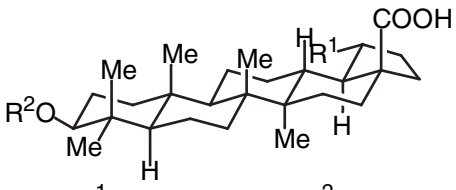
Presenter: Michael E. Jung, UC-Los Angeles

Collaborators: Brian Duclos, Aaron Novack

Principal Investigator: Michael E. Jung

UARP Award Number: ID02-LA-007

Good progress has been made toward the total synthesis of several structural analogues of the potent anti-HIV agents, the betulinic acid esters and diesters, 2 and 4, which we hope will have enhanced antiviral activity. In particular we have carried out several steps of this very long synthesis and are nearing the key step in the construction of these molecules. In particular we are examining two general approaches, one involving a [3,3] sigmatropic shift and the second a cycloaddition approach using either a direct [4 + 2] cycloaddition or a two-step process using first a [2 + 2] cycloaddition to an allene followed by a formal [3,3] sigmatropic rearrangement to generate the contiguous bis-quaternary centers in very hindered cyclohexene unit, that is one of the most serious synthetic challenges of this molecular skeleton which has never been synthesized before. We have completed an efficient synthesis of the two smaller components of the large pentacyclic molecule and are now close to attempting their coupling which will take several chemical steps. While the success of the synthesis is by no means guaranteed, we are confident that we can find methods or sets of conditions that will allow us to prepare these materials. Once they are in hand, we will carry out extensive antiviral testing to determine their activity and mode of action.



1 R^1 = CH(Me)=CH_2 R^2 =H
2 R^1 = CH(Me)=CH_2
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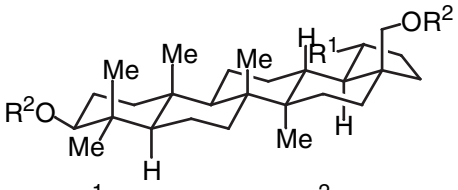


3 R^1 = CH(Me)=CH_2 R^2 =H
4 R^1 = CH(Me)=CH_2
R^2 =$COCH_2C(Me)_2CH_2COOH$

Basic Sciences

Structural and Functional HIV-1 Protease Determinants that Contribute to Protease Inhibitor Resistance

Presenter: Victoria D. Kutilek, The Scripps Research Institute

Collaborators: Dennis A. Sheeter, Holly Heaslet, Dave Stout, John H. Elder

Principal Investigators: Bruce E. Torbett, Victoria D. Kutilek

UARP Award Number: F03-SR-207

Protease and reverse transcriptase inhibitors are the current mainstay therapy against the Human Immunodeficiency Virus (HIV). The HIV-1 protease is an essential enzyme that is responsible for cleaving the viral proteins into individual structural and functional proteins in a sequential and ordered manner required for production of mature and infectious particles. All currently approved FDA protease inhibitors compete with the enzyme's natural viral substrates by binding directly to the active site of the protease, disrupting the enzymatic function of the protease, and thus, inhibiting the production of mature, infectious viral particles. While the current protease competitive inhibitors have been successful in extending the lives of many AIDS (Acquired Immune Deficiency Syndrome) patients by decreasing the HIV-1 replication rate to undetectable levels, a significant number of these patients, approximately 40%, experience a viral rebound due to the development of drug resistance. Furthermore, drug resistant variants of HIV-1 protease are frequently cross-resistant to all classes of protease inhibitors, a burgeoning and serious medical concern. The overall goal of my project is to determine the structure - function relationship of HIV protease as it acquires mutations that confer drug- resistance / cross- resistance. My study will identify regions of the protease that are critical for enzymatic function in addition to identifying regions of the protease that are invariant during the acquisition of drug resistance. These new insights into the mechanistic features of HIV-1 protease will aid in developing new drug design strategies.

Previous work by our laboratory revealed a series of mutations within protease that develop sequentially as HIV viral isolates are grown in the presence of the broad based protease inhibitor, TL-3. This experimental protease inhibitor has been shown to be effective against tissue culture adapted strains of HIV-1 and primary HIV-1 isolates resistant to commercial drugs as well as feline immunodeficiency and simian immunodeficiency viruses. Interestingly, while early mutations in protease only conferred resistance to TL-3, later mutations contributed to the development of cross-resistance. Identification of these pivotal residues in our panel of protease mutants has provided us with the ideal panel to study how the protease structure – function relationship evolves throughout the development of drug resistance and cross-resistance. This panel of drug resistant protease variants will be probed with a random library of RNA aptamers, oligonucleotides capable of discriminating proteins via their three- dimensional structure and altering their function. Using the well recognized SELEX protocol, systematic evolution of ligands by exponential enrichment, RNA aptamers will be generated and individual aptamers that bind to unique regions of each protease variant as well as to conserved regions within all the protease variants will be identified via epitope mapping and activity assays. Crystallographic studies of RNA aptamer – HIV protease complexes will be performed in collaboration with Dr. Stout's Laboratory at TSRI. The structural information obtained will help us elucidate the precise protease determinants recognized by individual aptamers as well as the mechanism in which the aptamer might

alter enzymatic function. Previous attempts to develop RNA aptamers and conduct biophysical studies of HIV-1 protease have had limited success due to the highly unstable biochemical nature of the enzyme. We have engineered a protease expression library, including an inactive form of the enzyme to prevent autoprocessing, that we believe will now allow us to perform comprehensive structural studies. We are currently in the process of expressing the inactive constructs of protease and assessing their capability of adapting the proper conformation via chromatography, mass spectrometry, and binding studies.

Once it has been determined that the conformation of the inactive protease is identical to that of the native, active protease, aptamer generation will be pursued. Furthermore, crystallographic studies and biophysical studies characterizing the stability and binding affinity of these drug resistant protease variants alone will also be performed simultaneously with aptamer production. Determination of these biochemical characteristics will provide us with extremely valuable information with regards to the regions of the protease that are being altered and conserved as the enzyme acquires drug resistant mutations, providing a functional understanding of my results obtained from structural studies using aptamers. The research proposed here addresses several of the primary concerns within the HIV community of California, namely, how does drug resistance develop and eventually result in drug failure. In addition, the information obtained from this study will aid us in determining new drug targets and strategies for drug design that will be more efficacious in inhibiting replication of HIV-1 in all of its various drug resistant forms.

Basic Sciences

Synthesis and Biological Evaluation of Novel HIV-1 Integrase Inhibitors

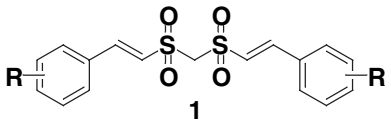
Presenter: Chris Meadows, UC-Davis

Collaborators: D. Christopher Meadows, M. J. Hadd, J. Gervay-Hague

Principal Investigator: Jacquelyn Gervay-Hague

UARP Award Number: D02-D-400

Integrase is one of three viral enzymes used by HIV and is a necessary part of the viral life cycle, responsible for inserting reverse-transcribed, double-stranded viral DNA into the host genome.[1, 2] As part of the ongoing HIV research occurring in the Gervay-Hague laboratories, we have developed a novel compound (general structure **1**) that potently inhibits HIV integrase in enzymatic assays.[3] It was found that the activity of the compounds could be changed by altering the substituents on the aromatic ring. We envision coupling a reverse transcriptase inhibitor to one of our novel integrase inhibitors creating one compound with a dual mode of action. This double-drug strategy has been successfully applied previously, but never with an integrase inhibitor.[4, 5, 6]



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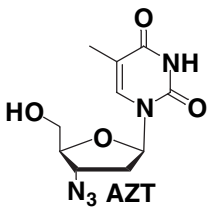
The first stage of this project was to determine if our novel integrase inhibitors would actually translate into anti-HIV agents in the cell, as many integrase inhibitors do not display antiviral activity.[7, 8] Once we had shown that these kind of compounds were indeed active in cellular assays we determined the most active compound to link to a reverse transcriptase inhibitor. To this end we synthesized a library of compounds based on structure (**1**) and tested them in cellular anti-HIV assays. Based on the data from these assays, we found the most active compound to be DCMII117 in table 1 (table 1 compares a novel integrase inhibitor to known anti-HIV drug AZT).

Table 1

Compound Tested	**Conc. Of Test Compound**	**% Reduction (ng/mL)***
DCMII117	10mM	87%
	10mM	98%

*ng/mL of p24 antigen

Having selected the appropriate integrase inhibitor, we are now ready to attempt conjugation of the reverse transcriptase inhibitor. Several methods of conjugation have been envisioned for this. This is where our future work will be focused. The results of the library cellular testing and enzymatic data will be presented.

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Basic Sciences

Inactivated HIV-1 Candidate Vaccine Derived from Human Blood Components

Presenter: Girish N. Vyas, UC-San Francisco

Principal Investigators: Girish N. Vyas, Chia-Rong Wu

Molecularly homogeneous and immunogenic HIV vaccine candidates (proteins/DNA) developed during the past decade have generally failed to induce broadly neutralizing antibodies (NAB) against primary isolates of HIV-1 (pHIV). Recombinant HIV DNA in various microbial vectors induces cytotoxic T-cells (CTL), which successfully prevent or delay the onset of AIDS because of viremia controlled at a very low level but fail to prevent the establishment of chronic HIV infection. Since both CTL and NAB are considered necessary for effective protection against exposure to cell-free as well as cell-associated HIV, a "prime-boost" approach to immunization using CTL-inducing DNA followed by NAB-inducing envelope glycoproteins is now in vogue for large-scale clinical trials.

The natural history of immune response to viral proteins could be mimicked by a novel candidate vaccine, termed HIVACC, which is composed of diverse pHIV-1 isolates propagated in CD4-enriched primary cell substrate (CD4-ECS) and inactivated by established methods that do not alter the immunochemical properties of genetically diverse virion proteins. Conventional HIV-1 culture methods were modified to optimize production of primary isolates of HIV-1 from plasma of blood donors found to have early acute infection when nucleic acid amplification test is positive and antibody response is negative by enzyme immunoassay. HIV-1 expansion was optimized by Immunomagnetic removal of CD8 cells and substitution of the fetal calf serum with serum from human group AB donor. HIV-1 inactivation by three methods is assessed by immunization of mice with HIV-1 inactivated by individual methods. HIVACC is designed to ultimately provide a safe and effective approach to prevention of the HIV-1 infection prevalent in a given population. Priming with CTL-inducing vectored DNA followed by boosting with HIVACC would be an appropriate approach to preventive vaccination against HIV-1. With the concerted effort for making HIVACC in conjunction with local blood services, indigenous production of this unique biological product is possible in developing countries that are most severely impacted by the AIDS pandemic.

Basic Sciences

Identification of small molecule inhibitors of Simian Immunodeficiency Virus Nef and the cellular p21-Activated Kinase

Presenter: Earl Sawai, UC-Davis

Collaborators: Scott W. Wong, Ruiwu Liu, Alan Lehman, Erwin F. Antonio, Michael Ye, Kit Lam, Earl T. Sawai

Principal Investigator: Earl T. Sawai

UARP Award Number: ID03-D-060

Nef is a viral protein encoded by the Simian Immunodeficiency Virus (SIV) and the Human Immunodeficiency Virus (HIV). Nef is capable of enhancing virion infectivity, downregulating CD4 and MHC-I proteins from the cell surface and participating in cellular activation. One way Nef increases cellular activation is by binding and activating the cellular serine-threonine kinase, p21-activated kinase (PAK). In our earlier in vivo studies using delta-Nef mutations, pathogenic revertants were found to restore PAK binding through the generation of truncated forms of Nef.

To further study this interaction, we will be identifying small chemical compounds that inhibit the Nef-PAK interaction. We have expressed wild-type SIV Nef in E.coli as a poly-histidine tagged fusion protein, and purified it using nickel affinity chromatography. The recombinant SIV Nef was used to screen one-bead one-compound encoded small molecule combinatorial libraries to identify ligands that bind Nef. These libraries consist of a functional small molecules attached to the surface of a bead while a coding tag attached to the bead interior can be identified by peptide microsequencing. Beads containing molecules that bind Nef will be identified using a colorimetric method.

In preliminary studies using the one bead-one compound small molecule libraries, several compounds have been identified that bind SIVmac239 Nef. These are being characterized for their ability to affect PAK binding and activation. Furthermore, these small molecules will be used to determine whether they are capable of inhibiting virus replication in cell culture. If they are found to be effective in vitro, lead compounds will be tested in vivo in the rhesus macaque model for SIV pathogenesis. It is hoped that compounds identified in these studies will represent a new class of anti-HIV inhibitors.

Basic Sciences

Enhancement of B cell activation and/or transformation in AIDS-associated B cell lymphoma

Presenter: Elizabeth Crabb Breen, UC-Los Angeles

Collaborators: Justin Ford, Marta Epeldegui, Amy McQuay, Laura Martínez, Larry Magpantay, Steve Miles, Otoniel Martínez-Maza

Principal Investigator: Elizabeth Crabb Breen

UARP Award Number: CC99-LA-002

Adults with HIV/AIDS have a greatly-increased risk of developing Non-Hodgkin's B cell lymphoma (AIDS lymphoma). In HIV infection, both immune deficiency (due to T helper cell loss) and immune hyperactivation (of B cells) are seen. It has been suggested that there are two processes which may contribute to the increased risk of AIDS lymphoma among HIV-infected persons: (1) loss of control of potentially immortal Epstein-Barr virus (EBV)-infected B cells due to immunodeficiency and (2) inappropriate and/or excessive B activation leading to potentially cancerous mutations. The original objective of our studies was to examine the ability of human interleukin-6 (hIL6) and its viral homologue, vIL6 (encoded by Human Herpesvirus-8 [HHV-8]), B cell stimulatory molecules that are overproduced in HIV infection, to enhance the activation and/or immortalization of B cells by EBV. The studies were expanded to include an examination of a recently-described gene, activation-induced cytidine deaminase (AID), which has been shown to play a role in somatic hypermutation in normal B cells and has been reported to be expressed in B cell lymphoma tumors. We previously reported that both hIL6 (50 units/ml) and vIL6 (5 units/ml) were capable of enhancing EBV-induced activation of normal peripheral blood B cells, increasing immunoglobulin production more than two-fold over EBV alone (Breen et al, Cell Immunol 212:118, 2001). We also evaluated the ability of vIL6 to enhance the transformation and immortalization of normal B cells by EBV by comparing cell numbers over one month in culture, but were unable to demonstrate a consistent effect, perhaps due to differences between blood donors. For additional studies, we have utilized human B cell lines established from AIDS-associated lymphomas (R, 2F7, 10C9, RRBL), non-AIDS lymphoma (Ramos), or from EBV-transformed normal peripheral blood B cells (71197) as models of malignant and/or immortalized B cells. All of the above cell lines except Ramos are EBV-infected; RRBL is co-infected with EBV and HHV-8. R, 2F7, RRBL, and 71197 could be activated by low doses of vIL6 (1 unit/ml) to levels comparable to that seen with much higher doses of hIL6 (50 units/ml), as evaluated by Western blotting for phosphorylated STAT3, a component of the intracellular signaling pathway for IL6; Ramos was activated weakly by vIL6 only. Since STAT3 has been linked to expression of LMP-1, an EBVencoded molecule associated with malignant transformation of B cells, preliminary experiments were performed examining levels of LMP-1 by Western blotting in response to treatment with hIL6. The R, RRBL, and 71197 cell lines showed significant levels of LMP-1 protein in the absence of hIL6 treatment, which did not increase following 48 or 72 hours of culture in 50 units/ml hIL6; in the productively EBV-infected B95-8 cell line, no difference in LMP-1 protein levels was seen even at 500 units/ml of hIL6. Based on recent reports in the literature and observations within our group of collaborators suggesting that AID may play a role in hypermutation of B cells and/or B cell lymphomas, perhaps in concert with EBV (see abstract from Epeldegui et al), we assessed the expression of the AID gene in the B cell lines by reverse-transcription PCR. The AID gene was strongly expressed in all of the immortal B cell lines examined, regardless of the source of the B cell line or the presence or absence of EBV.

However, AID was not expressed in an immortal monocyte cell line (THP-1), or in unstimulated, purified peripheral blood B cells from normal healthy donors. hIL6 and vIL6 can clearly enhance EBV activation of B cells as evidenced by increased immunoglobulin production, but further work needs to be done to evaluate the enhancement of B cell transformation/immortalization, especially by vIL6. The cellular approaches undertaken within the scope of this project, examining intracellular signaling and protein expression, could be extended to the molecular level by evaluating EBV gene transcription in response to IL6-induced STAT3. The observation of constitutive AID gene expression in immortalized B cells raises a number of new questions regarding the role of the AID protein in the development of B cell lymphoma, and whether an interaction between EBV infection and expression of AID could be an additional means of enhancing the B cell activation and/or transformation via hypermutation.

Basic Sciences

Identification of Temperance Factors of Human Cytomegalovirus

Presenter: Walter Dunn, UC-Berkeley

Principal Investigator: Fenyong Liu

UARP Award Number: D03-B-409

Human cytomegalovirus (HCMV), a member of the betaherpesvirus group, is a ubiquitous pathogen of significant importance as it is a major cause of disease among immunocompromised individuals. HCMV is capable of infecting a variety of tissues and has been observed to exhibit a broad spectrum of replication rates. In some tissues viral particles are readily detected while in others virus is present only in very low levels. The capacity of the virus to engage in cell specific replication rates is most likely a result of both viral and host factors. Identifying and understanding these tropism factors will be of the utmost importance in terms of treating AIDS related HCMV disease.

With the recent completion of the HCMV mutant bacterial artificial chromosome library, which contains mutant constructs for every predicted open reading frame of the virus, we have identified several viral mutants which have exhibited hypergrowth phenotypes in tissue culture models. Microarray analysis of both viral and host expression profiles are being conducted to understand how these mutant viruses are able to propagate at an enhanced rate.

Further studies will determine where these viral proteins localize during infection and which host proteins, if any, they interact with to facilitate temperance of viral replication. The phenomenon of limiting or tempering replication or virulence is not restricted solely to HCMV and has in fact been documented in other viruses and pathogenic organisms. We believe the loss of these temperance factors in viruses and other pathogens maybe related to emerging infectious diseases, especially those from previously benign strains. With further insight into the mechanisms of this phenomenon alternative therapies and strategies for treating infectious diseases may be developed.

Basic Sciences

Epstein-Barr Virus (EBV) Infection of B Lymphocytes Induces the Expression of Activation-Induced Cytidine Deaminase (AID)

Presenter: Otoniel Martínez-Maza, UC-Los Angeles

Collaborators: Elizabeth Crabb Breen, Jon Aster, Amy McQuay, Laura Martínez, Larry Magpantay, Steve Miles

Principal Investigator: Otoniel Martínez-Maza

UARP Award Number: ID02-LA-005

The overall aim of our work is to better define the immunological and molecular mechanisms that contribute to AIDS-associated non-Hodgkin's lymphoma (AIDS-NHL). AIDS-NHL are thought to result from errors in normal processes (IgH isotype switching, somatic hypermutation) that occur in antigen-activated germinal center (GC) B cells. AID is a recently-described RNA/DNA editing enzyme that plays a central role in the induction of both IgH isotype switching-related DNA recombination and somatic hypermutation of IgH variable region DNA, processes that occur in GC B cells. Incidental hypermutation of proto-oncogenes in GC cells is believed to contribute to the genesis of some forms of NHL. In the first year of work, we have developed many of the tools necessary to further our goals, including the development and refinement of PCR-based assays to assess *AID* expression, as well as an assay to detect *c-MYC:IgH* translocations in rare cells, using fluorescence *in situ* hybridization (FISH) combined with a computer-aided image analysis system. In preliminary studies, we unexpectedly discovered a variant form of *AID* mRNA (*AIDvar*), which appears to represent an alternative splice variant of *AID*, the function of which is not yet known. Some HIV+, but no HIV-negative, subjects were seen to have *AID* mRNA in their circulating lymphocytes. Nearlly all HIV+ and HIV-negative subjects were seen to express *AIDvar* mRNA. In recent preliminary studies, we have seen that infection of B cells by EBV results in the up-regulation of *AID* expression: B cells from PBMC showed clear *AID* mRNA expression (by RT-PCR) and EBV LMP1 expression (by Western blot) ten days after exposure to EBV-containing B95.8 supernatant. EBV-transformed B lymphoblastoid cells (B-LCL) also were seen to express *AID*. EBV-induced *AID* expression appears to be functional, as a clear, progressive increase in hypermutation was seen in a gene expressed in these EBV-infected cells (*AID* itself), but not in a gene that is not expressed in these cells (*BCL-6*). This is consistent with the known hypermutation-inducing properties of AID, which operates primarily on genes that are being actively expressed. These findings are of great interest, in that they point to a novel molecular mechanism (EBV-induced *AID* expression, and subsequent hypermutation activity) that may contribute to the genesis of NHL. We hope to integrate these findings into our continued study of GC-like B cells in HIV+ subjects, and hope that this new information provides new insights on how lymphoma arises and develops in the setting of HIV infection.

Basic Sciences

K-bzip of KSHV: Transcriptional properties and replication

Presenter: Yoshihiro Izumiya, UC-Davis

Authors: Yoshihiro Izumiya, Edward T. H. Yeh, Hsing-Jien Kung

Principal Investigator: Yoshihiro Izumiya

UARP Award Number: F03-D-206

Kaposis's sarcoma, a major malignancy associated with AIDS patients, is caused by KSHV (Kaposi's sarcoma-associated herpesvirus). The present study is aimed to understand the role of K-bZIP in the replication and pathogenesis of KSHV. K-bZIP is a basic-leucine zipper protein encoded by KSHV. It is the positional and structural homologue of Epstein-Barr virus (EBV) Zta, a molecule that behaves like a latent-to-lytic switch for EBV. Recent studies however found several surprising functions of K-bZIP, which are quite different from EBV Zta. K-bZIP alone does not turn on the lytic cycle, but rather K-Rta, another early gene of KSHV does. We found that one of the potential functions of K-bZIP is to modulate the transactivation potential of K-Rta, by repressing its function in a promoter dependent manner (J. Virol. 2003a). Further, we found K-bZIP directly interacts with CDK2-cyclin complex and inhibits its kinase activity (J. Virol. 2003b). The interaction causes G1 cell cycle arrest and helps viral DNA replication to proceed without competition from cellular DNA replication. These results show that K-bZIP plays versatile roles in KSHV replication.

In this study, we probe K-bZIP's potential to transcripitonally modulate host genes. A 293 cell line with tetracycline inducible K-bZIP was developed and the expression of host gene was analyzed by Affymetrix gene chips, before and after induction. Close to 600 genes with at least a three-fold change were detected upon the induced expression of K-bZIP. Amazingly, 99% of the genes are repressed and only three genes are activated. This suggests that K-bZIP is a strong general transcriptional repressor and may contribute to the host "shut-off" during the early phase of KSHV infection. The strong repressor phenotype of K-bZIP is unprecedented and only rivaled by strong cellular repressors such as Polycomb G.

There is a growing body of evidence suggesting that sumoylation plays a role in transcriptional repression and we noticed a consensus sumoylation site present in K-bZIP. We therefore asked whether K-bZIP is sumoylated and whether sumoylation is related to its repressor activity. We were able to demonstrate the sumoylation of a fraction of K-bZIP proteins in 293T and BCBL1 cells, by virtue of their higher molecular weight, and their sensitivity toward SUMO/Sentrin specific protease. Inclusion of SUMO specific protease gene in transactivation assay reverses the repression activity of K-bZIP. A K-bZIP mutant which can no longer be sumoylated has significantly reduced repression activity. Our data thus suggests that sumoylation is one mechanism whereby K-bZIP exerts its transcriptional repression activity.

Basic Sciences

Roles and Regulation of Efg1 in Candida albicans

Presenter: Prashna Raniga, UC-Irvine

Prinicpal Investigator: Prashna Raniga

UARP Award Number: F03-I-208

Oropharyngeal Candidiasis (OPC) is the most frequent oral manifestation of HIV infection. It is seen in 50-90% of AIDS patients. Given the limited number of suitable and effective antifungal drugs, the continuing increase in the incidence of Candida infections, together with increasing drug resistance, highlights the need to develop novel strategies to prevent and treat OPC. One of the virulence properties of C. albicans has been attributed to its unique ability to grow and switch to variety of morphological forms, such as, from a budding yeast to an elongating hypha, depending upon its environmental conditions. Such morphological flexibility plays a central role in the pathogenicity of this fungus.

A transcription factor known as Efg1 (Enhanced Filamentous Growth) plays a critical part in regulating hyphal development in C. albicans and Candida virulence because mutations that inactivate Efg1 block hyphal development and is avirulent in mice. The objective of this research has been to identify the regulation and function of Efg1 in order to understand how Efg1 contributes to the overall virulence of C. albicans. This project aims to identify proteins that interact directly with Efg1 in yeast and hyphal cells of C. albicans to elucidate how Efg1 is regulated, in addition to identify its direct targets in vivo. We are currently using Tandem Affinity Purification (TAP) strategy to purify proteins that interact directly with Efg1 in C. albicans. In parallel to TAP purification, DNA microarray analysis has been used to identify genes regulated by Efg1 in C. albicans. We are using Chromatin Immunoprecipitation to determine which Efg1-regulated genes are directly bound by Efg1 in C. albicans. Results of these experiments will be discussed.

The results should enable the understanding of Efg1 function and regulation and allow for further identification of other potential targets of Efg1 that contribute to pathogenicity in Candida.

Basic Sciences

In Vivo Function of Interleikin-6 of Human Herpesvirus-8

Presenter: Ting-Ting Wu, UC-Los Angeles

Collaborators: Ting-Ting Wu, Leming Tong, Elizabeth Crabb Breen, Julia R. Gage, Otoniel Martinez-Maza, Ren Sun

Principal Investigator: Ren Sun

UARP Award Number: ID01-LA-053

Kaposi's Sarcoma-associated herpesvirus (KSHV) or HHV-8, is associated with Kapsosi's Sarcoma (KS), primary effusion lymphoma (PEL) and multicentric Castleman's Disease (MCD). Remarkably, KSHV encodes a homologue of IL-6. It has been proposed that the cellular IL-6 cDNA may initially have been captured by KSHV and undergone changes conferring selective advantages for the virus. MHV-68 does not encode a homologue of IL-6, providing an opportunity to recapitulate this evolutionary event and to study the effects of vIL-6 and cIL-6 on viral infection. The expression cassette of vIL-6 or cIL-6 driven by the CMV promoter was inserted into the MHV-68 genome. An additional recombinant virus expressing a mutant form of vIL-6 (vIL-6m), bearing a two-amino-acid change and deficient in transducing signals, was also constructed. Expression of vIL-6 or cIL-6 did not affect the growth curves of the virus in cultured cells. However, the vIL-6 virus produced plaque morphology distinct from wild-type MHV-68, the vIL-6m virus or the cIL-6 virus. After infection of mice, the vIL-6 virus, but not the vIL-6m virus or the cIL-6 virus, generated seven-fold higher acute viral titers ($p<0.0001$) in lungs and four-fold higher number of latently infected spleen cells ($P<0.01$) at the peak time of latency (day 15 post-infection) as compared to wild-type MHV-68. The in vivo data indicate that the addition of vIL-6 to the MHV-68 genome promotes viral infection during both acute and latent phases.

Basic Sciences

Targeting of Hepatitis C Virus Core Protein to Mitochondria through a Novel C-Terminal Localization Motif

Presenter: T. S. Benedict Yen, UC-San Francisco, Northern California Institute for Research & Education

Collaborators: Björn Schwer, Shaotang Ren, Jürgen Kartenbeck, Katrin Kaehlcke, Thomas Pietschmann, Ralf Bartenschlager, T. S. Benedict Yen, Melanie Ott

Principal Investigator: T. S. Benedict Yen

UARP Award Number: ID02-NCIRE-040

Hepatitis C virus (HCV) co-infection is extremely common among people with HIV, and chronic hepatitis C is becoming a major cause of morbidity and mortality for this population. Hepatitis C tends to be more aggressive in HIV-positive individuals, likely due to a direct cytopathic effect of HCV that is exacerbated by immunosuppression and/or antiretroviral therapy. The core protein of HCV is a strong candidate for causing at least part of the cytopathic effect of the virus. This protein is not only a viral structural protein, but it also has multiple effects on host cell apoptosis, metabolism, transcription, and cell growth. Using a variety of microscopic and biochemical methods, we observed that a fraction of mature core protein colocalized with mitochondrial markers both in cells expressing only the core protein and in Huh7 cells containing the full-length HCV replicon. Protease digestion experiments showed that the core protein was predominantly exposed on the outer surface of the mitochondria. A domain of 10 amino acids within the hydrophobic C-terminus of processed core protein targeted a heterologous protein to the surface of mitochondria. These results indicate that a portion of mature HCV core protein is present on the outer mitochondrial membrane, possibly via a mechanism similar to that used by other mitochondrial outer membrane proteins, such as Bcl-2. The location of core protein in the outer mitochondrial membrane may allow it to modulate various critical cellular processes, including apoptosis, lipid metabolism, and oxidative phosphorylation.

Basic Sciences

Effect of senescent HIV-specific CD8 T cells on bone biology

Noteworthy Abstract

Presenter: Rita B. Effros, UC-Los Angeles

Principal Investigator: Rita B. Effros

UARP Award Number: ID03-LA-017

Clinical studies have documented the frequent association between chronic immune activation and osteoporosis. HIV disease, the quintessential example of prolonged chronic immune activation, is associated with a progressive increase in a population of memory CD8 T cells that have reached the end-stage of replicative senescence. In fact, > 65% of the CD8 T cell subset in some HIV-infected persons consists of senescent cells, underscoring the importance of comprehensive analysis of the entire spectrum of functional characteristics associated with this type of memory cell. Interestingly, there is already evidence of bone changes in persons infected with HIV, but the relative contributions chronic T cell stimulation versus anti-retroviral therapy have not been carefully analyzed. Indeed, it would be difficult or impossible to dissect the effects the drugs from those of the T cells using epidemiological data or even clinical studies on individual patients, where only non-causal correlations can be derived. By contrast, the unique cell culture system that has been exploited in our earlier studies on T cell senescence provides an unparalleled opportunity to address the specific interactions between T cells and the cells controlling bone mass. The central hypothesis of the this new facet of our HIV research is that the CD8 T cell replicative senescence associated with HIV disease not only affects anti-viral function, but also influences bone homeostasis.

The following are the objectives of the proposed UARP IDEA pilot project: (1) To compare the culture supernatants from HIV-specific CD8 T cells at various points in their antigen-driven proliferative "lifespan" for cytokines that are known to affect *osteoclasts,* the bone-resorbing cells; (2) To determine the effect of chronic stimulation of HIV-specific CD8 T cells on *osteoblastic* differentiation. Cytokine profiles (ELISA, Western blots, RT-PCR) as well as bioassays of bone cell maturation/activation will be used to determine how senescent HIV-specific CD8 T cells may become altered in their interaction with cells involved in bone remodeling. The potential link between prolonged CD8 T cell stimulation, high proportions of senescent T cells and alterations in bone mass represents a novel aspect of HIV disease pathogenesis which, to our knowledge, has not been previously investigated. HIV disease has a major impact on the health of the residents of California, with 44,855 persons in Los Angeles County alone diagnosed with AIDS by the end of 2002. The key role played by CD8 T cells in controlling/preventing HIV infection, as well as the intense vaccine efforts aimed at stimulating CD8 T cell protective immunity, highlights the importance of more complete characterization of the multiple aspects of CD8 T cell biology, including those not directly involved with anti-viral function.

Basic Sciences

Noteworthy Abstract

2D-MRS Cerebral Metabolits in HIV-Infected Children

Presenter: Margaret A. Keller, Harbor-UCLA Medical Center

Principal Investigator: Margaret A. Keller

UARP Award Number: ID02-REI-043

Although both CT and MRI have been used to assess structural central nervous system (CNS) damage in children with HIV, more sensitive, non-invasive, physiological techniques, such as proton magnetic resonance spectroscopy (^{1}H-MRS), are needed to evaluate non-structural CNS damage. We have detected abnormalities in cerebral metabolite concentrations for HIV-infected children compared to controls with one dimensional ^{1}H-MRS and have correlated these changes with performance in neurodevelopmental tests. Two dimensional MRS is potentially an even more sensitive tool to evaluate the extent of CNS involvement for children with HIV since 2D-MRS permits a nonselective detection of different metabolites that cannot be assessed by ID-MRS. This detection is facilitated by identifying J-coupled resonances that cannot be measured in ID-MRS due to significant overlap. 2D-MRS has not as yet been developed for clinical application. 2D-MRS resolves N-acetyl aspartate, free aspartate, choline, ethanolamine, phosphorylcholine, myo-inositol, glutamine/glutamate, gamma-aminobutyric acid, threonine, and the accepted reference creatine. Ratios of metabolites to creatine will be determined since it is not yet possible to generate absolute metabolite concentrations with two-dimensional MRS (localized, correlated spectroscopy, L-COSY). We will first study control adults to standardize our protocol for minimum voxel size with the best signal to noise ratio using a new receiver coil placed on the head. Our preliminary studies with 1D-MRS suggest that the frontal white matter and the basal ganglia are two brain areas with metabolite abnormalities that merit further study. Time for the scanning may limit study to one brain region per session. We will then pilot this new technique in 10 HIV-infected children and 10 age-matched controls. Localization and voxel size will be critical in applying this technique to children. When the feasibility of 2D-MRS (with its more reliable determination of metabolites) is confirmed in children, the next step will be to apply this technology to a large group of patients under uniform, optimized conditions and confirm the functional relevance of abnormal metabolites in the brain by correlating metabolite ratios with clinical parameters, such as viral load, CD4, and performance on neurodevelopmental assessment tests. The work would then need to be expanded to other brain regions such as the hippocampus and midfrontal gray matter. Ultimately, it is hoped that clinical application of 2D-MRS will provide a useful tool for monitoring the success of antiretroviral therapy in the brain.

Basic Sciences

Combined Toxic Effects of Methamphetamine and HIV in the Nervous System

Presenter: Eliezer Masliah, UC-San Diego

Collaborators: Dianne Langford, Aline Grigorian, Rosemary Hurford, Scott Letendre, Ron Ellis, J. Allen McCutchan, Igor Grant, Eliezer Masliah

Grant Numbers: NIH MH59745, MH45294, MH58164, DA12065, and HNRC pilot project award

The use of methamphetamine (METH) continues to increase the risk of HIV transmission within both homosexual and heterosexual drug abuser groups. Neurological studies indicate that the progression of HIV encephalitis is also enhanced by illicit drug use. Recently, our studies in the post-mortem brains of HIV-positive METH users have shown that the combined effects of HIV and METH selectively damage calbindin (CB) immunoreactive non-pyramidal neurons, which may enhance behavioral alterations observed in these patients. To better understand the mechanisms of neuronal toxicity associated with exposure to HIV and METH, survival, neuronal phenotypic markers, and mitochondrial potential were assessed in HT22 (mouse) and primary human neurons exposed to the HIV-Tat protein and/or METH in vitro. In combination, Tat and METH triggered more significant neuronal cell death than either of these toxins caused separately. Both Tat and METH were toxic to neurons in a time and dose dependent fashion. Neurons exposed to Tat and/or METH showed a profound decrease in CB and MAP2 immunoreactivity. Loss of CB immunoreactivity associated with the combined exposure to Tat and METH was accompanied by mitochondrial damage. The toxic effects of Tat and METH were inhibited by blocking mitochondrial uptake of intracellular calcium; whereas, blocking calcium flux in the endoplasmic reticulum or from the extracellular environment had no effect on Tat/METH toxicity. These studies indicate that in vitro, the combined effects of the HIV protein Tat and METH damage CB immunoreactive non-pyramidal neurons by dysregulating the mitochondrial calcium potential. In combination, Tat and METH may increase cell injury and death, thereby enhancing brain metabolic disturbances observed in HIV-positive METH-abusers in clinical populations.

Basic Sciences

Fc-γ Receptor IIIa Polymorphism and HIV Infection

Presenter: Donald Forthal, UC-Irvine

Authors: D. Forthal, T. Phan, L. Lin, G. Landucci, J. Becerra, C. Diamond, R. Larsen, C. Kemper, M. Witt, C. Miller, R. Haubrich, and the CCTG

Prinicipal Investigator: Donald Forthal

UARP Award Number: ID03-I-021

Background: Fc receptors for IgG (FcγR) are found on natural killer cells and macrophages and are required for critical host defenses such as clearance of immune complexes, antibody-dependent cellular cytotoxicity, and cross presentation of immune complexes to T cells. The FcγRIIIa gene occurs as two alleles, encoding either a phenylalanine (F) or valine (V) at amino acid 158. This polymorphism has been associated with differences in susceptibilities to infectious and autoimmune diseases; however, its role in HIV infection has not been previously investigated.

Methods: Using a PCR-based alleleic discrimination assay, we determined FcγRIIIa genotypes for 92 HIV-infected individuals from the CCTG 578 study who had either never received anti-retroviral therapy (ART) or who had discontinued ART for at least 3 months; all subjects were considered candidates for ART. We then determined if there was an association between genotype and plasma viral load. In addition, we compared the distribution of genotypes in our cohort of HIV-infected individuals with the genotype distribution in uninfected individuals obtained from 10 published studies.

Results: Mean viral load for all infected subjects was 5.31 (range=4.03-6.70 copies/ml) and was similar for all three genotypes: FF=5.27; FV=5.33; VV=5.30 ($p>0.1$). Furthermore, genotype did not predict CD4+ cell count in this group of patients. However, HIV-infected patients were much less likely to have the FF genotype (27%) than were uninfected individuals (41%; $p=0.009$).

Conclusions: Among subjects with fairly advanced HIV infection, we found no association between FcγRIIIa polymorphism and viral load. However, the association between the FF genotype and HIV infection suggests that the presence of the V allele (or absence of both F alleles) is a risk factor for acquiring HIV infection. Alternatively, the skewed distribution of genotypes in our infected patients resulted from selecting a population with fairly advanced infection; we are currently comparing genotypes in this cohort with those of long-term non-progressors.

Basic Sciences

Role of c-Mpl in HIV-1 Induced Cytopenias

Presenter: Srinivasa T. Reddy, UC-Los Angeles

Principal Investigator: Prasad S. Koka

UARP Award Number: ID01-LA-082

HIV-1 infection of the severe combined immunodeficiency mouse transplanted with human fetal thymus and liver tissues (SCID-hu Thy/Liv), inhibits multilineage hematopoiesis in the conjoint human organ. This inhibition, as evaluated by the myeloid, erythroid, and megakaryocytoid colony forming activity (CFA) of the human CD34+ cells derived from the infected Thy/Liv implants, is also accompanied by a severe loss of c-mpl expression on these progenitor cells. CFA inhibition is partially revived to about 40% of mock infected implants, following reconstitution of the CD34+ cells that were exposed to HIV-1 infection, in a new Thy/Liv stromal microenvironment of irradiated secondary SCID-hu recipients, at 3 weeks post-reengraftment. In addition, in these reconstituted animals, proportion of the c-mpl+CD34+ cells relative to c-mpl-CD34+ cells increased by about 25%, to 60% of mock infected implants, suggesting a reacquirement of c-mpl phenotype by the c-mpl-CD34+ cells. Treatment of the secondary recipient animals with the c-mpl ligand, thrombopoietin, further increased c-mpl expression and CFA of CD34+ cells previously exposed to virus in the primary transplanted animals, to about 50-70% over that of those CD34+ cells derived from untreated animals, following reengraftment. These results suggest a correlation between c-mpl expression and multilineage CFA of the human CD34+ progenitor cells that have experienced the effects of HIV-1 infection. Thus c-mpl may play a role in hematopoietic inhibition during HIV-1 infection and that control of its expression levels, aid in hematopoietic recovery and thereby reduce the incidence of cytopenias occurring in infected individuals.

Basic Sciences

How HIV Infects Resting CD4 T-cells in Lymphoid Organs

Presenter: Jason K. Kreisberg, UC-San Francisco, Gladstone Institute of Virology and Immunology

Principal Investigator: Warner C. Greene

UARP Award Number: D03-GI-401

One poorly understood aspect of the HIV viral life cycle includes the interplay of this virus with host factors that promote infection. For example, it is well recognized that HIV-1 fails to replicate in unstimulated peripheral blood CD4 T-cells. Conversely, HIV effectively infects unstimulated CD4 T-cells residing in lymphoid tissues. How the intracellular milieu of tissue-resident, CD4 T-cells differs from blood-derived CD4 T-cells leading to productive infection is unknown.

We have recently found that lymphoid organs elaborate one or more soluble factors that render tissue-derived, naïve CD4 T-cells permissive for HIV infection. Further, these same soluble factors can convert resting peripheral blood CD4 lymphocytes into permissive hosts for viral replication. Given the known ability of cytokines such as IL2, IL4, IL7, and IL15 to confer a permissive state for a single cycle infection, we have focused out efforts on exploring the potential role of these and other cytokines as permissivity factors. Depletion studies have suggested that IL2 and IL15 are key permissivity factors produced in lymphoid organs that make resting T cells susceptible to HIV infection. Further we have found that treatment of normally nonpermissive peripheral blood lymphocytes with high doses of IL2 or low doses of IL15 converts these cells to permissive hosts that support viral spread.

In addition to further defining the role of these cytokines as host permissivity factors for HIV infection of resting cell populations, we are seeking to identify the cells responsible for their production and the site of their action in the retroviral life cycle. These studies promise to extend our understanding of the interplay between HIV-1 and resting CD4 T-cells and could lead to new therapeutic approaches for controlling viral replication in vivo.

Basic Sciences

Hypothalamic Alterations Associated with AIDS: SIV-Induced Changes in Feeding and Temperature

Presenter: Lisa Madden, The Scripps Research Institute

Collaborators: Lisa J. Madden, Steven J. Henriksen, Howard S. Fox

Prinicipal Investigator: Lisa Madden

UARP Award Number: F02-SRI-209

HIV infection leads to a variety of complications. Fever/temperature dysregulation and wasting disorders can contribute to the morbidity and mortality induced by HIV. Furthermore, such disorders may also contribute, or be pathophysiologically linked, to the HIV-1 infection in the brain. SIV infection in the rhesus macaque is one of the best models for studying AIDS related changes in a controlled environment. Following infection with SIV, rhesus monkeys develop fever, as well as reductions in food intake and a wasting syndrome. The hypothalamus plays a critical role in physiological regulation and changes in this area following infection may play a role in the homeostatic alterations seen in HIV/AIDS. We have previously shown that during the acute period of SIV infection, IL-6 is elevated in the CSF and plasma, a period when fever and reduced food intake are also present. IL-6 is a critical element in the induction of fever, and with other factors, influences temperature by interactions with the hypothalamus. Such factors are also likely to be altered by infection, and likely interact with the hypothalamic homeostatic mechanisms involved in food intake and temperature regulation. We therefore tested the following hypothesis: SIV infection leads to hypothalamic changes resulting in temperature dysregulation and reduced food intake/wasting. Correlations between peripheral physiological changes and potential hypothalamic mechanisms in SIV-infected and non-infected rhesus macaques are examined in this study.

Basic Sciences

Tat inhibition of Nep may increase amyloid beta in the brain

Presenter: Lynn Pulliam, UC-San Francisco, Northern California Institute for Research & Education

Principal Investigator: Lynn Pulliam

UARP Award Number: ID02-NCIRE-045

Aging is a risk factor for Aβ accumulation and dementia. For individuals infected with HIV-1, availability of highly active antiretroviral therapies (HAART) has effectively lengthened their life expectancy thereby putting them at risk for age-related neuropathies. Since the brain is seeded early after infection by monocyte/macrophages migrating across the blood brain barrier, the central nervous system is exposed to HIV-1 for an extended period of time. We hypothesize that in the brain, long-term exposure to HIV proteins may initiate mechanisms of neurodegeneration not previously detected in acute HIV-associated dementia (HAD).

In this study, we show that an HIV-1 nonstructural protein Tat inhibits neprilysin (NEP), a major Ab degrading enzyme expressed in neurons. In a cell-free assay using membrane fractions from human brain cultures, NEP enzymatic activity was significantly reduced by full-length recombinant Tat. When recombinant Tat was added directly to brain aggregate cultures, there was a 125% increase in soluble Aβ 1-40, compared to non-treated cultures. These observations are consistent with Tat inhibiting NEP activity thereby increasing Aβ accumulation. In both assays, a cysteine-rich region in the Tat protein was found to inhibit NEP and elevate Aβ 1-40 in culture. To establish the relevance of this finding to patients with long-term HIV infections, frontal cortex from archived postmortem tissue was immunostained for Aβ. Using a monoclonal antibody, we found an increase in Aβ staining in patients diagnosed with HAD compared to similarly aged, non-infected controls. These findings demonstrate that Tat interferes with the enzymatic activity of an important zinc-metalloendopeptidase that is critical for Aβ catabolism. Accumulation of Aβ due to Tat inhibition of NEP, may have serious implications for long-term survivors of HIV-1-infection.

Basic Sciences

Characteristic Gene Expression Profile in GALT Distinguishes Long Term HIV-1 Infected Non-progressors from Individuals with High HIV-1 Viral Loads

Presenter: Sumathi Sankaran, UC-Davis

Collaborators: S. Sankaran, M. D. George, M. Guadalupe, E. Reay, S. Dandekar

Principal Investigator: Satya Dandekar

UARP Award Number: D03-D-408

Background: CD4+ T cell depletion is more pronounced in GALT than in peripheral blood early in HIV-1 infection. Since GALT is the largest lymphoid organ, it is an important site for host-virus interactions. Our study sought to determine the molecular basis of HIV-1 infection induced pathophysiologic and immunologic changes in intestinal mucosal tissue in patients whose immune responses failed to control the viral replication.

Methods: Immunophenotypic analysis and immunohistochemical (IHC) analysis from small intestinal biopsy samples obtained from 4 HIV-1 infected individuals with high plasma viral loads, 4 long-term non-progressors and 4 HIV-1 seronegative healthy controls were performed. Gene expression analysis was studied using DNA oligonucleotide microarray techniques. Gene expression in the microenvironment of the GALT was compared in order to identify a signature profile that could distinguish between long-term non-progressors and patients with high viral replication.

Results: Immunophenotypic and IHC analysis demonstrated a pronounced depletion of CD4+ T cells in GALT of individuals with high viral loads and a corresponding increase in CD8+ T cells. In contrast, GALT of long-term non-progressors had normal levels of CD4+ T cells and undetectable levels of viral RNA expression. DNA microarray analysis revealed that the gene expression profile of HIV-1 infected patients with high viral loads compared to that of HIV-1 negative, healthy controls reflected a marked increase in inflammation and tissue injury associated gene expression. Expression of genes regulating immune and antiviral responses, response to injury, cell cycle regulation and apoptosis was notably increased in correlation to high tissue viral RNA loads. In these individuals the enhanced expression of pro-apoptotic factors over-shadowed that of anti-cell death factors in GALT as detected by TUNEL assay as well as Annexin V staining. Gene expression regulating inflammatory pathways such as the complement pathway was also increased in expression. These changes were noticeably absent in LTNPs.

Conclusion: The data from this study demonstrated that HIV-1 infection led to complement mediated inflammation and increased apoptosis associated gene expression. In contrast, LTNPs had down regulation of apoptosis and inflammation related gene expression. Thus, improved regulation of cell death and inflammation may contribute to the improved maintenance of T cell homeostasis.

Basic Sciences

A Model of Latent/Persistent HIV Infection in Primary CD4 Cells

Presenter: Celsa Spina, UC-San Diego, VA San Diego Healthcare System

Principal Investigator: Celsa Spina

UARP Award Number: ID03-VASD-033

Current treatment of HIV infection does not lead to viral eradication or complete suppression of viral replication. HIV persists in various cell reservoirs; viral replication continues at some level and can be accelerated during in vivo episodes of immune activation. Latently-infected, quiescent CD4 lymphocytes represent an important, highly stable viral reservoir (estimated half life of 6-44 months), and thus present a major barrier to eradication of HIV infection. Studies of latently infected CD4 cells, and the potential effects of new therapies on this nonproductive viral state, are difficult to perform in vivo, due to the very low frequency of such infected cells in the peripheral circulation (1-10 per 10^6 CD4 lymphocytes). Before new treatment strategies can be rationally designed and targeted to latently-infected cell reservoirs, we must first understand the basic biologic mechanisms underlying the establishment and maintenance of persistent, nonproductive HIV infection in CD4 lymphocytes. To address the difficulties existing currently in this research area, we are using a well-defined, primary T cell model to elucidate the viral and host cell variables that interact to develop and maintain a persistent/latent HIV infection in quiescent CD4 cells.

In this model, primary CD4 cells are FACS-sorted into $CD45RA^+CD62L^+$ naive (RA) and $CD45RA^-$ memory (RO) subsets, infected with the NL4-3 clone of HIV-1, and stimulated by immobilized anti-CD3 plus anti-CD28 antibodies. Cultures are maintained, in the presence of selected cytokines (IL-2, IL-15, IFNb), for up to 21 days. Sequential analyses are done for: cell activation and proliferation, HIV DNA and p24 production. Integrated HIV DNA is measured by real-time PCR using gag-specific primers, following gel-separation of high and low molecular weight forms of extracted DNA. With induced proliferation, naive cells switch to an activated RO^+ phenotype, and infection spreads within the cultures. After several division cycles, cells return to a predominantly resting state ($G_{0/1}$) by day 14. HIV survives in an integrated state within the remaining cells (3-10 x 10^4 copies/500ng cellular DNA). A second round of cell activation is capable of inducing high levels of productive virus replication.

This long-term culture system provides a highly relevant biological model for the study of viral-host cell interactions that occur during the establishment and maintenance of persistent HIV infection in CD4 lymphocytes. Our cell model also has the potential to aid preclinical studies in the optimization of antiviral therapy strategies.

Basic Science

Inhibition of T cell development by Interferon-alpha

Presenter: Christel H. Uittenbogaart, UC-Los Angeles

Collaborators: Arnaud Colantonio, Beverly Redsar

Principal Investigator: Christel H. Uittenbogaart

UARP Award Number: ID03-LA-001

Plasmacytoid dendritic cells (pDC), or natural interferon type I producing cells play an important role in linking innate and acquired immunity. pDC express high levels of interleukin 3 (IL-3) receptor (CD123) and are present in cord and peripheral blood, T cell areas of the lymph nodes and in the thymus and have the capacity to produce high levels of IFN-α in response to viruses and other stimuli. Although IFN-a has antiviral activities this cytokine may also have a maladaptive role in T cell development. Virally induced IFN-α has been directly shown to suppress development of hematopoietic cells *in vivo* in an LCMV model and IFN-α impedes proliferation of human hematopoietic progenitor cells. Since IFN-α can interfere with T cell development in the mouse and mediate terminal differentiation of human thymic epithelial cells, IFN-α production in the thymus might be expected to have important effects on T cell development. HIV has been shown to induce IFN-α production by pDC. Furthermore, HIV infection is believed to impair thymic output of naïve T cells, and has been shown to deplete the $CD4^+CD8^+$ thymocyte subset in experimental models. A potential unifying hypothesis for these observations is that HIV-induced IFN-α production impairs early human T cell development. Consistent with this hypothesis is the report that an antibody to IFN-αR reduced the loss of $CD4^+$ cells in SIV-infected macaques. Our preliminary data show that exogenous IFN-α inhibits human T and NK cell development from $CD34^+$ cells in fetal thymic organ culture (FTOC). In addition, we find that thymic pDC infected with X4 or R5 HIV-1 express IFN-α *in vitro* and in the SCID-hu mouse model. Based on these results we hypothesize that IFN-a production induced by HIV directly or via immune activation interferes with T cell development in the thymus, thereby contributing to the impaired T cell regeneration in HIV infected patients.

We therefore believe it is important to define this potential pathway of immune dysfunction in HIV-1 infection by evaluating the mechanisms of HIV-induced IFN-a production in pDC, the quantitative and qualitative effects of IFN-α on developing T cells, and the possibility that IFN-α interferes with the IL-7 pathway that plays a crucial role for T cell development. In order to fully understand the potential impact of HIV infection on pDC/IFN-α networks, we need to better understand how IFN-α is induced and affects T cell development.

Centers & Institutional Support

Drew CARES

Principal Investigator: Eric G. Bing, The Charles R. Drew University of Medicine and Science Center for AIDS Research

UARP Award Number: IS02-DREW-705

The Charles R. Drew University of Medicine and Science Center for AIDS Research, Education and Services (Drew CARES) is an important resource to the under served minority communities of South and East Los Angeles. Serving over one million residents, Drew CARES brings together the many HIV resources that are available at Charles Drew University for people living with HIV and AIDS. Research conducted under Drew CARES includes behavioral studies on adherence to HIV medications, depression among HIV/AIDS infected people, HIV prevention interventions (including brief interventions in emergency rooms, three hour peer interventions, and week-long intensive interventions), and sexual partner notification and testing programs. Clinical/medical research includes studies on lipodystrophy and the role of alcohol on infectivity and activation of latent t-cells. Service programs at Drew CARES include mental health care, case management, home health programs, medical care, a food pantry, substance abuse counseling and assistance, physical exercise programs, adult education programs, anger management, peer counseling and social events. In addition to providing treatment education, Drew is also an AIDS Education Training Center site. In addition to operating in Los Angeles, Drew CARES has recently expanded its reach to Africa, where it currently works with the Angolan military on HIV prevention, voluntary counseling and testing and behavioral and serologic surveillance. Drew CARES has also been working with UCLA and UCSD/Naval Health Research Center in training Angolan physicians in HIV epidemiology research, diagnosis and treatment options.

Centers & Institutional Support

East Bay AIDS Research Institute

Principal Investigators: Jeff Burack and Jan Malvin, East Bay AIDS Center at Alta Bates Summit Medical Center

UARP Award Number: IS02-ABF-710

Introduction and Overall Objectives: The East San Francisco Bay Area collaboration of three institutions, East Bay AIDS Center at Alta Bates Summit Medical Center, Alameda County Medical Center/HIV Services Division, and UC Berkeley's School of Public Health, requested funds from UARP to establish the East Bay AIDS Research Institute (EBARI). The main objective of EBARI is to create and operate a unique model of client-centered research driven by consumers of HIV/AIDS care, community advocates, and scientists, to investigate issues of concern to the large, diverse population of historically under-served and under-researched patients in the East Bay. EBARI ties together a strong network of community-based AIDS services organizations with clinical care centers that serve about 1,500 patients. The broad goals of EBARI are to advance the quality of HIV/AIDS care and treatment, enhance the quality and length of life for patients, expand the impact and effectiveness of HIV/AIDS research, and nurture community-focused investigators to improve HIV/AIDS research and care.

Progress Toward Specific Aims: The chief aim in the first year of UARP emerging institutions support was to forge an operational infrastructure for EBARI that will support HIV/AIDS-related research projects. In addition, proposed first-year specific aims are to (1) convene a community board to provide planning and oversight related to the mission and vision of EBARI; (2) establish EBARI as a freestanding research organization built upon the foundation of clinical research activities at East Bay AIDS Center and Alameda County Medical Center; (3) create a five-year strategic plan for implementing community-focused research; (4) leverage UARP support to bring three new, community-focused studies in development by partner organizations under the EBARI umbrella. To date, significant progress has been made towards developing the operational infrastructure of EBARI. The Project Director was hired and an Executive Committee (EC) was assembled to set administrative policies and practices, prioritize potential research initiatives, and make decisions relevant to day-to-day operations of the organization. The EC meets on a monthly basis. The community board, or Research Advisory Committee (RAC), was recruited and convened for a half-day, professionally facilitated retreat in September. The RAC is comprised of people living with HIV, provider-scientists, and representatives of four local, well-established service organizations. Through quarterly meetings, this body will shape the research agenda, provide guidance on research protocols including recruitment and retention of participants, and advise on potential cultural, linguistic, and access issues related to research proposals. The first meeting focused on the collaborative process itself in the context of EBARI and resulted in a draft set of guiding principles for collaboration, as well as a list of tangible ideas for promoting EBARI within the community. Initial stages in the development of a five-year strategic research plan were accomplished by the RAC and the group decided to meet again sooner than a calendar quarter to expedite the attainment of this aim. Since UARP award notification, EBARI affiliates launched three research projects with EBARI's clinical population; and EBARI-affiliated investigators submitted three new research proposals to federal agencies.

Next Steps and Potential Impact on California: Specific aims for EBARI in the next phase of development are to recruit new community-focused HIV/AIDS researchers; cultivate collaborations with established researchers; refine the community-participatory research model; broaden the network of EBARI-affiliated individuals and agencies; apply for and receive funding to implement a variety of new studies, at least 50% of which are driven by community-generated ideas. EBARI's unique contribution to the research landscape in California will be to set new standards for collaborative research outside a university institutional base.

Centers & Institutional Support

UCSF Center for AIDS Research Center

Principal Investigator: John Greenspan, UC-San Francisco

UARP Award Number: CC02-SF-002

We will continue to conduct an integrated set of basic and clinical studies to understand better how to prevent infection with HIV and how to delay progression of the disease once a person is infected with HIV. We have chosen this theme of "Biomedical Approaches to HIV/AIDS Prevention" because it is scientifically important and the results of the studies will be clinically useful. Furthermore, the findings have great relevance to preventing HIV and AIDS in diverse populations in California. This CARC allows us to continue a coherent and unified program in an area which has not been developed elsewhere at the UCSF campus, namely fundamental studies that will lead to useful concepts for novel vaccine and therapeutic approaches to HIV prevention. We have developed innovative mechanisms for mentoring our scientists in this area of research and for cross-disciplinary research. We also have derived a set of principles and procedures for developmental efforts and growth of our research in this important area, notably a strong pilot studies program. This non-competing renewal proposal is the result of a process of internal and external peer-review, which has resulted in re-affirmation of our theme. We have modified each Project in the light of the work performed in the first two and a half years of the Center and have accordingly also made minor changes in the Cores.

We have effective mechanisms for maintaining excellent community input, for insuring maximum representation of all elements of the community in our studies, and for insuring that our results are disseminated quickly. Our efforts work to reach diverse populations, ranging from the Theme projects working with infected persons including women, children, MSM, and drug users; to our pilot studies which have focused on all infected populations, as well as special populations such as those recently infected, their partners, and the homeless. We use the Executive Committee, External and Internal Advisory Committees to do strategic planning for the CARC. In addition, to support this process, the Scientific Development and Mentoring Core works with the broader scientific community to support these plans with pilot projects and seminars. Levering of external funds from the work of the Theme Projects is being energetically pursued through RO1 proposals. Two such applications have also grown out of the work of the Clinic-based Cohort, now Core D. Leveraging from the pilot studies is listed in the table in Appendix 7, publications and presentations arising out of the first two years of CARC funding are listed in Appendix 10.

The CARC's science is advised by an External Advisory Board of scientists of national and international distinction and by a Community Advisory Board reflecting the epidemic in California, and we have in place effective strategies for including populations which are most affected by the epidemic and usually overlooked in research studies. The structure of the UCSF CARC was designed to be maximally responsive to the intent of the UARP

Centers & Institutional Support

UCSF AIDS Research Institute

Principal Investigator: John Greenspan, UC-San Francisco

UARP Award Number: IS02-SF-716

UCSF ARI responds to the HIV/AIDS epidemic by delivering high quality science that benefits the communities most in need of that science. We also care for a substantial portion of the people with HIV in San Francisco at three hospitals (San Francisco General, Moffitt-Long, and the VA Medical Center). Our progress report documents that UCSF-ARI achieved the goals we established for the first period of UARP infrastructure funding and that we can take funds, unattainable from any other source, and leverage those funds. Moreover, we have established self-sustaining mechanisms for the goals we established.

The epidemic continues to evolve in unfortunate ways, especially to affect the most vulnerable segments of our state and our world. Our response has also evolved, and we have developed a new set of goals consistent with our desire to continue to meet the challenges posed by the evolution of the epidemic. We are asking for funding under this initiative to support those things that will help us to be more successful: investments in people (Goal 1), in structures needed to support new research initiatives (Goals 2, 3, 4 and 5), in the stimulation of specific strategic research initiatives (Goal 6, 7 and 8), and in the continuation of proven strategies for stimulating investigator-initiated multidisciplinary research (Goal 9).

It might be tempting to conclude that UCSF ARI is strong and capable of achieving its goals without UARP infrastructure funding. Nothing could be further from the truth. UARP infrastructure funding is necessary so that we can pay for essential activities that Federal grants are not permitted to cover, and for critical services not provided by funding from UCSF. Specifically, UARP infrastructure funds will pay staff needed to bring faculty together, crossing over disciplinary lines to translate scientific discoveries into initiatives, to prepare applications, to support faculty, with particular attention to faculty who will contribute to our diversity and capacity to work closely with our HIV affected communities. We need to ensure that essential faculty and facilities are sustained, especially those essential to our ability to serve the impacted communities of California.

Nurture People: Develop Multidisciplinary and Multicultural Scientists

Goal 1: Increase the number of minority scientists devoted to HIV/AIDS at UCSF.

Develop Facilities to Support Multidisciplinary Research

Goal 2: Develop, implement, and evaluate a model program for prevention of HIV transmission among HIV+ individuals within the context of clinical care.

Goal 3: Stabilize the UCSF Women's and Children's HIV Clinic at Long-Moffitt/Parnassus.

Goal 4: Establish the UCSF Center for HIV and the Urban Poor.

Goal 5: Establish the UCSF California-Mexico-Latin America Collaborative HIV Research Center.

Pursue Strategic Multidisciplinary Research Goals

Goal 6: Initiate a program of multidisciplinary research to test and evaluate interventions to reduce disparities in access to care and prevention services in California.

Goal 7: Stimulate new approaches to research in prevention and care of HIV among men who have sex with men (MSM), with a special focus on minority MSM.

Goal 8: Initiate a program of international clinical research on HIV/AIDS.

Stimulate Investigator-Initiated Multidisciplinary Research

Goal 9: Stimulate and disseminate trans-disciplinary research across all UCSF-ARI organizations and priorities.

Centers & Institutional Support

The California Collaborative Treatment Group

Principal Investigator: Richard Haubrich, UC-San Diego

UARP Award Number: CC02-SD-003

Objectives: The California Collaborative Treatment Group (CCTG) is a UARP-funded, multi-center, clinical research organization which has integrated the efforts of investigators at five academic institutions in California (UCSD, UCI, UCS, Harbor / UCLA, and Santa Clara Valley / Stanford). Since 1996, CCTG studies have assessed emerging technologies for antiretroviral management in rigorous randomized trials. The CCTG has also contributed to: a) faculty development through mentoring of junior faculty; b) inclusion in research studies of ethnic minorities and women through our locations in hospitals that serve medically needy populations; and c) leveraging of private research support for our participating institutions.

Significant Findings and Conclusions: CCTG 575 evaluated the utility of HIV phenotypic susceptibility testing to aid in regimen selection for antiretroviral management. This randomized comparison of antiretroviral therapy that is selected with or without information on phenotypic resistance showed no overall difference in virologic outcomes. The benefit of phenotyping may have been compromised by misleading cut-points for D4T and DDI. Subgroup analysis of patients with extensive prior ARV experience suggested a virologic benefit in the phenotype group. The study found that resistance testing was most helpful for patients with complex resistance patterns and that interpretation of the test results (defining clinical cut-points) was key to optimal use of this expensive clinical test. A recent analysis by L. Miller (Harbor-UCLA) found that better medication adherence actually augmented the evolution of resistance during a failing regimen.

CCTG 576 was a partially NIHM-sponsored, randomized, multi-centered clinical trial conducted jointly by USC and the CCTG. It tested the efficacy of provider-based interventions to promote safer sex as a means to reduce HIV transmission and to improve adherence of therapy. The primary analysis performed by Jean Richardson and her colleagues at USC found that interventions for safer sex presented in "loss or consequences", but not the "gain or advantages," frame were effective in reducing unsafe sex in patients who have high risk sex.

CCTG 578 is a randomized factorial 3x2 comparison of three levels of adherence training (standard of care, counseling, and counseling with 2 weeks of practice using placebos) integrated with a study of therapeutic drug monitoring (TDM). This study was designed and funded in collaboration with two behavioral scientists at RAND, David Kanouse and Glenn Wagner as well as industry funding from Quest diagnostics. This study will complete accrual in December 2003. The synergy of studying TDM and adherence in the same patients makes this design both scientifically and logistically appealing. Thus, the CCTG has produced a series of pioneering studies of new technologies and behavioral interventions that promise to markedly improve management of antiretroviral therapy.

Centers & Institutional Support

Entre Fronteras: Behavioral Research Informing HIV/AIDS Control in Binational and Border Region Latino Populations

Principal Investigator: Melbourne F. Hovell, Center for Behavioral Epidemiology and Community Health, San Diego State University

UARP Award Number: IS02-CBECH-711

Since 1988, the Center for Behavioral Epidemiology and Community Health (CBEACH) has conducted AIDS prevention research with support from NIH, the World AIDS Foundation, State Office of AIDS, and the Universitywide AIDS Research Program. Our research has targeted racial and ethnic minority populations: high-risk youth, separated and divorced women, homeless individuals, injection drug users and men who have sex with men. Our experience has heightened concern about geographic and socio-culturally high-risk populations on both sides of the U.S.- Mexico border. Our initial UARP funding to support our emerging center provided the experience to consolidate a core group of investigators and extend our original geographic boundaries. Our current emerging center award extends the original and emphasizes activities that will enable support from NIH and other funding agencies and by which research directed to the prevention and control of HIV/AIDS may be sustained.

Specific Aims:

1. Develop more focused collaborative scientific and community partnerships, specific to high-risk Latino groups.
2. Prioritize a logical extension of our research agenda targeting Latinos in San Diego, Imperial and Madera Counties and from cross-border cities of Mexicali, Tijuana and others in Baja California as well as communities of origin for Mexican migrants.
3. Extend our previous and ongoing epidemiology and surveillance studies to set the stage for surveillance systems that inform prevention and control policies. Extend our research concerning reliable measures of risk practices and their social/behavioral determinants to enhance the quality of our epidemiological and community trials.
4. Increase professional capacity for bi-national and collaborative HIV prevention research by recruiting faculty level investigators and by obtaining NIH training support for pre and postdoctoral fellows.
5. Prepare and submit for NIH funding at least two epidemiological and two community intervention trials that concern the prevention and control of HIV along the border and among migrant populations.

Centers & Institutional Support

Center for the Study of Retroviral Inhibitors

Principal Investigator: Nathaniel R. Landau, The Salk Institute for Biological Studies

UARP Award Number: IS02-SI-704

Introduction and objectives: A core was established at The Salk Institute for Biological Studies through a grant from UARP for a center for the analysis of current or novel anti-retrovirals. The Center for Retroviral Inhibitor Analysis (CRIA) provides a service to California AIDS researchers for testing and evaluation of compounds with anti-retroviral activity. The center provides analytic assays and the expertise of Salk AIDS researchers who have developed laboratory means to analyze compounds or antibodies for anti-retroviral activity and to determine the specific step in the HIV-1 replication cycle at which they act. The center also serves as a resource for consultation and information to California researchers and around the country. The Center is currently utilized by academic and industrial researchers. The Center provides a means by which researchers can determine the activity of specific molecules rapidly and accurately. The assays provided by the Center are rapid, efficient and well established.

Specific Aims:

1. To evaluate compounds and antibodies from California researchers for activity against HIV-1 entry, integration and transcription.
2. To promote interaction between Salk researchers and other California researchers.
3. To serve as a resource for California researchers for consultation and information regarding the evaluation of HIV-1 inhibitors.

The Center is comprised of three cores: (1) HIV entry, (2) integrase and (3) viral transcription. The three cores are coordinated by a manager who analyzes the data, communicates results to clients and who interfaces with the outside users to plan analyses and report findings.

Next steps and potential impact on California: The Center has advanced research in small molecule antagonists of HIV coreceptors, peptides that block HIV fusion and mechanism of HIV accessory gene function. These resulted in more than eight primary publications this year. A website was established that provides information regarding services provided and procedures for requesting service. Its goal is to broaden the services provided and to engage more researchers to use the facility. In addition, the website will be expanded to serve as a laboratory information resource for AIDS researchers in California and in throughout the country.

Centers & Institutional Support

HIV Clinical Research Facility

Principal Investigator: J. Allen McCutchan, UC-San Diego

UARP Award Number: IS02-SD-701

UCSD's Institutional Support Grant was initially awarded in 1/99 and renewed for 1/03-12/05 to enhance infrastructure for our HIV program. We have found this support invaluable and accomplished many of our goals. Our current grant (1/03-12/05) supports the following important components of our programs:

1) Research facilities, communications and data management capacity, and recruitment of minority participants at the UCSD Center for Clinical HIV Research (CCHR).
To maintain cohesion and integration of our multidisciplinary programs of therapeutic and neurobehavioral research, we have supported rental costs for a building adequate to co-house these programs. We also are enhancing the wide-band telecommunications infrastructure at the CCHR and are integrating the data bases of patient-oriented research programs at UCSD with those of our Owen (HIV primary care) clinic.

2) HIV international research, education, and training
To enhance our developing program in international research, we have supported epidemiologic surveillance and training for clinical care of HIV-infected women and children in Tijuana. More recently we applied for an NIH (CIPRA) grant to develop a clinical research program in collaboration with the Autonomous University of Baja California, also in Tijuana.

3) Advanced biomathematics in HIV research
We have initiated a fellowship program to provide training in biomathematical analysis of HIV dynamics and evolution. This emerging area of research in epidemiology, virology, and pathogenesis promises to enhance the value of our clinical and basic sciences programs. We also support the analytical bioinformatics section of the UCSD HIV Genomics Center.

Centers & Institutional Support

UCLA Center for AIDS Research Center

Principal Investigator: Ronald Mitsuyasu, UC-Los Angeles

UARP Award Number: CC02-LA-001

For the past 4 years the UCLA CARC has been engaged in a number of research studies evaluating innovative approaches to the treatment and prevention of HIV. These studies have taken several diverse approaches reflecting the wide research expertise and the broad interest of UCLA faculty in various areas of AIDS research. The studies of the UCLA CARC have involved translating basic research finding to the clinic and the furthering multi-disciplinary collaborations and linkage building with the community. The goals of the UCLA CARC is to promote and facilitate the development and evaluation of new and potentially more effective treatment and prevention strategies for HIV. The CARC also seeks to evaluate novel behavioral and/or educational interventions that may impact on risk-taking behavior in selected at-risk populations. To accomplish these goals, the UCLA CARC maintains an administrative core, an outreach core and a limited clinical trials core to provide research nursing and statistical support for research CARC-sponsored and related projects. The CARC seed grant programs continues to support new investigators and innovative pilot studies in areas of translational, clinical and social-behavioral research. Due to reduction in funding earlier this year, the number of seed grants awarded had to be reduced to two awards. The major core projects and seed grants conducted during this past year include:

1. A study to evaluate in peripheral blood and mucosal tissues prostratin, and agent which can activate and mobilize HIV from latent viral reservoirs - PI: Peter Anton, MD.
2. An evaluation of a novel computer assisted risk-taking assessment versus a physician intervention on the behavior of HIV-iinfected individuals who may be engaged in high-risk behavior – PI: Marguerita Lightfoot, PhD.
3. A study on behavioral intervention to reduce HIV risk-taking behavior and to increase medical adherence and the development of a behavioral intervention specifically for gay male African Americans and Latinos – PI: Gail Wyatt, Ph.D.
4. A study to evaluate the effects of beta-adrenergic blockade on suppressing HIV replication infected individuals – PI: Steven Cole, Ph.D.
5. A pilot study to assess the impact of family on adolescent stage sexual behavior – PI: Carl Sneed, Ph.D.
6. Evaluating the care of HIV patients on Medi-CAL – PI: David Zingmond, MD.

By supporting these important clinical, social-behavioral and prevention research efforts and providing funds for new investigators to conduct pilot projects in HIV, the UCLA CARC is working to meet the evolving needs and priorities in AIDS research and prevention in California.

Noteworthy abstracts are of particular relevance to the conference theme or address a topic of special interest.

Clinical Sciences

Consumer Willingness to Participate in HIV Vaccine Trials among Communities at Risk (Project VIBE)

Noteworthy Abstract

Presenter: Sung-Jae Lee, UC-Los Angeles

Collaborators: Naihua Duan, Peter Newman, William Cunningham, Ellen Rudy, Danielle Seiden, Lisa Kakinami

Principal Investigator: Naihua Duan

UARP Award Number: CC02-LA-001

Purpose: The development of efficacious HIV vaccines through successful vaccine trials offers the best long-term hope of controlling the AIDS pandemic. Therefore, examination of potential barriers to HIV vaccine trial participation is critical. Underenrollment may limit the power of the trial; selective enrollment may limit the generalizability and relevance of the trial findings. The purpose of this study is to assess participants' willingness to participate in hypothetical HIV vaccine trials and the impact of vaccine trial characteristics on willingness to participate, among diverse potential trial participants at elevated risk for HIV.

Methods: Participants (n=123; median age=38.5 years; 69% male; 14% African American, 32% white, 37% Latino) were recruited using multisite (n=9) purposive, venue-based sampling from gay-lesbian community centers (n=3), needle exchange programs (n=3), and Latino primary care clinics (n=3) in Los Angeles. We assessed participants' willingness to participate for eight hypothetical HIV vaccine trials that are varied across seven dichotomous attributes, including provision of free medicine (yes vs. no), side effects (none vs. minor), follow-up period (3 years vs. 5 years), number of injections (2 vs. 5), testing HIV+ (vs. not testing HIV+), risk of HIV infection (no risk vs. small risk), and reimbursement ($75 vs. $25). Minor side effects were reported as temporary body aches, skin rash and fevers. A fractional factorial experimental design was used to construct the hypothetical vaccine trials. The importance placed by each participant on each attribute was estimated using an Analysis of Variance (ANOVA) model within each participant, then meta-analyzed across participants. We measured participants' willingness to participate in the hypothetical vaccine trials on a 100-point scale, with 0 = highly unlikely, 25 = somewhat unlikely, 50 = neither likely nor unlikely, 75 = somewhat likely, 100 = highly likely.

Results: Participants' willingness to participate in the eight hypothetical HIV vaccine trials ranged from a high of 70.3 (SD=37.9) for a hypothetical trial with free medicine, no side-effects, three years of follow-up, five injections, not testing HIV+, no risk of HIV infection and $25 reimbursement; to a low of 25.6 (SD=34.1) for a hypothetical trial with no free medicine, no side-effects, five years of follow-up, two injections, not testing HIV+, small risk of HIV infection and $25 reimbursement. Participants placed the greatest importance on the risk of HIV infection in their reported willingness to participate: a hypothetical vaccine trial that guarantees no risk of HIV infection is more attractive than a hypothetical vaccine trial that discloses a small risk of HIV infection, by a mean difference of 22.1 points on the 100-point scale (CI: 16.2, 28.0; p<.0001). Other significant attributes included testing HIV+ (13.4; CI: 8.8, 17.9; p<.0001), provision of free medicine (13.1; CI: 8.6, 17.6; p<.0001), and duration of follow-up (6.8; CI: 3.3, 10.2; p=.0002). Monetary reimbursement, number of injections, and purported minor side effects did not contribute significantly to participants' willingness to participate in an HIV vaccine trial.

Conclusion: The wide range of scores on willingness to participate in hypothetical HIV vaccine trials suggests vaccine trial characteristics, particularly risk of HIV infection and testing HIV+, may strongly influence participants' willingness to participate in a trial. Eliciting potential participants' preferences towards hypothetical HIV vaccine trials prior to the actual trial may improve the chances that participants will enroll in trials that are consistent with their interests and preferences. Informational forums that address potential participants' barriers and preferences may improve enrollment and ethics of such trials.

Next Steps: First, further analysis of the data is being undertaken to examine HIV vaccine trial participation and risk behavior change, and determinants of these outcomes, among diverse communities at risk. Second, several manuscripts are in preparation, including the comparison of trial participation data with the post-trial adoption data. Third, a pilot study has been initiated in collaboration with the Thai Ministry of Public Health to utilize conjoint analysis to assess HIV vaccine trial preparedness and post-trial acceptability in Thailand. Fourth, several new collaborations with UCLA researchers in Medicine and Public Health are underway to prepare for future HIV vaccines and other prevention innovations among diverse communities at risk.

Clinical Sciences

HIV Vaccine Acceptability and Risk Behavior Intentions among Communities at Risk: The Impact of Vaccine Characteristics (Project VIBE)

Noteworthy Abstract

Presenter: Peter A. Newman, University of Toronto

Collaborators: Naihua Duan, William Cunningham, Ellen Rudy, Sung-Jae Lee, Danielle Seiden

Principal Investigator: Naihua Duan

UARP Award Number: CC02-LA-001

Purpose: The development of efficacious HIV vaccines offers the best long-term hope of controlling the AIDS pandemic. Yet, future HIV vaccine availability does not guarantee adoption. Risk behavior increases subsequent to HIV vaccine availability could offset the benefits of partially efficacious vaccines. The purpose of this study is to assess HIV vaccine acceptability and post-vaccine risk behaviors, and the impact of vaccine characteristics on these outcomes, among diverse consumers at elevated risk for HIV.

Methods: Participants (n=143; median age = 36 years; 69% male; 22% African American, 31% Latino, 36% white) were recruited using purposive, venue-based sampling from gay/lesbian community centers, needle exchange programs, and Latino primary care clinics in Los Angeles. Consumer preferences, likelihood of adoption and risk behavior intentions were assessed in regard to eight different hypothetical FDA-approved HIV vaccines each with seven dichotomous attributes. Vaccine characteristics included efficacy (95% vs. 50%), duration of protection (10 years vs. lifetime), side effects (none vs. minor [temporary body aches, skin rash and fever]), doses (2 vs. 5), cross-clade (i.e., across multiple subtypes; vs. single-clade) protection, route of administration (oral vs. injection), and cost ($10 vs. $50). A fractional factorial experimental design was used to construct the hypothetical vaccines. The importance placed by each participant on each attribute is estimated using an Analysis of Variance (ANOVA) model within each participant, then meta-analyzed across participants. Participants' likelihood of adoption of the hypothetical HIV vaccines was measured on a 100-point scale, with 0 = highly unlikely, 25 = somewhat unlikely, 50 = neither likely nor unlikely, 75 = somewhat likely, 100 = highly likely.

Results: The likelihood of adoption of the eight hypothetical FDA-approved HIV vaccines ranged from 33.2 (SD=34.9) to 82.2 (SD = 31.3), with a mean likelihood of 60.0 (SD = 21.9) averaged across all eight hypothetical vaccines, substantially higher than the mean likelihood of 40.5 (SD = 22.1; p<.0001) for willingness to participate in hypothetical vaccine trials, averaged across eight hypothetical vaccine trials. Efficacy had the greatest impact (22.7; CI: 18.5, 27.1; p<.0001 ; e.g., almost one gradation from neutral to somewhat likely) on likelihood of adoption, followed by cross-clade protection (12.5; CI: 8.7, 16.3, p<.0001), side effects (11.5; CI: 7.4, 15.5; p<.0001) and duration of protection (6.1; CI: 3.2, 9.0; p<.0001). In response to hypothetical adoption of an FDA-approved HIV vaccine, 6.4%-12.2% indicated intentions to decrease condom use and 14.3%-16.6% to increase number of sexual partners, with no intention to increase needle sharing.

Conclusion: The wide range of acceptability of hypothetical FDA-approved HIV vaccines suggests vaccine characteristics, particularly efficacy, may strongly influence consumer adoption. While most consumers would

maintain or decrease risk behaviors, a small proportion indicated intentions to increase HIV risk behaviors subsequent to vaccine adoption. Given the likelihood that initial HIV vaccines will be only partially efficacious, educational, social marketing and behavioral prevention interventions tailored to different communities at risk may be vital to the success of future HIV vaccines in controlling the HIV/AIDS pandemic.

Next Steps: First, further analysis of the data will be undertaken to investigate HIV vaccine acceptability and risk behavior change, and determinants of these outcomes, among diverse communities at risk. Two manuscripts are in preparation and several others planned. Second, several grant applications have been submitted to continue and expand on this pilot study: 1) NIMH R-01 (Post-trial HIV Vaccines: Receptivity, Risk and Disparities) to study at risk populations in Los Angeles; 2) UCLA AIDS Institute International Seed Grant (Consumer Research on HIV Vaccines in Thailand); and 3) Canadian Institutes of Health Research (HIV Vaccine Acceptability among Black Women in Toronto). Third, a pilot study has been initiated in collaboration with the Thai Ministry of Public Health to utilize conjoint analysis to assess HIV vaccine trial preparedness and post-trial vaccine acceptability in Thailand. Fourth, several new collaborations with UCLA researchers in Medicine and Public Health are underway to conduct formative social marketing research, using conjoint analysis, in order to prepare for future HIV vaccines and other HIV prevention innovations among diverse communities at risk.

Clinical Sciences

Liver and Kidney Transplantation in Persons with HIV

Presenter: Peter Stock, UC-San Francisco

Collaborators: Michelle Roland, Les Benet, Lynda Frasseto, Mike McCune, Barry Bredt, Jeffrey Martin, Joel Palefsky, Norah Terrault

Principal Investigators: Peter Stock, Michelle Roland

UARP Award Number: TP00-SF-154

Patients with HIV infection are at significant risk for end stage organ disease. Prior to the advent of highly active antiretroviral therapy (HAART), such patients were often not considered as transplant candidates based on poor prognosis. However, with the use of HAART, HIV positive patients have experienced significant improvements in morbidity and mortality. Thus, increasing numbers of HIV+ patients with end stage kidney and liver disease are potential candidates for transplantation. This is a trial to determine the safety of solid organ transplantation in patients with HIV infection. This pilot single center, non-randomized, longitudinal study specifically investigates the effect of HIV on the alloimmune response, the effect of immunosuppression on HIV infection, and the complicated drug interactions between the anti-viral agents and the immunosuppressive agents.

14 subjects received kidney transplants, 9 received liver transplants, and 1 received a liver/kidney transplant (N=24) between 3/00 and 9/03. Subjects included 23 men and 1 woman, with a median age of 45 (15 – 64). 54% were White, 33% African American, 8% Asian and 4% Latino. Four (17%) subjects had a prior history of 5 opportunistic complications (CMV, cryptococcal meningitis, MAC, KS and TB). Median pre-transplant CD4+ T-cell count was 407 (104-973). HIV RNA was undetectable in kidney recipients; median HIV RNA was < 75 (< 75 – 55,100) in liver recipients. HCV infection was present in 4 (40%) liver and 4 (29%) kidney recipients. Median follow-up as of October 1, 2003 is 480 days (8 - 1254). Two subjects died: 1 liver recipient with recurrent HCV infection (15 months) and 1 kidney recipient with pneumonia (6 months). There was one case each of the following: Candida esophagitis, CMV esophagitis, and pulmonary Aspergillus infection. There was no recurrence of prior OIs. At follow-up, the median CD4+ T-cell count was 255 (8-902) and HIV RNA was < 75 (< 75- 9600). Rejection occurred in 10 (71%) kidney recipients, the liver/kidney recipient, and 1 liver recipient. There were 5 cases of delayed graft function in kidney recipients and 1 kidney graft loss due to rejection. Median creatinine is 1.6 (1.1 – 3.2) in kidney recipients. 1 liver recipient required re-transplantation due to a small for size graft lesion. Recurrent HCV has been documented in 2 liver recipients, 1 of whom received HCV treatment, and progressive HCV in no kidney recipients.

Conclusions: Liver and kidney transplantation appears to be associated with good patient and graft survival and minimal evidence of HIV disease progression despite CD4+ T-cell declines with rejection treatment. There is an unexpectedly high rate of kidney rejection. A national, 5-year multi-site study, which is sponsored by the University of California, San Francisco and supported by The National Institute of Allergy and Infectious Diseases (Peter Stock, PI; Michelle Roland, Co-PI) has been funded as a U01and has begun enrolling patients.

Clinical Sciences

Disparities in Perceived Barriers and Intentions to Adopt Future HIV Vaccines (Project VIBE)

Presenter: William Cunningham, UC-Los Angeles

Collaborators: Peter Newman, Naihua Duan, Jae Lee, Ellen Rudy, Danielle Seiden

Principal Investigator: William Cunningham

UARP Award Number: CC02-LA-001

Background: Developing and disseminating effective HIV vaccines is a primary public health objective, particularly among persons of color who are at greatest risk for HIV infection. However, little is known about how perceived barriers and intentions to adopt future HIV vaccines may vary by demographic groups. The objectives of this study were to examine attitudes and beliefs about future HIV vaccines that may act as barriers to adoption, and to examine their associations with demographic characteristics and adoption intentions.

Methods: Multisite (n=9) purposive, venue-based sampling was used to recruit and survey 143 participants (mean age 37, 31% female, 31% Latino, 22% Black, 43% High school or less educated, 36% uninsured) at risk for HIV infection from gay/lesbian community centers (n=3), needle exchange programs (n=3), and Latino primary care clinics (n=3) in Los Angeles.. The survey contained 22 items assessing concerns about HIV vaccines, belief in AIDS conspiracy, trust in providers, trust in government and discrimination from providers, as well as a measure of the likelihood of adoption of eight different hypothetical FDA-approved HIV vaccines on a 0-100 scale (0 = highly unlikely, 25 = somewhat unlikely, 50 = neither likely nor unlikely, 75 = somewhat likely, and 100 = highly likely). A fractional factorial experimental design was used to construct the hypothetical FDA-approved HIV vaccines.

Results: The mean overall adoption score for the sample was 60.0 (SD 21.9) . Potential barriers to future HIV vaccine adoption were commonly reported: 27% were concerned an HIV vaccine would lead to discrimination, 37% were concerned that getting HIV an vaccine would affect health insurance; 51% were concerned about confidentiality 51% believe that the government already has an HIV vaccine, but is keeping it from the public (blacks 50%, Latinos 55%, whites 37%, p<.05), 39% believe there is a cure for AIDS but the government is keeping it from us (blacks 46%, Latinos 27%, whites 33%, p<.05), 29% believe the government uses AIDS to kill off people not wanted by society, 32% believed they might be used as guinea pigs in research without their consent (Latinos 38%, Blacks 25%, whites 17%, p<.01), 31% believed Drs. experiment on people without their consent (Latinos 38%, Blacks 25%, whites 15%, p<.01), 31% do not trust their Drs. to put their health first (income <$5000 55%, income $5001-10,000 41%, income >$10,000 20%) 25% do not trust their Drs. to provide quality care (uninsured 42%, public insurance 18%, privately insured 15%, p<.01), and 17% had been refused service by providers. Furthermore, mean scores for overall intention to adopt future HIV vaccines were lower for those who believed Drs. experiment on people without their consent than for those who don't (55.0 vs. 61.8, p <.10), for those who trust their Drs. to provide quality care than for those who don't (53.1 vs. 61.9, p <.05), and for those who were refused service than for those who weren't (52.4 vs. 61.1, p< .10).

Conclusion: Overall, respondents reported a modest likelihood of adopting approved HIV vaccines. Attitudes and beliefs that could interfere with the adoption of future HIV vaccines were prevalent, more common in demographic groups at greatest risk for HIV infection, and some were negatively associated with intentions to adopt HIV vaccines. In order to effectively control the spread of HIV infection, extensive educational interventions to address barriers to adoption are needed among communities at risk long before approved vaccines are disseminated. Next steps include further analysis of the survey results to better understand the relationships between barriers, motivators, and adoption intentions. In addition, several follow-up grant applications have been submitted to examine these and other factors related to vaccine adoption in Los Angeles, Canada, and Thailand.

Clinical Sciences

Post-Trial HIV Vaccine Adoption and Behavioral Responses among Persons at Risk for HIV (Project VIBE)

Presenter: Dallas T. Swendeman, UC-Los Angeles

Collaborators: Peter A. Newman, Ellen T. Rudy, Kathleen J. Roberts, Naihua Duan

Principal Investigator: Naihua Duan

UARP Award Number: CC02-LA-001

Background: Future dissemination of HIV vaccines may encounter two key challenges that could subvert vaccine effectiveness in controlling the epidemic: 1) suboptimal adoption, as indicated by experience with existing vaccines, which may be exacerbated by HIV/AIDS stigma and mistrust; and 2) potential increases in risk behaviors, particularly important given the expectation that initial HIV vaccines will only be partially efficacious. Thus, it is vital to investigate consumer concerns and motivations regarding the adoption of hypothetical FDA-approved HIV vaccines, and consumers' intentions to change risk behaviors, before the vaccines become publicly available.

Method: Nine focus groups were conducted with participants (N = 99; median age = 33 years; 48% female; 22% African American, 44% Latino, 28% white) recruited from STD clinics, needle exchange programs, and Latino community based health organizations using purposive, venue-based sampling. Nine key informant service providers were also interviewed. A semi-structured interview guide elicited concerns, motivators and behavioral intentions in regard to hypothetical post-trial HIV vaccine adoption. Data were analyzed using narrative thematic analysis and Ethnograph qualitative software.

Results: Concerns included limited vaccine efficacy, vaccine-induced HIV infection and HIV-seropositivity, side effects, cost/access, trustworthiness, and relationship issues. Motivators included protection against HIV infection and the ability to safely engage in unprotected sex. Participants expected increases in risk behaviors among at least half of their peers. Both participants and providers urged HIV preventive interventions that: 1) address the consequences of limited efficacy vaccines, 2) combat "magic bullet" perceptions of HIV vaccines, and 3) provide sustained behavioral risk reduction in conjunction with vaccine dissemination.

Conclusion: Tailored interventions that facilitate future HIV vaccine adoption while preventing risk behavior increases will be vital to the success of future HIV vaccines.

Next steps: These findings were used to guide development of a survey instrument, which included preexisting measures and new items based on the qualitative data (e.g., relationship issues in regard to HIV vaccine adoption). Results from the survey (n=266) are reported at this conference (Newman, Duan, et al.; Lee, Cunningham et al.) and have been incorporated, along with qualitative findings, in several grant proposals. Based on the qualitative findings, a manuscript has been accepted for publication in Vaccine ("HIV Risk and Prevention in a Post-vaccine Context"), another manuscript is in revision, and two are in preparation.

Study supported by the Universitywide AIDS Research Program through a grant to the UCLA California AIDS Research Center CC99-LA-002; and The UCLA AIDS Institute and Palotta Teamworks AIDS Vaccine Rides

Clinical Sciences

Developing an HIV Sensor for Rapid Diagnosis and Viral Load Testing

Noteworthy Abstract

Presenter: Robert Beatty, UC-Berkeley

Collaborators: P. Robert Beatty, Turgut Aytur, Jonathan Foley, Wilfredo Lim, Bernhard Boser, Mekhail Anwar, Eva Harris

Principal Investigator: Eva Harris

UARP Award Number: ID03-B-043

We are using micro-scale sensor technology to develop a novel instrument for rapid point-of-care diagnostic assays, called the ImmunoSensor. The ImmunoSensor combines inexpensive computer chip technology and common clinical diagnostic tests to detect the presence of infectious agents, active infection and/or past infection. The ImmunoSensor uses integrated circuit chips modified with a gold overlay to allow efficient interaction with biological molecules (e.g. antibody, antigen, DNA) that determine disease specificity. Small magnetic beads attached to the bound proteins (antigens or antibodies) are detected using a magnetic sensor array. The magnetic beads, when bound near the surface of the chip, create a magnetic field that interacts with the electronic sensor in the chip itself. This information is then transmitted to a handheld device, such as a PDA, as easily-interpretable numeric results. We are able to detect 20 picograms per milliliter of protein, which is equivalent or better sensitivity than many current enzyme-linked immunosorbent assays (ELISAs).

Currently, we have developed the ImmunoSensor for diagnosis of infection with dengue virus (DEN). We are optimizing the prototype sensor based on an antibody detection immunoassay that allows diagnosis of active DEN infection. We are testing the reliability and accuracy of disease diagnosis using the ImmunoSensor compared to the prevailing clinical ELISA tests using human serum samples. Field testing of the ImmunoSensor in Nicaraguan clinical settings is scheduled for early 2004. In addition, a wireless configuration is currently under development that will allow remote detection of assay results.

Application of the ImmunoSensor technology to HIV detection awaits receipt of the UARP award. The HIV-specific sensor will analyze human serum specimens to determine the amount of HIV virus and anti-HIV antibodies that are present. It will also have the potential to simultaneously detect common opportunistic viral or bacterial infections that are often associated with HIV infection. The ImmunoSensor tests will be inexpensive due to the low cost of manufacturing large numbers of computer chips and will provide rapid results. It will also be significantly automated, allowing for use in community clinic settings.

Clinical Sciences

Noteworthy Abstract

Towards the electronic detection of HIV

Presenter: Arica A. Lubin, UC-Santa Barbara

Collaborators: Chunhai Fan, Alan J. Heeger

Principal Investigator: Kevin W. Plaxco

UARP Award Number: ID03-SB-008

While current HIV detection technologies are more than adequate for use in the developed world, they are far too costly in terms of dollars, time and other resources for widespread use in the developing world. To meet the challenging goal of rapid, sensitive HIV detection in an inexpensive, field portable platform we are developing an inexpensive, reusable electronic method for the sensitive, near real-time detection of oligonucleotide hybridization (gene and RNA detection). The approach employs a reagentless electrochemical probe of hybridization in a reusable, miniaturizable, solid-state platform. Initial experiments demonstrate that the approach is feasible and, after only limited optimization, robustly capable of sequence-specific DNA detection at target concentrations below 10 pM and with better than million-fold selectivity. We are currently attempting to improve the sensitivity of the technology to levels sufficient for the reagentless, near real-time detection of HIV via the direct, electronic detection of HIV RNA.

Clinical Sciences

Infectious Diseases Pathogen Chip

Noteworthy Abstract

Presenter: Jeremiah Tilles, UC-Irvine, California Collaborative Treatment Group

Collaborators: X. Y. Jia, M. Berger, J. G. Tilles

Principal Investigator: Richard Haubrich

UARP Award Number: CC02-SD-003

Correct and timely identification of the pathogens in an infected individual is essential for effective treatment of diseases. The classic approach usually uses separate tests for each potential pathogen. This approach is slow, expensive, complicated and impractical for treating acutely ill patients. A simplified and automated format that could detect multiple pathogens could dramatically improve clinical diagnoses and should lead to efficient treatment. A pathogen microarray (pathogen chip) including all common respiratory pathogens has been developed and preliminary studies show it to be powerful in detecting pathogens. Samples to be queried are applied to the master array to establish the presence of specific pathogens. A method was also developed for detection of low concentration pathogens in clinical samples using a pre-amplification step for sensitive detection. Detection algorithm, the assay procedures and software for computer data analysis is being developed. Our research goal is to develop a microarray based pathogen detection system to simplify the complexity of pathogen identification and develop it into a single automated format for detecting multiple pathogens. The pathogen chip should be useful for the diagnosis of infectious diseases, surveillance of the pathogen population, monitoring environment. It could also be used for research, emerging infectious diseases and responding to bioterrorism.

Clinical Sciences

Differentiation of Antibody Reactivity between HIV Progressor and Long Term Non Progressor Using Random Peptide Libraries Displayed on Phages

Presenter: Jeremiah Tilles, UC-Irvine, California Collaborative Treatment Group

Collaborators: M. M. Berger, J. G. Tilles, M. Cho, O. Paez, M. Dionisio, A. Tran, D. N. Forthal, M. M. Addo, B. D. Walker, X. Y. Jia

Principal Investigator: Richard Haubrich

UARP Award Number: CC02-SD-003

Although human immunodeficiency virus type 1 (HIV-1) infection leads to the development of AIDS within an average of 8-10 years, there exists a small group of HIV infected patients who remain asymptomatic for a long time. This later group of HIV infected patients are classified as long-term non-progressor (LTNP) and represent less than 5% of all HIV infected patients. The factors responsible for the lack of HIV progression in LTNP are largely unknown. Several reports have demonstrated that antibodies play a critical role in the defense against viruses. Therefore we compared the humoral immune response of HIV progressor and HIV long term non progressor (LTNP) with each other. Epitopes which were predominantly reactive to sera of HIV progressor or LTNP were isolated from the sera by using random peptide libraries displayed on phages (RPLP) combined with a differential immunoscreening approach. Using this technique, 14 epitopes were isolated, 3 of these epitopes were LTNP specific, 5 HIV progressor specific and 6 were reactive to both subject groups in the same way. As demonstrate from these results both HIV groups are able to produce antibodies against HIV, however, the focus of the antibody production to sinlge epitopes is different. If these difference in antibody production against different epitopes is important for virus control and disease progression has to be investigated further. The understanding of the distinct antibody response in HIV infected patients with different disease states may lead us to a better understanding why a small group of HIV infected individual can control virus infection and disease progression and the other group will unavoidable progress to AIDS.

Clinical Sciences

Dramatic Increase in Anal Cancer Diagnoses in the Era of Highly Active Antiretroviral Therapy

Presenter: Catherine Diamond, UC-Irvine, California Collaborative Treatment Group

Principal Investigator: Richard Haubrich

UARP Award Number: CC02-SD-003

Background: We sought to determine how the availability of highly active antiretroviral therapy (HAART) influenced rates of anal cancer among AIDS patients.

Methods: We performed a match between the AIDS & cancer registries for San Diego County. Registry data were complete from 1988-2000 but no cases of anal cancer were diagnosed before 1992.

Results: We identified 39 cases of anal squamous cell carcinoma. All were men & 38 (97%) were men who have sex with men (MSM). The median age was 42 years (range: 25-59); 28 (72%) were white; 2 (5%) were Black; 7 (18%) were Latino & 2 (5%) were unknown race/ethnicity. The median CD4 count was 120/MCL (range: 2-551). Among the 36 patients diagnosed with HIV prior to or simultaneous with their anal cancer diagnoses, the median duration of known HIV infection was 78 months (range: 0-175). The median duration of HIV infection in the pre-HAART era (1992-1995) was 29 months while post-HAART (1996-2000) it was 84 months (p=.01). Eight cases (21%) were diagnosed pre-HAART, while 31 (79%) were diagnosed post-HAART. The number of cases increased each year between 1996-2000 (3 (8%) in 1996; 4 (10%) in 1997, 5 (13%) in 1998, 8 (21%) in 1999 & 11 (28%) in 2000) despite a declining incidence of AIDS in San Diego County. Thus, the rate of anal cancer increased from 2.8 per 1000 AIDS cases in 1992 to 24.7 per 1000 in 2000 (r=.83, p =.005). Pre-HAART, 3 (38%) of 8 cases were in-situ while post-HAART, 8 (26%) of 31 were in-situ (p=.51). Twenty-eight patients (72%) received surgical treatment. One (3%) received radiation therapy & 1 (3%) received chemotherapy; 16 (41%) received both & 21 (54%) received neither. Twenty (51%) were alive at most recent follow-up. Among the 19 deceased, 6 (32%) died of HIV/AIDS; 6 (32%) died of anal cancer & 7 (37%) died of other/unknown causes. The median survival was 37 months (range: 2-104). Data limitations include lack of information regarding HAART usage, smoking status & anal cancer rates in HIV-infected persons without AIDS & uninfected MSM in San Diego County.

Conclusions: Cases of anal cancer among AIDS patients in San Diego County have increased since the introduction of HAART. This could be related to increased screening for anal cancer or increased longevity with the use of HAART. Fewer in-situ tumors in the post-HAART era argue against a screening phenomenon. The longer duration of HIV infection post-HAART suggests that HAART increases the time at risk for the development of anal cancer.

Clinical Sciences

Pneumocystis Colonization in HIV-Infected Patients

Presenter: Laurence Huang, UC-San Francisco

Collaborators: Kristina Crothers, Alison Morris, Gena Groner, Melissa Fox, Joan Turner, Shary Eiser, Jeffrey Jones, C. Ben Beard

Principal Investigator: Laurence Huang

UARP Award Number: ID03-SF-027

Although significant advances have been made in our understanding of Pneumocystis and Pneumocystis pneumonia (PcP), the reservoir of human Pneumocystis, *P.* jiroveci, remains unknown. Increasingly, studies indicate that humans are a reservoir for P. jiroveci. Several potential human reservoirs have been suggested, including persons with active PcP, persons living with or caring for patients with active PcP, infants, pregnant women, adults with underlying lung disease, and immunocompromised individuals, including HIV-infected persons. However, the extent of colonization and the clinical characteristics associated with colonization in these different populations remain unclear. The objectives of this study were to determine the proportion of HIV-infected patients without microscopic evidence of PcP who are colonized with *P.* jiroveci and to examine potential risk factors for and consequences of colonization.

Subjects were HIV-infected patients admitted to San Francisco General Hospital with clinically suspected PcP from May 2000 through May 2003. This population was chosen because these patients were at the highest risk for PcP and therefore presumably at a high risk for Pneumocystis colonization. The University of California San Francisco and the Centers for Disease Control and Prevention Institutional Review Boards approved the study. Study specimens were obtained by sputum induction (SI) or bronchoalveolar lavage (BAL) that were performed for clinical diagnosis of PcP. Specimens were shipped to the Centers for Disease Control and Prevention for molecular analysis. Polymerase chain reaction (PCR) amplification and DNA sequencing was performed at the P. jiroveci mitochondrial large subunit (mtlsu) ribosomal RNA (rRNA) and the dihydropteroate synthase (DHPS) loci. Clinical data were obtained from standardized chart abstraction performed six weeks after hospital admission. The investigators who collected the clinical data were blinded to the PCR and sequencing results, and the investigators who performed the molecular analysis were blinded to the clinical status of the patient. Prior to unblinding, patients were classified as PcP-negative if (1) the SI/BAL specimen microscopic examination was negative for Pneumocystis, (2) PcP treatment was discontinued, and (3) the patient recovered from their pneumonia. PcP-negative patients were then classified as colonized with Pneumocystis if P. jiroveci DNA was detected by PCR and confirmed by DNA sequencing. Statistical analysis was performed using Stata version 8.0 (Stata Corporation, College Park, Texas, USA). Colonized and non-colonized patients were compared to identify potential risk factors for Pneumocystis colonization. Dichotomous predictors were compared using chi-square or Fisher exact tests while continuous predictors were compared using Student's t-test or Wilcoxon rank sum.

Overall, 32 patients were classified as PcP-negative. PcP treatment was discontinued in all 32 patients after a median of two days of therapy (range 0 to 8 days) and all of the patients recovered from their pneumonia. Twenty-two of the 32 PcP-negative patients (69%) had evidence of Pneumocystis colonization. These patients were classified as colonized with Pneumocystis on the basis of a confirmed P. jiroveci sequence at the multi-copy mtlsu rRNA locus (n = 22); six of these patients also had a confirmed P. jiroveci sequence at the single-copy DHPS locus. No patient had a positive DHPS sequence in the absence of a

positive mtlsu rRNA sequence. There were no significant differences between colonized and non-colonized patients in terms of demographic factors such as gender, race/ethnicity, or factors traditionally associated with the risk of PcP, including CD4 cell count, HIV RNA level, prior PcP, use of PcP prophylaxis (within the preceding three months) and, if receiving prophylaxis, specific PcP prophylaxis regimen. All patients were discharged from the hospital, except for a single patient who developed a subdural hematoma unrelated to the pulmonary disease. No patient subsequently developed PcP during the 6-week follow-up period.

The current study found that the majority of HIV-infected patients without microscopic evidence of PcP were colonized with P. jiroveci. In this study, the proportion of HIV-infected subjects who were colonized (69%) was higher than previously reported (range 9% to 44%). The higher rate in our study may result from differences in the patient populations studied or the type of respiratory specimen examined. In particular, the fact that our subjects were at a high risk for PcP by virtue of advanced HIV disease and had symptoms that were suggestive of PcP may have contributed to the high rate of colonization observed. This rate may be quite different in asymptomatic subjects with less advanced HIV disease. The current sample size undoubtedly limited our ability to find statistically significant clinical predictors of colonization, and large-scale studies are needed to further delineate risk factors for colonization. No patient developed PcP during the study period; however, it is unclear whether colonization increases the risk of PcP over a longer period of time. In addition, it is unclear whether the use of PcP prophylaxis or combinations of antiretroviral therapy may alter the risk of Pneumocystis colonization as both have been demonstrated to decrease the risk of PcP. Although the clinical consequences of Pneumocystis colonization in humans are unknown, these preliminary findings raise the possibility that a substantial number of HIV-infected patients may be at risk for transmitting the disease to others, as animal models suggest that animals colonized with Pneumocystis may infect others of the same species. Future research, including the development of non-invasive means for obtaining respiratory specimens that can be applied to large-scale studies and the comparison of different PCR assays to determine which assay offers the highest sensitivity to detect colonization, are needed to understand better the epidemiology and clinical consequences of Pneumocystis colonization.

Clinical Sciences

Screening for Asymptomatic Sexually Transmitted Diseases (STDs) in HIV-Infected Men Who Have Sex with Men (MSM)

Presenter: Gunter Rieg, Harbor-UCLA Research and Education Institute

Collaborators: G. Rieg, R. Lewis, M. Witt, D. Smith, J. Wong, E. Daar

Principal Investigator: Gunter Rieg

UARP Award Number: ID03-REI-040

Background: STDs have been shown to be increasing, particularly among MSM. The presence of STDs correlates with unsafe sexual practices in the community and can contribute to HIV transmission. Moreover, there is an increasing frequency of asymptomatic infection with gonorrhea (GC) and chlamydia (CT). The literature reports asymptomatic urethral infection caused by GC and CT ranging from 1-6%, and perhaps as high as 18% in select settings. An audit of annual STD screening by urine nucleic acid amplification (NAA) methods from 300 HIV-infected patients in our clinics revealed 12 (3.3%) with asymptomatic GC or CT. In light of the relationship between STDs and HIV transmission the most recent Centers of Disease Control and Prevention STD guidelines recommend assessment of sexual risk, client centered prevention counseling, and routine screening for urethral, pharyngeal and rectal infection in at-risk MSM. It is recommended that screening be performed at least annually, and more frequently in those considered to be at highest risk. Since there are few data regarding how to define the optimal frequency for screening, and what group constitutes those at highest risk, the guidelines are based primarily on expert opinion.

Study Aims: This study will explore the utility of screening studies for asymptomatic STDs in HIV-infected MSM in two urban HIV clinics. Aim 1 will prospectively determine the prevalence and rate of new asymptomatic syphilis, GC and CT infection in this group. Aim 2 will prospectively define factors associated with increased rates of these STDs in asymptomatic individuals. Aim 3 will define the optimal frequency and cost effectiveness of screening for these STDs in asymptomatic subjects. Aim 4 will determine the impact treating asymptomatic urethral GC or CT has on HIV viral load in genital secretions.

Study Design: These Aims will be addressed in this study by prospectively screening 300 HIV-infected MSM every six months for serologic evidence of syphilis and by culture and NAA for asymptomatic urethral, rectal and pharyngeal GC and CT. Behavioral information will be collected at each time of testing. Those identified with urethral GC or CT will have seminal mononuclear cells and plasma assayed for quantitative HIV DNA and RNA prior to and after specific treatment. This study will determine how often new cases of asymptomatic infection are identified, whether there are select groups whose behaviors predict that they are at greatest risk for incident cases of STDs, and the cost effectiveness of testing these subjects based upon demographic and risk-taking behaviors. Finally an exploratory study will be performed to determine whether treating asymptomatic STDs will reduce the amount of HIV present in genital secretions.

Perspective: These studies will systematically collect data to define the optimal strategy and utility of performing STD screening in asymptomatic, at-risk HIV-infected MSM.

Clinical Sciences

An Enhanced Approach for Studying the Causes of Diarrheal Disease in an HIV+ Population: The Enteric Pathogens Microarray Study

Presenter: Sona R. Saha, UC-Berkeley

Collaborators: Jeffery Burack, Jamie Mandelke, Brian C. Thomas, Patricia Holman, Alan E. Hubbard, Lee W. Riley, John M. Colford, Jr.

Principal Investigator: Joseph Eisenberg

UARP Award Number: ID02-B-048

Although microarrays have been employed for transcript profiling and gene expression analysis, the potential power of microarrays as diagnostic tools for infectious pathogens has been largely untapped. Using such an array, we would need to test a clinical specimen only once to detect the presence or absence of numerous pathogens or differentiate pathogenic from non-pathogenic strains. We are currently designing a pilot diagnostic microarray to detect the presence of a broad range of infectious agents associated with gastrointestinal illness in stool specimens. This enteric pathogens microarray is composed of 40mer oligonucleotides derived from species specific and conserved rRNA sequences from approximately 45 bacterial and protozoan organisms including pathogenic E.Coli, Shigella, Salmonella, Mycobaterium, Cryptosporidum, Entamoeba and Microsporidia species.

In parallel, we are conducting a case control study investigating the etiology of gastrointestinal illness among HIV+ individuals. Stool specimens are being collected from 150 HIV+ patients with and without diarrheal symptoms from a community AIDS clinic; we will compare the performance of the microarray to that of standard clinical microbiological analysis. This application of the array is of particular relevance to HIV+ individuals as they represent a sensitive subpopulation at increased risk for infectious gastroenteritis.

HIV+ patients from the East Bay AIDS Center with acute, chronic or no diarrhea are being recruited to provide stool specimens and complete a brief questionnaire on gastrointestinal symptoms and potential risk factors (e.g. travel, sexual behavior, food and water consumption, animal contact). This sampling design represents a case-control study with two comparison arms (Cases=acute diarrhea; control arm #1=chronic diarrhea; control arm #2=no diarrhea). The stool specimens will be analyzed by a clinical laboratory using standard methodologies and by the enteric pathogens microarray in development. Information on medications, HIV viral load and CD4 count is also being abstracted from participant medical records. Recruitment began in April 2003 and 142 participants have been enrolled and submitted specimens as of November 15, 2003.

Our principal objectives for this pilot enteric pathogens microarray study are to: 1) design, develop and validate an enteric pathogens microarray to detect bacterial and protozoan organisms from fecal specimens, 2) evaluate the association of specific organisms with acute, chronic and no diarrhea in HIV+ patients using standard microbiological methods and the enteric pathogens microarray, and 3) determine if organisms previously unrecognized as pathogens are associated with symptoms of gastrointestinal illness. Study results are anticipated in summer 2004. Although this pilot study focuses on bacterial and protozoan organisms, we plan to develop a more comprehensive microarray in the future that will include key enteric viruses.

Clinical Sciences

Noteworthy Abstract

Novel Approach for Evaluating Pasteurization Methods to Inactivate HIV in Breast Milk

Presenter: Kiersten Israel-Ballard, UC-Berkeley

Authors: K. Israel-Ballard, R. Donovan, B. Enge, M. Gesner, M. Scott, H. Sheppard, A. Sage, C. Chantry, B. Abrams

Background: Mother-to-child transmission of HIV-1 via breast milk (BM) causes an estimated 350,000 infants to contract HIV each year in developing countries. Heat-treatment of expressed BM is one alternative infant feeding option advocated by WHO and several methodologies have been proposed. However these methods have not been systematically evaluated, in part because present culture-based methods of evaluating the efficacy of inactivating HIV in breast milk are insensitive, slow, technically demanding, and lack precision. This work describes two pasteurization methods, Flash-heating (FH) and Pretoria Pasteurization (PP), and uses a new approach for measuring HIV inactivation based upon the destruction of reverse transcriptase (RT) activity that is sensitive, rapid and precise.

Methods: Fresh BM was obtained from 5 healthy women volunteers and spiked with $1x10^8$ copies/mL of an HIV-1 subtype C isolate. Field conditions were simulated using a 1 Qt. aluminum pan, 16 oz. glass peanut butter (PB) jars, and an open flame. Heating methods included: 1) FH - 50 mL of BM in uncovered PB jar was placed in 450 mL of water in aluminum pan over flame until the water began to boil, then BM was immediately removed from the water and heat, and allowed to cool to room temperature; 2) PP - 450 mL of water was brought to a boil in an aluminum pan, removed from the flame, a covered PB jar with 50mL BM was placed in the water for 20 minutes, then removed and allowed to cool to room temperature uncovered. Aliquots of BM also served as unheated ('No Heat') and unspiked ('No Virus') controls. Temperatures were tracked using a DuaLogR Thermocouple. One mL samples of FH, PP, No Heat, and No Virus were quantitatively assessed for RT activity using appropriate dilutions in the ExaVir Quantitative HIV-RT Load assay (Cavidi, Uppsala, Sweden).

Results: A representative temperature recording of FH and PP is presented at left. Comparison of RT activity in 5 BM samples treated according to the 4 methods is shown at right.

Conclusions: Both the FH and PP methods inactivated 3 logs or more of HIV-1 RT activity. However, the FH method appeared superior to the PP method in eliminating residual RT activity. This approach, utilizing simulated field conditions, accurate and continuous temperature monitoring, and the exquisite biologic sensitivity and range of the RT assay, should allow the direct assessment of HIV-1 inactivation in breast milk from HIV-infected mothers.

Clinical Sciences

Source and Mechanisms of Perinatal HIV Transmission

Presenter: Ruth Dickover, UC-Los Angeles

Principal Investigators: Ruth Dickover, Yvonne J. Bryson

UARP Award Number: ID02-LA-021

Human Immunodeficiency Virus infection is spreading rapidly among women of child-bearing age throughout both the developed and developing world today. Knowledge of the means by which HIV is transmitted from infected mother to infant is essential for the development of specific intervention strategies. The primary objective of this study is to evaluate potential sources of maternal virus inoculum in both in utero and intrapartum perinatal HIV transmission. Through these studies we hope to obtain a better understanding of the mechanisms involved in transmission of HIV from infected mothers to their infants in order to develop future intervention strategies for both in utero and intrapartum perinatal HIV transmission. To date, we have completed cloning HIV env gene regions obtained from a variety of infected mother/infant pair sources including maternal PBMC and cervicovaginal secretion as well as infant PBMC and gastric aspirates from all three mother / infant pairs in the study. DNA sequencing has been performed on a total of 100 HIV env gene region clones from mother / infant pairs 1 and 2 and the data generated has been edited and we have begun an in depth phylogenetic analysis. Preliminary sequence analysis of the data collected to date indicates that unique viral strains are present in the compartments analyzed (peripheral blood, gastric aspirates and cervico vaginal secretions) which can readily be identified by their sequence patterns. Phylogenetic analysis of the sequences obtained from mother / infant pairs 1 and 2 by the neighbor-joining method indicate a very high degree of genetic relationship between HIV isolates obtained from time of birth infant gastric aspirates and the viral env gene region sequences found in the peripheral blood of the infected infants. The infant gastric aspirate sequences are however, distinct from both maternal peripheral blood and vaginal secretion env gene clones, suggesting the presence of HIV in amniotic fluid, prior to delivery. Such HIV may then have been swallowed by the infants during gestation, resulting in perinatal transmission in utero. Phylogenetic data from mother / infant pair 3, an intrapartum transmitting pair, will help the further elucidate the role of amniotic fluid and vaginal secretions in perinatal HIV transmission. In summary data collected so far indicates amniotic fluid may serve as a source of HIV transmitted perinatally via a mucosal route. These data suggest the need to develop specific means for lowering amniotic fluid viral load and avoiding mucosal perintal HIV transmission.

Clinical Sciences

Modelling the Effectiveness of Nevirapine, HIV Vaccine and HIV-Specific Monoclonal Antibody on Mother to Child Transmission (MTCT) of HIV from Intrapartum and Breast-Feeding

Presenter: Myungshin Sim, UC-Los Angeles

Collaborators: Yvonne Bryson, Naihua Duan

Principal Investigator: William Cumberland

Studies have shown mother to child transmission (MTCT) rates of up to 35%(including transmission in utero, intrapartum, and through breast feeding) in Africa where antenatal care, antiretroviral therapy, and formula feeding are not always feasible. The use of Nevirapine has reduced MTCT of HIV during labor and delivery up to 50%. However, the overall MTCT at 36 months shows that the beneficial effect of intrapartum Nevirapine decreases with continued breast-feeding. Large scale use of antiretroviral therapy is not practical due to its complexity, unavailability, side effects, development of resistance, and the cost; therefore the ultimate prevention method is believed to be an effective HIV vaccine with or without HIV specific monoclonal antibody (HIV-Ab) in infants. However little is known about the potential efficacy of vaccines so the purpose of this study is to develop a model that would predict the potential effects of various interventions including combinations of vaccine, HIV-Ab, and NVP on mother to child intrapartum and breast-feeding transmission of HIV at various ages.

We used rates reported from several longterm mother infant intervention studies in Africa to estimate the scale and shape parameters of a Weibull hazard function. Two separate Weibull functions were modeled for non-treated and NVP-treated groups. Models were developed to accommodate different levels of protective immunity and waning immunity following various vaccine regimens, to predict the primary outcome measure of cumulative transmission of HIV at 36 months of age from both intrapartum and breast-feeding (CTR_{36}). The protective Immunity(PI) of one dose vaccine is modeled to be 50~95% and with a second and third dose it is assumed to be boosted to 75.5~99.5%. PI is allowed to wane from its peak level of protection. Nevirapine, HIV-Ab, and 1st dose of vaccine are assumed to be given at birth. Graphical methods are developed to display model prediction for different prevention interventions and the variety of assumptions for the purpose of showing effectiveness of various prevention strategies. The predictions from the models are illustrated under the following assumptions. Vaccine; PI 95%(1 dose), 98.5%(2 doses), 99.5%(3 doses), 11% waning over 10 years, and for the HIV-Ab; 70% PI, 50% waning per month. The model suggests that when vaccine is used along with NVP, CTR_{36} reduces to 1.81~2.11% depending on number of vaccine doses. Combined use of Nevirapine, HIV-Ab, and vaccine can further reduce CTR_{36} to 0.71~ 0.74%. Less ideal vaccine such as 50% PI(1 dose), 65%(2 doses), 75.5%(3 doses) and 11%/10 years waning rate used with NVP can reduce CTR_{36} to 3.32~6.19%. The addition of HIV-Ab in this case further reduces CTR_{36} to 1.78~5.95%.

These results from the models indicate that even imperfect vaccine can greatly reduce MTCT especially when it is used along with NVP. These results have an important implication in countries where antiretroviral therapy and formula feeding are not feasible. Further research is underway to incorporate into the model the cost effectiveness of different prevention options.

Clinical Sciences

Effect of Prostratin on Latent Viral Reservoirs

Noteworthy Abstract

Presenter: Peter Anton, UC-Los Angeles

Collaborators: Stephen J. Brown, Marjan Hezareh, Julie Elliott, Marie Fuerst, Ian M. McGowan, Peter A. Anton

Background and Significance: The persistence of latent reservoirs for human immunodeficiency virus type 1 (HIV-1) represents a major barrier to virus eradication in patients on combination anti-retroviral therapy. It has been proposed that treating infected individuals simultaneously with HAART and agents that activate cells to express HIV-1 might eliminate the latent reservoirs. One promising candidate for such strategy is prostratin, a phorbol ester and protein kinase C (PKC) agonist. Unlike other phorbol esters, prostratin is a potent anti-tumor promoter. Prostratin displays dual functions with regard to HIV activity: (i) it activates viral expression from all models of latency studied so far (ii) it limits the spread of viral infection. Therefore, prostratin may be an important potential adjunct therapy to activate latently infected cells simultaneously limiting viral spread in subjects on HAART. This project is a condensed drug development and phase I safety study for prostratin addressing latency, with particular focus in the mucosal compartment.

Material and Methods: Currently prostratin is undergoing pre-clinical toxicology under auspices of the NIH-Inter-Institute program for the Development of AIDS Related Therapeutics (IIP-DART). Additional standard IND toxicology is the next development step. Preliminary toxicological results are presented below.

Results: Single dose range finding studies in rats indicates a dose dependent reversible hepatotoxicity with a maximum tolerated dose (MTD) between 0.2 and 0.4 mg/kg. The MTD (via IV bolus) in Rhesus Macaques is estimated at between 0.4 and 0.6 mg/kg. Repeat dosing at 0.4 mg/kg was tolerated with reversible toxicity. Human microsomal experiments indicate time dependent loss of parent compound with a single metabolite representing less than 17% of total amount, and rapid distribution of the drug. Urinary excretion was less than 5%. Oral bioavailability is estimated at 28%. Simulations of various activation levels reveal that prostratin, used as a single agent, would require multiple cycles of administration to achieve a detectable 3-log decrease in latent virus. Additional dosing to determine whether toxicity is related to "Cmax" effect or total exposure (i.e., AUC) is planned. These studies will help determine the optimal dosing schedule, i.e. single maximum dose vs. multiple smaller daily doses per cycle. The initial clinical trial design will attempt to determine the MTD of prostratin, and the time to return to baseline of any toxicities seen. The initial endpoints will be determinations of activation markers, "blip' in plasma and tissue (gut mucosal) viral RNA and changes in proviral DNA in plasma, tissue and HIV co-culture.

Conclusion: Clinical attempts to target viral reservoirs face challenges in designing interventions, which can measure if changes in planned endpoints can reasonably be monitored, whether the changes measured are clinically significant and whether such interventions warrant the potential risks to patients. Most likely, several targeting modalities will need to be combined to be successful.

Clinical Sciences

Noteworthy Abstract

Role of T-Cell Activation in Determining CD4+ T-Cell Count Changes Among HIV-Infected Patients with Drug-Resistant Viremia

Presenter: Jeffrey Martin, UC-San Francisco

Collaborators: J. Martin, T. Neilands, E. Sinclair, P. Hunt, B. Bredt, M. Krone, E. Hagos, T. Liegler, R. Grant, S. Deeks

Principal Investigator: John Greenspan

UARP Award Number: CC02-SF-002

Background: CD8+ T-cell activation is associated, independent of viral load, with disease progression in untreated HIV infection. Among patients with drug-resistant viremia, while T-cell activation has been shown to be diminished relative to wild-type viremia, little is known about the role of T-cell activation markers in predicting progression.

Methods: We examined antiretroviral-treated patients in the "Study of the Consequences of the Protease Inhibitor Era" (SCOPE), a clinic-based cohort of HIV-infected adults, who had stable detectable plasma HIV RNA and evidence of genotypic resistance to at least one drug class. T-cell activation, defined as the % of CD8+ T-cells co-expressing CD38 and HLA-DR, was measured once and subsequent changes in CD4+ T-cells were assessed by repeated measures analysis. CD4+ T-cell count was square-root transformed to meet model assumptions, and observations were censored upon any change in drugs.

Results: Among 47 antiretroviral-treated patients examined, the median (IQR) values at the time of the baseline T-cell activation measurement were: age 45 (41-50) yrs, viral load 3.5 (2.3-3.9) $\log_{10}$ copies/ml, and CD4+ T-cells 340 (220-498) cells/mm^3. Median % of activated CD8+ T-cells was 18.6 (range 1.7-53; IQR 15.5-26.6). After a median follow-up of 1.1 years, there was no evidence for overall change in CD4+ count (-0.035 √CD4 cells/month, p = 0.17). In unadjusted analyses, higher levels of baseline CD8+ T-cell activation (p=0.01) and viral load (p=0.006) were both associated with lower subsequent CD4+ T-cell counts. In a multivariable model, after adjustment for baseline viral load and CD4+ T-cell count, the rate of change of CD4+ cells over time differed according to the baseline level of T-cell activation (p for interaction term = 0.004). Among patients with median values of baseline viral load and CD4+ count, those with the lowest levels of T-cell activation had stable to slight gains in CD4+ cells while those with the highest levels of T-cell activation had declines in CD4+ cells.

Conclusions: Higher levels of CD8+ T-cell activation are associated with faster rates of CD4+ T-cell decline in patients with drug-resistant viremia. This provides further evidence of the independent role of CD8+ T-cell activation in predicting disease course and prompts consideration of larger scale testing of whether measurement of T-cell activation is useful in deciding when to switch antiretroviral drugs among patients with drug-resistant viremia.

Clinical Sciences

Repeated Measures Longitudinal Analyses of Adherence to Antiretroviral Medications and HIV Virologic Responses

Noteworthy Abstract

Presenter: Loren Miller, Harbor-UCLA Research and Education Institute

Collaborators: Loren G. Miller, Andrew H. Kaplan, Ron D. Hays, Tongtong Wu, Carol Golin, Neil S. Wenger, Honghu Liu

Principal Investigator: Honghu Liu

Background: Adequate adherence to antiretroviral medications is essential for HIV viral suppression, but the measurement tools and statistical methods for handling and analyzing adherence have not been well developed. Previous investigations of the relationship between adherence and virologic outcomes have focused on cross-sectional analyses with adherence measures that are error-prone. Furthermore, the exact compliance-response curve between medication adherence and virologic outcomes remains poorly defined. We performed a detailed examination of changes in HIV RNA over time as a function of antiretroviral medication adherence controlling for other important clinical covariates.

Methods: We examined data from the Adherence and Efficacy of Protease Inhibitor Therapy (ADEPT) study, a rigorously designed longitudinal investigation of adherence to antiretroviral medication in 141 subjects initiating a new regimen. On a monthly basis for 12 months we measured HIV RNA, HIV drug resistance and adherence, which was determined using multiple measures including electronic bottle caps. Log_{10} HIV RNA was modeled using over 1,200 HIV RNA measures over time using a repeated measures linear mixed models as a function of medication adherence while controlling for patient demographics, clinical factors, genotypic sensitivity score, and dose-timing error (which was determined using electronic bottle caps data). Optimal covariance structures of the repeated measures models were selected through Akaike Information Criterion(AIC). The potential non-linear relationship between virologic outcomes with adherence and other continuous measures was modeled and tested through restricted cubic spline functions.

Results: Mean viral load declined significantly over time ($p<0.001$) despite a slight overall downward trend for adherence. There were larger variations in dose-timing error for adherence at lower levels of adherence than at its upper levels ($P<0.05$.) Through restricted cubic spline functions, adherence demonstrated a significant non-linear relationship with HIV viral load ($p<0.03$ with multivariate Wald-test). Controlling for patient age, gender, education, race/ethnicity, protease inhibitor naïve status at baseline, primary language spoken, HIV risk factor, CDC stage, history of alcohol abuse, psychiatric disease, dose-timing error and genotypic sensitivity score, viral load was significantly predicted by medication adherence ($p<0.005$), genotypic sensitivity score ($p<0.001$), alcohol /drug abuse ($p<0.05$) and CD4 count ($p<0.008$).

Conclusion: Adherence is non-linearly related to HIV viral load over time. Other independent predictors of HIV RNA include genotypic sensitivity measure, CD4 count, and alcohol/drug abuse. Overall, there is a slight downward trend of medication adherence and a significant decrease in viral load over the 12-month period.

Clinical Sciences

T-cell Responses to HIV and Opportunistic Pathogens Following Patient Initiated Interruption of Antiretroviral Treatment

Presenter: Rachel Schrier, UC-San Diego

Collaborators: R. Schrier, D. Durand, S. Letendre, A. McCutchan, the HIV Neurobehavioral Research Center and R. Ellis

Principal Investigator: Rachel Schrier

UARP Award Number: ID03-SD-018

The consequences of antiretroviral treatment interruption remain controversial. Temporary exposure to HIV antigens may boost immune responses to HIV. However, increased virus production and circulation could also seed new viral reservoirs and sequester or deplete helper T lymphocytes.

Methods: 12 subjects who were self motivated to halt antiretroviral therapy agreed to be monitored clinically and immunologically in exchange for information as to HIV RNA levels. Treatment could be re-initiated at any time by patient request. Prior to monitored treatment interruption (MTI), CD4 T-cell levels ranged from 202-620 and 8 of the 12 subjects had HIV RNA plasma levels <400 copies/ml. T-cell memory lymphoproliferative (LP) responses to HIV and opportunistic agents were assayed at weekly intervals, before, during, and after MTI. HIV antigens consisted of chemically inactivated HIV MN (NCI) and a Protein Sciences gag reagent. Opportunistic pathogen antigens were: CMV, Candida, MTB,and Toxoplasma. Time from TI to rebound (plasma HIV RNA levels above 5000 copies/ml) and peak RNA levels were determined.

Results: With cessation of antiretroviral treatment, viral loads in all 12 subjects rebounded to over 100,000 copies/ml in plasma within 6 weeks. CD4 levels did not drop significantly over 2-3 months follow-up. Immune responses to opportunistic pathogens, which may vary even when virus and treatment are stable, showed remarkable uniformity. LP responses to opportunistic pathogens fell significantly as plasma HIV RNA rose ($p=0.0004$) and tended to normalize as HIV RNA plateaued. Loss of pathogen memory response was temporally associated with virus rebound rather than withdrawal of treatment. In contrast to opportunistic pathogen responses, LP responses to HIV antigens neither fell ($p=0.205$), nor were they boosted by exposure to antigen, even after restarting antiviral treatment. Levels of HIV immunity prior to TI did not influence interval from TI to HIV RNA rebound, which varied from 1 to 6 weeks. However, a strong HIV specific response prior to TI was associated with lower peak HIV RNA levels following TI ($R2=0.625$).

Conclusions: Rising HIV plasma levels following TI corresponded to a temporary loss of peripheral immune surveillance to opportunistic pathogens. Strong HIV specific LP responses prior to TI predicted lower peak HIV RNA rebound. HIV specific LP responses were neither boosted, nor initiated by re-exposure to HIV antigens during TI.

Clinical Sciences

When to Change Antiretroviral Therapy: Testing the Guidelines

Noteworthy Abstract

Presenter: Starley B. Shade, UC-San Francisco

Collaborators: Steven Deeks, Ricardo Alvarez, Stephen O'Brien

Principal Investigators: Donald I. Abrams

UARP Award Numbers: CR02-SF-610, CR02-MNHC-611, CR02-EBACA-612

Introduction: Much time and care has been devoted to developing and updating federal guidelines for the clinical care of people with HIV. However, little is known about whether patients are treated in accordance with guidelines, whether there are any demographic factors that predict adherence to guidelines, and whether patients whose care is consistent with the guidelines have better outcomes than patients whose care is not consistent with guidelines. This study examines adherence to clinical guidelines for when to change antiretroviral therapy.

Topic addressed: 1025 HIV-positive patients in the Community Consortium's Observational Cohort Study and 435 HIV-positive patients in the San Francisco General Hospital Cohort were followed to assess: (1) Adherence to the clinical guidelines for when to change antiretroviral therapy; (2) demographic differences in adherence to these guidelines; (3) and virologic, immunologic and clinical outcomes associated with adherence to guidelines.

Progress toward specific aims: (1) We identified 542 individuals who started a new HAART regimen during study follow-up. Overall, 345 (64%) experience failure of their treatment regimen based on guidelines (failure to mount a virologic response, virologic rebound, immunologic decline, or emergence of a new opportunistic infection or malignancy). Median time from initiation of HAART regimen to failure was 91 days (IQR=73-118). Among those who failed, 198 (57%) subsequently changed their treatment regimen after a median of 116 days (IQR=50-227), 110 (32%) changed their treatment regimen within 120 days of treatment failure, 80 (40%) changed all of the drugs in their regimen, 97 (49%) changed only part of their regimen, and 21 (11%) stopped some or all of their antiretroviral medications. (2) Older (HR=0.83; 95% CI=0.70, 0.99; p=0.04) participants waited longer after failure to change treatment. Younger age (OR=0.79; 95% CI=0.63, 0.98; p=0.03) and pre-treatment viral load greater than or equal to 30,000 copies/mL (OR=0.71; 95% CI=0.28, 6.60; p=0.01) were significantly associated with changing therapy within 120 days of failure. Younger patients were also more likely to change all of the drugs in their treatment regimen (OR=0.61; 95% CI=0.41, 0.90; p=0.01 per 10 year increase in age). (3) Among the 198 participants who changed therapy after treatment failure, we have follow-up information for 151 (76%) of these individuals. Median follow-up after treatment change was 10.0 months (IQR=2.9, 17.1). Median viral load decline was -0.02 $\log_{10}$ copies/mL per month (IQR=-0.17, 0.04), median CD4+ T cell count increase was 3.1 cells per month (IQR=-6.2, 12.8), 9 individuals experienced a new opportunistic infection or malignancy, and 13 people died. These results did not differ by whether patients changed therapy within 120 days of treatment failure. Patients who changed all drugs in their regimen experienced larger decreases in viral load compared to others (median= -0.07 vs. -0.01; IQR=-0.28, 0.01 vs. -0.08, 0.05 $\log_{10}$ copies/mL per month).

Impact: Two-thirds of patients with HIV are not being treated in accordance to clinical guidelines for their care. However, we found few demographic differences in adherence to clinical guidelines. Only younger age was associated with shorter time to treatment change after treatment failure and changing all drugs in a treatment regimen. Changing all drugs in a patient's regimen was associated with larger declines in viral load after treatment change. During our second year, we will explore differences in adherence to clinical guidelines in patients' first, second and third treatment regimens.

Clinical Sciences

Noteworthy Abstract

High-Level Dual and Triple Class Multidrug Resistance (MDR) in a Large Health Maintenance Organization: Prevalence, Risk Factors, and Response to Salvage Therapy

Presenter: Robert W. Shafer, Stanford University

Collaborators: W. J. Fessel, S. Y. Rhee, L. Hurley, D. P. Nguyen, S. Slome, S. Smith, D. Klein, M. Horberg, J. Flamm, S. Follansbee, M. J. Gonzales, R. W. Shafer

Principal Investigators: W. J. Fessel, R. W. Shafer

UARP Award Number: CR03-ST-524

Background: The prevalence, risk factors, and response to salvage therapy in persons with MDR HIV have not been well characterized.

Methods: We analyzed 3,320 sequences from 2,324 persons in the KPMC Program in Northern California who had genotypic resistance testing 1998-2002. Genotypes were submitted to a computer program that assigned resistance to 18 HIV drugs. High-level 3-class resistance was defined as intermediate or high-level resistance to all 18 HIV drugs. High-level 2-class resistance was defined as intermediate or high-level resistance to each drug within 2 drug classes with complete susceptibility to drugs in the 3rd class. Sustained response was defined as RNA levels <50 copies/ml for ≥6 months; transient response was defined as ≥1 RNA <50 copies/ml for <6 months.

Results: 74 (3.2%) persons had high-level NRTI/PI 2-class resistance; 21 (0.9%) had high-level NRTI/NNRTI 2-class resistance; 82 (3.5%) had high-level 3-class resistance. The duration of HIV therapy was >4 years in 92% of persons. Of 74 persons with high-level NRTI/PI 2-class resistance, 59 changed therapy: 30/59 (51%) had an RNA response, which was transient in 12 and sustained in 18. Of 21 persons with high-level 2-class NRTI/NNRTI resistance, 12 changed therapy: 10/12 (83%) had an RNA response, which was transient in 5 and sustained in 5. Of 82 persons with high-level 3-class resistance, 60 changed therapy: 17/60 (28%) had an RNA response, which was transient in 11 and sustained in 6. Response to therapy was more likely in persons with NRTI/NNRTI (83%, p=0.001) and NRTI/PI (51%, p=0.02) 2-class resistance than with 3-class resistance (28%). In univariate analyses, treatment with ≥5 drugs (counting boosted PIs as 2 drugs, p<0.001), lopinavir (p<0.001), and tenofovir (p<0.001) were associated with RNA response. 10 persons with high-level NRTI/PI 2-class resistance developed 3-class resistance following unsuccessful salvage therapy.

Conclusions: High-level 2- and 3-class resistance occurred almost exclusively in persons who began HIV drugs in the pre-HAART era. In persons with high-level 2-class resistance, salvage therapy with a regimen containing ≥1 drug belonging to the 3rd drug class often leads to a dramatic reduction in RNA levels, particularly in persons receiving ≥5 drugs. However, this response is frequently not sustained. Studies are needed to compare 1 vs. 2 new drug classes (e.g. an NNRTI and a fusion inhibitor) in persons with high-level 2-class resistance.

Clinical Sciences

Is Early HIV Evolution Determined by the HLA Class 1 Genotype?

Presenter: Eric Delwart, UC-San Francisco

UARP Award Number: ID02-SF-075

The immune system loses to HIV after a long struggle during which the virus gradually reduces the number and function of CD4 cells. The immune system is initially effective in controlling a high level of viremia but because the virus rapidly becomes resistant it can then escape immune responses. It is thought that cellular immune responses are responsible for this early control of viremia. The exact regions of HIV recognized and targeted by cellular immune responses are thought to be determined in part by a highly diverse part of the human genome called the HLA locus (the same human genome region that determine organ transplant compatibility). Because the HLA locus in the human population is so genetically diverse it is expected that the cellular immune response of different individuals will target different regions of HIV. In order to test this hypothesis we have been analyzing the evolution of HIV very early following primary infection. Whole genomes of HIV have been sequenced at the earliest date available following primary infection and then again several weeks later. The difference between the two genomes reflects the evolution undergone by the viruses as they adapted to the unique immune responses generated by each individuals. We also determined the exact HLA genotype of each recently infected individual. We have determined which regions of the HIV genome shows the greatest concentration of mutations in primary infection and may therefore be targeted by early immune responses. Unlike what has been observed in non-human primate model system the HIV tat gene did not appear to evolve rapidly in primary infection. We are now analyzing the exact location of the HIV mutations to determine if they fit into the regions of HIV expected to be targeted in people of their specific genetic background (i.e. HLA type). We have found that only a minor subset of early mutations were potential cellular immune response target sites based on the subjects' genetic background. Selection forces other than HLA type are likely to contribute to the early evolutionary path of HIV following transmission. We are generating further HIV genome sequences and continuing our analysis of the mutational pattern of HIV in relation to the patients' HLA.

Clinical Sciences

Quantitative CD38 Expression on CD8 T-Cells as a Predictor or CD4 T-Cell Maintenance among Patients Falling Salvage Antiretroviral Therapy

Presenter: Miguel Goicoechea, UC-San Diego

Background: CD38 is a lymphocyte surface marker of immune activation. High expression of CD38 on CD8 lymphocytes is a predictor of decline in CD4 cell count independent of plasma HIV-1 viral load. With viral control (VC) during antiretroviral therapy (ARV) CD38 expression declines, but does not reach levels seen in uninfected subjects. We investigated whether patients with virologic failure (VF), who achieve low T-cell activation in response to treatment were better able to maintain their CD4 cell numbers.

Methods: Data were extracted from a sub-study of CCTG 575, a randomized prospective ARV salvage trial of 238 patients with > 6 months of ARV therapy and VF at entry. Markers of T-cell activation were measured at baseline and 6 months. Low T-cell activation was defined as the 90th percentile of: the number of CD38 molecules on CD8 cells and the total % of activated (DR+/CD38+) CD8 cells found in patients with VC (< 50 RNA copies/ml) at month 6. This value was used as a threshold to identify a subset of patients with VF (> 1000 RNA copies/ml) with low T-cell activation after 6 months of ARV therapy. Change in CD4 cell counts at 6 months was then compared between two groups of patients with VF: those with low vs. high T-cell activation levels.

Results: Sixty-one patients with VF had T-cell activation markers at 6 months. Forty-four of these subjects had low levels of activated CD8 T-cell (< 56% CD8+/DR+/CD38+) and 37 subjects had low CD38 expression (< 8754 molecules/CD8 cell). Low CD38 expression was significantly associated with an increase in CD4 cells from baseline (p=0.002), whereas the % of activated CD8 cell was not correlated (p=0.66). In multiple linear regression analysis, adjusting for baseline log HIV RNA, change in HIV RNA at 6 months and baseline CD4 count, patients with lower levels of CD38 molecules/CD8 cell had higher CD4 cell numbers (p=0.02). Patients with low CD8 cell activation had 58 more CD4 cells gained at 6 months than those with higher CD8 cell activation.

Conclusions: Among patients failing salvage ARV therapy those who achieved low levels of CD8 activation (CD38 molecules/cell), similar to levels in patients with viral control, showed greater CD4 cell gains after 6 months of therapy than those with higher CD8 activation, even after accounting for change in plasma HIV-1 viral load. Reduced T-cell activation may explain the discrepancies in therapy induced CD4 cell response in the setting of ongoing viral replication.

Clinical Sciences

HIV Protease Inhibitors Alter Notch Processing, Expression, and Localization in Cerebral Endothelial Cells

Presenter: Aline Grigorian, UC-San Diego

Collaborators: Rosemary Hurford, Eliezer Masliah, Dianne Langford

Grant Numbers: NIH DA12065, MH59745, MH45294

HIV-1 enters the brain soon after initial infection via the migration of infected monocytes across the blood-brain barrier (BBB). Protease inhibitors (PI) are frequently used to control plasma viral load in HIV patients, but have little impact on brain viral load due to inefficient transport of the drugs across cerebral endothelial cells (EC) of the BBB. Cerebral EC of the PI-adherent HIV patient are however, in continual contact with these drugs and are subject to PI-mediated signaling alterations. Since PIs block the activity of the HIV protease, it is possible that they may also inhibit the activity of other aspartyl proteases, including g-secretase. Notch proteins are processed by the g-secretase enzyme complex and upon activation, an intracellular domain (NICD) is cleaved and translocated to the nucleus where it promotes the transcription of target genes. Since the Notch signaling cascades are important in EC fate and in regulating genes involved in angiogenesis, potential alterations in these pathways caused by HIV PIs may be important in maintaining BBB integrity during HIV infection.

The potential role of PIs on cerebral EC signaling and BBB integrity has not been considered. We hypothesize that PIs used to treat HIV alter Notch processing in EC, and thereby, render cells more vulnerable to challenge by HIV proteins during viral rebound. In this context, the main objectives of this study are to investigate the effects of chronic PI exposure on Notch1 and Notch4 signaling, and localization in cerebral EC, and to determine the potential affects on cell fitness. Western Blot, immunocyto-chemistry, gene transfer, and fitness assays were used to investigate Notch signaling in HBMEC (human brain microvascular endothelial cells) exposed to PIs. Comparison of changes in Notch processing and expression after PI treatment indicate that some PIs alter Notch processing and expression, whereas, others have no effect.

In the era of rapidly increasing classes of anti-retroviral drugs and development of resistance mutations, understanding the mechanisms of crosstalk between PIs, HIV proteins, and EC in regulating BBB integrity is critical to managing the treatments administered to AIDS patients. Furthermore, since anti-retroviral drugs have significantly contributed to increased longevity of the adherent patient, understanding the potential affects of long-term treatment is important in understanding the progression of NeuroAIDS in the HAART era.

Clinical Sciences

Shared Patterns in HIV-1 Coreceptor Utilization during Antiretroviral Therapy

Presenter: Christina Kitchen, UC-Los Angeles

Collaborators: Sean Philpott, Harold Burger, Barbara Weiser, Marc A. Suchard, Christina M. R. Kitchen

The rapid evolution of HIV-1, particularly in response to antiviral treatment, has complicated efforts to treat and prevent infection. There is substantial evidence for the on-going replication of HIV-1 in various compartments, even in individuals receiving highly active antiretroviral therapy (HAART). Viral evolution in the presence of antiviral therapy needs to be studied when developing new therapeutic strategies. Phylogenetic analyses can be used for this purpose, but may give rise to misleading results if rates of intra-patient evolution differ significantly. To improve analyses of longitudinally sampled sequences of HIV-1 evolution, we developed a Bayesian hierarchical model that incorporates all available sequence data while simultaneously allowing the phylogenetic parameters of each patient to vary. We used this method to examine evolutionary changes in HIV-1 coreceptor usage in response to treatment.

We examined three patients whose viral strains exhibited a shift in HIV-1 coreceptor utilization in response to therapy. In each patient, X4 strains emerged or began to predominate over time but later reverted back to R5 following initiation of new antiretroviral regimens. By phylogenetically reconstructing the evolutionary relationship of HIV-1 obtained longitudinally from each patient, it was possible to examine the origin of the re-emergent R5 virus. Using our Bayesian hierarchical approach, we found that the re-emergent R5 strains arose from an archived or latent source rather than through continued evolution of circulating HIV-1.

Clinical Sciences

A Statistical Method for Combining Results from Bayesian Phylogenetic Analyses

Presenter: Li-Jung Liang, UC-Los Angeles

Principal Investigators: Li-Jung Liang, Robert E. Weiss

Our objective is to develop a statistical model and computational algorithm for combining results from a number of complex Bayesian phylogenetic analyses from a number of exchangeable data sets that contain HIV-1 aligned DNA sequences for the envelop, gag and pol genes. The individual analyses have already been fit independently using standalone phylogenetic software that fits a complex phylogenetic Bayesian model using Markov Chain Monte Carlo (MCMC) simulation. Each individual analysis is computationally intensive and MCMC output from each of these complex Bayesian phylogenetic analyses is available. We are interested in estimating the ratios of the transition rate over the transversion rate across analyses for each of the envelop, gag and pol genes.

Instead of attempting to construct a single large complex model involving all the original HIV-1 sequences data sets, which may be difficult if not impossible to implement, our strategy is to use the existing MCMC samples of the individual posteriors. We place a hierarchical model across the individual analyses for estimating parameters of interest within and across analyses. This allows us to improve on the inferences from the individual analyses. Our method has two key features. We use a mixture of Dirichlet process prior for the parameters of interest to relax parametric assumptions and to ensure that the prior distribution for the parameters of interest is continuous. The conventional Gibbs sampling technique cannot be directly used to carry out our approach since we are using existing MCMC samples. Therefore we use an importance reweighting algorithm within Gibbs to sample values of the individual parameters.

Our method not only provides researchers with a flexible and practical way of combining results from multiple phylogenetic analyses of HIV-1 sequences data sets, but also results in improvement on the inferences from the individual phylogenetic analyses.

Clinical Sciences

Developing Computer Artificial Intelligence Systems to Interpret HIV Drug Concentrations

Presenter: Miguel Goicoechea, UC-San Diego

Authors: Andrea Vidal, M. Goicoechea

Collaborators: A. Vidal, E. Capparelli, M. Goicoechea, A. Rigby, R. Haubrich, and the California Collaborative Treatment Group

UARP Award Number: ID01-SD-029

Background: Treatment failure with potent antiretroviral therapy is associated with many factors, including sub-optimal plasma concentrations of protease inhibitors (PIs) and non-nucleoside reverse transcriptase inhibitors (NNRTIs). Therapeutic drug monitoring (TDM) allows for individual pharmacologic evaluation with the intent to tailor dose recommendations to a specific patient. The aim of this study is the development of a computer-based expert system for modeling and interpreting pharmacologic data of various antiretrovirals and to assist in therapeutic decision making.

Methods: Data were extracted from CCTG 578, a prospective study of TDM with approximately 220 patients enrolled. An expert committee of HIV clinicians and pharmacologists evaluated real-time pharmacologic data and made therapy recommendations to study investigators. From these recommendations, decision algorithms are being generated to interpret plasma concentrations. These algorithms will form the knowledge base of the expert artificial intelligence (AI) system.

Results and Current Status: Subject samples were analyzed for PI and NNRTI concentrations by using a Bayesean nonlinear curve fitting approach to estimate individual pharmacokinetic (PK) parameters. Subject values are compared to a standard population and assessed as above/below the 25^{th}, 50^{th} or 75^{th} percentile. The AI system will compute estimated trough, 4-hour post dose and PK metrics. These will then be compared to the Bayesean estimates. The data from the TDM modeler as well as clinical data are being entered into an interface engine which will then determine one of three solutions: increase, decrease or maintain drug exposure. With further development this project could ultimately lead to: 1. TDM guidelines to interpret PI and NNRTI concentration data and 2. A TDM web site to aid clinical decision making. The system will then be validated by comparing the recommendations of the AI system to those by the TDM expert committee.

Clinical Sciences

Relationship Between Lopinavir (LPV) Concentration and Changes in Lipid Levels at 24 Weeks

Noteworthy Abstract

Presenter: Brookie Best, UC-San Diego

Authors: B. Best, S. May, M. Witt, C. Kemper, R. Larsen, C. Diamond, P. Heseltine, F. He, E. Capparelli, A. McCutchan, R. Haubrich, and the California Collaborative Treatment Group (CCTG)

Background: The relationship between LPV concentration and cholesterol elevation is not clear. The objective of this analysis was to explore associations between LPV concentration metrics and change in lipid values.

Methods: Data were analyzed from CCTG 578, an on-going, randomized, 3x2 factorial study of three adherence interventions crossed with therapeutic drug monitoring. LPV and RTV levels were drawn pre-, 2- and 4-hours post a witnessed week 2 LPV dose from nave or experienced patients. Concentration data from the study was used to develop a population pharmacokinetic model. Post-hoc Bayesian estimates of individual subjects LPV exposure measures were calculated (C2, C4, and C12 for estimated 2, 4 and 12 hour concentrations). Fasting lipids (total cholesterol (TC), HDL, LDL and triglycerides (TG)) were measured at day 0 and week 24.

Results: For the 37 patients, the average $\log_{10}$ baseline HIV RNA and CD4 were 5.0 and 172. Mean (SD) 2, 4 and 12 hour LPV levels in mcg/mL were 6.9 (3.5), 8.1 (3.5) and 5.6 (3.0). Baseline to week 24 TC increased from 157 to 202 while TG increased from 196 to 317. Neither LPV nor RTV levels were associated with TG, LDL or HDL changes. Increasing LPV concentrations (both C2 and C4) were associated with lower changes in week 24 TC ($p<0.02$). LPV C12 and RTV C2 and C4 showed trends in the same direction ($p<0.15$), but were less predictive. Multivariate models, controlling for gender, continued to demonstrate the same LPV effect; for every one mcg/mL increase in LPV C2, the average week 24 change in TC was 5.9 mg/dL less ($p =0.008$).

Alternative models (2 piecewise linear forms) were explored due to a suggestion of differential effects of LPV concentration on TC depending on LPV concentration (initial increase in TC up to a level of 7 mcg/mL and then decrease in TC as LPV concentration rose). In this model, increasing LPV levels (up to 7 mcg/mL) were accompanied by non-significant TC increases ($p=0.7$) while increasing LPV levels at higher concentrations (above 7 mcg/mL) were significantly related to TC reductions ($p=0.005$).

Conclusions: In contrast to previous studies, this analysis did not find that higher LPV or RTV levels were accompanied by greater lipid increases. In fact, patients with higher LPV concentrations had smaller TC increases at week 24. LPV levels 2 and 4 hours after a witnessed dose were the best predictors while trough (C12) was not predictive of lipid changes.

Clinical Sciences

Noteworthy Abstract

Recombinant Human Leptin in the Treatment of HIV-associated Lipodystrophy

Presenter: Hootan Khatami, UC-San Francisco

Collaborators: Morris Schambelan, Kathleen Mulligan, Joan C. Lo, J. M. Schwarz, Gerald Matson, Giorgos Sakkas, Viva Tai

Principal Investigator: Hootan Khatami

UARP Award Number: CF02-SF-302

Despite dramatic reductions in mortality and morbidity attributed to highly active antiretroviral therapy (HAART), there is increasing concern among clinicians and patients about the development of potentially deleterious metabolic side effects, including insulin resistance, increases in cholesterol and triglyceride levels, peripheral and/or facial fat loss (lipoatrophy), and central fat accumulation. These findings, commonly referred to as the "lipodystrophy syndrome," are reminiscent of metabolic syndrome X, which is a major risk factor for cardiovascular disease.

Leptin is a hormone secreted by body fat, with an emerging role in glucose and fat metabolism in normal physiology, as well as a potential therapeutic role in non-HIV-infected humans with acquired or congenital lipoatrophy. Under this proposal we are performing a proof-of-principle study of recombinant human leptin in 12 patients with HIV-associated lipodystrophy who have below-normal leptin and high triglyceride levels. We are testing the hypotheses that, in this group of patients, treatment with leptin will (1) improve peripheral and hepatic insulin sensitivity and ameliorate abnormalities in glucose metabolism, assessed by euglycemic hyperinsulinemic clamp, oral glucose tolerance testing, and stable isotope studies of endogenous glucose production, gluconeogenesis and glycogen flux; (2) ameliorate abnormalities in lipid metabolism, by measurement of fasting lipids and lipoproteins and stable isotope studies of whole-body lipid turnover and hepatic *de novo* lipogenesis and very low density lipoprotein turnover; and (3) decrease visceral fat, liver volume and intramyocellular lipid content, measured by magnetic resonance imaging and spectroscopy. The safety of leptin is also being evaluated in such patients.

This study employs a paradigm based on intensive metabolic ward assessments in which each subject serves as his or her own control. Subjects undergo the aforementioned assessments during 5-day admissions to the General Clinical Research Center at San Francisco General Hospital at baseline and after 3 and 6 months on study. Two different dosing levels of leptin are evaluated in successive 3-month periods: during the first 3 months, the dose is 0.01 or 0.02 mg/kg twice daily in men and women respectively, a dose that is intended to bring serum leptin levels into the low-normal range; for the following 3 months, the dose of leptin is increased to 0.03 and 0.06 mg/kg twice daily.

To date, 6 subjects, all male, have been enrolled in the study. These subjects range in age from 42 to 62 years; median duration of HIV infection is 13 years. At baseline, all subjects had CD4+ lymphocyte counts >200/mL and were on stable HAART regimens, 3 of which contained a protease inhibitor. All six subjects had clinical evidence of lipoatrophy, with total body fat ranging from 6.6 to 22.4%. Triglyceride levels at baseline were above the upper limit of normal in all subjects, despite the fact that five of the six were using lipid-lowering agents. As of now, 3 subjects have completed the 6-month study, and the remainder are on treatment, so efficacy results are not yet available. To date, leptin has been very well tolerated, with no treatment-related adverse events.

In the coming months, we plan to complete the evaluation of the subjects currently enrolled in the study and to continue enrollment toward completion of the target 12 subjects.

Clinical Sciences

The Acute Effects of Protease Inhibitors on Peripheral Glucose Disposal

Noteworthy Abstract

Presenter: Grace A. Lee, UC-San Francisco

Collaborators: Tara Seneviratne, Mustafa A. Noor, Joan C. Lo, Jean-Marc Schwarz, Francesca T. Aweeka, Kathleen Mulligan, Morris Schambelan

Principal Investigator: Carl Grunfeld

UARP Award Number: ID01-SF-014

Introduction: Since the introduction of protease inhibitors to HIV therapy, abnormalities in carbohydrate and lipid metabolism including diabetes, hyperglycemia, and hyperlipidemia have occurred. However, it was unclear whether these changes were due to protease inhibitors, restoration of health, immune reactivation or changes in body composition. To determine the direct effects of protease inhibitors, we studied HIV-negative healthy negative volunteers. Previously, we have shown that indinavir treatment for four weeks inhibits peripheral glucose uptake without affecting lipids. Here we examined the acute effects of the protease inhibitors, indinavir and lopinavir/ritonavir, on glucose metabolism.

Significant Findings: Treatment with a single dose of indinavir 1200 mg decreased insulin-mediated glucose disposal from 14.1 ± 1.2 to 9.2 ± 0.8 mg/kg/min per ?U/ml ($p<0.001$) during the euglycemic hyperinsulinemic clamp. After indinavir treatment, there were no changes in lipid profile or body composition (abdominal CT or DEXA). Single dose treatment with lopinavir/ritonavir did not inhibit peripheral glucose uptake during the euglycemic hyperinsulinemic clamp. However, lopinavir/ritonavir treatment did cause an increase in 2 hour glucose (4.6 ± 0.3 vs. 5.9 ± 0.6 mmol/l; $p<0.05$) during oral glucose tolerance testing (OGTT). Insulin decreased at 30 minutes (396 ± 53 vs. 276 ± 54; $p<0.10$) during the OGTT. Impaired insulin secretion during the OGTT thus may be a cause of impaired glucose tolerance during lopinavir/ritonavir treatment. Lopinavir/ritonavir also increased VLDL levels from 15.1 ± 2.6 to 20 ± 3.3 mg/dL ($p<0.05$) and free fatty acid levels from 0.33 ± 0.04 to 0.43 ± 0.06 mmol/l ($p<0.001$). Lopinavir/ritonavir caused no changes in body composition. Currently, we are studying the acute effects of ritonavir on insulin-mediated glucose disposal, and the study has not been unblinded yet.

Summary: Protease inhibitors have drug-specific effects on glucose and lipid metabolism. Indinavir decreased insulin sensitivity after both chronic and acute treatment, suggesting that indinavir acutely inhibits insulin-mediated glucose disposal. In contrast, lopinavir/ritonavir did not affect insulin sensitivity but did increase VLDL and free fatty acid levels. These findings suggest that protease inhibitors should be studied individually for their effects on metabolism.

Clinical Sciences

HAART, HIV-1 and heart disease: gp120 causes cardiomyocyte apoptosis and azidothymidine (AZT) induces interendothelial gaps

Presenter: Milan Fiala, UC-Los Angeles

Collaborators: Milan Fiala, Kenneth P. Roos, Maria Jordan, Waldemar Popik, James Arthos

Authors: M. Fiala, F. Chiappelli, P. Provo

Grant Numbers: NHLBI 29576 and 29997

Dilated HIV cardiomyopathy and coronary heart disease are increasing complications of AIDS patients on HAART therapy. HIV-1 invades the heart by macropinocytosis and Trojan transport and is replicated in macrophages and T cells infiltrating the heart. The virus envelope protein gp120 and TNF-alpha induce cardiomyocyte apoptosis. Compared to the information gleaned about HIV-1 effects, the mechanisms of HAART drugs in cardiovascular disease have been elusive. Dyslipidemia is frequently found in patients on protease inhibitors. In our rat Alzet model gp120 infusion produced myocardial and epicardial inflammation, cardiomyocyte drop-out and myocardial fibrosis. In cell culture gp 120, but not AZT, caused apoptosis of cardiomyocytes and endothelial cells; AZT, however, disrupted endothelial cell cytoskeleton producing interendothelial gaps. These results suggest that the toxicities of HAART drugs affect mainly endothelium and vessels whereas HIV and HIV proteins damage both cardiomyocytes and endothelial cells.

Clinical Sciences

Effects of HIV Protease Inhibitors on P-Gylcoprotein on Endothelial Cells of the Blood Brain-Barrier

Presenter: Dianne Langford, UC-San Diego

Collaborators: Dianne Langford, Aline Grigorian, Rosie Hurford, Anthony Adame, Eliezer Masliah, and the HNRC Group

Grant Numbers: NIH MH59745, MH45294, MH58164, DA12065, and an HNRC pilot project award

The HIV patient of today is likely experienced with long-term HAART use and, having switched regi mens frequently due to viral rebound or intolerable side effects, may have developed drug resistant variants. Making their debut in the mid-90s, PIs have proven successful at treating systemic HIV infection. However, the efflux transport pump, P-gp, imposes a serious constraint on PI treatment of HIV infection of the brain. While progress has been made toward understanding the structure-activity relationships of P-gp and agents that may inhibit its function, it is unclear how HIV anti-retroviral drugs modulate P-gp signaling with cerebral endothelial cells (CEC) of the blood brain barrier (BBB). P-gp is located on the apical surface of CEC of the BBB that provide the first line of defense to prevent HIV from entering the brain. It is well established that P-gp functions in both efflux-dependent and efflux-independent pathways required for cell fitness. Efflux-independent mechanisms of P-gp include the regulation of cell survival and fitness signaling pathways. Alterations in these or other efflux-independent functions of P-gp have potentially important consequences for maintaining BBB integrity upon viral rebound. In the HAART-era, HIV encephalitis (HIVE) has shifted from a subacute condition to a chronic disease and a more severe form of HIV leukoencephalopathy has emerged. Furthermore, subtle behavioral and psychiatric conditions associated with NeuroAIDS have become more prevalent. In light of the increasing CNS involvement observed in HIV-infected patients, and the development of drug-resistant variants of the virus, understanding the mechanisms by which long-term use of anti-retroviral agents might modulate P-gp signaling is of significant importance in managing the treatment of NeuroAIDS. To address the potential effect of chronic exposure of PIs on BBB signaling, we treated CEC with saquinavir, indinavir, nelfinavir, or retonavir and assayed cells for P-gp expression, localization and activity. These studies revealed that P-gp expression, localization and activity are affected by exposure to some PIs, whereas, other PIs have no effect. Furthermore, host-derived trophic factors are known to play an important role in protecting cells of the CNS from HIV toxicity. Disruptions in trophic factor signaling pathways may result in loss of protection from HIV proteins such as gp120. Therefore, to address the potential contribution of PIs to trophic factor signaling, CEC treated with PIs, were exposed to angiotrophic factors and then challenged with HIV gp120. Chronic exposure to indinavir blocked the ability of basic fibroblast growth factor to protect CEC from gp120-mediated toxicity. Taken together, these studies indicate that chronic exposure of CEC to HIV-PIs interferes with P-gp efflux-independent signaling and disrupts growth factor protection against HIV protein toxicity. Thus, potential signaling alterations at the BBB caused by chronic exposure to PIs are of significant importance to treat and manage NeuroAIDS.

Clinical Sciences

The Effects of Protease Inhibitors on Glucose Metabolism

Presenter: Grace A. Lee, UC-San Francisco

Collaborators: Jean-Marc Schwarz, Mustafa A. Noor, Joan C. Lo, Kathleen Mulligan, Morris Schambelan

Principal Investigator: Carl Grunfeld

UARP Award Number: CF03-SF-301

Introduction: HIV protease inhibitor therapy is associated with abnormalities in glucose metabolism including peripheral insulin resistance. In studies performed in HIV-negative healthy volunteers, we found that four weeks of indinavir caused glucose intolerance and decreased insulin-mediated glucose disposal and storage. This study reports the effects of indinavir on hepatic glucose metabolism.

Methods: Endogenous glucose production (EGP), glycogenolysis, and gluconeogenesis were measured using stable isotope tracer techniques in nine healthy HIV-negative men before and at the end of treatment with indinavir, given 800 mg three times daily. Measurements were made under conditions of both fasting and hyperinsulinemia (euglycemic hyperinsulinemic clamp).

Significant Findings: Fasting EGP increased with indinavir (12.6 ± 0.3 vs. 13.5 ± 0.3 μmol/kg*min; [p<0.03]) This increase was driven by proportional contributions of glycogenolysis (9.5 ± 0.3 vs 10.2 ± 0.3 μmol/kg*min; [p<0.03]) and gluconeogenesis (3.0 ± 0.2 vs. 3.3 ± 0.2 μmol/kg*min; [p<0.14]). Both glycogenolysis and gluconeogenesis measured during the clamp were higher after 4 weeks of indinavir (4.7 ± 0.9 vs. 6.6 ± 1.2 μmol/kg*min [p<0.02]; and 0.2 ± 0.03 vs. 0.3 ± 0.04 μmol/kg*min [p<0.009] respectively).

Conclusion: Four weeks of indinavir increase fasting EGP moderately and blunts the suppression of EGP by insulin. Thus hepatic insulin resistance contributes to the effects of indinavir on altered glucose metabolism. The mechanism by which indinavir induces hepatic insulin resistance is unknown.

Clinical Sciences

The Effects of Protease Inhibitors on Insulin Secretion

Presenter: Grace A. Lee, UC-San Francisco

Collaborators: Tara Seneviratne, Mustafa A. Noor, Joan C. Lo, Jean-Marc Schwarz, Francesca T. Aweeka, Kathleen Mulligan, Morris Schambelan

Principal Investigator: Carl Grunfeld

UARP Award Number: ID01-SF-060

Introduction: HIV protease inhibitor therapy has been associated with abnormalities in glucose metabolism including hyperglycemia and peripheral insulin resistance. The main objective of this study was to determine the effects of protease inhibitors on insulin secretion. We studied indinavir and lopinavir/ritonavir, and compared their effects on insulin secretion.

Methods: Ten HIV-negative men were given either indinavir 800 mg three times daily or 400 mg lopinavir/100 mg ritonavir twice daily for four weeks. Fasting glucose and insulin, glucose tolerance test (GTT) insulin sensitivity by euglycemic hyperinsulinemic clamp were determined before and at the end of four weeks of treatment.

Significant Findings: During lopinavir/ritonavir treatment, 30 minute insulin during GTT decreased from 395.6 ± 52.6 to. 276 ± 53.9 pmol/l ($p<0.10$), and 120 minute glucose increased from 4.6 ± 0.3 to 5.9 ± 0.6 ($p<0.05$). The increase in 120 minute glucose can not be explained by induction of peripheral insulin resistance because there was no effect on lopinavir/ritonavir on insulin sensitivity during the euglycemic hyperinsulinemic clamp. Therefore impaired insulin secretion at 30 minutes during the GTT may explain the increase in 120 minute glucose.

During indinavir treatment, a similar defect in insulin secretion was observed during the GTT. Unlike lopinavir/ritonavir, indinavir caused insulin resistance (10.4 ± 1.4 versus 8.6 ± 1.2mg/kg/min per ?U/ml insulin; $p<0.01$). During the OGTT, 120 minute glucose increased from 5.1 ± 0.4 to. 6.5 ± 0.6 mmol/l ($p<0.05$). However 30 minute insulin was not significantly increased in the presence of insulin resistance, suggesting an inappropriate insulin response to peripheral insulin resistance.

Conclusion: In summary we found that indinavir and lopinavir/ritonavir had effects on insulin secretion. Lopinavir/ritonavir decreased insulin secretion at 30 minutes during GTT with no induction of peripheral insulin resistance. In the setting of increased peripheral insulin resistance during indinavir treatment, insulin secretion failed to appropriately increase during GTT. These findings suggest that both lopinavir/ritonavir and indinavir may directly inhibit insulin secretion. We plan to study these protease inhibitors by hyperglycemic clamp to better understand the effects of protease inhibitors on insulin secretion.

Noteworthy abstracts are of particular relevance to the conference theme or address a topic of special interest.

Prevention, Health Services & Contexts of Health

Association Between Unprotected Sex and Antiretroviral Use and Adherence in HIV Clinic Patients

Presenter: Catherine Diamond, UC-San Diego

Principal Investigator: Richard Haubrich

UARP Award Number: CC02-SD-003

Objective: To determine the relationship between unprotected sex and antiretroviral use and adherence.

Methods: This was a cross sectional survey conducted in 1998-1999 in 874 randomly selected, sexually active patients at six public HIV clinics in California. Patients completed a standardized interview regarding sociodemographics, HIV-related characteristics, sexual behavior, use of illicit drugs or alcohol, depression and health beliefs, experience with the medical system and antiretroviral use and adherence. We defined unprotected sex as anal or vaginal sex without a condom over the past three months.

Results: The majority of patients (79%) took antiretrovirals. One third reported having unprotected sex and one quarter reported <95% adherence to antiretroviral therapy. Antiretroviral use was associated with decreased odds of unprotected sex, OR 0.5 (95% CI 0.4-0.7, p < .001); this negative relationship persisted in most stratified analyses and was significant in multivariate analysis, OR 0.7 (95% CI 0.5-1.0, p= .04). Marijuana use and site and duration of clinic attendance confounded the relationship between unprotected sex and antiretroviral therapy in multivariate analysis. Among patients taking antiretrovirals, a self-reported undetectable HIV RNA was associated with a decreased odds of unprotected sex, OR 0.7 (95% CI 0.5-1.0, p= .04). Adherence to antiretroviral therapy of >95% was associated with decreased odds of unprotected sex, OR 0.6 (95% CI 0.4-0.8, p = .001); this negative relationship persisted in most stratified analyses but was not significant in multivariate analysis, OR 0.8 (95% CI 0.5-1.2, p= .22). Number of sexual partners and amphetamine use confounded the relationship between antiretroviral adherence and unprotected sex in multivariate analysis. Seven percent (N=57) of patients agreed with a statement that a low viral load would protect against HIV transmission and these patients had higher rates of unprotected sex than patients who disagreed with the statement. However, even among these 57 patients, those taking antiretrovirals still reported less unprotected sex than those who were not taking antiretrovirals (39% vs. 63%, p= .22); similarly, those were >95% adherent with antiretroviral therapy were less likely to have unprotected sex than those were less adherent (31% vs. 70%, p= .03).

Conclusion: Use of and better adherence to antiretroviral therapy are associated with decreased unprotected sex but multiple factors confound these relationships.

Prevention, Health Services & Contexts of Health

Predictors of Non-Adherence to HAART among Women with HIV/AIDS in Los Angeles County

Presenter: Denise Johnson, Los Angeles County Department of Health Services

Collaborator: Amy R. Wohl

Background: Highly active antiretroviral therapy (HAART) has been successful in reducing viral loads for individuals with HIV; however, strict adherence to prescribed regimens is required. We examined factors that are associated with non-adherence to HAART among women with HIV/AIDS in Los Angeles County, as there are very little data on patterns of adherence to HAART among women.

Methods: This analysis focuses on 125 HIV-infected women who were on HAART when they were interviewed for the Supplement to HIV/AIDS Surveillance (SHAS) Project in Los Angeles from September 2000 through September 2003. SHAS is a cross-sectional, population-based study that enhances routine AIDS surveillance by providing supplemental clinical and behavioral data on persons recently reported with HIV or AIDS. Participants who reported not always taking their medications over a 30-day period exactly as their doctor prescribed were considered non-adherent to HAART. Logistic regression analysis was used to examine the association between non-adherence and race, alcohol and drug use, and the health and emotional status of participants in the 30 days before their interviews.

Results: The study group of women included 61% Latinas, 33% African Americans, and 6% whites. Twenty-nine percent were non-adherent to their HAART regimens and 54% said they were non-compliant because they "often forget to take their medications". Participants who self-reported poor general health were more likely to be non-adherent than those who reported good or fair health (p=.01). Controlling for CD4 count, predictors of non-adherence were African American race/ethnicity (p<.01), alcohol use in the past 12 months (p=.04), frequent sadness or depression in the past month (p=.05), and frequent anxiety or tension in the past month (p=.05). Injection and non-injection drug use were not found to be associated with adherence among these women with HIV or AIDS.

Conclusion: These data suggest that there are variations in patterns of HAART adherence among women with HIV and AIDS by race, quality of life, mental health, and alcohol use. Clinicians may consider referral of patients for treatment of anxiety and depression before prescribing HAART.

Prevention, Health Services & Contexts of Health

Innovative Strategies in Medical Adherence and Risk Reduction

Presenter: Judith Resell, UC-Los Angeles

Principal Investigator: Ronald Mitsuyasu

UARP Award Number: CC02-LA-001

Introduction and objectives: The purpose of "Innovative Strategies in Medical Adherence and Risk Reduction" was to test the efficacy of a brief psychoeducational intervention in reducing HIV-related sex and drug risk behaviors and increasing medical adherence among HIV positive women and men, with particular attention to ethnic minorities. Specific aims were to (1) conduct a randomized controlled trial of a brief psychoeducational intervention with 120 HIV positive women and men and to (2) develop an assessment of health care providers' criteria for readiness to adhere to HIV medication.

Summary of progress: 120 HIV positive men and women were recruited from community-based HIV care providers and enrolled in a randomized controlled trial during 2001 and 2002. Of the total study participants, 56 percent were African-American, 23 percent white, 17 percent Latino and 45 percent were women. Participants were randomly assigned to one of two groups: the "Innovative Strategies for Medical Adherence and Risk-Reduction" curriculum, an eight-week one-on-one psychoeducational intervention or an attention control standard care group. Both interventions were taught by a trained health educator and conducted in participants' homes. All participants had been prescribed combination antiretroviral therapy.

Findings: One hour assessments were administered at baseline and at posttest, with 3-month follow ups. We attained a 93 percent follow-up rate at post and 88 percent of the posts were reinterviewed at 3-months. A total of 416 hours of health education and psychological support were provided to 52 individuals living with HIV as the intervention portion of the project. In addition, the data collection required 320 hours of one on one personal interviewing with patients, for a total of 736 one hour home visits completed by project staff.

The intervention was effective in removing barriers to medical adherence and sexual risk reduction. Strengthening social support ($p=.05$). Improving coping skills ($p=.04$). A trend of reducing the use of illegal drugs ($p=.06$). A trend of decreasing depression ($p=.08$). Compared to HIV positive men, HIV positive women had fewer sex partners ($p=.01$), were more likely to be abstinent sexually ($p=.05$), were more likely to have histories of child sexual abuse ($p<.001$), were more likely to live with their families ($p<.001$), and reported higher levels of social support ($p=.05$). Compared to HIV positive women, HIV positive men were more likely to have used illegal drugs in the 6 months prior to the interview ($p=.001$), and were more accepting of themselves ($p=.05$).

Next steps: Full results of the randomized controlled trial of the intervention, including analysis of persistence to the three month follow-up measurement has been submitted for a Special Issue of *AIDS Education and Prevention.* Funding for a follow-up study of an intervention with gay men of color has been received and is under HSPC review.

Potential impact: Funding will be sought from NIDA or NIMH for interventions demonstrating efficacy in risk reduction and medical adherence. Multivariate statistical models predicting HIV medical adherence will be used to specify criteria for clinical assessment of adherence readiness. Thus far, we anticipate that there will be gender specific and HIV specific readiness assessment generated for clinicians in the future.

Prevention, Health Services & Contexts of Health

Measuring Adherence Support as Part of Usual Care Practices in a Randomized Adherence Intervention for HAART

Presenter: Susan Cheng, Los Angeles County Department of Health Services

Collaborators: S. Cheng , W. Garland, A. Wohl, K. Squires, M. Witt, A. Kovacs, R. Larsen, S. Hader, P. Weidle

Clinicians may change the type, frequency and intensity of adherence support provided to patients for highly active antiretroviral therapy (HAART) and these changes may influence the outcome of an adherence intervention trial. We report on the process of assessing adherence support as part of usual care from a randomized adherence intervention for HAART.

As part of a larger adherence study, clinicians at two medical centers in Los Angeles were mailed a biannual survey (Time 1: surveys sent in Nov 2001 and May 2002, Time 2: surveys sent in Nov 2002 and May 2003) to evaluate the types of adherence support for HAART that are provided as standard care. The Wilcoxon rank-sum and chi-square tests were used to test for statistical significance.

Of the 130 surveys sent out, 70 (54%) were returned. The median number of patients seen per week (time 1: 24/week vs. time 2: 22/week) and the median patient load per provider (time1: 150 vs. time 2: 200) did not differ over time. There was an increase in the frequency of adherence education provided from time 1 to time 2 (36% vs 65% of providers reported always providing adherence education, p=.0344). However, no differences (p>.05) were found between time 1 and time 2 on the other five measures of adherence support, including average time spent with HIV/AIDS patients (avg. 15-30 minutes, 59% vs. 62%), frequency of oral discussion used as the main education tool, (97% vs. 91%) and frequency that providers always discussed the coordination of HAART taking behaviors with patients' daily routines (18% vs. 22%).

While most measures of adherence support did not differ significantly between time1and time 2, providers have increased the frequency of HAART adherence education provided over time. This difference should be described and accounted for in adherence intervention studies.

This study is funded through the Centers for Disease Control and Prevention.

Prevention, Health Services & Contexts of Health

The Association between Demographics, Drug, or Alcohol Use to Recent Self-Reported HAART Adherence among Patients Entering an Adherence Intervention Trial in Los Angeles, California

Presenter: Wendy Garland, Los Angeles County Department of Health Services

Collaborators: W. Garland, A. Wohl, S. Cheng, K. Squires, M. Witt, R. Larsen, A. Kovacs, S. Hader, P. Weidle

Principal Investigator: Amy Wohl

There are inconclusive associations between HAART adherence and demographics, drug, or alcohol use. We report a preliminary analysis of factors associated with self-reported HAART adherence among patients entering an adherence intervention trial.

HIV-infected patients who had been on HAART > 30 days before entering a randomized clinical trial of three adherence support programs for HAART were asked whether they missed any doses of HAART in the past 2 weeks before they entered the trial. We evaluated the association between missing any HAART and demographics, alcohol use, or drug use.

From Nov 2001 through Jul 2003, 123 patients (62% Latino, 24% African-American; 80% males; 40% > 40 years old; 63% foreign-born; 33% current smokers; and 55% with an annual income <$10,000) were assessed. In the past month, 22% of patients reported injection or non-injection drug use, 24% reported alcohol use > 2 times per week; 26% reported alcohol use < 3 times per week; and 50% reported no alcohol use. 24% reported missing any HAART doses in the past two weeks. No association was found between missing any HAART and race/ethnicity [(White vs. Latino OR=0.75, 95%CI=0.33-1.74): (White vs. African-American OR=0.72, 95%CI=0.26-1.97)], male vs. female (OR=1.47, 95%CI=0.54-3.99), age (OR=1.01, 95%CI=0.44-2.34), foreign-born (OR=0.72, 95%CI: 0.31-1.662), smoking (OR=1.47, 95%CI=0.63-3.45), income (OR=0.76, 95%CI=0.33-1.72), alcohol use [(no alcohol vs. >2 times/week OR=0.98, 95%CI=0.37-2.60), (no alcohol vs <3 times/week OR=1.61, 95%CI=0.66-3.96)], or drug use (OR=0.86, 95%CI=0.31-2.37).

Demographics, alcohol use, or drug use did not predict self-reported HAART adherence immediately before entering this trial in this population of patients from public care. Considering these characteristics to determine who might be nonadherent to HAART before enrollment into an adherence intervention trial does not appear to be useful.

Prevention, Health Services & Contexts of Health

Noteworthy Abstract

Translating Street Smart for Use with Latino CBO Serving YMSM (Life Smart: Nuestras Vidas)

Presenter: George Ayala, AIDS Project Los Angeles

Collaborators: Uyen Bui, Fernando Cadavid, William Garcia, Julian Hernandez, Monica Nuno, Sergio Pineda, Ariel Rivera, Rosemary C. Veniegas, Rocio Yong

Principal Investigators: George Ayala, Steve Shoptaw, Oscar de la O, Richard Zaldivar

UARP Award Number: TR02-APLA-500

There is a significant need among HIV prevention service providers for effective interventions for gay, bisexual, and MSM populations who continue to be heavily impacted by the epidemic. Specifically, there is a need for research on the process of translating evidence-based interventions for implementation in community organizations that serve these populations. Funded to study the process of translating and implementing an evidence-based HIV prevention intervention for use by Latino-run community-based organizations, the "Life Smart: Nuestras Vidas" project aims to explore the role that ongoing training, technical assistance, consultation and consumer input can play in facilitating the adaptation, adoption and client satisfaction of "Street Smart," an intervention originally designed for homeless and runaway youth. Targeting YMSM (ages 18-24) the Life Smart: Nuestras Vidas project will specifically describe: organizational characteristics of adopting agencies; inter-organizational communication patterns of key project partners; adaptations made to the original intervention; integration of the adapted intervention into prevention activities for Latino YMSM within adopting agencies; fidelity to the core elements of the adapted intervention; and participant self report ratings of satisfaction with the intervention. Project investigators hope to evaluate the extent to which program activities helped or hindered the adaptation and adoption of Street Smart.

Organizational records have been collected and are being systematically reviewed to obtain information about organizational structure (type – ASO vs. CBO, size – large vs. small, scope of prevention services offered – HIV testing only vs. multi-level approach & budget of prevention programs); staff characteristics (demographic profile of staff delivering prevention services); and organizations' ideological commitment to HIV prevention and to MSM. Organizational records include annual reports, reports to funding agencies, strategic plans, program policy and procedures, organizational charts and mission statements. Analysis of organizational documents collected will be completed in year 2 of the project.

Feedback from potential consumers –young Latino gay and bisexual men - was solicited through the use of focus groups. A pre-determined set of open-ended questions and a brainstorming format in which participants were asked to generate thoughts and ideas uninterrupted by deliberation were used. Input concerning the format, content, themes and staffing characteristics of the proposed intervention were audio taped and transcribed for review. A total of seven focus groups were conducted (5 in English and 2 in Spanish) with a total of 42 young Latino gay and bisexual men. Information generated by the focus groups was used to tailor Street Smart. Five main themes emerged from preliminary content analysis of the qualitative focus group data. Focus group participants expressed: 1) a desire for a family-like environment and opportunities to establish and sustain supportive networks during their involvement with HIV prevention interventions; 2) concern about lack of role models and unity within the Latino gay community; 3) the need for comprehen-

sive prevention programs and initiative that didn't only address HIV/AIDS; 4) interest in learning how to deal with family on sexuality issues; and 5) a preference for gay-friendly spaces over gay-only spaces. Analysis of focus group data will continue through year 2.

Next Steps. 8-12 semi-structured interviews with prevention staff will be conducted. HIV prevention staff in each of the adopting organizations will be interviewed. Semi-structured interviews will be designed to gather information related to the following domains: staff characteristics (demographic profile of staff delivering prevention services, their beliefs and attitudes concerning the intervention being adopted) and the organizations' ideological commitment to HIV prevention and to MSM. Pending their consent, staff will be asked to supply demographic information including their role and job title in the organization, their educational and training backgrounds, race/ethnicity, gender, age, sexual orientation and tenure at the agency. Staff will also be asked about their prior experience adopting evidence-based interventions, and their knowledge and experience with the target population as a way to tap organizational ideologies concerning HIV prevention and MSM. Semi-structured interviews are scheduled to begin shortly.

When adopting organizations begin implementation of the adapted intervention now known as "Life Smart: Nuestras Vidas," adherence to the core elements of the intervention will be measured using an index of fidelity developed for use during quality assurance reviews of the adapted intervention sessions. The index of fidelity will permit a systematic rating of the presence or absence of the core elements of the intervention, documentation of adaptations and organizational decisions made regarding recruitment of clients, scheduling, and staffing of the intervention.

Clients who complete the adapted Street Smart intervention will be invited to participate in a brief client satisfaction and behavioral risk survey. The survey was developed to assess a client's overall satisfaction with the quality and accessibility of the evidence-based intervention being adopted. Information obtained will include client demographics, health behaviors, self-report ratings of satisfaction with the intervention, technical expertise, competence and accessibility, cultural relevance and areas for improvement. Using a Likert scale ranging from 1=strongly agree to 4=strongly disagree, satisfaction ratings will be collected anonymously in addition to logging the number of sessions received. Client satisfaction surveys will be collected from 72 and 96 clients completing the intervention. A final version of the Life Smart: Nuestras Vidas curriculum will be made available upon completion of the project.

Prevention, Health Services & Contexts of Health

Noteworthy Abstract

Translating an HIV Prevention Intervention for Young Gay/Bisexual Men to Young African American MSM and Black AIDS Organizations in California

Presenter: Susan Kegeles, UC-San Francisco

Collaborators: Gregory Rebchook, Roosevelt Moseby, Valerie Wagner, Orenda Warren, Phill Wilson, Robert Williams, Brady Ralston

Principal Investigator: Susan M. Kegeles

UARP Award Number: TR02-SF-510

Substantial research effort has gone into developing and evaluating HIV prevention interventions that are based on current theories of behavior change, utilize rigorous research designs, and focus on groups at high risk for HIV. The CAPS/UCSF investigators have developed one such intervention for young gay/bisexual men called the Mpowerment Project. It is the only HIV prevention intervention that has been shown to have evidence of effectiveness (defined as studies that have been tested via randomized, controlled trials of efficacy). However, little is known about how to translate this research-based intervention, or any other research-based intervention into practice at community-based organizations (CBOs). Even less is known about how communities of color can apply this research to their settings and populations. In addition, the Mpowerment Project was shown in previous research to reach young mainstream gay/bisexual men (white, acculturated Latino and middle class Black men who socialize within the mainstream gay community), but did not successfully reach young African American MSM (YAAMSM) who predominantly socialize and live in the Black community. Yet YAAMSM are the group at greatest risk for HIV/AIDS in the U.S., with HIV infection rates exceeding those in some sub-Saharan African countries.

To help address these problems we are conducting a collaborative study between researchers and community providers at four institutions: 1) the Center for AIDS Prevention Studies (CAPS), University of California, San Francisco; 2) the Sexual Minority Alliance of Alameda Country (SMAAC) in Oakland; 3) the Black AIDS Institute (BAI) in LA; and 4) the Minority AIDS Project (MAP)/Unity Fellowship Church, in Los Angeles. For the past thirteen years, the CAPS researchers have developed and evaluated the effectiveness of the Mpowerment Project. In response to many requests from community-based organizations (CBOs) for assistance in implementing the Mpowerment Project, the researchers have developed a collaborative system of training, technical assistance (TA) and a replication package that is designed to facilitate the translation of the research-based intervention into practice (called the Mpowerment Project Technology Exchange System). However, very little is known about how well this system works for CBOs serving young African American MSM (YAAMSM). This lack of knowledge is problematic because California YAAMSM are contracting HIV at very high rates, and California African American AIDS Service Organizations are being urged to implement interventions that have evidence of effectiveness.

This study has two major phases: 1) the tailoring of the existing intervention so that it is appropriate for YAAMSM and the development of strong collaborative ties between the researchers and the CBOs; and 2) the implementation of the intervention at the three CBOs. The specific aims of this two-phase collaborative study are:

- To tailor the Mpowerment Project to make it culturally appropriate for YAAMSM;
- To use the collaborative technology exchange system to facilitate the translation of research into practice at the three African American CBOs listed above;
- To evaluate the success of the translation process at the CBOs by collecting process data throughout the project implementation period, conducting interviews with CBO staff and volunteers at four time points, analyzing data from TA interactions, and measuring intervention implementation and fidelity;
- To identify organizational, setting, and population characteristics that facilitate or impede implementation of the intervention using the above methods.

We are currently in the first phase of the project, of developing strong collaborative relationships and of translating [I'm not sure which word I like better. It seems to me that this phase is just the beginning of the ultimate translation, so I think of it more like tailoring, but I'm not sure it matters one way or the other.] the intervention to YAAMSM. During this first year, each of the three AIDS organizations and CAPS investigators have developed and agreed upon memoranda of understanding (MOUs) regarding the collaborative relationships. Meetings have been held with each CBO and CAPS investigators to explore the goals of the study to reach mutual understandings of expectations of the study and roles of the various agencies in this project. The following issues have been discussed at various times: different expectations and desires regarding outcomes of the study by researchers and practitioners; how to ensure that the perspectives and feelings of the communities about research are taken into account; how to get the research results back to the community; and ethics of conducting research in the Black community.

In addition, two Boards of Cultural Experts (BOCEs) have been convened, one in Oakland/San Francisco and one in Los Angeles. The BOCEs are comprised of African American gay/bisexual/same gender-loving/and heterosexually-identified men and lesbians who have engaged in substantial thinking, volunteer work, or career involvement in the psychosocial and cultural issues affecting young Black MSM. Potential BOCE members were identified through collaboration between CAPS, MAP and BAI in Los Angeles and CAPS and SMAAC in Oakland/San Francisco. There is considerable diversity among the men on the BOCEs in terms of education, socioeconomic status when growing up, careers, involvement in a church and age. The BOCEs have 10-12 members each, and the CAPS team has met individually with each BOCE member to describe the study, the intervention, the purpose of the BOCE, and preliminary thoughts that the BOCE members have about issues facing YAAMSM. The BOCEs are currently actively involved in the process of deconstructing the Mpowerment Project to determine what issues are not currently addressed that need to be focused on in the intervention and how to revamp the intervention to make it culturally appropriate for YAAMSM. After an initial training regarding the Mpowerment Project in its current form, the BOCEs will participate in 5 – 6 more meetings to formulate recommendations about the creation of a "Black Mpowerment Project." Four focus groups each in Los Angeles and Oakland/San Francisco, comprised of YAAMSM, will be conducted in the next few months and this information will also be used in the creation of the new program. The intervention will then be implemented in each of the three CBOs beginning in April, 2004, for at least one year. Besides focusing on primary prevention, the new intervention will also address testing and getting into treatment if one is HIV-positive. The presentation at the UARP meeting will also address issues that have arisen regarding how to alter the intervention.

Prevention, Health Services & Contexts of Health

Noteworthy Abstract

An Enhanced HIV Prevention Intervention for MTF Transgenders

Presenter: Cathy Reback, Friends Research Institute, Inc.

UARP Award Number: CR03-FRII-522

Objectives: Transgendered (male-to-female) women are exposed to several socio-cultural conditions that contribute to their risk of HIV infection, such as low income, high unemployment, lower levels of education, and unstable housing. These transgendered women engage in extremely high levels of injection use of hormones, unprotected sex, sex work, and substance use. Many of the high-risk activities in which transgender women engage in, such as unmonitored hormone use, are unique to their social circumstances and transgender identity. The objectives of this study are: (1) to implement an evidence-based intervention that provides enhanced HIV prevention case management (PCM) and that delivers a set of services consistent with the recommendations from the UARP-funded Los Angeles Transgender Health Study; and (2) to evaluate the implementation of these services to determine the impact of HIV prevention case management as measured by the following outcomes: (a) reducing sex work by facilitating legitimate employment; (b) lowering HIV injection risks by helping transgendered women to obtain legal and monitored hormones; (c) reducing substance abuse by helping transgendered women with the decision to enter treatment and facilitating the referral process when the decision for treatment is made; and (d) reducing homelessness by helping transgendered women to obtain stable, affordable housing.

Methods: Beginning February 2004, 60 transgendered women will be recruited to enroll in the study, which will add a high intensity enhanced PCM intervention to a low intensity standard transgender risk reduction program. The impact of the PCM will be assessed using 2 methods: (1) using longitudinal models to assess the effect of time in reducing risk behaviors and increasing access to services and quality of life; (2) using between-group comparisons of a sample of transgendered women matched on age and ethnicity who participated in the prior Los Angeles Transgender Health Study along outcomes that are parallel to estimate the impact of adding PCM to the standard services. Outcomes measures will include: (a) high-risk sexual behaviors, (b) hormone misuse, (c) substance abuse, and (d) homelessness. Correlational analyses will be conducted to describe the sociodemographic, behavioral, psychosocial, and psychiatric characteristics of transgendered women who are best able to utilize the enhanced services. Findings from this project will inform policy makers on the level of services that produce maximal behavior changes in this vulnerable group of individuals at extremely high risk for HIV transmission.

Prevention, Health Services & Contexts of Health

Evaluation of Counseling Outcomes

Presenter: Diane Binson, UC-San Francisco

Collaborator: LeRoy Blea, City of Berkeley Department of Public Health; William J. Woods

Principal Investigators: Diane Binson, LeRoy Blea

UARP Award Number: CR03-SF-520

The planned research involves collaboration between researchers at the University of California San Francisco (UCSF) and the Director of the AIDS Office in the Department of Public Health, Berkeley, California, who organized and oversees an HIV counseling and testing program at a local gay bathhouse. The planned research will evaluate counseling outcomes (i.e., engagement in a "risk reduction plan" and decreased sexual risk) for a new rapid testing program at the bathhouse. Data will be collected from patrons accessing the program utilizing rapid testing with a 20-minute wait for results. These data will be compared to an existing database with counseling outcome data from patrons who accessed the program when it had a standard, 1-week wait for results.

In the United States, MSM have the highest HIV infection rates among all risk groups with an estimated 42% of annual new infections continuing to occur in this population. 77% of men who reported unprotected anal intercourse with casual partners also reported going to gay bathhouses or sex clubs. To reach high-risk men, the Berkeley AIDS Office has provided a standard HIV/STI counseling and testing program in a local gay bathhouse for the last three years.

At the end of 2003 the Berkeley AIDS Office will introduce rapid testing, providing a patron's HIV serostatus within a single counseling session rather than providing results after a one-week follow-up. Counseling outcomes may be compromised with rapid HIV testing. The planned research will evaluate the new on-site rapid testing program at the bathhouse by replicating the instruments and methodological protocol from an earlier study that examined counseling outcome data of a standard counseling and testing program at the same bathhouse. The planned study will address the following specific aims: (1) a comparative evaluation of counseling outcomes of rapid versus standard testing, specifically, engagement in a risk reduction plan, and reduction in sexual risk behavior; and (2) a process evaluation of rapid C&T.

Prevention, Health Services & Contexts of Health

Preventing AIDS in Young MSM-IDU, The Saint UFO Study

Presenter: Deborah Cohan, Saint James Infirmary

Principal Investigators: Deborah Cohan and Paula J. Lum, UC-San Francisco

UARP Award Number: CR02-SF-316

Background: In the year 2000, estimated HIV seroprevalence among men who inject drugs and have sex with other men (MSM-IDU) was greater than that reported for either MSM or IDU alone. Local research has indicated that HIV transmission in MSM-IDU is primarily sexual. Young MSM-IDU in San Francisco, many of whom engage in sex work, may be at even greater sexual risk of HIV infection. To reduce the transmission of HIV in young MSM-IDU, researchers at the University of California San Francisco (UCSF) and their community collaborators at the St. James Infirmary (SJI) and the San Francisco Department of Public Health's STD Prevention and Control Services are conducting a pilot investigation to determine the feasibility and acceptability of a community-based HIV-STD intervention in young MSM-IDU. HIV counseling, testing, and referral (CTR) programs have become a standard component of HIV prevention efforts. Because HIV shares similar transmission routes with other more common sexually transmitted diseases (STDs), an intervention that combines HIV CTR with enhanced screening, counseling, and treatment for sexually transmitted infections may further reduce HIV risk behavior, subsequent infection, and co-infection among high-risk populations.

Objectives: We will collect behavioral data on 200 MSM-IDU (under age 30), measured at baseline and six months following the multi-infection CTR intervention.

Secondly, we will collect biological data to estimate the prevalence of HIV, syphilis, herpes simplex virus-2 (HSV-2), gonorrhea, and chlamydia in young MSM-IDU, and we will examine the epidemiological relationships between these STDs and HIV.

Finally, we will describe the process outcomes by which young MSM-IDU are willing and able to participate in prevalence and behavioral studies to reduce HIV risk behavior.

Methods: Young MSM-IDU are recruited to two community sites in San Francisco by street outreach workers familiar with both young male IDU (UCSF) and young male sex workers (SJI). Eligible subjects are male under the age of 30, report injecting drug use in the prior 6 months, and report sex with another male in the prior 6 months. Trained field staff consent subjects, administer structured interviews, conduct multi-infection risk reduction counseling, and collect biologic specimens. Blood is tested for HIV, syphilis, and HSV-2. Urethral, pharyngeal, and rectal specimens are tested for GC and CT. Participants return to study sites one week later to receive test results, treatment, partner treatment, referrals, and follow up risk reduction counseling. At 6 months, participants return again to study sites for interviews, multi-infection CTR, and treatment.

Progress to date: In our first six months of fieldwork (April-October 2003), we obtained baseline data from 61 eligible MSM-IDU. Behavioral risk data, including numbers of sex partners and numbers of unprotected sexual episodes, have been collected but not yet entered for analysis. A preliminary review shows that 67% of participants reported receiving cash or other goods and services in exchange for sex within the past 6 months. Of these 30% received cash only, 11% received non-cash payment, and 27% received both.

Of the 61 baseline subjects, 28 (46%) tested positive for one or more of HIV, syphilis, HSV2, GC, or CT. Baseline prevalence of HIV was 25%, -HSV-2 23%, GC 13%, and CT 1%. The one case of syphilis that was detected was a previously-treated case in an HIV-positive subject. Co-infection was common, with 14 of the 28 testing positive for more than one infection. Two-thirds of the HIV-infected participants tested positive also for HSV-2 (n=7), syphilis (n=1), GC (n=2), or CT (n=2).

No eligible participant has declined to participate in the study to date, and few (4 persons) have declined rectal swab testing for GC and CT. Feedback from street-based outreach workers suggest that study participation is limited by the time required to travel to one of our field sites and the time (~1 hour) to participate in the study. Potential participants who do choose to visit the field sites are usually highly motivated by the opportunity to be tested and potentially treated. The pre-existing street-reputations of the UFO Study and the Saint James Infirmary also appear to have a significant role in reducing barriers to participation.

Next steps: HIV and STD infections are common among young MSM-IDU. Multi-infection CTR interventions should emphasize the role that common STDs play in facilitating the transmission of HIV. The Saint UFO Study plans to conduct additional fieldwork in the Tenderloin/Polk and Castro neighborhoods. We will continue to enroll baseline patients through the end of March 2004 and complete follow-up visits in September 2004.

Prevention, Health Services & Contexts of Health

The Social Ecology of HIV Prevention for Latino MSM

Presenter: Ross Conner, UC-Irvine

Collaborators: Eduardo Archuleta, Julio Rodriguez-Maciel, S.O.L.A.A.R Project

Principal Investigators: Ross Conner, Lois Takahashi

UARP Award Number: PE00-I-145

Although researchers have called for community-based and culturally appropriate HIV prevention interventions, there is little research evidence that indicates which types of strategies are effective. This project seeks to address this gap in scholarly and policy understanding by evaluating the effectiveness of an HIV prevention program directed at Latino MSMs in Long Beach that aims to be socially and culturally appropriate. The program is called Proyecto S.O.L.A.A.R. (Superacion, Orgullo y Lucha Atraves de Amor en Relaciones; un programa de prevencion y educacion del VIH para hombres latinos; Empowerment, Pride and Struggle through Love in Relationships: An HIV Prevention and Education Program for Latino Men). The core of the program is an intensive retreat with small groups of self-identified Latino MSMs, promoting action toward HIV risk reduction through healthy, long-term relationships, new social networks and social capital formation. The retreat is followed one month later with a reunion meeting of the group members. Based on efforts by the study implementers and evaluators, the program is now using social marketing to increase the number of attendees at S.O.L.A.A.R. sessions.

Our research study is seeking to answer the following questions: (1) How effective are the retreats-reunions in changing and sustaining participants' dating and relationship behaviors? and (2) How effective are the retreats-reunions in improving self-esteem and self-efficacy and in maintaining HIV prevention practices? To answer these questions, we have crafted an evaluation design that involves assessing participants at several different times to monitor changes in the men's knowledge, attitudes and behaviors due to the retreat and reunion. The current evaluation plan involves surveying men before the retreat, just after the retreat, again after the reunion and six months later. The survey content focuses on men's self-esteem and self-efficacy, dating and relationship behaviors (including issues such as communication, sharing, expectations and anger management), and HIV prevention practices. The evaluation study plan for the current year includes a quasi-experimental control group, composed of men who register for a retreat but do not show up at the session. Based on experiences and reports from last year, the non-attendees appear to be generally similar to those who attend the program. We are confirming the comparability of the program attendees and non-attendees, to be sure that their data can be meaningfully used. We are surveying non-attendees at three points in time, similar to the surveys of retreat attendees. Once we confirm the comparability of the attendee and non-attendee groups, we will be using the data from these groups to answer our study questions.

Prevention, Health Services & Contexts of Health

Understanding HIV Testing among Young Adults in Los Angeles: Beliefs about HIV Testing, Attributions for a Negative Test Result, and Their Associations with HIV Risk Behavior

Presenter: Christine DeRosa, Childrens Hospital Los Angeles

Principal Investigators: Christine De Rosa and Cynthia Davis, Charles Drew Univ.

UARP Award Number: CR01-CHLA-024

Most people who are tested for HIV learn that they do not have the virus. These individuals vary in their reasons for seeking HIV testing, levels of behavioral risk for HIV, and many other factors. Little is known about how persons testing negative interpret their test result in light of their previous behavior, or to what they attribute their negative HIV status. Some researchers and health professionals have expressed concern that HIV testing does little to reduce behavioral risk for HIV among those testing HIV-negative, and, at worst, may reinforce high-risk behavior. It is important to understand the impact of testing HIV negative on a person's thoughts and beliefs about HIV risk. This study was undertaken to better understand how young persons (aged 18-30) testing for HIV understand the testing experience, their behavioral risk for HIV, and what the HIV test tells them. It is being conducted in three phases. The first consisted of qualitative work to develop measurement scales. In the second, persons testing for HIV and receiving a negative test result from two community-based agencies are being interviewed immediately after their HIV post-test counseling, and again 3 months later to assess changes in beliefs over time. Because of lower numbers of Phase 2 respondents than anticipated, the age range was recently expanded to include persons aged 18 and older. By doing so, it will be possible to include age comparisons on key variables. In the third phase, results of the study will be disseminated to local stakeholders.

In Phase 1, 20 persons between the ages of 18 and 30 years who were tested for HIV at two collaborating community-based agencies underwent a semi-structured interview asking questions about their reasons for being tested, perceived likelihood of HIV infection, and interpretation of their negative HIV test result. Based on these interviews, scales were developed assessing beliefs about what the HIV test determines and attributions for the negative test result. In Phase 2, persons aged 18 and over who are tested for HIV and receive a negative result are undergoing a structured survey interview at baseline and 3 months later, assessing the same constructs in addition to HIV risk behavior. Data are still being collected. To date, 107 HIV-negative persons between the ages of 18 and 30 have been recruited into the baseline survey interview, and 32 have completed a 3-month follow-up. Of the initial 107 baseline respondents, 54% were female. More than half (52%) of respondents were within the ages of 18-21; the remaining 48% were 22 to 30 years of age. The sample is ethnically diverse, with 40% Latino, 25% African-American, 15% Caucasian, 15% Asian/Pacific Islander, and 6% of other or mixed ethnicities. For 47% of respondents, the current HIV test was their first, while 26% were tested for the second time and 27% for the third time or more. Eighty-one percent were sexually active within the last 2 months, 46% of whom had multiple partners. The median number of sex partners in the last year was 3 and ranged from 0 to 60.

Subsequent analyses will consist of data reduction to create scales out of individual items developed from the qualitative data, determination of internal consistency within newly developed scales, and associations with number of times tested and behavioral risk factors. Baseline data collection will end in early 2004, with follow-up interviewing to be completed approximately 3 months later. After analyses of the data are completed, a set of recommendations for future HIV testing services will be developed and disseminated.

Prevention, Health Services & Contexts of Health

Increasing HIV Testing Through a Health Promotion Focus

Presenter: Frank H. Galvan, Charles R. Drew University

Collaborator: Rocio Yong, Bienestar Human Services

Principal Investigators: Frank H. Galvan, Rocio Yong

UARP Award Number: CRO2-DREW-600, CR02-BHS-601

Effective HIV prevention is based in part on the extent to which efforts to promote HIV testing among individuals engaging in high-risk activities are successful. However, some individuals in California participating in high-risk behaviors have still not yet been tested for HIV and thus are unaware whether they may be HIV-positive. In order to reach such individuals, innovative methods need to be developed which facilitate their getting tested in a timely manner.

This study focuses on Latino men who have sex with men and attempts to examine the extent to which presenting the HIV test in the context of offering other health- and mental health-related tests is a more effective HIV testing protocol than one which offers only an HIV test. Thus, this study proposes to compare a standard HIV testing outreach protocol (HIV only protocol) to an HIV testing outreach protocol that incorporates HIV testing within the context of tests for other health and mental health conditions, such as sexually transmitted diseases, depression and substance abuse (health promotion protocol). The specific objectives of this project are as follows: (1) to increase the rate of individuals who agree to take the test for HIV, and (2) to increase the rate of individuals who are identified as being HIV-positive.

The work to date has focused on laying all the necessary preparations for taking the project into the field, such as hiring project staff, obtaining approval from the Institutional Review Board of Charles Drew University, finalizing all study instruments, and responding to challenges that have arisen. Two major events occurred which required making modifications to the project's original study protocol. The first was the discovery that the mobile van that was intended to be used in the field for the health promotion arm of the study needed to be substituted with one better equipped in order to be able to conduct all the intended tests. This issue was resolved by our entering into a subcontract with the Los Angeles Gay and Lesbian Center's Mobile Health Program in order to partner with them in their own outreach in the community. The second event that occurred was the federal government's approval of the rapid HIV test. Given that this study involves HIV testing, it was necessary for the project to incorporate into its protocol the most current technology to be used by service providers. Approval was received from UARP to delay the start of the recruitment of study participants in order to be able to incorporate rapid HIV testing into the study protocol. Subsequently, the California State Office of AIDS approved the guidelines for the use of rapid HIV testing and the requirements for the certification of rapid testing counselors. This month the Los Angeles County Office of AIDS Programs and Policy began the trainings for this certification, and the project collaborators have been receiving this training.

The next steps will include the recruitment of the research participants in the field. Subsequent to this, the data from the field will be analyzed. This analysis will determine to what extent an HIV testing outreach protocol that incorporates a broader health promotion differs from one which focuses solely on HIV in terms of the rate of individuals who agree to test for HIV and the rate of people identified as HIV-positive. Such findings can be of great benefit to California agencies which have HIV testing and counseling programs. They can lead to the development of HIV testing programs for use with individuals who may be more inclined to test for HIV when this test is presented as part of a broader health promotion.

Prevention, Health Services & Contexts of Health

Psychiatric Symptoms among HIV Patients Attending Two Public Health Care Clinics

Noteworthy Abstract

Presenter: Dennis M. Israelski, Stanford University

Collaborators: R. Power, D. E. Prentiss, G. Balmas, P. Garcia, C. Koopman

Principal Investigators: Dennis M. Israelski, Cheryl Koopman

UARP Award Number: CR01-ST-090

Background/Objectives: High prevalence of mental distress and psychiatric disease among PLWHA suggests that access to quality psychiatric services may significantly affect incidence of HIV transmission in community and clinical outcomes in patients with HIV/AIDS. Posttraumatic stress disorder (PTSD), acute stress disorder (ASD) and depression, for example, are often undetected or misdiagnosed by primary care providers. Recent data reports elucidate associations between trauma history and increased HIV-related risk behaviors; depression and decreased adherence to antiretroviral treatment; and ASD with quality of life. Detection of previously untreated psychiatric disorders with subsequent referrals to treatment, could therefore enhance efforts aimed at secondary HIV prevention, optimize likelihood of HIV suppression, and improve overall quality of life. This abstract describes the baseline prevalence of symptom criteria for PTSD, acute stress disorder (ASD), and depression among HIV outpatients, as obtained using standardized, structured screening tools.

Methods: HIV-infected patients were consecutively recruited from the adult population of two public health clinics in Northern California. Informed consent procedures and structured screening assessments were conducted by trained, bi-lingual (English-Spanish) research interviewers. Assessment tools included: the PTSD Checklist (Weathers, et al. 1993) to detect diagnostic symptom criteria of posttraumatic stress disorder (PTSD); the Stanford Acute Stress Reaction Questionnaire (SASRQ) for acute stress disorder (ASD); and the Beck Depression Inventory (Beck & Beamesdefer, 1974). Demographic data and baseline utilization of psychiatric and social services were also collected. Statistical methods generate percentages of diagnostic criteria for the study population and across gender and ethnic groups. Mantel Haenszel odds ratios and corresponding 95% confidence interval estimates were calculated using SPSS 11.0.

Results: From April 2002 to July 2003, 210 participants were screened representing more than half of the approximately 350 current patients attending the two clinic sites. Participants were primarily male (71%), and the mean age was 42 years. Ethnic breakdown of the sample was: 34% African-American, 33% Latino, 26% Caucasian, and 7% other ethnicity. Preliminary analysis of crossectional data indicated high prevalence of diagnostic symptom criteria for ASD (43%), depression (38%), and PTSD (34%). Women in this sample were more likely to meet diagnostic criteria for ASD than men (55% vs. 38%, OR=1.94, $CI_{95\%}$=1.1-3.5), however, virtually no gender differences were detected for presence of PTSD or depressive symptoms. Rates of ASD were the highest among African-American participants (51%) and whites (50%), compared with Latinos (32%) and mixed/other (37%). Symptoms of depression appear slightly more among whites (44%), compared to all other groups (31-38%) (OR=1.43, 0.8 – 2.7). Latinos presented the lowest rates of PTSD (29%) compared to the other groups (35-37%) (OR=0.7, 0.4-1.3), while not statistically significant, may have clinical relevance. At the time of enrollment, 24% of participants reported receiving psychotherapy services and 35% reported taking psychiatric medications.

Conclusions: Preliminary evaluation of this ongoing screening and referral program confirms high prevalence of symptom criteria for PTSD, ASD, and depression among HIV-infected patients. These findings emphasize that patients receiving HIV/AIDS care may require routine, detailed screening for symptoms of mental health disorders and appropriate treatment. Increased attention to psychiatric needs may significantly impact patients' health care service utilization. Longitudinal research is warranted to examine the value of this type of screening program for reducing secondary HIV transmission and improving clinical outcomes.

Prevention, Health Services & Contexts of Health

High-Risk Sexual Behavior in HIV-Infected Adults with Genotypically Proven Antiretroviral Resistance

Presenter: P. V. Chin-Hong, UC-San Francisco

Collaborators: S. Deeks, T. Liegler, E. Hagos, M. Krone, R. M. Grant, J. Martin

Background: The substantial frequency of drug resistance in persons recently infected with HIV implies exposure among HIV-uninfected individuals to HIV-infected persons with drug-resistant virus. While there is an increasing emphasis on understanding high-risk behavior among HIV-infected patients in general, little work has focused on those with drug-resistant virus.

Methods: We examined HAART-treated patients in the Study of the Consequences of the Protease Inhibitor Era (SCOPE), a clinic-based cohort of HIV-infected adults. Sexual behavior was ascertained by self-administered questionnaire. Genotypic drug resistance testing was performed on patients with viral load (VL) > 100 RNA copies/ml.

Results: Among 287 patients on HAART, 177 had VL >100 copies/ml; 168 (95%) of these had resistance to at least one drug. The prevalence of high-risk sexual behavior in the prior 4 months in the drug-resistant viremia group was comparable to those with either VL <100 copies/ml or with >100 copies/ml with wild-type viremia:

	Drug Resistant Viremia		Undetectable VL or Wild-type viremia		P value
Homosexual men	N=133	%	N=93	%	
Any unprotected anal sex	36/133	27	29/93	31	0.50
Any unprotected anal sex with HIV negative/unknown partner	23/133	17	12/93	13	0.37
Heterosexual men and women	N=35	%	N=26	%	
Any unprotected vaginal or anal sex	6/35	17	6/26	23	0.56
Any unprotected vaginal or anal sex with HIV negative/unknown partner	2/35	6	4/26	15	0.21

In a multivariable logistic model of predictors of unprotected anal or vaginal sex with a HIV-uninfected or status unknown partner, among the 168 patients with drug-resistant viremia there was strong evidence for an effect of age £35 (OR 8.8, P<0.01), depression (OR 3.4, P<0.05) and sildenafil use (OR 5.4, P<0.01), moderate evidence for lower education (OR 9.2, P=0.09), alcohol use (OR 4.3, P=0.12) and use of poppers, ecstasy, metamphetamines or GHB (OR 2.9, P=0.06) but no evidence for sexual orientation or adherence (p > 0.15).

Conclusions: Among HIV-infected patients with drug-resistant viremia, there is a substantial prevalence of high-risk sex with HIV-uninfected partners. This frequency of high-risk behavior is comparable with other treated patients (most of whom have undetectable VL), suggesting that a potentially significant group of transmitters is not being systematically identified for direct intervention. The presence of definable risk factors for unsafe sex suggests a role for targeted rather than broad intervention, particularly when resources are limited.

Prevention, Health Services & Contexts of Health

Receipt of Case Management Services Is Associated with Improved Health Status and Increased Use of Health Services among a Probability-Based Sample of HIV-infected Urban Poor

Presenter: Grant Colfax, San Francisco Department of Public Health

Collaborators: Annemarie Heineman, Herminia Palacio, Kathleen Ragland, Caroline Shiboski, David Guzman, Misty Schultz, Andrew Moss, David Bangsberg

Principal Investigator: Grant Colfax

UARP Award Number: CT00-SFDPH-002

Background: The impact of case managers (CMs) on health is largely unexplored. We examined the association of receiving CM services on the health and medical service use of the HIV-infected, marginally housed urban poor.

Methods: Participants were selected from shelters, meal programs, and SRO hotels, using probability-based sampling. 86% of eligibles enrolled. Interviews and CD4 counts were performed quarterly. CMs were contacted and verified meeting with the clients. Analyses included multivariate linear and Poisson regressions.

Results: Of 280 participants enrolled, 217 (78%) completed the study within one year. Median age was 42, 57% were persons of color, 80% reported substance use, 25% reported at least one homeless night in the prior 3 months. At baseline, 59% of participants met with a CM; 91% of CMs discussed medical care with their client; 62% spoke with a medical provider on the client's behalf. At one year follow-up, median CD4 count of participants with a CM at baseline was 71 cells/ml greater than persons with no CM ($p= .001$), adjusting for baseline CD4 count and retroviral use. Compared with no CM at baseline and adjusting for CD4 count, persons with a CM also reported more visits to their primary care provider (13.7 vs. 11, $p <.001$), emergency room visits (1.4 vs. .72, $p < .001$), and hospital admissions (.95 vs. .42, $p <.001$).

Conclusions: Receiving CM services is associated with improved health status and greater use of medical services, suggesting that CMs are facilitating increased but appropriate medical care in this vulnerable population.

Prevention, Health Services & Contexts of Health

Decreased Cases of and Improved Survival from AIDS-Associated Non-Hodgkin's Lymphoma in the Era of Highly Active Antiretroviral Therapy

Presenter: Catherine Diamond, UC-San Diego

Principal Investigator: Catherine Diamond

UARP Award Number: CC02-SD-003

Background: We sought to determine how the availability of highly active antiretroviral therapy (HAART) changed the epidemiology, presentation, treatment and outcomes of AIDS-associated non-Hodgkin's lymphoma (NHL).

Methods: We performed a match between the AIDS and cancer registries for San Diego County. Registry data were complete from 1988-2000. We defined the pre- and post-HAART periods as 1988-1995 and 1996-2000, respectively.

Results: Among 537 AIDS-NHL cases, 410 (76%) were diagnosed pre-HAART and 127 (24%) were diagnosed post-HAART. The rate of NHL among reported AIDS cases in San Diego decreased from 61.8 per 1,000 in 1988 to a nadir of 35.9 per 1,000 in 2000 (r=.47, p=.11). This rate peaked in 1994 at 64.8 per 1,000, as did the number of AIDS-NHL cases (N=65). Although the number of AIDS-NHL cases gradually decreased each year from 1996-2000 (32 in 1996, 31 in 1997, 25 in 1998, 23 in 1999 and 16 in 2000), the concurrent decrease in AIDS cases in San Diego moderated the decline in the rate of NHL among reported AIDS cases. Among all NHL cases in San Diego, a greater percentage were AIDS-related in the pre- vs. post-HAART period (12.8% vs. 5.5%, p <.001). Pre-HAART, 15% of AIDS-NHL patients were diagnosed with HIV after their NHL diagnosis vs. 8% post-HAART (p=.04). The median duration of diagnosed HIV infection was shorter pre-HAART than post-HAART (21 vs. 64 months, p<.001). Comparing the histology of cases diagnosed pre- and post-HAART, the percentage of intermediate grade NHL increased from 27% to 43% and the percentage of high grade NHL concomitantly decreased from 30% to 18% (p <.01). Pre-HAART, 41% of patients received chemotherapy vs. 63% post-HAART (p <.001). Pre-HAART, 28% of patients had primary central nervous system (CNS) lymphoma vs. 17% post-HAART (p=.01). Among systemic NHL cases, the median CD4 count was 74/MCL pre-HAART vs. 105/MCL post-HAART (p =.04). Among CNS NHL cases, the median CD4 count was 20/MCL pre-HAART vs. 22/MCL post-HAART (p =.60). Among systemic NHL cases, the median survival was four months pre-HAART vs. nine months post-HAART (p <.001). Among CNS NHL cases, the median survival was two months pre-HAART vs. one month post-HAART (p =.39).

Conclusions: The number of AIDS-NHL cases decreased in San Diego County with the availability of HAART. AIDS patients with systemic NHL survived longer in the post-HAART era, presumably because of higher CD4 cell counts, less aggressive NHL disease and treatment with chemotherapy.

Prevention, Health Services & Contexts of Health

HIV Prevention for Positives in the Clinical Setting: The Sexual Health in Positives Study (SHIPS)

Presenter: Greg Greenwood, UC-San Francisco

Collaborator: Rod Mason

Principal Investigator: Frederick Hecht

UARP Award Number: ID01-SF-120

This pilot study aims to develop and pilot test an innovative web-based prevention program designed for HIV+ MSM in primary care. We have performed focus groups with HIV + MSM in clinical care and interviewed providers to inform the development of the intervention. This process has identified a series of issues including concerns of patients about how they work with their providers, especially with sensitive topics*)*. Based on this input we have developed a prototype web-based prevention program. It has two prominent features: (1) A suite of decision- making and support tools for patients to self-manage their sexual health and risk; (2) A set of integrated modules to promote patient-provider communication and partnerships for health. We are pilot testing the intervention with 30 HIV+ MSM from a public clinic. The pilot is assessing intervention feasibility and collecting initial efficacy data in preparation for a large scale randomized controlled trial. Pre- and post-assessment data will also be used to describe sexual risk behavior at three different time points.

Successful development of an interactive web-based risk reduction intervention for high-risk HIV+ MSM patients has required (1) a genuine collaborative approach among major stakeholders (HIV prevention researchers, HIV care providers, and eHealth web developers), and (2) a strategic development plan for website design and buildout. We offer key lessons learned and recommendations. From usability and pilot tests with patients, we will report user responses, navigational success and difficulties, overall user satisfaction, and patient demographics and sexual risk behavior during the past 3 months.

Prevention, Health Services & Contexts of Health

Body Image in Patients with HIV and AIDS: Assessment of a New Psychometric Measure and its Medical Correlates

Presenter: Carol Kemper, AIDS Community Research Consortium

Collaborators: Carol A. Kemper, Shay M. Martinez, Catherine Diamond, Glenn Wagner, J. Allen McCutchan, and California Collaborative Treatment Group

Introduction: HIV infection may alter self-perception of body image, with significant implications for medication adherence, anxiety and depression, and quality of life. We assessed the psychometric properties of a newly developed Body Image Scale (BIS), a subjective measure of body image perception, in persons with HIV-infection and AIDS, as well as the scale's relationship to HIV-related symptoms, disease progression, and other demographic factors.

Methods: HIV-positive men (n=129) and women (n=21) attending two outpatient HIV clinics were administered the BIS survey along with a one-page demographic questionnaire. A subset (n=38) were administered the survey on two occasions a median of 7 weeks apart (range, 2 to 25 weeks). The BIS is a 12-item self-report scale developed by the authors as a subjective measure of perceived body image function. The 12 items were designed to assess body image perception as defined by 5 different possible components (comfort, competence, appearance, predictability, existential self). The BIS was framed in three different contexts: how patients feel about themselves *now* knowing they are living with HIV, how they felt about themselves *before* they learned of their HIV-infection, and how they think *others* view people with HIV.

Results: Sixty-nine patients (46%) had a diagnosis of AIDS, and 37 (25%) had a CD4 count less than 200 cells/mm^3 within the prior 3 months. The *now* context of the BIS had good internal consistency reliability (Chronbach's alpha = 0.91), and a unidimensional factor structure, suggesting that the five proposed components of body image perception were not significantly different. Comparing data from the subset who completed the scale on two occasions, the BIS survey had excellent test-retest reliability ($r=.71$, $p<.001$), after controlling for the time interval between assessments. Patients current perception of their body image was significantly lower than their perception of themselves before they were infected with HIV ($p < .001$), but significantly higher than their perception of how others view people with HIV infection ($p <.001$). The presence of HIV-related symptoms and side effects ($p < .001$) and a diagnosis of AIDS ($p = .02$) were each significantly associated with a lower perceived body image (higher BIS score). Other factors (age, gender, ethnicity, partnership status, HIV risk factor, and CD4 count and HIV viral load within the prior 3 months) did not appear to affect the BIS response.

Conclusion: The BIS has good construct validity and is a reproducible measure of self-perception of body image in HIV-infected patients. Factor analysis found that body image perception in these patients with HIV-infection is essentially unidimensional and not built of separate components, as originally proposed. Symptoms of HIV infection, including side effects of treatment, and an AIDS diagnosis negatively contribute to body image but laboratory markers of disease progression do not. We plan to further explore the relationship of body image to medication adherence, and other aspects of psychological well-being.

Prevention, Health Services & Contexts of Health

Sexual Risk and HIV Disclosure Behaviors of HIV+ MSMW (In the Mix)

Presenters: Matt G. Mutchler and Leonardo Colemon, AIDS Project Los Angeles

Collaborator: Mark A. Schuster

Principal Investigators: Matt G. Mutchler, Mark A. Schuster

UARP Award Number: ID02-APLA-038

Introduction: The 'Sexual Risk & HIV Disclosure Behaviors of HIV+ MSMW' study or 'In The Mix' began data collection in early August 2003. This is a cross-sectional examination of the HIV risk and disclosure behaviors among HIV+ men who have sex with men and women (MSMW). Guided by the Disclosure Decision Making model, our primary hypothesis is: HIV+ MSMW who do not always disclose their HIV status to sexual partners will be more likely than those who always disclose to report unprotected anal or vaginal intercourse compared to HIV+ MSMW. We will also test for mediators and moderators in our regression models. Specific objectives in this cross-sectional investigation are to: (1) Test our hypothesis that HIV status disclosure is associated with increased condom use or risk reduction among HIV+ MSMW, (2) Determine if discussions of safer sex and safer sex practices are associated with increased condom use among HIV+ MSMW, (3) Characterize the sexual risk, sexual behavior and HIV disclosure patterns among HIV+ MSMW, (4) Identify demographic, health, and behavioral factors associated with unprotected intercourse among HIV+ MSMW, & (5) Identify demographic, behavioral, and health factors associated with HIV disclosure patterns among HIV+ MSMW

Progress: We have collected completed surveys from 41 members of the target sample of 150.

Next Steps: Data collection continues and data will be analyzed for demographic patterns and trends. Bivariate tests (chi-square) will be conducted. We will build regression models including variables with significant bivariate associations and run multiple logistic regression analyses to identify predictors of sexual risk behaviors and test our primary hypothesis. We will also assess community integration data to identify additional venues for the recruitment of participants for future studies. Our long-term goal is to use findings from this pilot study to inform a larger investigation of an HIV prevention intervention targeting HIV+ MSMW.

Prevention, Health Services & Contexts of Health

Secondary Syringe Exchange among Users of 23 California Syringe Exchange Programs

Noteworthy Abstract

Presenter: Ricky N. Bluthenthal, Charles R. Drew University

Collaborators: Jennifer Lorvick, Andrea Scott, Kara Riehman, Rachel Anderson, Neil Flynn, Alex H. Kral

Principal Investigator: Ricky Bluthenthal

This paper describes the secondary syringe exchange practices (SSE) of attendees of 23 California syringe exchange programs during 2002 (N=539). SSE was highly prevalent: 75% of IDUs reported participating in SSE in the six months prior to interview. Program characteristics, such as legal status, SSE policy and exchange policy, did not affect the prevalence of SSE among SEP clients. Infectious disease risk behaviors were significantly more common among SSE participants than non-participants. SSE participants were more likely to share syringes ($p<.001$) and cookers ($p<.001$) in the previous six months. SSE was significantly associated with being stuck with another person's syringe (needle-stick), a little-discussed "occupational hazard" of this practice. In multivariate analysis, the adjusted odds ratio of needle-stick among SSE participants was 2.8 (CI 1.3, 6.0). The high prevalence of SSE, and the infectious disease risk associated with it, warrant additional research to determine the causal direction of these associations. In the interim, SEPs should consider reinforcing HIV prevention education messages and training IDUs who engage in SSE in safe handling of biohazardous materials.

Prevention, Health Services & Contexts of Health

Noteworthy Abstract

Socio-Cultural Determinants of Methamphetamine Use: San Diego Homeless Youth

Presenter: Audrey Shillington, San Diego State University

Collaborators: C. Bousman, E. Blumberg, M. Hovell, M. Ji, S. Lehman, J. D. Clapp, C. Sipan

Principal Investigator: Audrey Shillington

UARP Award Number: PE00-SDSU-153

Background: Methamphetamine use has increased rapidly in the United States and is now considered to be the fastest-growing illegal drug in the country. The purpose of this cross-sectional study was to estimate the prevalence of methamphetamine use and identify possible social and cultural risk factors among homeless/runaway youth in a Southern California city.

Methods: Youth ages 14-24 were recruited into the CARRE Project at three urban drop-in centers. For the purposes of this study data from two centers were used. A total of 113 homeless and/or runaway youth were recruited and administered a thirty-minute survey using state-of-the-art audio-computer assisted survey instrument (A-CASI) technology. Based on the Behavioral Ecological Model, several protective and risk factors for substance use were selected. Peer modeling and pressure, school factors, exercise and parental monitoring were examined using hierarchical regression analysis.

Results: Results showed lifetime use of methamphetamine use was reported by 48% of participants. Peer modeling and low levels of parental monitoring were shown to be strong predictors of methamphetamine use after controlling for age, gender, ethnicity and all other factors selected. The use of methamphetamine among homeless youth is a trend that will continue to grow without immediate intervention.

Implications: These findings suggest integration of parental figures into homeless youth services and interventions focused on creating healthy youth social networks and relationships with other peers.

Prevention, Health Services & Contexts of Health

The Success of California's Bridge Project in Linking HIV-Positive Injection Drug Users of Color to HIV/AIDS Care, Treatment, and Prevention

Presenter: Arthur Aguirre, ETR Associates

Collaborators: Kama Brockmann, Jenny Waltermeyer, Marisol Mendoza

Principal Investigator: Fred Molitor and ETR Associates

Introduction: The Bridge Project is part of California's state-funded Early Intervention Program (EIP), a comprehensive HIV/AIDS care, treatment, and prevention program. The purpose of the Bridge Project is to decrease the time between a person becoming aware of their HIV status and enrolling in comprehensive HIV/AIDS care, treatment and prevention services as well as working to re-engage clients who have been lost to care. Bridge Workers are members of the EIP team and come from the communities of color in which they work. As client advocates and treatment educators, Bridge Workers build relationships with clients to encourage them to enroll or re-enroll in comprehensive HIV services. The Bridge Project is located in 22 EIP sites, serving clients in 16 of 58 California counties.

Objectives: To determine, among Bridge Project clients, the average number of days from most recent HIV-positive test date to date of engagement with a Bridge Worker and the average number of days to refer and link clients into comprehensive HIV/AIDS care, treatment and prevention services. A linkage occurs when the client begins receiving services. We report and compare these averages between two subgroups: injection drug users (IDU) and non-IDU clients. In addition, we assess Bridge Workers' average number of contacts with clients, by group, and the average number of months in contact with clients. We perform these comparisons among clients who most recently tested positive for HIV in year 2001 or 2002.

Results: We assessed data from 448 participants. Among IDU clients (n=86) 73.3% were male, 46.5% African American, 36% White, 14% Latino, 20.9% MSM, and most (74.4%) were between the age of 30 and 49. Among non-IDU clients (n=362) 79.0% were male, 43.1% African American, 41.0% Latino, 12.7% White, 59.1% MSM, and most (68.8%) were between the age of 30 and 49 years. Among IDUs, 23.3% had no prior history of medical care. IDU clients took one month longer than non-IDUs to meet a Bridge Worker after their HIV positive test result (mean = 183.33 vs. 153.6 days). While Bridge Workers report that the length of time in contact with IDUs (mean = 3.94 months) was about the same as non-IDUs (mean = 4.12 months), they report having to contact IDU clients more often (mean = 3.08 vs. 2.25 contacts) to link this group to service. Bridge Workers referred 55.0% and linked 44.2% of IDU clients to comprehensive HIV/AIDS services. In comparison, Bridge Workers referred 50.0% and linked 38.7% of non-IDU clients to comprehensive HIV/AIDS service. Data indicate that the average time for a Bridge Worker to refer (mean = 21.3 vs. 30.6 days) and link (mean = 5.1 vs. 8.5 days) IDU clients into comprehensive HIV/AIDS services was slightly less than the average time to refer and link non-IDU clients.

Impact of Findings: This study suggests a client advocate can successfully link IDUs into comprehensive HIV/AIDS care, treatment, and prevention services. Overall, the Bridge Worker referred over 50% of clients to comprehensive services while providing linkages to approximately 40% of clients, which is comparable to the referral and linkage rate for non-IDUs. Results further indicate that, on average, IDU clients of color will be without comprehensive services, including medical care, longer than non-IDUs. However, while requiring additional effort, once engaged, IDUs will have successful service outcomes. Future analysis will assess the percent of clients who receive medical services and how frequently clients receive these services.

Prevention, Health Services & Contexts of Health

Condom Attitudes, Preferences, and Behaviors of Injection Drug Users Participating in California Syringe Exchange Programs

Presenter: Laura Bogart, RAND Corporation

Collaborators: Alex H. Kral, Rachel Anderson, Neil Flynn, Ricky N. Bluthenthal

Prior research has found low levels of condom use among injection drug users (IDUs). However, few prevention efforts have targeted IDUs' sexual risk behavior, and little is known regarding predictors of consistent condom use among IDUs. The results of prior research, conducted mainly with non-IDU samples, suggest that individuals' failure to use condoms can be understood within the context of condom-related attitudes. The present research therefore investigated condom attitudes, preferences, barriers, and use among a sample of 550 injection drug using clients of syringe exchange programs in California.

Results indicated significant relationships between condom attitudes and condom use. Specifically, in multivariate tests, positive attitudes toward condoms were significantly associated with consistent condom use for vaginal sex (OR = 1.2, 95% CI = 1.1-1.3, $p < .001$), anal sex (OR = 1.3, 95% CI = 1.1-1.5, $p < .01$), and oral sex (OR = 1.2, 95% CI = 1.1-1.3, $p < .01$) in the past six months, beyond the effects of confounding socio-demographic and HIV risk variables. In free responses, participants commonly cited partner-related barriers to condom use, such as reluctance to use condoms with steady partners (34%). Almost a quarter of the sample cited dislike of condoms (e.g., because of reduction in pleasure) as a barrier. In addition, a third of respondents stated specific preferences regarding condom brands, sensitivity, sizes, and textures.

These findings suggest that interventions that increase awareness about positive aspects of condom use and sexual risk from steady partners may be successful in increasing condom use among IDUs. In addition, SEPs and condom distribution programs in California may want to conduct brief initial surveys of client preferences in order to determine which condoms to offer. Condom distribution programs that are tailored to the preferences of their clientele are likely to reduce barriers to condom use. Understanding condom use barriers, attitudes, and preferences is a first step to changing sexual risk behavior.

Prevention, Health Services & Contexts of Health

Cognitive Distance, Mobility Patterns, and Drug Use among MSM

Presenter: Vincent J. Del Casino Jr., CSU-Long Beach

Principal Investigator: Vincent J. Del Casino Jr.

UARP Award Number: ID02-CSULB-042

Project Summary: This project investigates the relationship among the social and spatial organization of the urban environment, designer drug use, and risk behaviors related to HIV transmission among men who have sex with men (MSM) in Long Beach, California. The specific aims of this study include the following: 1., enhance our understanding of the key aspects of the social and spatial organization of the urban environment that affect designer drug use and high-risk behaviors, such as patterns of mobility related to drug seeking and risk taking behaviors among MSM; 2., compare how one is constructed in relation to different ethnic groups, in this case Latino, African-American, and White men in Long Beach, CA; 3., develop a set of qualitative mechanisms for collecting data and analyzing individual level cognitive maps of the social and physical environments in which MSM live that can be used by others; and 4. inductively generate new hypotheses that can be tested in a larger research/intervention project. Data include 25 in-depth, life history interviews with MSM from three distinct racial/ethnic groups: Whites, Blacks, and Latinos.

Findings: To date, 16 of the 25 interviews have been completed. We have interviewed 6 Latino MSM, 6 White MSM, and 3 Black MSM. Several designer drugs are used in Long Beach, including ecstasy, ketamine, GHB/GHL, and, acid among MSM. Many of these drugs are taken in conjunction with "crystal" (methamphetamine), cocaine (particularly crack cocaine), and alcohol. Some subjects have reported "slamming" (injecting) combinations of ketamine and crystal, while others have reported snorting crystal and ecstasy in opposing nostrils. Designer drugs are used in at least five different locations in Long Beach: MSM attending bars, clubs, circuit parties, gay organizations; younger (approx. 18-25 years) MSM who attend garage parties/mini-raves; older (approx. 25-50+ years) MSM who attend sex parties; MSM (approx. 25-50+ years) who meet and socialize with other men through the internet; and MSM (approx. 18-50+ years) who encounter and use designer drugs only occasionally. These are not discreet spaces but they do reflect unique cognitive maps of the city's drug culture and gay culture. Mobility is also important in designer drug use and MSM report using these drugs in a number of sites within and outside Long Beach, including West Hollywood, Orange County, Palm Springs, and local and national "circuit parties." While private cars are used by many MSM, the Metro system in Los Angeles County provides homeless MSM access to designer drugs, sex, and hustling opportunities in other parts of Los Angeles County. Designer drug use can be found in all three ethnic groups. No distinct patterns within ethnic groups have yet been found. This might be a reflection of the intermixing of ethnic groups in Long Beach or a limitation of the study to only English-speaking MSM. These drugs are also used across class lines; homeless MSM have reported use of designer drugs. Many MSM report decreased inhibitions when using designer drugs and that those drugs increase opportunities for sex. Almost all report little or no condom use when using drugs while having sex. Several MSM report drug use throughout the life course in almost all sexual contexts. The life history methodology has been valuable for locating points in time and space where designer drug use takes place. Some follow up interviews have been done in the field, following MSM through a "typical day" of partying. Methodologically, it is possible to trace where MSM who use designer drugs are going on a day-to-day basis and under what circumstances they encounter these drugs. We are also able to link these data to HIV risk contexts.

Future Initiatives: Over the next six months we will continue to collect data from MSM who have used designer drugs through life history interviews. We will also expand our in the field follow ups, collecting more baseline data related to where, when, and how designer drugs are used and their relationship to increased HIV transmission risks. Data analysis has been and continues to be an on-going process and preliminary results have already been used to submit an intervention proposal to Substance Abuse and Mental Health Service Administration (SAMHSA) in conjunction with Dennis Fisher of the Center for Behavioral Research and Services of California State University, Long Beach. This proposal was funded in October 2003. Additional intervention and research proposals will be developed using this database for the National Institute of Drug Abuse (NIDA) and the Centers for Disease Control (CDC). Research results will also be disseminated through key publications and presentations in the field of HIV prevention and drug abuse/use research. This research project has the potential to significantly help in our interventions to reduce HIV transmission and designer drug use among MSM in California. One set of interventions will not suffice. There are multiple patterns and practices of designer drug use, each of which has a discreet set of factors related to HIV. Different sites within the urban environment provide space for different sub-groups within the larger MSM population to gain access to designer drugs and potentially practice unsafe practices leading to the transmission of HIV. Interventions to reduce HIV transmission, particularly as this is related to designer drug use, must be as mobile and diverse as the MSM who are using designer drugs themselves.

Prevention, Health Services & Contexts of Health

Preventive Effectiveness of Behavioral Health Risk Assessment

Presenter: David Gibson, UC-Davis, and Peter Simpson, Harm Reduction Services

Principal Investigators: David Gibson, Peter Simpson

UARP Award Number: CR02-D-617, CR02-HARM-618

Injecting drug use now accounts for 33% of cumulative AIDS cases, and 36% of AIDS cases for calendar year 2002. Health risk assessment, a non-labor intensive individualized intervention which involves a careful examination of a person's health habits, a qualitative assessment of his/her future risk of disease and death, and counseling and education about how to alter one or more personal risk factors, has been used successfully in promoting a wide variety of health behaviors, and shows potential as a cost-effective strategy for preventing HIV/AIDS. In this study, we are evaluating individualized behavioral risk assessments as an HIV prevention modality with methamphetamine-using injecting drug users (IDU). After conducting baseline interviews, we are randomizing 200 methamphetamine injectors to receive either the experimental health risk assessment intervention or a packet of educational brochures. Follow-up interviews will be conducted nine months after baseline to assess the effectiveness of the intervention in reducing high-risk sexual and injection behaviors. In addition, to better understand the mechanism of the intervention's impact, we will examine whether the effects of the intervention are mediated by changes in AIDS-related attitudes and beliefs.

Prevention, Health Services & Contexts of Health

Mobilizing Methamphetamine Users to Prevent HIV/AIDS

Presenters: David Gibson, UC-Davis, and Peter Simpson, Harm Reduction Services

Principal Investigators: David Gibson, Peter Simpson

UARP Award Number: CR00-D-131

As the U. S. HIV epidemic continues to unfold, injecting drug use is accounting for an ever-increasing proportion of HIV infections. Current prevention efforts have failed to adequately slow the spread of HIV among injecting drug users. The spread of HIV is especially serious among methamphetamine injectors, who are much more likely to practice high-risk behaviors and be infected with HIV. Community-level interventions have been successful in promoting a wide variety of health behaviors, and have the potential for diffusing health-related norms to entire communities or populations of people. Recent studies demonstrate the effectiveness of community-level interventions in preventing HIV among segments of a community. In this study, we propose to evaluate a promising small group intervention, which if effective, could help mobilize communities of methamphetamine injectors' around prevention of HIV and other bloodborne infectious diseases. After conducting baseline interviews, we randomized approximately 40 friendship networks consisting of 200 methamphetamine injectors to the experimental intervention or to the comparison group, which will receive brief oral feedback about how their behaviors may place them at risk of infection with HIV. Follow-up interviews were conducted an average of nine months after baseline to assess the effectiveness of the intervention in reducing high-risk sexual and injection behaviors; we reached approximately 65% of respondents for the follow-up interview. Data analysis is proceeding to determine impact of the small group intervention and whether effects of the intervention are mediated by changes in peer norms for safer behaviors, and peer communication about the need for behavior change.

Prevention, Health Services & Contexts of Health

A Study of the Feasibility of Retaining a Cohort of Traveling Young IDU

Presenter: Judith Hahn, UC-San Francisco

Collaborators: David Bangsberg, Paula Lum, Kim Shafer, Andrew Moss

Principal Investigator: Judith Hahn

UARP Award Number: ID03-SF-006

Young injection drug users (IDUs) are at high risk for becoming infected with viruses that are transmitted through blood, such as HIV, hepatitis C virus (HCV), and hepatitis B virus (HBV). However, because the number of persons infected with these increases with age and duration injecting, young IDUs are in the window of opportunity for disease prevention. Most interventions, such as immunization against vaccine-preventable diseases or behavior change models, require retention of participants over a period of time. These models assume a degree of stability that is not the case among young IDUs. Money spent on developing, evaluating, and implementing HIV interventions among IDUs is wasted if there is a high degree of attrition. We found a high degree of travel in a previous study of young IDUs in San Francisco. In this study, the median time in San Francisco prior to the study was two months, and two thirds had been traveling in the prior three months. The median number of cities to which they had traveled in the prior three months was two. Effective methods that address the high mobility of young IDUs are essential for testing and implementing interventions to prevent HIV infection. We plan to test the feasibility of following young IDUs who travel, utilizing current technology such as ATM cards to give participants instant financial incentives and online interviewing systems for follow up interviews. We will also determine young IDUs' rate of accessing services while traveling. This approach, if successful, could be used to increase the ability to test and implement interventions to prevent HIV in this crucial at-risk population.

Prevention, Health Services & Contexts of Health

Noteworthy Abstract

Mexican Farm Workers and Day Laborers' Attitudes and Beliefs about HIV and STD Testing

Presenters: Norma Aguirre and Carlos Vera, PROCABI

UARP Award Number: CM02-PROC-801, CM02-SDHHS-805, CM02-VCC-804

The purpose of this study is to shed some light on the attitudes and beliefs of Migrant Farm Workers and Day Laborers regarding biological sample collections for a research study. A total of 48 Mexican migrant farm workers and day laborers participated in a pilot-test as part of the California-Mexico Epidemiological Surveillance Pilot (CMESP). Recruitment took place at 6 venues throughout San Diego County, over a two-week period in November (from 15th to 29th, 2003). Of the total sample, 93.75% (45/48) were males, and their age ranged from 19 to 71 years, with a mean age of 45 years. During the biological sample collection in the field, participants shared with the project's Phlebotomist their impressions about participating in research and providing biological samples. Sixty-five percent (31/48) of participants had never tested for STD's before. Fifty percent of participants (24/48) believed that their blood would be sold and that they would never get their results back. Seventy percent of participants (34/48) were interested in being tested for HIV, but were not aware that they could be tested for other STD's. Sixty percent (29/48) were not aware that they had access to health care, regardless of their legal status. Taking the time to address the fears, beliefs and misconceptions can greatly benefit research studies among this hard to reach population. This information can be used to enhance outreach activities for both community clinics and research studies.

Prevention, Health Services & Contexts of Health

The California-Mexico Health Partnership: Fresno

Noteworthy Abstract

Author: Shahla Rahmani, Department of Community Health, Fresno

Collaborators: Shahla Rahmani, Alvaro Garza, Patsy Montgomery, Lorena Ayala-Lawless, Joe Matthew Stanich

Principal Investigator: David Luchini

UARP Award Number: CM02-FCDCH-803, CM02-SF-806, CM02-PPMM-800

This project brings together a collaboration of academics, community-based organizations, and State and local public health agencies. The goal of the partnership is to implement the California-Mexico Epidemiological Surveillance Pilot (CMESP) project in Fresno County. CMESP is a bi-national collaborative project that aims to improve methods of identifying and addressing the specific health needs of the Mexican migrant/immigrant population, with an emphasis on HIV/AIDS, sexually transmitted diseases, and tuberculosis. The partnership is structured to maximize the collaborative and individual expertise of all parties involved.

The collaborating agencies and their contributions are:

Fresno County Department of Community Health (DCH), they provided background information for the initial implementation of the pilot. The CMESP local team leader is housed in the DCH and operates under the umbrella of public health activities in Fresno County. DCH staff have contributed ongoing feedback and consultation and have acted as the liaison for communications and interactions with other programs and organizations. In addition, the DCH public health lab has provided blood tests. UCSF-Fresno Latino Center for Medical Education and Research (LaCMER) provided data management and analysis support, as well as consultation on activities with Fresno communities and organizations. Specifically, LaCMER has established a computerized database for data management and analysis. LaCMER has also disseminated information about the pilot project to health professionals. Planned Parenthood Mar Monte (PPMM) provided staff to assist the CMESP local program manager in completing the fieldwork and activities specified by the project protocols. Four PPMM health educators working under the direction of a project team leader conducted 11 key information interviews, six focus groups, enumeration and ethnography in seven rural communities. The State Department of Health Services, STD Control Branch-Fresno field office has provided training support. They have been responsible for medical chart abstraction through the use of active surveillance of the selected reportable diseases at various healthcare sites within the targeted communities.

This partnership will continue to employ its cross-programmatic and multi-disciplinary approach for the next two years and will monitor and evaluate the success of the pilot activities. The partners will disseminate the results of the findings to area and State community bodies and organizations. The pilot also has implications for the collaborative agencies themselves, who may choose to adopt some of the multiple methodologies for disease and behavioral surveillance along with the appropriate prevention and intervention activities that the project will be employing and assessing. Finally, we also foresee further research or prevention project partnerships among these agencies on other health issues to benefit our migrant populations.

Prevention, Health Services & Contexts of Health

Noteworthy Abstract

Evaluation of Two School-Based HIV Prevention Interventions in the Border City of Tijuana, Mexico

Presenter: Ana P. Martinez-Donate, Center for Behavioral Epidemiology & Community Health, San Diego State University

Collaborators: Melbourne F. Hovell, Carol L. Sipan, Jennifer Zellner, Elaine J. Blumberg, Claudia Carrizosa

Principal Investigator: Melbourne F. Hovell

UARP Award Number: IS02-CBECH-711

HIV is a pandemic and adolescents are at increased risk. The mixing of Mexican and American cultures may increase the risk for HIV infection among adolescents living in the Mexican border region. To date, no HIV prevention interventions for adolescents in this region have been formally tested. This study was aimed at evaluating the individual and combined effectiveness of an HIV prevention workshop and a free condom distribution program in four high schools in the border city of Tijuana, Mexico. Adolescents (N=320) completed baseline measures on sexual practices and theoretical correlates and participated in a two-part study. In Study 1, students were randomly assigned to an HIV prevention workshop or a control condition, with a 3-month follow-up assessment. Results indicate that the workshop significantly delayed sexual initiation ($p<.001$), increased access to condoms ($p<.001$), and reduced traditional beliefs regarding condom ($p=.016$) use and acquisition ($p=.001$). In Study 2, a condom distribution program was set up on two of the participating schools, with students completing a 6-month follow-up assessment. Results suggest that exposure to the workshop followed by access to the condom distribution program moderated sexual initiation ($p<.001$) and increased condom acquisition ($p<.001$). Access to the condom distribution program alone also had a significant moderating effect on sexual initiation ($p<.001$), but no effects on other behavioral and psychosocial correlates of HIV infection. These results suggest that a three-hour HIV prevention workshop represents an effective tool to reduce the spread of the infection among high school students in Tijuana. This study also demonstrates that condom distribution programs do not hasten sexual initiation, although these programs may need to be implemented in combination with education programs to prevent HIV infection in this population. In the context of increased migration from Mexico and the degree of interaction between Tijuana and San Diego residents, these interventions may contribute to reduce the risk for HIV infection among youth in both Mexico and California.

Prevention, Health Services & Contexts of Health

HIV Risk in Populations of Mexican Origin

Presenter: Héctor Carrillo, UC-San Francisco

Collaborator: Jorge Fontdevila

Principal Investigator: Héctor Carrillo

UARP Award Number: ID02-SF-004

In California, Latino populations have been found to be disproportionately affected by HIV. Not all Latinos/as in the state however, have the same levels of HIV risk. Differences in HIV risk and sexual behavior can be found among subgroups of Latinos defined by their degree of acculturation and U.S.-born vs. immigrant status. The literature suggests that such differences may be related to the subgroups' sexual norms and values (or, more broadly, to the sexual cultures and ideologies prevalent in each subgroup). Paradoxically, several studies have reported lower levels of HIV risk among less acculturated Latinos/as and recent immigrants when compared with U.S. born and highly acculturated Latinos/as. Currently, we do not understand fully the cultural patterns and social mechanisms that explain this health paradox.

This study's specific aims are to (1) compare the sexual cultures and ideologies of heterosexual Mexican Americans and Mexican recent immigrants, and link their cultural norms, values, and ideas about sexuality and sex with their sexual decision making, sexual behaviors, and HIV risk; and (2) assess the feasibility of a larger-scale study on this topic. We have conducted forty semi-structured, qualitative interviews with Mexican American and recent Mexican immigrants living in San Diego. Participants also responded to the questions contained in two of the acculturation scales that are most widely used in behavioral research with Latino populations.

We are currently initiating analysis of these interviews and will present preliminary findings. After an initial round of reading, the interview transcripts will be coded for analysis using ATLAS.ti, a software package for qualitative analysis. Our analysis will include a comparison between the content of interview transcripts and the results obtained in the acculturation scales, and will help formulate questions for a larger study on this topic. We anticipate that our results will also suggest possible directions in the creation of HIV prevention programs that respond more specifically to the needs of Mexican American and Mexican immigrant populations in California.

Prevention, Health Services & Contexts of Health

Characteristics of HIV in Hispanic Migrants: An Emerging Vulnerable Population in California?

Presenter: Vivian Levy, Stanford University, San Mateo Medical Center

Principal Investigators: V. Levy, D. Prentiss, G. Balmas, K. Page-Shafer, D. Katzenstein, D. Israelski

UARP Award Number: CF02-SMCHC-300

Globally, migrants have emerged as vulnerable populations in the HIV epidemic and often as strategically important core groups linking populations. In our northern California county, foreign born HIV infected patients, predominantly from Latin America, are more likely to present undiagnosed with opportunistic infections (OIs). In an effort to explore the role of migratory and social networks among Hispanic immigrants and elucidate barriers to HIV diagnosis and treatment, we conducted in-depth interviews with 20 Hispanics consecutively diagnosed with HIV in the last year.

Among these 20, 18 were male. The two females were sexual partners of newly presenting males. Ninety percent were born in Mexico/Central America; 10% were US born. Thirty percent had been in the US less than five years and 85% chose to be interviewed in Spanish. The mean CD_4 count at HIV diagnosis was 307 cells/mm3 (17%). Half had OIs at first HIV diagnosis, 2/20 have died.

The interviews revealed varied paths to HIV testing and clinical presentation. However, among nearly all, migration, housing and social networks are closely intertwined. Migration and initial establishment in the US is sponsored by shared binational networks, usually with strong familial ties. Most migrants meet their sexual partners through these networks. Sexual transmission was the mode of HIV acquisition for 95% of this cohort. One third of men described their current sexual identity as homosexual/gay or bisexual, yet one half of men reported men who have sex with men (MSM) contact in the preceding six months. Virtually half of patients (45%) were sexually active in the six months prior to HIV diagnosis with no condom use; 25% reported a personal history of sexually transmitted disease (STD) treatment. Precipitants for current HIV testing included: Partner with HIV/STD infection (35%), OIs (30%), and Unprotected MSM exposure (15%). HIV disclosure to recent sexual partner(s) was more common than to family and housing members. Geographic mobility is common: 25% had lived in more than one city in the last six months; 35% had returned to Latin America within the last year.

Latin American migrants in California are likely an important bridge population in HIV and STDs. California outreach and testing should focus on recently arrived migrants in venues such as labor recruitment sites and language schools. Culturally appropriate, effective education and partner notification strategies in this vulnerable population need to be explored.

Prevention, Health Services & Contexts of Health

Prevalence & Correlates of HIV-Related Practices among Mexican Migrants

Presenter: Ana P. Martinez-Donate, Center for Behavioral Epidemiology & Community Health, San Diego State University

Collaborators: Melbourne F. Hovell, Gudelia Rangel, Carol L. Sipan

Principal Investigator: Melbourne F. Hovell, Gudelia Rangel

UARP Award Number: CR01-CBECH-100

Mexican migrant laborers might represent a high-risk group for HIV infection in the U.S. Previous studies have found low HIV rates but high prevalence of sexual transmitted infections (STI) and HIV risk behaviors, suggesting a link between migration to U.S. and increased risk of HIV infection. More knowledge about the magnitude and the dynamics of the infection in this population is needed.

This study was aimed at estimating the prevalence and determinants of HIV risk practices among Mexican migrants traveling across the San Diego-Tijuana border. An HIV-related interview has been added to an on-going Mexican survey of migration in Tijuana. A sub-sample of the respondents has also been tested for HIV status. The extended survey has been completed by 1,413 Mexican migrants (88% males and 12% females). Among them, 1,066 have been tested for HIV infection. Results indicate relatively high prevalence of unprotected sexual practices with casual partners and sex workers, needle sharing, and reported STIs. In contrast, none of the migrants tested positive for HIV infection. A preliminary analysis of the role of migration to the U.S. indicates that, after controlling for gender, age, education, marital status, and socioeconomic level, individuals with a history of migration to the U.S. are more likely to have had vaginal sex with casual partners ($p=.023$), sex with an IV drug user ($p=.03$), and in exchange for money or other goods ($p=.048$) during the last 6 months. In addition, migration to the U.S. was positively associated with the likelihood of having shared needles ($p<.001$), been tested for STI ($p<.001$), and visited a clinic/doctor office regarding a STI ($p<.001$) during the last 6 months.

The results suggest that the prevalence of HIV infection among Mexican migrants is lower than .09% (less than 1 out of 1,066) and that migration to the U.S. is associated with increased risk for HIV infection. Unprotected sexual practices with casual and prostitute partners, as well as needle sharing practices, place migrants and their regular partners at risk for HIV infection and should be targeted by prevention programs directed to this population in both Mexico and California. Future analyses will address the estimation of the prevalence and multivariate models of risk practices at different stages of the migration process and will inform interventions for the prevention, control, and treatment of HIV infections on both sides of the Mexican/U.S. border. Further, the degree of generalization of these results to the overall migrant population traveling across the Tijuana-San Diego border region (i.e. analysis of non-response bias and estimation of adjusted models) will be assessed.

Prevention, Health Services & Contexts of Health

Gender Differences in Condom-Related Behaviors and Attitudes among Mexican Adolescents Living on the US-Mexico Border

Presenter: Ana P. Martinez-Donate, Center for Behavioral Epidemiology and Community Health, San Diego State University

Collaborators: Melbourne F. Hovell, Elaine J. Blumberg, Jennifer Zellner, Carol L. Sipan, Audrey M. Shillington, Claudia Carrizosa

Principal Investigator: Melbourne F. Hovell

UARP Award Number: IS02-CBECH-711

There is extensive evidence that Mexican adolescents are at increased risk for HIV infection. Previous studies suggest that risk factors and behaviors linked to HIV infection are likely to differ between Mexican male and female adolescents. Research on gender differences in risk behaviors and determinants is needed to develop effective HIV prevention interventions targeting Mexican adolescents. However, studies of gender and condom use among adolescents have suffered from methodological limitations. Failure to control for gender differences in the likelihood of having had sex when estimating the effect of gender in the use of condoms creates a situation of sample selection that may bias the estimation of true gender differences in condom use. Thus, estimation about gender differences in condom use would not be able to be generalized to the general population of adolescents, but only to the sub-sample who are sexually active.

This study examined gender differences in the likelihood of unprotected sex and theoretical correlates among high school students in the border city of Tijuana, correcting for this methodological problem. 370 high-school students completed a face-to-face interview and a self-administered survey on HIV-related risk practices and theoretical behavioral and cognitive correlates. Differences between male and female adolescents in sexual initiation, condom use, intentions to use condoms in the future, and attitudes towards condoms in this population were assessed, using multivariate models. A version of the Heckman method was used to correct for sexual history bias when estimating the effects of gender on the use of condoms. Results indicate that male students are more likely to have initiated sexual practices than females (OR=2.83, $p<.001$). However, after controlling for the probability of having had sex during the last 3 months, females are more likely to have had unprotected sex than males (B=-.40, $p<.05$). In contrast, female adolescents perceive themselves as more likely to avoid unprotected sex in the future (OR=2.28, $p<.01$), report higher levels of self-efficacy to refuse having sex without condom (OR=4.77, $p<.005$), hold more favorable attitudes about condoms (B=-1.20, $p<.01$), and less traditional views about condom use (B=1.12, $p<.001$). Overall, these findings suggest that Tijuana female high school students are at higher risk for HIV infection than their age-matched male peers and may be a greater need of risk reduction interventions. HIV prevention programs targeting Mexican adolescents need to be gender-based and intervene on specific barriers for safe sex among female and male youth. More structural changes at social, cultural, and economic level may be necessary to lower the risk for HIV infection among Mexican women.

Prevention, Health Services & Contexts of Health

Demographics of Migratory Mexican Day Laborers

Presenters: Shanna O'Reilly and Saul Estavillo, PROCABI

Principal Investigators: Shanna O'Reilly, Saul Estavillo, Victor Pereda, Robin Slade

UARP Award Number: CM02-PROC-801

The California-Mexico Epidemiological Surveillance Pilot (CMESP) is a bi-national collaborative between academic institutions, public health departments, and community-based organizations. In San Diego County the collaborative is represented by the University of California, Office of the President, Vista Community Clinic, and the Bi-National AIDS Advocacy Project (PROCABI). The objective is to test methods of identifying migration patterns, and address health needs of Mexican migrants/immigrants in San Diego County. As part of this objective, enumeration activities have been conducted throughout the County to assess population flow and volume, and determine the population's state of origin within Mexico, through intercept questions on demographics. A total of 441 people were enumerated at 28 sites from end of July through end of November 2003. Seventy-one percent (314/441) migrate between California and Mexico, the majority (64%) arriving at Baja California and Jalisco once in Mexico. Sixty-Two percent, of the 314 people (169/314) who migrate, travel between California and Baja California, and 10% (32/314), travel between California and Jalisco. This data demonstrates the need for future epidemiological and ethnographic studies on the trends of communicable disease transmission, between California and the population's return state. Such studies aid in designing prevention and treatment programs throughout California and Mexico.

Prevention, Health Services & Contexts of Health

HIV and Related Risk Behaviors among Young Latino MSM at the California-Mexico Border; Imperial, California-Mexicali, Mexico

Presenter: Assunta Ritieni, California Department of Health Services, Office of AIDS

Collaborators: Juan Ruiz, Arturo Hernandez, Enrique Gomez, Mirna Salazar

Principal Investigators: Juan Ruiz, Assunta Ritieni, Arturo Hernandez

UARP Award Number: CR02-CDHS-606, CR02-CDHS-607, with support from the Centro Nacional para la Prevención y Control del VIH/SIDA (CENSIDA)

Background and Study Summary: Every year since 1987, Latinos have represented a greater percentage of new annual California AIDS cases than the year before, representing 33.4 percent of new cases in 2000. Of the 24,440 Latino individuals that have been diagnosed with AIDS, roughly 70 percent had been diagnosed between the ages of 20 and 39. Ninety-one percent were males and of these males over 63 percent had been exposed through homosexual contact. Furthermore, a significant percentage of these Latinos are of Mexican descent. As a result, this study in the Imperial-Mexicali border area is being conducted to assess HIV prevalence, incidence and related risk behaviors among young (18-29) Latino men who have sex with men (MSM). Each participant is administered a 35-45 minute questionnaire which inquiring about the subject's socio-demographic characteristics, access to healthcare, and HIV-related risk and preventive behaviors. A blood sample is collected and analyzed for HIV antibodies and, if positive, for CD4 count and viral load. Detuned assay is performed on positive specimens to determine whether seroconversion occurred within the 120 days prior to blood collection. A subset of HIV-positive specimens will undergo genetic subtyping analyses.

Study Progress and Findings: Formative research was conducted between January and April of 2003 and included focus groups, informational interviews, observations and enumerations. The data collected during this phase were used to develop recruitment and sampling frameworks for the study. Recruitment and survey data collection began in late June 2003. Preliminary data for Mexicali participants are currently available. Of the 62 individuals interviewed, 32 percent were born in a state in Mexico other than Mexicali. Approximately 80 percent indicated having lived in the Mexicali area for more than 5 years. Fifty-six percent stated that they do not have health insurance and 22 percent indicated that they do not have a regular source of healthcare. Among the MSM interviewed, insertive anal sex appears to be more common than receptive anal sex: 87 percent and 69 percent respectively. Fifty-eight percent have had sex with a female. All of these individuals have engaged in vaginal intercourse. Only 39 percent have had anal sex with their female sex partner(s). Prevalence of unprotected sex, both lifetime and recent, varies with gender of sex partner. Approximately 87 percent have had either insertive or receptive unprotected sex. Roughly 72 percent of MSM who have had sex with females have engaged in either unprotected vaginal or anal sex with their female partner(s). Among those who had sex in the past four months, unprotected sex is also prevalent. Sixty-two percent of the 47 men who had sex in the past four months with a male partner, had unprotected insertive or receptive sex. Thirty-four percent of these MSM had unprotected sex with either an anonymous or exchange male partner. Roughly 75 percent of the 16 MSM who had a female sex partner in the past four

months, engaged in either vaginal or anal unprotected sex. Seventy-five percent of these MSM had unprotected sex with either an anonymous or exchange female partner. Interestingly, fifty-one percent of all MSM feel that they are at little or no risk of infection and 26 percent indicated that hearing about new HIV/AIDS medical treatments would influence their behavior.

Of 58 participants who agreed to have their blood tested, 19 percent tested positive for HIV. None of these participants were aware of their status. Seven indicated having previously tested for HIV and having tested negative, and three of these got tested within the past 2 years.

Implications/Next Steps: Unprotected sex with males and females is placing both the MSM and female population at high risk for HIV infection. Unprotected sex with exchange or anonymous partners, low risk perception, and lack of health insurance or regular healthcare for this population is worrisome. Unfortunately, the HIV prevalence observed thus far validates these concerns. Data collection will continue through September 2004, at which time the data should allow for more accurate estimates of HIV prevalence and related risk and preventive behaviors among the MSM population in this border region.

Prevention, Health Services & Contexts of Health

HIV in Mixtec Workers: A Model Surveillance System

Presenter: Carol Sipan, San Diego State University

Collaborators: Melbourne Hovell, Fernando Sañudo, Carol Sipan, Arturo Jimenez

Principal Investigator: Melbourne Hovell

UARP Award Number: CR02-SDSU-627

This study is designed to provide epidemiological data to inform California/Mexico collaboration for the control of HIV/AIDS among Mexican migrants traveling between Mexico and California. Results will also inform policy with regard to the feasibility of establishing surveillance systems for tracking risk practices and their probable determinants. This study will increase knowledge of the prevalence of HIV, risk practices for HIV and the social determinants for risk practices and infection for Mixtec migrant farm workers residing in northern San Diego County and in San Quintín, Northern Baja California. This population represents one of the largest groups of Mexican indigenous people who migrate from Mexico to San Diego County and other areas of California, yet they are understudied. Anecdotal information and limited epidemiological data from Mexico indicate potential for acquisition of HIV by male farmworkers during their time away from Oaxaca. The Specific aims of this study are:

- To determine the degree to which migration history, utilization of preventive and healthcare services, and social/behavioral and environmental factors based on a behavioral ecological model are associated with Mixtec males' risk profile and key risk practices;
- To determine the degree to which specific risk practices (e.g. sexual intercourse without a condom) and conditions (e.g. STI and TB history) are associated with HIV infection;
- To estimate the prevalence of HIV and related behavioral risk factors for Mixtec migrants;
- To estimate the prevalence of Mixtec migrants' use of U.S. and Mexican healthcare services; and
- To determine the degree to which social/cultural factors are associated with access to preventive and healthcare services in the U.S. and in Mexico.

Year 1 has been dedicated to activities critical to successful completion of data collection. Data have been collected regarding the location and numbers of male migrant farmworkers in North County. Data collection sites have been determined based on existing relationships between growers and Vista Community Clinic, and the access to Mixtecs at those sites. Focus groups have been conducted with male and female Mixtecos regarding the conduct of the study and the sensitive nature of the topics to be studied. Decisions have been made after numerous meetings between the collaborating partners and with Mixtec community leaders regarding data collection procedures and translation requirements. Staff for the North County portion of the study has been hired and staff training is underway. IRB approval at SDSU has been obtained with the exception of the approval of the final data collection instrument, and data collection is scheduled to begin in North County at the beginning of Year 2 following translation into Spanish and Mixtec. With the completion of the data collection instrument, IRB approval will be sought from Mexican authorities. Visits have been made to San Quintín to discuss plans with local health authorities for accessing the Mixtec farmworker population at the camps and to determine staffing for data collection. Data collection for the San Quintín component will be conducted in the Spring and Summer. Data analyses will be conducted in the Fall of Year 2.

Prevention, Health Services & Contexts of Health

HIV Prevention Policies of Latino/non-Latino Businesses in Two San Diego Communities

Presenter: Gabrielle Foley, Center for Behavioral Epidemiology & Community Health, San Diego State University

Collaborators: Gabrielle Foley, Melbourne Hovell, Carol Sipan

Author: Carol Sipan

UARP Award Number: IS02-CBECH-711

The Latino population in the United States has been severely affected by Acquired Immune Deficiency Syndrome (AIDS). Educationally based intervention strategies are only somewhat effective in preventing HIV transmission. Applying an ecological approach to HIV prevention behavior may provide a more comprehensive and representative view of the factors that control these behaviors in Latinos. In many communities, especially those in low-income urban settings, businesses hold a unique potential to influence HIV prevention efforts through company employee policies and consumer interactions. This study is designed to identify current policies and practices among Latino owned/servicing businesses in the San Diego area to promote HIV prevention, and compare them to the practices and policies of non-Latino owned/servicing businesses. Descriptive data will be collected from 100 businesses, approximately 50% of which will be Latino owned or managed. Half of the businesses will be selected from a low HIV prevalence community and the remainder from a high HIV prevalence community. Data will be collected by means of telephone and face-to-face interviews with key managerial personnel. The interview will assess current practices of businesses regarding their promotion of general health and HIV prevention, and the practices that they may be willing to adopt in the future. Results will provide a description of current practices and will be examined for differences between low prevalence and high prevalence communities and between Latino and non-Latino owned or managed businesses. Resulting information from this study will quantify which potential business-based policy options, financial incentives, and educational interventions employers are willing to initiate related to HIV prevention. It may also identify model business practices for advancing HIV prevention efforts specifically for Latino communities.

Prevention, Health Services & Contexts of Health

Maquiladora Employment as a Determinant of HIV-related Risk Behaviors in Tijuana Adolescents

Presenter: Claudia Carrizosa, Center for Behavioral Epidemiology & Community Health, San Diego State University

Collaborators: Claudia Carrizosa, Melbourne Hovell, Carol Sipan

Principal Investigator: Carol Sipan

UARP Award Number: IS02-CBECH-711

Studies about HIV prevalence among Street Youth (Norris, 2000), men who have sex with men (MSM) (Rangel, 1998), migrants (Rangel, 1998) and women (Wortley, 1997) have raised concern about the spread of HIV in the California-Mexico border region. Research suggests that young people have been disproportionately affected by the AIDS epidemic, as half of all new infections occur in the population between the ages of 15 and 24 (PAHO, 2002). The area in and around the border city of Tijuana presents with the highest AIDS mortality rate in all of Mexico, with estimates ranging from 11.4 to 21.7/100,000 deaths (Instituto Nacional de Salud Publica, 1998) as compared to the national AIDS mortality rate of 4.2/100,000 deaths. (Magis et al, 2000). Over 86% of all known cases among adolescents in Mexico can be attributed to sexual transmission (SSA, 2000; Amigos contra el SIDA, 2002). Thus, the period of adolescence, when many youth initiate and engage in sexual activity, may present significant risk for adopting high-risk sexual practices and acquiring sexually transmitted diseases, including HIV infection. The maquiladora industry in Mexican cities along the U.S.-Mexico border tends to employ large numbers of young, single, low education, low socioeconomic status (SES) individuals. Maquiladora employees constitute a large segment of the low-wage working population in the border region, and the industry continues to attract young people who migrate to northern border cities in search for better opportunities. These factors may contribute to higher rates of risk behavior in this population.

The purpose of this study is to describe HIV-related risk behaviors and prevention needs of 16 to 19 year-old male and female maquiladora workers in the border city of Tijuana, Mexico, as compared to other same-aged youth who are not employed in the maquiladora sector. In order to understand the contribution of maquiladora employment to HIV risk behaviors, data will be collected from 150 maquiladora-employed youth and 300 non-maquiladora employed youth, matched on area of residence, gender and age. The study will examine HIV-related knowledge, attitudes, and beliefs, estimate the prevalence of HIV-related behaviors, and identify social and environmental determinants for HIV-related risk practices. This study will contribute to understanding Mexican youth's sexual risks, particularly for those who live in the Mexican northern border region. It will also help inform HIV prevention efforts and needs for these youth.

The specific aims of this study are: (1) to describe HIV-related knowledge, attitudes and beliefs of maquiladora-employed youth and non-maquiladora employed youth in Tijuana, Mexico, (2) to describe the prevalence of HIV-related risk behaviors of maquiladora-employed youth and non-maquiladora employed youth in Tijuana, Mexico, and (3) to describe determinants for HIV-related practices, including social, cultural, environmental, economic, behavioral and cognitive predictors of maquiladora employed and non-maquiladora employed youth in the border city of Tijuana, Mexico. The impact of transborder interactions will also be examined.

Prevention, Health Services & Contexts of Health

Simplified Syndromic Assessment among Farm-workers and Day Laborers in North San Diego County

Presenter: Angie Valencia, Vista Community Clinic

Collaborators: Angie Valencia, Julio Cesar Quintero, Jose Conde, Carlos Vera, David Hurtado, Fernando Sanudo

UARP Award Number: CM02-VCC-804

The purpose of the proposed study was to identify people with disease symptoms among rural venues where migrant farm workers and day laborers congregate. Clinic outreach workers would regularly approach the target population at different venues using a standardized syndromic assessment questionnaire that includes sections on gastrointestinal disorders, respiratory diseases, nervous system diseases, febrile exanthems, vector diseases, chronic diseases, nutritional diseases, dermatological diseases, sexually transmitted diseases, poisoning, accidents, and poorly defined illnesses. A total of 212 participants volunteered their information at 20 different sites located in North County, in San Diego. The mean age was 44.5 years, ranging from 18 to 71 years; 87.3 % were males (185/212). Sixty-nine percent of participants were healthy (146/212), 31.1 % had "poorly defined diagnosis" (66/212). Training outreach staff at community clinics to conduct syndromic assessments as part of their outings in the community will allow members of the community to access much needy services. Community clinics will be able to use this information to request further funding on health-related areas that are currently affecting the community.

Prevention, Health Services & Contexts of Health

Noteworthy Abstract

Project VIBE: A Dynamic Partnership between Community Agencies and Research Staff

Presenter: Danielle Seiden, UC-Los Angeles

Collaborators: Naihua Duan, Terry Hair, Tiffany Horton, John Kirby

Principal Investigator: Naihua Duan

UARP Award Number: CC02-LA-001

Purpose: With the need for collecting field data, academic research studies are often set in local community-based organizations (CBO). As data collection is indisputably one of the most essential elements of any research study, CBO executives and their staff are a crucial, yet often under-recognized, source of frontline expertise in ensuring sound data collection processes, such as access to clients that represent the study's target population. Similarly, social service agencies can equally benefit from direct interaction with researchers, especially in order to generate and interpret empirical data to justify program design and intervention models, a requirement increasingly called for by funding agencies. While agencies may have access to published research that describes the larger demographic and geographic populations that they serve, their programs and associated funding requests can be substantially strengthened by collaborating with researchers to collect and analyze data specific to their client population. With this perspective in mind, the administration of Project VIBE (Vaccine Interest and Benefit Evaluation), a study evaluating consumer receptivity toward HIV vaccine trials and future vaccines, expanded the traditionally one-dimensional 'data supply and demand relationship' to create an integrative research environment fostering a dynamic partnership between community agencies and research staff. Not only did this approach improve the validity of the collected data but it also encouraged site personnel to consult with research staff for formulating their own research and program ideas. Consequently, this circular exchange of information and ideas led to a productive work environment that has influenced the HIV/AIDS provider and research community well beyond the scope of Project VIBE.

Methods: Before implementation of the field work, the project director met with each site individually to communicate the goals of the data collection process and to discuss any concerns that the sites may have had about the upcoming fieldwork. A common concern that was raised referred to the tendency of research projects to impose on the daily routines of sites leading to the interruption of provided services. Compromises were therefore developed to ensure the smooth continuation of services while enabling a statistically sound data collection strategy. Sites also advised on recruitment hours to provide access to the most representative study populations and offered valuable insights into recruitment strategies. As the study progressed, site representatives were invited to strategic meetings and continued to be important resources informing the project administration of the research population's expressed attitudes toward the study and the changing needs in the field. At the same time, site personnel consulted with the project's research staff to foster their organization's development strategies to serve Los Angeles' communities living with and at risk of HIV.

Conclusion: Both the Project VIBE administration and agency site staff have greatly benefited from this dynamic partnership between community agencies and research staff. For instance, without the continued input and feedback from sites, the collected data's generalizability to a larger population may have been significantly compromised if the project administration had not learned of program changes or other aspects

affecting the demographics of clients present during recruitment hours. Similarly, as site staff interacted with project staff throughout – and beyond – the administration of the study, they gained important insights into issues affecting their clients while establishing a long-lasting relationship with researchers to further improve their agency services.

Next Steps: With Project VIBE's data collection process being completed, the project administration and site staff have developed a long-lasting relationship that is anticipated to foster beyond the scope of this project. Currently, Project VIBE investigators are collaborating with several of the participating research sites to apply for funding and to provide support in other areas of the agencies' realm of activities. Among these consultation activities, VIBE researchers have recently assisted the Long Beach Gay and Lesbian Center with their proposal entitled *Positive Directions,* a program to reduce the likelihood of HIV transmission among HIV infected individuals who receive care at specific sites in Long Beach. The study's project director also continues to act as a liaison between the agencies and the research community by connecting representatives of both arenas to collaborate on future projects.

Prevention, Health Services & Contexts of Health

HIV Testing Sites and On-Premise Signage: Appearance and Context

Presenter: Naihua Duan, UC-Los Angeles

Collaborators: Oscar Grusky, Aimee-Noelle Swanson, Michela Woodbridge, Typhanye Penniman, Jennifer Leich

Principal Investigator: Oscar Grusky

Objectives: HIV testing sites face enormous challenges to reach out to potential consumers. On-premise signage is a potentially cost-effective way for HIV testing sites to conduct outreach, but little is known about the use of on-premise signage as an outreach vehicle for HIV testing sites, and the goals and barriers envisioned by HIV testing sites in making decisions about on-premise signage. We aim to estimate the prevalence of on-premise HIV testing signage, to assess its association with service accessibility, and to explore the HIV testing sites' perspectives.

Methods: We enumerated non-hospital HIV testing sites in Los Angeles County, and conducted a non-intrusive photographic survey of 83 of those sites. The photo survey data are linked to a telephone survey that included measures of service accessibility, including testing frequency and telephone attendant orientation in terms of friendliness, helpfulness, knowledge, proclivity, and focus (factor-analyzed into an attendant orientation measure) when available. We also conducted informant interviews with the staff at several HIV testing sites regarding their experience in decision-making for on-premise signage.

Results: Only 18% of HIV testing sites in Los Angeles County display on-premise signage for HIV testing. Having such signage is associated positively with testing frequency and service attendant orientation. A handful of HIV testing sites use a variety of innovative on-premise signage for outreach. Among the three sites interviewed, no major barriers to on-premise signage were reported. One site reported evidence that on-premise signage was successful at inducing people to get tested. One site currently does not use on-premise signage because it was never considered; the director reported that she might consider adopting on-premise signage for outreach now that she has come across this idea.

Conclusions: The low level of use of on-premise signage to promote HIV testing services may indicate opportunities missed. Despite the small sample size, there is a strong indication that on-premise signage is associated with accessibility to HIV testing sites, although the current study does not allow a strong causal inference to be drawn. Further work is required to gain a better understanding of the causal relationship between signage and site functioning, and factors that determine the distinction between consumer-oriented vs. non-consumer-oriented HIV testing sites. Sites that do not use on-premise signage might have over-looked this vehicle for outreach unintentionally. Further work is required to gain a better understanding of the decision process for or against the use of on-premise signage as an outreach vehicle, with the eventual goal of developing an intervention program to facilitate effective and cost-effective use of on-premise signage.

Prevention, Health Services & Contexts of Health

Men Who Have Sex with Transgenders: An Overlooked HIV Priority Group

Presenter: Don Operario, UC-San Francisco

Principal Investigator: Don Operario

UARP Award Number: ID03-SF-009

Men who have sex with male-to-female transgenders (MSTGs) are an overlooked HIV risk group. Very little is known about MSTGs, and no known HIV interventions have addressed this category as a priority group. There is strong indirect evidence suggesting that MSTGs confront overwhelming risk for HIV and merit increased attention from the public health sector. Findings from our prior research with male-to-female (MTF) transgenders found multiple behavioral and psychosocial risk factors urging the need to understand the dynamics contributing to HIV vulnerability among MSTGs. The goal of the current investigation is to understand the HIV-related attitudes risk behaviors, identities, and sexual mixing patterns of MSTGs.

We know from the perspective of MTF transgenders that MSTGs may not define their sexual orientation according to conventional categories such as heterosexual, bisexual, or homosexual. MSTGs are likely to engage in high-risk behavior, including unprotected sex and sex while under the influence of drugs with MTF transgenders. Furthermore, some MSTGs do not exclusively have sex with MTF transgenders; they may concurrently have sexual relationships with biological females and men, thereby posing a potential bridge for transmission of infectious diseases across groups.

This research will complement prior studies of MTF transgenders by explicitly acknowledging MSTGs as a population that warrants public health research and intervention. We will identify and describe behavioral, psychological, and community factors related to HIV risk among MSTGs, and use these findings to guide the development of HIV prevention approaches for this group.

Prevention, Health Services & Contexts of Health

Understanding the Impact of Spatial Variations in Access to HIV/AIDS Services

Presenter: Paul Robinson, Charles R. Drew University

Principal Investigators: Paul Robinson, Keisha Paxton, Arleen Leibowitz

Introduction: This project explores the relationship between persons living with HIV/AIDS, the geographic distribution of primary and ancillary services in Los Angeles County, California, and post antiretroviral treatment mortality rates (1996-2002). The principal research objectives were 1) to determine how HIV/AIDS service providers are stratified geographically and by type within the study area. 2) How the locations of these services correspond with the residence areas of HIV/AIDS patients. 3) To determine the relationship between distance to HIV/AIDS services and AIDS longevity in Los Angeles County.

Progress and Findings: The AIDS Project Los Angeles comprehensive HIV/AIDS services database was geo-coded. Estimated number of Persons Living with AIDS in each Zip Code was calculated. Service availability by type of service was analyzed by Service Planning Area. Distances between each zip codes weighted population centers and primary and ancillary services were calculated. Estimated annual AIDS mortality rates (1988-2002) were calculated for zip codes.

The location of AIDS service intake points is an important influence upon the longevity and quality of life of PLWA. The Antelope Valley has a shortage of services of all types. South Los Angeles has a shortage of targeted youth services. Geographic distance from a AIDS medical service provider is an important factor in the longevity of PLWA. This relationship is moderated by distance to ancillary service providers.

Next Steps: Currently we are writing the research manuscript for this project. After submitting these initial findings, we plan to obtain better data and refine our statistical methods to try and learn more about the relationships between the distribution of primary & ancillary AIDS services and the health of PLWA in other California counties, as well as nationally.

Prevention, Health Services & Contexts of Health

For Every Outcome There Is a Process!

Presenter: Shanna Starke-Livermore, California Department of Health Services, Office of AIDS

Collaborators: S. Livermore, J. Bernstein, S. Truax, L. Clark

Project Introduction/Objectives: In response to federal program evaluation requirements, the California State Office of AIDS (OA) designed and implemented an innovative web-based process evaluation system for its HIV prevention providers. The goal of the Evaluating Local Interventions (ELI) system is for California's HIV prevention providers to be able to systematically collect and access client-based information critical to tracking program activities and evaluating their programs. The process began by conducting needs assessments across the State in collaboration with the University of California AIDS Research Program (UARP) to define core measures that target program implementation and risk behavior. Data collection forms for various types of encounters were developed in conjunction with the system. Statewide training and technical assistance on the use of ELI and evaluation were co-developed by the OA and the UCSF Center for AIDS Prevention Studies (CAPS) to introduce providers not only to the system, but to the basics of process evaluation and data utilization as well.

Progress/Findings: Throughout 2002, a minimum of two individuals from each of the 61 local health jurisdictions (LHJ) in California successfully completed training on the use of ELI and evaluation basics. On-going training is currently provided every other month around the State. Statewide implementation of ELI began July 1, 2002, and ELI generated reports indicate that as of November 14, 2003, there are 3,275 interventions defined with 915,613 client contacts recorded. The majority of those client contacts come from street outreach interventions. 1,181 users from 205 community-based organizations in 61 LHJs utilize the system. This is the first time basic information regarding HIV prevention services other than HIV counseling and testing has been summarized on a statewide level. The ELI system continues to evolve based on provider feedback. The quality of the data in the system has been improved over the past year by provision of on-site technical assistance to agencies.

Impact/Next Steps: Community and LHJ participation in the development of ELI was crucial to its successful launch in July 2002. Developing a flexible system that could be updated to meet the specific needs of providers was an essential feature of the ELI system. Providers were enthusiastic when forms were made available in Spanish. Training evaluations have been very positive and supportive of the ELI system, although suggestions have been made to create specific trainings for different types of users and levels of data/computer experience, i.e., basic and advanced ELI training. Feedback has also suggested greater emphasis on the reports generated from ELI, combined with specific examples of how the data could be used for evaluating programs. This feedback has provided great insight into both the data needs and data use capacity for agencies throughout the State. Finally, due to frequent communication and in-depth examination of LHJ and their subcontractors' interventions, ELI has provided its funder (Office of AIDS) with valuable information on the state of HIV prevention interventions in the State of California. Next steps include integration of ELI with other process evaluation mechanisms used by the Office of AIDS, advanced system trainings, two-tiered technical assistance, in-depth quality assurance analysis, program enhancement, and ongoing maintenance.

Prevention, Health Services & Contexts of Health

Geographic Disparities in HIV-Testing in LA County: A Multi-Level Analysis

Presenter: Stephanie Taylor, RAND Corporation

Principal Investigator: Stephanie Taylor

UARP Award Number: CR03-LA-512

Three studies have examined variations in HIV-testing across geographic regions and two explored a possible regional characteristic associated with that variance, leaving many compelling regional characteristics unexamined. None of the studies examined areas with concentrations of residents having "higher risk" behaviors. This study examined the variation in HIV-testing across all Los Angeles (L.A.) County ZIP codes and across "higher-risk" regions. L.A. County is a widely diverse area whose metropolitan area had the third largest number of AIDS cases nationally in 2001. We examined eleven ZIP code characteristics as potential correlates of that variation, controlling for eleven individuals' characteristics.

We addressed two questions, "Were residents of some ZIP codes more likely to test for HIV in the previous two years than residents elsewhere?" and "What ZIP code characteristics were associated with the geographic variation in testing, controlling for individuals' characteristics?". We addressed these questions in two samples: 1) respondents in all L.A. County ZIP codes, enabling examination of individuals' testing across the full range of areas and 2) the subset of respondents in regions having larger percentages of respondents reporting higher-risk sex behaviors. We examined the latter sample because, given limited resources, it is important to focus HIV prevention efforts where they could have the greatest impact – where concentrations of residents at higher-risk for HIV live.

This paper is important for understanding HIV-testing decisions because it documents the role of individuals' residential areas and their risk and demographic factors. It does so in both the entire sample of L.A. ZIP codes and higher-risk regions. Identifying ZIP code-level correlates of low testing rates, particularly in higher-risk areas, is potentially important to public health agencies nationally. They can use these insights to increase their outreach efforts in areas where many higher-risk people in need of testing reside.

Methods and Results: We used a 1999 random probability sample of Los Angeles (L.A.) County adults to conduct a multi-level analysis of HIV-testing among respondents. We did so in two samples: 1) all 5,267 persons in 233 ZIP codes and 2) only the 923 persons in the 20 higher-risk regions. The eleven ZIP code characteristics examined were: 1) cumulative number of AIDS cases in 1999, 2) the number of publicly funded HIV test sites, 3) racial/ethnic composition, 4) . Their sources are noted in Table 1. Regarding test sites, we focus on publicly-funded sites, including community, non-profit, and family planning clinics. (The latter account for 17% of L.A. County women's HIV tests in the previous two years.) Although hospitals and private medical offices offer HIV-testing, their geographic location should have little impact on decisions to test due to their relative ubiquity. Seven additional neighborhood-level variables were obtained from the 2000 Census including: higher-risk sex indicators such as 1) percentage of single adults and 2) male same-sex partner households; 3) median household income, 4) education and 5) unemployment rate; 6) residential stability (being in the same household as five years prior) representing social networks; 7) percentage of non-English speakers representing language barriers to care, and 8) the proportion of respondents having higher-risk sex behaviors. The latter was a region-level variable obtained from aggregating individuals' survey responses in each region. Data for eight variables were from the 2000 Census, and AIDS and test site data was from the L.A. County Department of Health Services. The eleven individual-level characteristics controlled for were: unmarried and not living w/someone, unmarried and living w/someone, higher-risk sex (defined as, in the past year, not always using condoms and having multiple partners),

gay/bisexual male, race/ethnicity, age, gender, education, spoke English/not, insurance status, employed/not, annual household income (adjusted for household size), having a regular source of medical care.

We focused on how neighborhood characteristics relate to individuals' HIV-testing because testing is a function both of individuals' behaviors and their residential contexts. There are at least two ways to conceive of neighborhoods' influence on testing. First, neighborhoods may offer residents more opportunities for sex with higher-risk partners if they have more: unmarried residents, persons having higher-risk sex, or persons with HIV/AIDS, (including gay males or Latinos and African Americans because they disproportionately are affected by HIV/AIDS). Individuals acting on those opportunities may perceive themselves at higher-risk for HIV and, subsequently, may be more likely to test. Neighborhoods also could represent structural-level phenomena affecting testing. For example, a neighborhood's supply of testing sites could affect testing because the demand for preventive health care, which is more responsive to price than other types of health care, may depend on travel as well as financial costs. Predominately Latino or African American neighborhoods or areas with higher HIV/AIDS prevalence could be proxies for increased outreach efforts by HIV prevention organizations. They also could represent increased awareness about HIV/AIDS.

The results show that HIV-testing rates varied widely across all ZIP codes and slightly among higher-risk regions. Throughout L.A. and higher-risk regions, residents of predominately African American ZIP codes were more likely to test than residents of predominately White or Latino areas, regardless of their own race/ethnicity or ten other individual characteristics. Residents of predominately Latino ZIP codes were not more likely to test than residents of predominately White areas. Also, Residents of mostly single ZIP codes also were more likely to test than residents of predominately married ZIP codes. All results held while controlling for ZIP codes' number of AIDS cases, testing sites and the seven other ZIP code characteristics.

Possible explanations for the finding regarding African American residential areas stem from the fact that HIV/AIDS disproportionately affects African Americans. First, HIV prevention outreach efforts may be targeting African American neighborhoods more than others. Also, residents of these neighborhoods might be relatively more aware of HIV/AIDS because of increased knowledge of local acquaintances who are infected, and this awareness may lead to testing. Residents of these neighborhoods may perceive themselves to be at increased risk for HIV due to the greater likelihood of encountering HIV-positive sex partners, and subsequently may test.

The relatively low rates of HIV testing among residents of Latino areas is a concern because Latinos accounted for 45% of the county's newly diagnosed AIDS cases in 2002; similar rates are seen in the ten West and Northeast states where Latinos with HIV/AIDS are clustered. The relatively stronger HIV/AIDS stigma among Latinos may partially explain this. Alternatively, a false sense of security regarding HIV may prevail among residents of White and Latino higher-risk neighborhoods, with residents thinking that HIV does not exist in their social group. This finding also could reflect greater difficulty accessing testing in Latino neighborhoods due to language barriers, lack of insurance or greater reliance on non-traditional providers who do not offer testing. Residents of predominately single neighborhoods may perceive themselves at higher risk for HIV due to more opportunities to meet new sex partners (bars and clubs) relative to areas where married residents predominate.

Implications. Public health officials and HIV/AIDS service organizations in L.A. and elsewhere in the nation might want to examine the testing messages and outreach efforts occurring in African American neighborhoods for guidance on possible interventions to increase testing in higher-risk, predominately Latino and White areas. Additional research, perhaps qualitative, also might address this issue. The potential mechanisms leading to increased testing might involve social marketing efforts, social networks, or other factors such as routine HIV-testing practices, as was recently advocated by the CDC. The next step for the paper authors is to obtain a grant to comprehensively examine these and other potential mechanisms in a variety of high- and low-testing African American, Latino, and White higher risk areas. The first step would involve eliciting from individuals the possible reasons they tested for HIV and culling out those higher-level social norm and structural explanations. Once a comprehensive list of these potential mechanisms is compiled, their prevalence will be assessed.

Prevention, Health Services & Contexts of Health

Maximizing the Benefit: A decision-support tool to prioritize HIV prevention interventions using cost-effectiveness

Presenter: Shinyi Wu, RAND Corporation

Collaborators: Deborah A. Cohen, Thomas A. Farley

Principal Investigator: Deborah A. Cohen

Background and Objectives: The goal of HIV prevention is to prevent as many new infections as possible. We developed a decision-support tool to help local communities select the best combination of strategies to address their local epidemics. This presentation demonstrates how the tool may be used to inform the prioritization and resource allocation of HIV prevention.

The tool, which we have named "Maximizing the Benefit," is an Excel spreadsheet that compares the cost-effectiveness of 26 evidence-based HIV prevention strategies, including individual behavior-change, biomedical, and structural interventions. It also allows users to specify their own interventions. Users input local data on the size and HIV prevalence of the target group, intervention effectiveness, and local costs. The tool then uses Bernoulli models and proportionate-change models to estimate the number of HIV infections prevented and the cost per infection prevented. The tool also contains a multi-attribute utility model that allows users to weigh the importance of various factors, such as cost-effectiveness of an intervention, strength of the evidence, feasibility of replication, and acceptability of the intervention by the local community, to help them make decisions about priority-setting and allocation of resources among interventions. We applied the tool to a local epidemiological profile to estimate an optimal HIV prevention strategy and compared it to a typical resource allocation plan for HIV prevention dollars.

Progress and Findings to Date: The tool shows that the most important factors in determining the cost-effectiveness of the interventions are the HIV prevalence of the targeted population and the cost per person reached by the intervention. For low-prevalence populations (e.g. heterosexuals) the only cost-effective interventions were structural interventions (e.g. mass media, condom distribution), whereas for high-prevalence populations such as men who have sex with men (MSM) and injecting drug users (IDUs), individual and small-group interventions were still relatively cost-effective. Among the most cost-effective strategies overall were showing videos in STD clinics and raising alcohol taxes.

We used the tool and the linear programming method to estimate the optimal allocation of a $12 million HIV-prevention budget, based on Southern California community epidemiological profile and the local cost to reach the population by each intervention. Our objective was to maximize the sum of the weighted ratings of various factors to be considered in resource allocation. We assumed three factors to be important in considering an intervention – its cost-effectiveness (0.5 weights in the 0-1 scale of our weighting scheme), the strength of the evidence (0.2 weights), and feasibility and acceptability (0.3 weights) – and rated the 26 interventions in the tool. We also assumed $500,000 would be required to allocate to individual counseling and testing for each of the four risk groups – MSM, IDUs, MSM/IDUs, and women.

The tool selected 14 interventions, which were estimated to reach over 1.8 million people at risk and prevent over 1200 cases of HIV infection. In comparison, following current guidelines for HIV prevention that focus on individual and small-group interventions, a typical plan could reach a fraction of that, about

360,000 people at risk and prevent only 250 new infections. The decision-support tool recommended several structural interventions such as alcohol taxes and mass media campaign, which are often overlooked in local HIV prevention plans.

Next Steps and Study Implications: Comparing estimates of the cost-effectiveness of HIV interventions provides insight that can help local communities optimize their HIV prevention strategies. Other implementation factors should also be considered in the resource allocation decisions. Our decision-support tool can help California communities generate a portfolio of plans to maximize the benefit of their HIV-prevention resources.

Prevention, Health Services & Contexts of Health

Applying Quality Management for Successful HIV Survey Research (Project VIBE)

Presenter: Shinyi Wu, RAND Corporation

Collaborators: Danielle Seiden, Naihua Duan, Peter A. Newman

Principal Investigator: Naihua Duan

UARP Award Number: CC02-LA-001, CC99-LA-002

Background and Objectives: Investigators who conduct surveys or other interventions aimed at people with, or at risk for, HIV/AIDS face many challenges. Because of the persistent stigma of HIV/AIDS and the routes of infection, the population is often difficult to reach. Identifying high-risk individuals usually requires working with understaffed agencies, community groups, or clinics for whom research, understandably, may not be a priority. Additionally, often interviewers and research staff are recruited on a project-by-project basis. Thus, team cohesion and functioning may not be optimal. Moreover, the frequent limitations of research funding and resources may make it difficult to bring together the variety of knowledge and skills needed to ensure successful implementation of the research plan.

Quality Management (QM) is an approach for continuously improving the quality of goods and services delivered, through the participation of the entire organization. Influential in the success of many corporations in the manufacturing sector, QM has been increasingly applied by health care organizations, including Ryan White CARE Act grantees, to ensure the quality of HIV care and services delivery.

The current study tested whether applying principles of quality management (QM) could ease the challenges of conducting research with communities at elevated risk for HIV. This study examined the benefits of QM in a pilot project investigating future adoption of HIV vaccines by at-risk individuals. A tailored QM intervention, guided by the management principles on which the International Standards Organization's 9000-series QM standards are based, was used to improve research performance and meet the goals of the project. The QM intervention includes: 1) leadership commitment to an open, bottom-up, and intellectually stimulating management style; 2) research staff empowerment through extensive training, communication, ownership, teamwork, and feedback; 3) a customer focus to approach and involve survey participants with respect and sensitivity; 4) building participatory and partnering relationships with the study sites; and 5) use of quality improvement tools, such as a flowchart for process planning and a checklist for quality review of the survey instrument.

The pilot project had two goals. One goal was to test the feasibility of a conjoint analysis survey of people at risk for HIV, to assess the acceptability of HIV vaccines and vaccine trials. Conjoint analysis involves the measurement of psychological judgments (such as consumer preferences) or perceived similarities or differences among alternative choices. Such analysis allows for the study of joint effects, such as multiple product attributes or characteristics. Our survey presented a series of complex hypothetical scenarios about HIV vaccines and vaccine trials and asked respondents to describe their reactions to each hypothetical scenario, a substantially more involved and complex task for the respondents than most surveys. The second goal was to complete 200 surveys by a predetermined date with persons at elevated risk for HIV.

Progress and Findings to Date: We were able to meet our two project goals. We found that participants were able to maintain interest in and complete the complex survey; we completed 266 surveys. The mid-term and end-of-project interviews with the two project investigators, the five project staff and interviewers, as well as the staff at each of three study sites showed the team attributed the successful implementation of the project to the QM intervention.

The investigators reported that the QM intervention had resulted in a committed, motivated, and mobilized project team, which was key to their informed decision-making and the success of the pilot project. The staff and interviewers reported that the QM intervention had encouraged the free flow of ideas, knowledge, and creativity as well as their commitment to take initiative for continual quality improvement. In our study, we saw that these changes led, in turn, to an improved relationship with survey participants and study sites. A respectful and sensitive customer relationship with the survey participants encouraged cooperation among a hard-to-reach population. A participatory partnership with the survey sites made even overburdened site staff willing to go the extra mile to contribute to this difficult research project. The staff at the study sites complimented the project team for being the best research team that they had worked with and told the team they would always be welcome to return to conduct further research.

Next Steps and Study Implications: This study demonstrates that QM can be an effective approach to enhance research quality and efficiency. Investigators should apply QM principles to train staff and encourage teamwork, provide a positive environment and incentive for staff to take initiative and ownership, and offer feedback for continual improvement. QM also demonstrated the potential to facilitate a mutually beneficial relationship between health service researchers and the HIV community in California. All investigators who conduct HIV survey research should consider implementing quality management.

Prevention, Health Services & Contexts of Health

Referrals to Outside Services in HIV Prevention Counseling and Testing Sessions: Are Clients Getting What They Need?

Presenter: Loriena Yancura, California Department of Health Services, Office of AIDS

Collaborators: S. Truax, D. S. Webb

Principal Investigator: Loriena Yancura

Background: Referrals to other services are an important component of community-based HIV prevention programs. Clients who visit testing sites to test for HIV would often benefit from other social services, such as prevention support groups, alcohol and drug treatment or needle exchange programs.

Methods: Clients at a cross-section of State-funded testing sites were asked to complete a two-page survey after being counseled and tested for HIV. A total of 1824 surveys were returned for a 48% response rate. Of these, survey responses from 1678 clients were matched to behavioral, demographic and referral data gathered by the counselors during the counseling session. Most of the respondents reported that they were white (58.3%) and African-American (13.3%). Over two-thirds of the sample reported that they self-identified as heterosexual (70.6%), while nearly one-fifth self-identified as gay men (19.9%). The present study examines patterns for client interested in referrals and compares client interest in learning more about available referral services to counselor reports of actually making these referrals to clients.

Results: Factor analyses of referrals that clients were interested in yielded two main factors. The first factor, counseling and general services, included items such as 'more sessions with an HIV counselor' and 'learning how to talk with your partner to reduce your risk'. The second factor, 'outside referrals', included items such as 'needle exchange program', 'social services' and 'domestic violence counseling'. Comparisons of client interest in referral services and counselor referrals revealed that very few (12-34%) of the clients who were interested in specific referrals received those same referrals from counselors.

Implications: These findings suggest that there are two main categories of clients needing referrals: those needing only general services and those needing referrals for more critical issues. These findings also indicate that there is a need for additional counselor training to match client needs and referrals.

Prevention, Health Services & Contexts of Health

"Don't Ask, Don't Tell": Patterns of HIV Disclosure among HIV Positive Men Who Have Sex with Men (MSM) Practicing High Risk Behavior in Los Angeles and Seattle

Noteworthy Abstract

Presenter: Pamina Gorbach, UC-Los Angeles

Collaborators: B. Amani, A. Shin, C. Fernandez-Ortega, C. Celum, H. Hansfield, M. Golden

Principal Investigator: Pamina Gorbach

UARP Award Number: ID02-LA-033

Background: Continuing high incidence of STIs including HIV along the West Coast suggests HIV positive MSM may not disclose their HIV status prior to having unprotected sex with partners of unknown status.

Objective: To identify themes around disclosure among MSM in LA and Seattle.

Methods: 55 MSM HIV positive MSM (24 in Seattle, 31 in LA) reporting recent STI or unprotected anal intercourse with serostatus discordant or unknown partners were recruited from STD clinics in Seattle and LA and underwent indepth interviews that were tape-recorded, transcribed verbatim, coded and content analyzed for themes using Ethnograph.

Results: Ages ranged from 24-52 years (mean 39). Mean years since HIV diagnosis was 9 years and 6 years with one-third and one-half diagnosed in the past 5 years in LA and Seattle respectively. Most interviewed in LA (67%) and some (29%) in Seattle were minority. Themes around disclosure include MSM being more likely to disclose when having sex in a home, context of dating, when feelings for a partner, had a previous positive disclosure experience, or feel responsible for transmission. Nondisclosure themes included not being asked about HIV status, not having insertive anal intercourse, having bathhouse sex, anonymous partners, fearing of rejection, overcome by passion, and using methamphetamines. Many minority MSM in LA reported disclosing because of fear of legal prosecution. MSM reported disclosing indirectly by introducing condoms, asking for low risk sex, showing medications, not listing status online, and displaying HIV materials. Some MSM felt partners should ask for HIV status; many assumed if not asked partner must be positive.

Conclusions: Our findings suggest many HIV positive MSM either do not disclose or disclose HIV status indirectly and engage in high risk sex with partners with unknown serostatus, fueling incidence of STIs/HIV in Seattle and LA. Indirect ways to disclosure may offer promise.

Prevention, Health Services & Contexts of Health

Noteworthy Abstract

Mens' Health Research Project

Presenter: Judith Resell, UC-Los Angeles

Principal Investigator: Ronald Mitsuyasu

UARP Award Number: CC02-LA-001

Objectives: The objectives of the Mens' Health Research Project are to: (1) conduct focus groups and discussions to better understand ethnic minority MSM's self-perceptions and how sexual abuse compounds HIV-related risk-taking; (2) adapt a curriculum developed for use with HIV positive women having histories of child sexual abuse for use with men; and (3) enroll 130 African-American and Latino MSM in a randomized controlled trial to test the intervention.

Summary of progress toward achievement of specific aims and findings to date. Four 60 minute focus groups (2 Latino and 2 African-American) were conducted during May, 2003 with 20 gay men of color. Two groups were gay-identifying and two were non-gay identifying. Key themes from the focus groups included:

Risk reduction:

- Anonymous sex is important in the Latino MSM community and they do not form sexual groups or circles
- Drug use and sex clubs create an "anything goes" environment for sex—unprotected sex, and multiple partners, sex with both men and women
- Drug use is associated with having sex with strangers

Self-acceptance as a gay man of color:

- Being the inserter in anal sex or recipient of oral sex allows a man to not think of himself as gay
- Alcohol is frequently used as an "excuse" for having sex with men, especially by older Latinos
- Many gay men have an image of the "African-American family" taught in home and church and marry women to maintain an image. Sometimes this results in emotional needs being met by a woman and sexual needs by men on the side. Similarly, Latinos are very familistic, and are encouraged to get married and have children; as a result, Latino MSM receive great emotional reward from their wives and children, but are sexually satisfied by men
- Because many Latinos are Roman Catholic, most MSM are extremely secretive and seek out anonymous sex in discreet places like bathhouses and parks
- Sexually conservative Catholic Latinas may not want to engage in oral or anal sex, which may also contribute to sexual satisifaction with male partners and emotional rewards from women and children

Disclosure:

- The community is closed, tightknit, with little relating to white gay men
- African-American men tend to have sex within a small circle of friends and who you have sex with is not discussed; body language is important in sexual communication
- Because of the cultural value of "machismo", the strong male head of the family, disclosing male-male sex behaviors or child sexual abuse is very difficult. These disclosures also violate the strong cultural norm of privacy.
- Latino families will "turn a blind eye" to MSM behavior if the man is discreet

Child sexual abuse:

- The experience of abuse affects sense of self-worth and increases fear of physical harm
- The fact that sex is not discussed places boys at risk of sexual abuse
- Violence and emotional abuse is common in the community

Thus far, an intervention for African-American and Latino men and an attention control group has been developed. The results of the focus groups were used to adapt a risk reduction curriculum addressing sexual abuse for use with MSM of color. Sections were added to the curriculum to deal with self-acceptance as a gay man of color and coping with HIV and sexual abuse. Sections on children and family were shortened and sexual risk reduction and drug use skills were strengthened. The intervention will be piloted on 20 men.

Next steps to be taken on the project and potential impact of the results in California. Protocols for a randomized controlled trial of the curriculum are under review and the trial is scheduled to be completed during 2004. If the trial demonstrates efficacy of the intervention, funds will be sought for translational work to incorporate brief behavioral interventions addressing experiences of sexual abuse into HIV clinical care settings in Southern California.

Prevention, Health Services & Contexts of Health

Noteworthy Abstract

Turning HIV prevention inside out: Youth and community perspectives on interventions targeting YMSM in two unique Southern California communities

Presenter: Erin Wilson, Children's Hospital Los Angeles

Collaborators: Melissa Cribbin, Delia Easton, Ellen Iverson

Principal Investigators: Wes Ford, Ellen Iverson

The proposed presentation will focus on the challenges and solutions to HIV prevention that were uncovered through CITY (Community Intervention Trial for Youth) an HIV prevention intervention research project for young men who have sex with men (YMSM). The project was funded in 1995 by the Centers for Disease Control and Prevention and implemented in six different communities throughout the US. This presentation will focus on two very distinct communities of YMSM in Southern California in which the intervention took place - West Hollywood and Orange County. The West Hollywood intervention team worked with an ethnically mixed group of youth, while the Orange County intervention took place in a conservative and suburban area south of Los Angeles, focusing on young Latino men who were primarily monolingual Spanish-speaking or bilingual and relatively new to the US. The CITY teams created a common intervention framework, and then adapted the design to meet the needs of the local youth and community. The goal of CITY was to affect individual and community-level change among YMSM with a multi-dimensional intervention design that incorporated youth leadership development, peer-to-peer education and safer-sex trainings with social marketing, small group workshops, social events and collaborations with local agencies. The CITY intervention ended in 2002, and the team is currently in the process of analyzing and disseminating findings from the evaluation.

Youth participants and community partners (N=87) discussed challenges to HIV prevention for these communities during a series of qualitative interviews. Both groups were able to identify a wide variety of challenges to effective HIV Prevention for YMSM. Specifically, they discussed challenges in finding appropriate, accessible services for youth, a community to which youth could connect, and an environment where youth felt supported. Youth and partners identified challenges related to intervention strategies and funding structures that did not meet the needs of these two groups of young men. For example, they found that current HIV prevention efforts failed to be age-specific or culturally appropriate for the more "hidden" at-risk youth community. Others discussed more structural challenges such as individual and institutional experiences with poverty, racism and homophobia.

This presentation will provide a thorough discussion of the experiences youth and community partners described during the qualitative interviews, with special attention to their perspectives on the challenges they identified as well as the strategies that were introduced to overcome these challenges. Lastly, we will provide lessons learned from the process of developing and implementing the intervention, which we hope will help guide other researchers and providers looking to find spaces for youth.

Prevention, Health Services & Contexts of Health

Viagra Use and HIV Risk in Older MSM: A Qualitative Study

Presenter: David W. Coon, Institute on Aging, San Francisco

Collaborator: David Latini

Principal Investigator: David W. Coon

UARP Award Number: ID03-IOA-045

Older men who have sex with men (MSM) are at substantial risk for becoming infected with the virus that causes AIDS. However, the research on older MSM remains very limited. Older men, including MSM, are also at greater risk for difficulties in having and maintaining an erection sufficient for sexual activity. For MSM, this difficulty may force them into sexual practices that carry greater risk for becoming infected with the virus that causes AIDS. At the same time, Viagra and other medicines that treat sexual dysfunctions have become very popular among older men, including MSM. Younger (under 50) MSM also have begun using Viagra as a way of enhancing their sexual activity. In studies of younger MSM, those who used Viagra were almost four times as likely to have anal sex without a condom with men who had or might have had HIV. As California's population ages and individuals are living longer with HIV, researchers, practitioners and program planners need information regarding older MSM, their risk behaviors, and Viagra use.

Beginning in January 2004, this recently UARP-funded project will recruit 30 MSM who are 50 years old or older from the practices of physicians that treat male sexual dysfunction, community-based organizations that serve older MSM, the Internet and newspapers. Half of the study participants will have self-identified as HIV positive and 40% as ethnic minorities. The research team will interview the study participants about their sexual behavior and HIV prevention practices, including their use of Viagra or other medications for sexual dysfunction erectile dysfunction, and the interpersonal contexts of how they meet men and negotiate sex. The qualitative data collected will be analyzed using content analyses and grounded theory techniques to understand the range and variation in the sexual experiences of older MSM with erectile dysfunction and the central themes that pervade their sexual experience and HIV prevention practices, including their use of Viagra.

Results from the study will deepen our understanding of an important sub-group within the MSM community that may be at heightened risk for HIV transmission and suggest ways in which existing HIV prevention interventions can be tailored to encourage safer sexual practices in these men. Once the study's themes and patterns have been identified, results will be disseminated at scientific meetings and through the release of a report to key stakeholders and AIDS and Aging services organizations in California. The report will include recommendations that health departments and AIDS prevention organizations can use to create or adapt existing prevention programs for older men who have sex with men, particularly related to the use of Viagra and other medications for sexual dysfunction.

Prevention, Health Services & Contexts of Health

Sexually Transmitted Diseases and Sildenafil Use: Risks for HIV Transmission among MSM

Presenter: Lydia Drumright, UC-San Diego

Collaborators: P. M. Gorbarch, S. J. Little

Prinicipal Investigator: Susan J. Little

UARP Award Number: D03-SD-400

Introduction: The incidence of sexually transmitted diseases (STDs) and human immunodeficiency virus (HIV) among men who have sex with men (MSM) has been increasing in California, however the relationship between the increased incidence in HIV and STD has not been well characterized. Moreover, the use of sildenafil (Viagra) has not been thoroughly examined in terms of HIV transmission and acquisition.

Objectives: To compare MSM recently infected with HIV with HIV negative MSM who were referred for testing to determine the role that the current increases in STDs are playing in HIV transmission, and to examine HIV transmission risks associated with sildenafil use.

Methods: One-hundred MSM recently infected with HIV and 100 HIV-negative MSM recruited from the Antiviral Research Center (AVRC) in San Diego will be screened gonorrhea, Chlamydia, syphilis, herpes simplex virus II (HSV II) and hepatitis B virus and will complete a computer assisted survey instrument (CASI) behavioral questionnaire to assess sildenafil use. Presence of STD and amount sildenafil use will be compared among HIV positive and negative MSM using contingency tables (for analyses such as chi-square), t-tests and multivariate logistic regression to determine if those with HIV have more STD and use sildenafils more than those without HIV.

Progress: 69 individuals with primary HIV infection and 9 individuals who are HIV negative have been interviewed and tested for STDs. Currently there is too little data to examine statistical associations, however prevalence of Viagra use and STD are available. 19% of primary HIV cases and none of the HIV negative controls reported Viagra use with the last 3 partners. Bacterial STD (Chlamydia, gonorrhea and syphilis) and HSV II antibody test results were available for 78% (54) and 48% (33) of the primary HIV patients respectively and 100% (9) and 89% (8) of the HIV negative patients respectively. There was no difference in STD between HIV positive and negative MSM, 8% of positives and 11% of negatives had a bacterial STD and 21% of positives and 38% of negatives had antibody for HSV II ($p>0.05$).

Projected Implications: Data from this study may provide insight to the current relationship between HIV and STD among MSM in California and could determine potential risk of Viagra use in HIV transmission.

Prevention, Health Services & Contexts of Health

Beyond Focus Groups: A New Method to Text HIV Prevention Ads

Presenter: Maria L. Ekstrand, UC-San Francisco

Principal Investigator: Maria L. Ekstrand

UARP Award Number: ID03-SF-015

Twenty years into the HIV epidemic among gay and bisexual men, many community-based groups consider it a challenge to develop advertising materials that continue to grab the attention of their target groups. It is also becoming increasingly difficult for AIDS prevention ads to stand out from the general background of all the other ads to which the gay community is exposed on a daily basis. Yet, with increasing rates of sexual risk taking and rising STI and HIV incidence among urban gay men, it is as important as ever for AIDS Service Organizations (ASOs) to get their messages out. Recent attempts to develop more provocative, sexually explicit ads to attract increased attention were met with disapproval by the federal government, which disputed the notion that such ads are necessary and asserted that federal money can not be used to fund "obscene" materials. As a consequence, the San Francisco based STOP AIDS Project had to undergo two separate audits before being cleared of these charges. Given this tension, it is crucial that we develop objective, feasible and low cost methods of assessing the effectiveness of HIV prevention ads for this population. To date, most agencies that use advertising research have relied primarily upon focus groups to help them develop targeted campaigns. Commercial advertising research agencies, on the other hand, have a long history of using different qualitative and quantitative methods to conduct more comprehensive assessments of advertising in both formative and evaluative phases of their campaigns. The overall goal of this pilot project is thus to attempt to adapt state-of-the-art advertising research approaches so that ASOs and public health researchers can use more rigorous methods of advertising testing to evaluate HIV prevention ads.

Prevention, Health Services & Contexts of Health

Executive functioning and condom use: A pilot study with young MSM

Presenter: David M. Latini, UC-San Francisco

Collaborators: David W. Coon

Principal Investigator: David M. Latini

Grant Number: NIMH, NIH R03-MH56567-01

Introduction and Objectives: Rates of both HIV risk behaviors and new sexually transmitted infections are increasing in young men who have sex with men (MSM) in spite of extensive research on predictors of risk and ongoing prevention programs. Among the various psychosocial characteristics studied by HIV prevention researchers, a number of studies have focused on general qualities of impulsiveness or sensation-seeking as measured by pencil-and-paper tests. These studies hypothesize that the degree to which a person can self-regulate their behavior in sexual situations is governed by a general quality of impulsiveness or sensation-seeking that is not specific to sexual situations. We suggest that work examining the general quality of impulsiveness measured by paper-and-pencil scales in other studies would be included in executive functions located in the brain's frontal lobe and can be detected using standardized tests of executive functioning. This paper reports results of a pilot project that used a performance-based standard neuropsychological measure to examine the relationship between executive functioning and condom use in young MSM.

Progress and significant findings: Twenty-eight self-identified young gay men, age 18-25 completed a computerized version of the Wisconsin Card Sorting Test, a standardized measure of executive functioning that focuses on cognitive flexibility and perseveration, and a questionnaire about key psychosocial characteristics. The questionnaire included validated scales of constructs from Social Cognitive Theory previously identified as important predictors of HIV/STD risk. Based on responses about their sexual behavior in the three months before study enrollment, respondents were characterized as either higher risk (inconsistent or no condom use for anal intercourse) or lower risk (consistent condom use for anal intercourse or sexually inactive). Nonparametric methods were used to characterize the sample and test the study's hypotheses. We hypothesized that higher in comparison to lower risk young men would show significantly higher scores on 1) number of perseverative errors and 2) perseverative errors as a percent of total errors. Although no significant differences were found on the psychosocial characteristics of HIV-related self-efficacy, partner expectations, or peer norms, there was a significant difference between the two groups on the adoption of HIV prevention as a goal measure ($p < .03$), with higher risk participants scoring higher than those at lower risk. In terms of executive functioning, higher risk young men committed significantly more perseverative errors ($p < .05$) and obtained significantly fewer categories than lower risk young men ($p < .01$), indicating they may be lacking in cognitive flexibility often useful in adapting to novel situations. However, no differences were found between the two groups on perseverative errors as a percent of total errors or on the cognitive index variable.

Implications for HIV/STD prevention in California: The goal of this pilot study was to test the relationship between executive functioning and HIV/STD sexual risk using a novel assessment approach. Unlike previous studies of this relationship, the current study assessed executive functioning using the Wisconsin Card Sorting Test, a widely studied measure of frontal lobe functioning shown to differentiate between

children with impulse control problems and control children. As hypothesized, young men who reported higher risk of HIV/STD transmission in the months before the study had significantly more perseverative errors on the WCST. The lack of cognitive flexibility may affect their ability to adapt to changing conditions in their sexual encounters and put them at greater risk of HIV transmission, and suggests that these young men need simple and concrete skill-building intervention approaches to help them with effective decision making and communication with partners in order to negotiate safer sex encounters or remove themselves from unsafe situations. These higher risk young men reported significantly higher scores on the HIV prevention as a goal measure, suggesting that they may be aware of their need for additional development of these skills. However, their lack of cognitive flexibility indicates that they may require different intervention approaches than other MSM.

Prevention, Health Services & Contexts of Health

Late Night Buffet: Methods and Approach for a Novel HIV/STD Outreach Program

Presenter: Valerie Rose, San Francisco Department of Public Health

Collaborators: Willi McFarland, Charles Klein, Michael Pendo

Principal Investigator: Valerie Rose

UARP Award Number: ID-03-SFDPH-013

Introduction. Previous research has demonstrated the need for HIV/STD prevention interventions targeting late night populations of men who have sex with men (MSM) in San Francisco. This pilot study will evaluate the feasibility of providing an HIV/STD prevention intervention to late night populations of MSM. The intervention will consist of needle exchange, harm reduction information on specific drugs commonly used by late night populations, brief counseling, referrals to health and substance use agencies, HIV testing, and STD testing delivered via a mobile van. The mobile van will be stationed 3-4 nights per week from 1:00 a.m. to 6:00 a.m. in 3 or more neighborhoods where late night populations of MSM are known to congregate or hang out. The van will rove between sites to extend service exposure and reach. The number of people accessing services, the types of services used by location and date of delivery will be documented. Individuals who select harm reduction counseling, testing or needle exchange will be asked to complete a brief survey on site in the van and asked if they would be willing to be contacted three months later for a follow-up interview. The surveys will ask about HIV risk behaviors, drug use, and linkages to HIV and other social services. Locating information will be collected for all individuals who agree to participate. Primary outcome measures will include service use, acceptability, preferences and satisfaction; client risk profile, referral follow through and prevention impact.

Specific Aims and Progress to Date: The specific aims of the study are to 1) assess the feasibility of conducting late night HIV prevention activities and other brief harm reduction interventions and 2) to assess whether MSM reached during late night hours with brief interventions can be linked to more intensive interventions. The project was designed in 5 distinct phases and is projected to run for 18 months. Initial meetings with substance use and HIV prevention providers were held to inform implementation strategies, identify key locations and venues, and to define survey areas of inquiry.

Next Steps: Three focus groups with a late night population of MSM will be conducted to gain input into overall study design. To ensure participants' safety and protection, discussions with law enforcement will be arranged to elicit support for these late night activities. Subsequent to analysis of focus group data, venues will be selected and local businesses will be alerted to our presence. Research staff will be hired and trained in outreach techniques, harm reduction theory and counseling approaches, and HIV/STD testing procedures. Field implementation is projected to begin in April, 2004 and end in September 2004.

Prevention, Health Services & Contexts of Health

Racial and Ethnic Disparities in Access to Physicians with HIV-Related Expertise: Findings from a Nationally Representative Study

Noteworthy Abstract

Presenter: Kevin C. Heslin, Charles R. Drew University

Collaborators: Susan L. Ettner, William E. Cunningham

Principal Investigator: Ronald M. Andersen

UARP Award Number: D01-LA-080

Professional medical associations recommend that physicians who treat patients with human immunodeficiency virus (HIV) have some form of disease-specific expertise, based on evidence from the United States that certain types of board certification and high HIV patient volume (or "experience") are associated with lower patient mortality, increased use of appropriate medications, and fewer hospitalizations. It is known that racial/ethnic minorities with HIV generally have worse access to health services than do whites; however, previous work has not examined disparities in access to HIV-expert physicians. African Americans and Latinos have fared poorly on each of the outcomes that evidence suggests are improved by the care of physicians whose training or clinical experience would make them eligible for certification as "HIV specialists." Compared with whites, members of these minority groups have greater odds of dying, lower odds of receiving antiretroviral therapy, and more frequent hospital admissions. The objective of this study was to examine racial/ethnic disparities in access to physicians with HIV-related expertise, because the lack of work on this subject represents a considerable gap in the health disparities literature.

Using data from the nationally representative HIV Cost and Services Utilization Study (HCSUS), we estimated the association of the race/ethnicity of patients with the board certification and HIV patient volume (or "experience") of their physicians, while also accounting for the potential effects that health status, socioeconomic status, other demographic characteristics, and geographic variation in specialist supply might have on this measure of access. The HCSUS is a prospective cohort study of a representative sample of 2,864 persons in care for HIV infection in the U.S. Investigators also conducted a cross-sectional survey of physicians identified by these patients as their regular source of care. In multivariate analyses, African Americans had two-thirds the probability of seeing an infectious diseases specialist (risk ratio = 0.66; 95% CI = 0.56, 0.81) and half the probability of seeing a high-volume physician (risk ratio = 0.47; 95% CI = 0.37, 0.68) as a regular source of care, compared with whites. Analyzing the HIV volume variable in continuous form showed that the physicians seen by African Americans had, on average, 55 fewer HIV patients than did the physicians seen by whites (predictive margin = -55; 95% CI = -92, -6). We found no differences in physician use between Latinos and whites or between persons of "other" racial/ethnic backgrounds and whites.

These findings have potentially important implications for the provision of HIV health services in California. Recognition of the value of physician expertise in HIV care is evidenced by the passage of the "Standing Referral Law" in 1999, which requires that managed care plans allow their HIV-positive enrollees to self-refer to specialists. However, relatively generous insurance provisions do not guarantee that HIV patients will see physicians who are best suited for treating their health problems. In this study, we found that African Americans were less likely to have physicians with HIV expertise, even after controlling for

insurance coverage characteristics and other important determinants of access to care. This suggests that policymakers should employ a variety of strategies to reduce disparities in access to physicians with HIV expertise. In addition to legislation, support for cultural competence training and educational loan forgiveness for service in minority communities should also be considered. The availability of effective HIV treatments makes coordinated efforts to reduce racial/ethnic disparities in access to care more important than ever. An article that describes and discusses these findings is currently being reviewed for publication by a peer-reviewed journal.

Prevention, Health Services & Contexts of Health

The Intersection of Stigma and HIV in Young African American MSMs' Lives

Noteworthy Abstract

Presenter: Susan Kegeles, UC-San Francisco

Principal Investigator: Susan Kegeles

Collaborators: Gregory Rebchook, Brady Ralston

Young African American MSM (YAAMSM) in California and the U.S. are contracting HIV at alarmingly high rates, and there are no scientifically developed and empirically tested HIV prevention interventions for them. Very little research about YAAMSM has been conducted even though this group is at highest risk for HIV infection in the U.S. in general, and in California in particular. In this pilot study our goal was to conduct formative research that would inform us about how to tailor an HIV prevention intervention we have developed previously for "mainstream" (gay-identified, middle class, and largely white and Latino) young gay men appropriately for young AAMSM. Through the use of semi-structured qualitative interviews with professionals who provide YAAMSM with HIV prevention services ("providers") and sexually active HIV-positive and HIV-negative YAAMSM we proposed to:

- Gain an understanding of different segments of the YAAMSM community and how members of these groups relate to each other. Within the major segments, we will seek to determine levels of sexual risk behavior, size of the segment, where they congregate, their age range, sexual identity, and other related topics.
- Gain an understanding of the impact of various psychosocial variables on YAAMSM's sexual risk-taking behaviors. The variables of interest include religiosity, bisexuality, the influence of the family and community, sexual identity, homophobia and economic issues.
- Gain an understanding of the contextual issues surrounding YAAMSM's high and low risk sexual encounters by eliciting information about when and where the sexual encounters took place, knowledge about partner's serostatus and how this was determined, substance use, feelings and thoughts prior to and during the sexual encounters, attitudes towards condoms, sexual communication and negotiation strategies, feelings about and attraction to the partner and partner characteristics.

Three groups of individuals were interviewed using semi-structured qualitative interview methods: sexually active HIV-positive YAAMSM (N = 17); sexually active HIV-negative YAAMSM (N = 14); and professionals who provide YAAMSM with HIV prevention services ("providers"; N = 10). Interviews lasted 1 – 2 hours. The men were recruited from diverse agencies in Oakland/San Francisco and from other community venues. The young men ranged in age from 19-30 years, with a mean of 26 years. While all reported sex with men in recent past, they had diverse identities: 74% identified as gay, 16% as bisexual; 6% as same gender loving;; and 3% as "straight and loves men." 58% were unemployed. The men had lived in the Oakland/San Francisco area for an average of 10 years. The interviews were tape-recorded and transcribed and entered into the software program Atlas TI. A codebook was developed through iterative readings of the interviews, by the first and second authors. Thematic analysis of the interview data is being conducted currently.

Many different subgroups were mentioned by providers, including: young homeless men, sex workers, transgenders, young professionals, men into the arts (including visual arts as well as hip-hop/spoken word artists), men who have sex on the "DL" ("down low", indicating that they do not identify as being gay or same gender loving, and are very closeted about their same sex sexual interactions); incarcerated men; young

men who live with gay "families" or "houses" (groups of MSM who form their own family units); college students; club kids; "pre-club" kids (those who socialize around clubs but are too young to get in); bisexual men; church-involved men. Providers felt that there are few boundaries between the groups because men can easily belong to more than one group simultaneously, have friends/acquaintances with men from the various groups, and have sex with men from other groups. There was consensus that all of the groups of men were at significant risk for HIV infection and that with the possible exception of transgenders, all of the groups were equally vulnerable to contracting HIV (transgenders were perceived as being at highest risk).

Stigma about attraction to and having sex with men is a dominant theme that arises in the interviews, both in the past and in the present. Multiple sources of significant stigma were identified, including: family of origin; churches; community; and school. HIV-positive men also perceive significant stigma from other YAAMSM. While all of the men reported having to cope with stigma, preliminary analyses indicate that HIV-positive men experienced significantly greater stigma prior to seroconversion than did HIV-negative men from these various sources. In contrast to the HIV-positive men, HIV-negative men had more positive experiences of support and acceptance that seemed to help them be more resilient to stigma. For example, most men reported that their families were initially upset at learning that their sons had same sex desire, but the men who remained HIV-negative reported experiencing subsequent support and acceptance from their families. The HIV-positive men more often reported enduring rejection from families; in addition, several had no family due to the death of family members. Nearly all of the men reported having been very involved with the church as they were growing up, and most remained spiritual in adulthood. However, while many men had found supportive and accepting churches in which they were currently involved, others felt very alienated and were not currently connected to a church. Many men reported never having heard anything about HIV/AIDS in their childhood or early adolescence and if they had heard of HIV/AIDS, it was discussed as a "white gay man's disease" and therefore was not personally relevant. Many men talked about growing up hearing many negative comments about men who were effeminate and/or homosexual, at a time that many of the respondents said that they had been realizing that they were "different," i.e., not heterosexual, and not very masculine. Most men, regardless of their serostatus, had friends, other young Black men, who had died of AIDS. Many men avoided initial or repeat HIV-antibody testing because they feared the stigma associated with a positive result. Yet there were also many stories of resiliency, and many reported support from families, friends and churches in the face of stigma they had endured. In contrast to abundant reports about mainstream gay men's increasing rates of unsafe sex, most providers felt that there had been no change over time in YAAMSM's sexual risk behavior in response to treatments for HIV. Their perceptions were that YAAMSM's risk behavior never declined earlier in the epidemic, and had not increased in response to the newer antiviral treatments.

These preliminary findings have many implications for interventions. They clearly suggest a need for an HIV prevention program that reaches both HIV-positive and HIV-negative men, and one that discusses issues beyond HIV/AIDS. Such a program must involve the creation of a supportive community of young Black men, which does not require any particular sexual identity to be involved. It must reach men who only have sex with men as well as those who have sex with men and women. Poverty, Christianity/spirituality, stigma and testing must be addressed in a program. These findings are currently being used in a separately funded, collaborative project by the UARP and the California State Office of AIDS in translating the Mpowerment Project, an HIV prevention intervention for young gay/bisexual men, so that it is culturally appropriate for YAAMSM. Three Black community-based organizations will then implement the tailored intervention.

Prevention, Health Services & Contexts of Health

Finding Prevention Strategies that Work: Meeting the Needs of California's Growing Asian Pacific Islander College Population

Noteworthy Abstract

Presenter: Amy G. Lam, Health Psychology Program, UC-San Francisco

Principal Investigators: Nolan W. S. Zane, UC-Davis, and Amy G. Lam

UARP Award Number: D02-D-403

Asian Pacific Islander Americans (APIAs) comprise the largest ethnic minority group across California colleges and universities, accounting for over 40% of the undergraduate populations in some schools (University of California Office of the President Information Digest, 2002; Wong & Mock, 1997). Because of the large number of API students in the California university systems, HIV prevention interventions in these institutions must provide health education programs that are consistent with the cultural frameworks of their diverse students (Michal-Johnson & Bowen, 1992). Unfortunately, current approaches for interventions, including assertive and direct safer sex negotiations, may be in stark contrast to cultural norms and practices of APIAs (Yep, 1997).

To address this concern, the present study evaluated the importance of condom negotiations among 447 Asian (Chinese and Filipinos) and White American college women. Given that the ability to persuade one's partner about condom use has been empirically demonstrated to be one of the most important correlates to condom use behavior (Sheeran, Abraham, & Orbell, 1999), the study investigated *how* individuals persuaded their sexual partners to use condoms. More importantly, the study examined what negotiation strategies were effective in producing condom use. In particular, more commonly studied strategies (verbal and direct), were contrasted to strategies that may be more culturally appropriate to the communication styles of Asian Americans (nonverbal and indirect).

Findings indicated that ethnic culture played a significant role in the types of condom negotiation strategies that women used and found to be effective. In fact, while both verbal-direct strategies (e.g., directly telling partner) and nonverbal-direct (e.g., placing condom on bed) were important for White Americans, only nonverbal-direct strategies were important for Asian Americans.

The study's findings have important implications for HIV interventions in university settings, especially for Asian Americans. Current HIV interventions in the California university system should incorporate condom negotiation skills that are more congruent with the behaviors of their Asian American students. While verbal-direct strategies are important in negotiating condom use, they are not the only method. By normalizing other forms of safer sex communication strategies, including nonverbal-direct techniques, sexual health educators can help women to broaden their repertoire of effective negotiation skills.

Prevention, Health Services & Contexts of Health

Noteworthy Abstract

A Comparison of High-Risk Behavior among Urban and Rural Latino Adolescents

Presenter: Audrey Shillington, San Diego State University

Collaborators: K. Mueller, A. Shillington, N. Roy, J. Clapp, S. Lehman, E. Blumberg, M. Hovell, C. Sipan

Principal Investigator: Audrey Shillington

UARP Award Number: PE00-SDSU-153

Latinos are the fastest growing and youngest ethnic group in the U.S. Adolescent pregnancy and sexually transmitted disease rates are substantially higher among minority youth than among white adolescents. To better understand the risk behaviors of these youth, the Centers for Adolescent Risk Reduction Evaluation Project (CARRE Project) was designed to evaluate youth drop-in centers in southern California. These drop-in centers offer youth a place to voluntarily spend time and provide HIV-related information including contraception use, sexually transmitted diseases, HIV testing, and substance use. This study is part of this larger evaluation project and compares high-risk behaviors among Latino youth who attended an urban drop-in center with those youth who attended a rural drop-in center. An audio-computer assisted survey instrument (A-CASI) was used to assess self-reported HIV-related risk behaviors in Latino youth (between the ages of 14-24 years old) who agreed to participate. Those behaviors include sexual activity, condom use, and substance use.

One-hundred sixty-four Latino youth completed an interview. Of those youth, 57.3% were male and the mean age was 15.9 years old. With respect to sexual orientation, a majority of the youth self-identified as heterosexual (76.3%). Analysis of sexual behavior showed that youth attending the urban center were more likely to have ever had vaginal sex (OR=2.46, $p<.05$) and to have used condoms during vaginal sex in the past 3-months (OR=3.17, $p<.05$) in comparison with the youth attending the rural center. Regarding substance use, Latino adolescents attending the urban center were more likely to have ever used cigarettes (OR=2.55, $p<.05$), alcohol (OR=4.34, $p<.001$), and marijuana (OR=3.29, $p<.001$) compared to the rural adolescents. These findings suggest that Latino adolescents living in an urban environment may be at greater risk for sexual activity and substance use than their counterparts in a rural environment. Although the urban youth had greater lifetime vaginal sex (54.3% vs. 32.5%), they also practiced greater condom use during vaginal sex in the last 3-months (54.3% vs. 27.3%). This evidence suggests that the urban youth demonstrate a protective behavior, which appears to be lacking in the rural youth.

This study provides information to aid in the design of programs to reduce high-risk behavior among Latino youth, while taking into consideration the influence of urban and rural environments. Further analysis will examine psychosocial and environmental factors related to risky behaviors such as family closeness, parental monitoring, depression, religiosity, peer influence, and neighborhood perception as predictors of high-risk behavior among these Latino adolescents. Additionally, analysis will examine any gender differences in high-risk behaviors after controlling for drop-in center location.

Prevention, Health Services & Contexts of Health

Role of Religion and Spirituality in Reducing Risky Behaviors

Presenter: Shahrzad Bazargan-Hejazi, Charles R. Drew University

Principal Investigators: Eduardo D. Lam, Jonathan Dyreyes, Mohsen Bazargan, Eugene Hardin, Shahrzad Bazargan-Hejazi

Background: Studies indicate that spirituality and religiosity may influence risky behaviors differently.

Specific aim: To assess how individual's perception of his/her own religiosity and spirituality may relate to reporting risky behaviors especially risky sexual behaviors.

Method: This was a cross-sectional study that surveyed consecutive patients presenting to an inner-city Emergency Department in Los Angeles, California. Four hundred and twelve (412) structured interviews were completed during the months of March and April of 2001 on a 24-hour basis. The outcome variable (number of risky behaviors in the last 12 months) was constructed by adding participants' responses to questions regarding (1) having more than one sexual partners; (2) reporting alcohol use within two hours of having sex, (3) reporting drug use within two hours of having sex, (4) reporting "very likely", "likely" to have sex with someone just met; (5) scoring positive on Rapid Alcohol Problems Screen (RAPS-4); and (6) scoring positive on illicit drug use.

Results: Only 3.6% of the sample reported no risky behaviors, whereas slightly over 80% and 16% reported between 1-3 and 4-6 risky behaviors, respectively. Multivariate analysis showed that among demographic variables, gender, age, and ethnicity were significantly associated with risky behaviors. Male (t= 7.096), younger age (t= -5.3), and African American (t= 3.8) were more likely to report a higher number of risky behaviors. In addition, controlling for demographic variables, those who reported suffering from depression symptoms (t= 2.4), and reported lower level of risk perception (t= 5.2) were also more likely to report a higher number of risky behaviors. Yet, controlling for all other variables, those who reported a lower level of religiosity (t= 2.2) were more likely to report a higher number of risky behaviors. Interestingly, the multivariate analysis revealed that the degree of spirituality was not associated with taking risky behaviors (t= 1.7).

Conclusion and Discussion: We find that personal religiosity rather than personal spirituality, plays a significant role in reducing the likelihood of participating in risky behaviors. Traditionally, spirituality has been defined as one's beliefs in existence of a Supreme power a faith that positively affirms life. Religion, on the other hand is an institution, a social phenomenon with defined beliefs, rituals, and governance, and many functions one of which is to develop spiritual individuals. However, spiritual individuals do not necessarily belong to a religious affiliation. Interventions are needed to mobilize religious organization in reducing of risky behaviors.

This study was supported by Center for Minority Health and Health Disparities through the National Institute on Alcohol Abuse and Alcoholism (U24AA11899-05).

Prevention, Health Services & Contexts of Health

Clique Influences on Adolescent Sexual Roles and HIV Risk

Presenter: Margaret Dolcini, UC-San Francisco

Principal Investigator: Margaret Dolcini

UARP Award Number: ID02-SF-079

Introduction: African American adolescents who are sexually active are at disproportionately high risk for HIV and other sexually transmitted infections (STIs). Sexual roles (i.e., perceived or proscribed roles specific to sexual behavior) impact sexual behavior, but little is known about the cultural and social factors that influence the development and maintenance of sexual roles during adolescence. Scientific advancement in this area is dependent on developing culturally relevant research and theory on sexual roles and sexual behavior. This pilot project represents a first step toward that goal. The objectives of this study are to use qualitative methods to 1) examine how previously identified sexual role related themes are related to risk behavior of African American adolescents living in an urban low-income community; 2) examine how adolescents' close friendship networks shape and reinforce beliefs and expectations about sexual roles that promote safe and unsafe sexual behavior; and 3) begin the development of a culturally relevant model of peer social influences on sexual roles and sexual behavior among low-income African American youth.

Progress toward specific aims: To date, we have hired and trained project staff and have made contact with community gatekeepers who work with youth, met with such individuals, and established procedures for recruiting youth from community centers. We have developed, pilot tested, and revised our interview protocol. The interview was pilot tested with youth that are similar in characteristics to the youth being targeted in the study. These initial interviews provided important feedback on areas of strength and areas for improvement in the interview. We have revised the protocol and begun interviews at two sites in the study community. To date we have conducted 10 interviews and this work is continuing. Transcription of interviews has begun.

Future direction and impact: Over the next year we will complete the interviews for this pilot study, transcribe the tapes, analyze the data and develop a culturally appropriate model of sexual roles and their impact on safe and unsafe sexual behavior in an urban African American community. The results from this project will influence future theoretical and applied work in the area of adolescent sexual roles and HIV related behavior.

Prevention, Health Services & Contexts of Health

Formative Work on Clique-based HIV Interventions for Youth

Presenter: Margaret Dolcini, UC-San Francisco

Prinicipal Investigator: Margaret Dolcini

UARP Award Number: R00-SF-050

Introduction: Sexually active African American youth are disproportionately at risk for HIV/STIs and innovative programs are needed to address this population. One promising intervention approach involves the incorporation of social networks in the construction of intervention groups and in program content. Prior community based research indicates that African American youth have longstanding intimate friendships which provide avenues for information exchange and norm development. Thus, social network interventions may be particularly effective with this high-risk population.

Topic Addressed: The present study examined the feasibility and acceptability of an innovative friendship based HIV/STI half-day intervention with inner city African American youth. The primary goals of this study were to: 1) modify an existing intervention to increase cultural relevance and to incorporate friendships into the program: 2) determine the feasibility of recruiting friendship groups for the program, and 3) to evaluate youths' response to the program immediately following the intervention and three months later.

Progress toward Specific Aims: Our findings demonstrate acceptability, feasibility, and preliminary efficacy of the friendship based HIV/STI program. A total of 20 friendship groups (10 Male, 10 female, N=78) completed the program. Youth responded positively to the program, noting that attending with close friends had a number of benefits including, greater comfort at the workshop, greater disclosure of sensitive information and increased confidentiality of the group discussion. We found significant increases in HIV/STI knowledge, perceived risk, safer sex norms, and intentions to use condoms. At three-month follow-up we found decreases in risky sexual practices and increases in seeking HIV/STI testing.

Future Directions: Based on our positive findings we have received federal funding to conduct a controlled test of the friendship-based intervention.

Impact: Preliminary evidence provides strong support for the value of this friendship based HIV/STI intervention. These findings provide new evidence for adolescent network based interventions that can be delivered in a community setting. This program has the potential to provide a new avenue for HIV/STI prevention with inner city adolescents.

Prevention, Health Services & Contexts of Health

Noteworthy Abstract

Evaluating an HIV Prevention Program for IDU Women: Looking at Early Change in Condom and Needle Exchange Use Behaviors

Presenter: Nancy Brown, Palo Alto Medical Foundation Research Institute

Collaborator: Veronica Luna

Principal Investigator: Nancy Brown

UARP Award Number: PE00-PAM-147

The CA High Risk Initiative funded Santa Clara County, in collaboration between the County and three community-based organizations, to offer a harm reduction program to female injection drug users (IDUs) or the sexual partners of IDUs. The goals of the intervention — a series of four HIV prevention workshops, in conjunction with STI and HIV testing — were to teach women to recognize their HIV risk, access available health services, and initiate and sustain drug-related and sexual practices that prevent HIV. The Palo Alto Medical Foundation Research Institute (PAMFRI) is evaluating the process and outcome of that collaboration using a prospective cohort design.

This presentation summarizes early results from the outcome evaluation (N=200) involving up to three interviews completed between three months and one year after participating in the intervention. The evaluation participants in this multi-ethnic sample were typically over the age of 36 (66%), not married (84%), had at least a high school education (59%), and had at least one previous STI (62%). In addition, 50% of this sample lived in temporary housing, 33% defined themselves as Bisexual or Lesbian, 83% had been incarcerated, 21% reported testing positive for Hepatitis B, 61% reported being positive for Hepatitis C, and three participants knew they were HIV positive. Most participants reported a history of physical (69%), emotional (93%), and/or sexual abuse (76%).

Stage of Change (SOC) was assessed at baseline and each follow-up interview using conventional algorithms for application of the SOC model. Early results suggest that there were significant changes between baseline and each follow-up with regard to SOC for condom use for vaginal sex ($p= 0.0359$) and the number of women who carried condoms ($p= 0.0075$), felt confident they could put a condom on a male partner properly ($p= 0.0011$), and used needle exchange services ($p= 0.0094$; all p-values refer to the last follow-up).

Prevention, Health Services & Contexts of Health

Feasibility and acceptability of voluntary rapid HIV testing strategies on pregnant women

Noteworthy Abstract

Presenter: Rolando Viani, UC-San Diego

Prinicipal Investigator: Rolando Viani

UARP Award Number: ID03-SD-029

This pilot study will seek to evaluate the feasibility and acceptance of voluntary rapid HIV testing strategies on pregnant women with unknown HIV status, who present to Tijuana General Hospital for prenatal care, or in active labor. In addition by means of a questionnaire we will evaluate the knowledge and attitudes regarding HIV risks on pregnant women.

Pediatric HIV infection is an important public health problem in both the industrialized and developing world. The great majority of HIV infection in children around the world results from mother-to-child transmission. Over the past several years, the University of California San Diego (UCSD) Pediatric AIDS research group has developed a collaboration with pediatricians and obstetricians delivering HIV care in Baja California. The goal of these activities is to expand opportunities for research, provide education and clinical efforts along the bi-national border. AIDS is a major health crisis along the US-Mexico border. Mexico ranks third in the Americas for AIDS cases with 29.9 cases per 100,000 residents. According to CONASIDA, Baja California including Tijuana, has the highest rates of AIDS in Mexico with 62 AIDS cases per 100,000 residents. The obstetric department at the Hospital General of Tijuana has an average of 426 deliveries per month of whom only 60% have some degree of prenatal care. In addition prenatal HIV testing and treatment to prevent maternal-fetal transmission is not fully implemented.

Eligible women will be offered counseling and rapid HIV testing. Women found to be HIV infected will be offered antiretroviral therapy and follow-up care. Their exposed infants will receive preventive antiretroviral therapy and follow-up care. The estimated sample size will be 3,600 pregnant women over a period of 12 months. Written informed consent will be obtained from all women before any study-related procedures are performed. After consent for the study has been obtained, a questionnaire regarding the knowledge and attitudes on HIV risks will be filled by every pregnant women, blood will be drawn for rapid HIV testing (Determine“ HIV-1). Determine HIV-1, is an in vitro immunochromatographic rapid test, is based on a sandwich immunoassay technique. Pregnant women with positive rapid test will have a confirmatory HIV EIA and Western blot and will receive post-test counseling.

This pilot study will allow us to determine the HIV prevalence in pregnant women who seek care at Tijuana General Hospital. In addition it will allow us to intervene with antiretrovirals in a timely fashion to prevent mother-to-child HIV transmission. The information collected from the questionnaires will provide insights into the attitudes and knowledge among pregnant women in Tijuana regarding HIV testing during pregnancy, and will provide an opportunity to design intervention and educational strategies to be implemented in the near future at Tijuana General Hospital.

Prevention, Health Services & Contexts of Health

HIV Testing Patterns and Sexual Behaviors of Latina Migrant and Seasonal Farm Workers in Three California Counties

Presenter: Arsen Aslanyan, UC-Berkeley

Collaborators: Community Medical Centers, Inc., and Centers for Diseases Control and Prevention

Principal Investigators: Renato A. Littaua, Vanessa Miguelino

Background: The number of migrant and seasonal farm workers in California is estimated to be around 1 million, 28% of which are women. Little is known about California's female migrant and seasonal farm workers and this is the first comprehensive study to identify their HIV testing patterns, risk factors, knowledge, beliefs and sexual behaviors. The goal of the survey was to assess HIV testing patterns and the prevalence of risk factors for getting HIV in this population.

Methods: Anonymous face-to-face interviews were conducted among 400 migrant and seasonal farm workers in Fall 2002 in the counties of San Joaquin, Solano and Yolo. The structured survey instrument included questions on demographics, sexual behavior, HIV perceptions, alcohol/drug use, pregnancy and HIV testing patterns. All interviews were conducted in Spanish.

Results: There were 139 females participating in the survey. Eighty-nine percent were born in Mexico, 60% were between 18 and 35 years of age, 50% had no education or had primary schooling, 73% were married, 53% had a monthly income between $500 and $1,000; and 36% had Medi-Cal insurance.

Forty-five percent (63/139) of females reported ever having an HIV test. Fifty nine percent (37/63) had tested only once and 15% (21/139) reported testing for HIV regularly. Eighty seven percent (55/63) always got their test results back. The most frequent motives for females to get an HIV test was their desire to learn their serostatus (55%), being pregnant or having desire to have a child (48%) and following their doctor's recommendation to get tested for HIV (47%). Some women delayed testing for HIV because they believed they were HIV negative (58%) or they thought that it was unlikely for them to get HIV (48%).

Among women who were pregnant in the last five years, only 50% (29/58) had an HIV test during their pregnancy. Women who did not get an HIV test during the last pregnancy either perceived themselves as not being at risk for HIV or they thought they did not need it because they had been tested before. Twenty-two percent (13/58) of pregnant women reported they were not offered an HIV test at a clinic/hospital.

Eighty five percent of females (118/139) reported being sexually active during the past 12 months and all of those women reported having only one male partner. Sixty four percent of them (76/118) never used a condom during vaginal sex. Fifteen percent (18/118) reported having anal sex with their male primary partners and in 83% of the cases (15/18) they never used a condom.

Conclusion: There is need for increased HIV/AIDS education and prevention as well as HIV testing programs directed at migrant and seasonal farm worker women in California. While we find that women in this survey were not engaging in high risk behaviors supporting their self-perception that they are not at risk for HIV, 17% (28/165) of males who had primary partners reported having casual sex partners in the past year and engaging in high risk sex behaviors which may put their female partners at risk. Migrant and seasonal

farm working women, particularly those, who are pregnant, should be encouraged to test for HIV regardless if they have tested negative in the past. Getting medical providers attending to migrant and seasonal farmworker women to encourage their patients to take the HIV test may increase testing rates. Providing linguistically and culturally appropriate information and anonymous HIV testing are equally essential for preventing the HIV/AIDS epidemic in this population.

Prevention, Health Services & Contexts of Health

Demographics and HIV Behavioral Risk Characteristics among Women Served by Publicly Funded HIV Counseling and Testing Services 1990-2002, California

Presenter: Hong Chen, California Department of Health Services, Office of AIDS

Collaborators: David Webb, Steve Truax

Introduction/Objectives: Women are one of the fastest growing populations being infected with HIV. Through the end of 2001, more than 49,226 women have been infected with HIV and the percentage of AIDS cases more than tripled from 7% in 1985 to 25% in 2001 among adolescent and adult women (CDC, 2002). A similar trend is seen in California, where the proportion of new AIDS cases among women especially African American and Latino women are increasing (Office of AIDS, 2003). This research investigates trends in HIV testing, and exams client demographics and HIV behavioral risk among California women served by publicly funded HIV counseling and testing (C&T) services in order to guide the development of HIV prevention programs. We collected the information through the California HIV Counseling Information System that records HIV test results, risk behavior, and demographic data for clients who tested at publicly funded HIV counseling and testing sites. Analyses are based on female client visits within three different time frames, 1990 to 2002 (N= 1,324,621), 1995 to 2002 (N=709,595) and 1998 to 2002 (N=381,592). Study sample includes those women aged 12 years and older tested for HIV with valid HIV test results excluding those who reported a previous HIV positive result.

Findings: The proportion of HIV testing among White women decreased 20% from 61.4% in 1990 to 40.1% in 2002 while it increased gradually among all other women. The percent of overall HIV positive test results was the highest at 0.68% in 1990, declined sharply to 0.46% in 19991, and has remained relatively stable at around 0.40%. African American women have the highest percent of overall HIV positive test results (1.25%), followed by Native American (0.53%), Other race (0.39%), Latina (0.34%), White (0.25%) and Asian American/Pacific Islander (0.22%). The percent of HIV positive tests among African American women gradually decreased from 2% in 1990 to 0.9% in 2002 and remains the highest among all women from 1990 to 2002. The percent of overall HIV positive test results was the highest among women aged 30 to 49 years old (0.61%). The percent of reported injection drug use (IDU) (13%), sex for money (8.5%) or drugs (7%), sex with an HIV infected sex partner (3.5%) or IDU partner (18%) were most reported among women 30 to 49 years old. However the percent of reported STDs decreased as age increased. The percent of overall HIV positive test results was the highest among women who reported having had an HIV infected sex partner (2.7%), followed by sex for money or drug (1.1%), injection drug use (IDU) (0.9%), sex worker partner (0.8%) and IDU partner (0.6%). The percent of reported IDU increased annually from 5.3% in 1995 to 9.8% in 2002; sex for money or goods and sex for drugs also increased annually from 2.7% in 1995 to 7.3% in 2002 and from 2.1% in 1995 to 5.4% in 2002 respectively. The percent of reported STDs was 13.8% in 1995 but increased to more than 18% in 2002.

Implications/Next Steps: African American women have the highest percentage of HIV positive tests from 1990 to 2002. The high percentage of HIV positive tests among African American women and among women age 30 to 49 years represents a population that is important to target for HIV interventions. The high percentage of HIV risk behaviors such as having an infected sex partner, injection drug use, sex for money or drugs among women age 30 to 49 years and the increased percentage of STDs suggest that the prevention services need to be targeted towards these women. An increased focus on providing C&T services in outreach interventions targeting woman with these risk behaviors should be an important component of HIV prevention programs.

Prevention, Health Services & Contexts of Health

Does Victimization Predict Changes in HIV Risk Behavior?: A Prospective Study of Impoverished Women in Los Angeles County

Presenter: Joan S. Tucker, RAND Corporation

Collaborators: Suzanne L. Wenzel, Grant N. Marshall, Marc N. Elliott, Stephanie Williamson, Daniela Golinelli

Principal Investigators: Joan S. Tucker, Suzanne L. Wenzel

Victimization and domestic violence have been identified as important HIV risk factors for women, particularly poor women of color. Women in abusive relationships report greater fear that their partner will respond violently if asked to use a condom and are less likely to practice safe sex than other women. Other factors that likely contribute to abused women's greater susceptibility to HIV include having high-risk sexual partners, perceiving that they have little control over safe sex, and being subjected to coerced sex. In general, relationship violence can erode women's sense of coherence and personal control, which may in turn adversely affect their inclination and ability to engage in HIV self-protective behavior. The goal of this study, which is part of a larger National Institutes of Health-sponsored project, was to investigate whether recent experiences of violence were prospectively associated with increases in sexual risk behavior over a 6-month period.

Structured interviews were conducted at baseline and six months later with a probability sample of 810 women living in temporary shelters and low-income housing in Los Angeles County. Baseline victimization was conceptualized as any sexual or physical violence during the past 6 months. Outcome variables were frequency of sex, frequency of unprotected sex, having multiple partners, and having high-risk partners. Control variables included baseline sexual behavior, demographic characteristics, and substance use. Victimization at baseline was significantly associated with decreased frequency of sex in a typical month and engagement in unprotected sex, but increased tendency to have multiple partners and high-risk partners at follow-up. These associations may be partially due to the fact that victimized women were more likely than non-victimized women to lose primary partners and gain casual partners during the follow-up period. Further, baseline housing status and substance use accounted for some of the association of victimization with increases in multiple and high-risk partners over time.

These findings and others from our project have several implications for HIV prevention services. For sheltered women, there is an obvious need for stable housing and income that may, among other benefits, result in less vulnerability to victimization and engagement in high-risk survival-based activities. In the case of housed women, our findings indicate that most victimization comes from a primary partner, suggesting a need for more services that focus on safety and on supporting and promoting financial independence from abusive partners. Better access to substance abuse treatment services is also warranted given the strong links of substance abuse with victimization and sexual risk behavior in this population.

Prevention, Health Services & Contexts of Health

Does Residential Instability Contribute to HIV Risk Behavior Among Impoverished Women?

Presenter: Suzanne L. Wenzel, RAND Corporation

Collaborators: Joan S. Tucker, Grant Marshall, Marc Elliott, Stephanie Williamson, Daniela Golinelli

Principal Investigators: Joan S. Tucker, Suzanne L. Wenzel

Homeless persons, including shelter users, are at especially high risk for HIV/AIDS. It has been suggested that housing instability may contribute to high-risk behaviors, but this possibility has not been investigated to our knowledge. HIV/AIDS is furthermore a critical public health problem in the lives of impoverished and homeless women. The incidence of HIV/AIDS among women has grown over the past decade and much of this is attributable to heterosexual contact with men. Understanding the relationship between residential instability and HIV risk among impoverished women is therefore a public health concern of very high priority. This study, which is part of a larger National Institutes of Health (NIH)-sponsored grant, has its goal to understand the extent to which residential instability and experiences of homelessness are uniquely related to HIV risk among impoverished women in Los Angeles County.

We conducted structured interviews at two time points (baseline and 6-month follow-up) with a representative probability sample of 460 impoverished women in Los Angeles County. Women were sampled from a variety of temporary settings in the County including homeless and transitional shelters. We examined the contribution of residential instability and homelessness to HIV risk relative to other potential contributors to risk including substance use, trauma, and mental health. Risk was defined as frequency of sex with primary, casual and need-based partners; having sex with high-risk partners (intravenous drug users, non-monogamous); and having unprotected sex. Women who reported a greater number of homeless episodes in their lifetime also reported greater sexual activity at follow-up. Women who described themselves as homeless were more likely to have sex with a high-risk partner at follow-up, although substance use was a stronger predictor of sex with a high-risk partner. Residential instability and homelessness did not contribute to having unprotected sex at follow-up, although having poor mental health did.

These longitudinal analyses provide some evidence for a unique impact of residential instability and homelessness on HIV risk, particularly frequency of sexual activity and having sex with a high-risk partner. Women with more severe cases of housing deprivation and histories of homelessness may need special services—namely, stable housing may be important to reducing risk among impoverished women. The results also indicate that substance use and mental health must continue to receive attention in HIV prevention efforts for women; however, these must be offered in a context that recognizes women's need for a stable and safe environment.

The findings from this study are being considered along with those emerging from our other work to better understand key public health epidemics among impoverished women in Los Angeles County. The next steps are to use the collection of results from this and other studies to inform prevention and intervention efforts for women in Los Angeles County and other regions of California. Because these studies have randomly sampled women from diverse settings throughout the County, they provide policy makers and providers with a comprehensive and generalizable picture of need among impoverished women in the County. The findings of the present study suggest another of many humanitarian reasons to provide affordable housing in our communities: prevention of HIV/AIDS.

Prevention, Health Services & Contexts of Health

Secondary Analysis of HIV Intervention Studies

Noteworthy Abstract

Presenter: Martha Lee, UC-Los Angeles

Principal Investigator: Martha Lee

UARP Award Number: ID01-LA-038

Objectives: This project is a secondary analysis study of four existing data sets. These data sets are from four randomized controlled prevention trials on youth at high risk of transmitting HIV: runaway youth (n=312), gay youth (n=154), Youth Living with HIV (n=351), and Youth with Parents with AIDS (n=423). In collaboration with a Community Advisory Group, the consistency of the findings across four longitudinal data sets were examined in order to:

1. Estimate the size of the relationships among sexual behavior, substance use, mental health problems, delinquency, school problems, and employment over time within and across data sets.

2. Examine the evidence for the generalization of positive intervention effects from sexual risk acts to substance-use, problems at school, delinquency, pregnancy, and emotional distress and the consistency of these effects across samples.

Progress and Significant Findings: As a result of the meetings between the PI, Dr. Martha Lee and the Community Advisory Board of the Center for HIV Identification, Prevention, and Treatment Services (CHIPTS), the research directions of this project have been identified to focus on: 1) HIV status disclosure to partners and related factors, 2) ethnicity is considered in the analyses, 3) attendance of interventions, 4) social support data are integrated into the analyses.

We examined 243 Youth Living with HIV (YLH) aged of 13 to 23 years. YLH had disclosed their positive serostatus to about half (48%) of their 547 sexual partners in the 3 months period prior to the recruitment. YLH who had longer time since the HIV diagnosis or had fewer sexual partners were more likely to disclose. Moreover, YLH were more likely to disclose their HIV status to their sero-positive or regular partners.

The profile of YLH's attendance at intervention sessions was studied. About one-fourth of YLH (26%) had missed all module 1 or 2 intervention sessions. YLH had attended an average of 15 sessions (out of a total of 23 sessions). Factors related to attendance include not having a full-time job, more likely using social support or spiritual hope, or less likely to use self-destructive as coping strategies and having fewer sexual partners.

The bivariate relationship between sexual behavior and substance use among runaway gay adolescents over time was examined. Log transformation was used on the percent condom use of anal sex acts and the number of drugs used. Based on a mixed model for multivariate repeated measures, a negative correlation between the percent of condom use and the number of drugs used was obtained.

Future Steps and Potential Impact of the Results in California: The results will be presented in a series of forums in conjunction with the Community Advisory Board. In addition, CHIPTS has ongoing community collaborations with about 18 CBO in Los Angeles. Therefore, the results will have implications for mounting adolescent preventive interventions in community settings. CBO will gain important information on whether to narrowly target sexual risk or to offer more generalized skills training programs in their agencies. Economists will also gain information on whether HIV prevention programs may be beneficial in reducing a broad range of adolescent's problem behaviors.

Prevention, Health Services & Contexts of Health

Noteworthy Abstract

A Comparison of Youth Reporting Risky Sex While under the Influence and Youth Reporting to Have Sex Sober

Presenter: Audrey Shillington, San Diego State University

Collaborators: J. D. Clapp, S. J. Lehman, E. J. Blumberg, C. L. Sipan, M. F. Hovell, K. Mueller

Principal Investigator: Audrey Shillington

UARP Award Number: PE00-SDSU-153

Background/Objectives: In the U.S., data indicate that youth and minorities account for a growing proportion of new AIDS cases. Given the extended latency period for demonstrable infection, it is likely that most young adults diagnosed with HIV contracted the infection during adolescent years. AIDS is now the 9th leading cause of death for youth ages 15-24. Adolescence is a developmental stage known to be when people experiment with drug use and risky sexual behaviors. Although it is known that youth who use alcohol or other drugs (AOD) are also more likely to be involved in other risk taking behaviors, little is known about the co-occurrence of both AOD use and sexual risk taking.

Methods: Youth were recruited into the CARRE Project at one of three urban drop-in centers. An audio-computer assisted survey instrument was used to measure HIV-related risk and AOD use behaviors. For each sexual behavior queried, the youth was asked if they did such behavior first under the influence of alcohol and second, if they did the behavior under the influence of other drugs.

Results: A total of 270 youth were recruited with a mean age of 17.1 and a mean education of 10 years with 58% male and 72% ethnic minority with largest group being Hispanic which accounted for 43% of the sample. 70% of the youth reported past sexual behavior with a mean age at onset for vaginal or anal sex of 14.6 years, a mean number of partners of 8.7 for lifetime. For AOD use, 88% reported lifetime use of at least one substance, and 75% during the past 3 months.

It was found that 25% of youth reported being sexually active while under the influence of AOD. Results indicate that for the youth who combined both behaviors concurrently were at significantly higher risk for HIV and other public health problems compared to youth who did not combine the two behaviors.

Those who reported both behaviors concurrently were significantly more likely to report past 3 month vaginal sex (90%. v 47%), past 3 month anal receptive sex (76% v 32%) and insertive sex (69% v 40%), sex with injection drug users (33% v 11%), group sex (36% v 13%), report more school problems, less religiosity, and less parental monitoring. The youth who combined both risky sex and AOD use were significantly more likely to report lifetime and current cigarette, marijuana, alcohol use, binge drinking, methamphetamine use, ecstasy use and needle sharing behaviors. Analyses will be conducted to understand the unique risk and protective behaviors for these two groups.

Conclusions: Implications of this study are important for prevention interventions with youth. Although HIV prevention information is important for youth because of their developmental stage and experimentation, it is clear that the prevention efforts need to also include strong alcohol and drug use treatments as well. Youth who are involved in both concurrently are much more likely to put themselves and their partners at risk for HIV than youth who are multiple risk takers but not concurrent.

Prevention, Health Services & Contexts of Health

Differentiated Video-Enabled Early Abstinence Promotion

Presenter: Stephen L. Eyre, UC-San Francisco

Principal Investigator: Stephen L. Eyre

UARP Award Number: ID02-SF-026

Purpose: This goal of this research is to learn how early adolescents conceptualize and seek to influence social problems related to their age group. The long-term goal is to develop effective peer-authored messages about sexual risk taking for this age group.

Methods: Thirteen male and 15 female adolescents, ages 13 to 14 years, formed teams in an 8th grade middle school class to script and produce videos portraying, "a problem people your age have involving people your age." Teams were asked to write scripts that told a story and were trained to direct, film, and edit videos based on these scripts. The process of video production as well as the content of the resulting videos were analyzed using narrative analysis and grounded theory.

Results: Students formed 3 predominantly female and 3 predominantly male teams to make videos. The social problem addressed and the style of argument appeared to be tied both to the gender composition and the developmental level of the videographer teams. The female teams chose to focus on popularity, gossiping, and teen pregnancy. The male teams focused on bullying, marijuana use, and suicide. All of the female videos depicted complex social interactions with substantial verbal exchange among characters, whereas none of the male videos had this characteristic. For example, the female video on gossiping featured a large number of cast members in complex web of friendship loyalties and jealousies. In contrast, the most sophisticated of the male videos, that on suicide, featured only 4 characters in straightforward relationships to each other (friend, sibling), and minimal dialogue. Differences in developmental level among both female and male teams were striking. Among female teams, the least sophisticated group made a video in which the main character was an extremely negative caricature of a popular student who was ultimately defeated. The most developmentally sophisticated female group made a video about teen pregnancy in which characters had both positive and negative traits, without a happy or romanticized ending. A similar progression was seen in the male videos.

Conclusions: When given free choice to divide into teams, the class divided into teams representing distinctly different gender and developmental interests and made videos, which advocated these interests. This reflects the strong gender and developmental diversity of this age group, which leads to the greatest crowd differentiation of adolescence upon entry to high school the following year (Brown, et. al., 1986; Brown, 1990; Maccoby, 1990; Youniss, McLellan & Strouse, 1994). We conclude that a problem with educational messages directed at this age group is that one message can never effectively reach the entire group. In the next stage of this research, we will be assisting 8th graders to produce differentiated peer-authored abstinence-promoting video messages that will then be shown to self-selected subgroups of 8th graders.

Prevention, Health Services & Contexts of Health

Using Multiple Imputation in a Couple-Focused HIV Prevention for Adolescent Parents

Presenter: Tanya A. Henneman, UC-Los Angeles School of Public Health

Collaborators: Tom Belin, William Cumberland, Evelyn Gonzalez-Figueroa, Deborah Koniak-Griffin

Principal Investigators: William Cumberland, Deborah Koniak-Griffin

UARP Award Number: PC99-LA-2011

In health studies with incomplete data an available-case analysis can result in biased parameter estimates, the reduction of information or the elimination of potentially relevant variables from the analysis. Various imputation techniques have been developed in order to impute missing observations and allow the researcher to perform statistical analyses appropriate for complete-data. With data collected in a couple-focused HIV/AIDS prevention for adolescent parents, we explore the use of a multiple imputation technique (Little and Rubin, 1987) to assess the effect of an experimental intervention with outcome measurements missing for some individuals. In a joint effort between the UCLA School of Nursing, Bienvenidos Family Services and the National Latino Fatherhood and Family Institute, forty-nine couples were recruited and randomized into a control or experimental group. Data were collected from a baseline questionnaire and from questionnaires administered at three different post-intervention time points. Outcome measures of interest include AIDS knowledge, behavioral intention to use condoms, and the number of unprotected vaginal sex episodes in the past three months. The goal of this project is to develop a framework for analyzing longitudinal data with couple clusters where subjects have differential attrition rates.

To determine if any significant differences in outcomes exist between the two treatment groups, we apply a multiple imputation inference technique to combine parameter and standard error estimates from analyses made on imputed complete data sets, specifically, we compare results from two imputation strategies. The first strategy uses a crude approximation using a multivariate normal model. An alternate multiple imputation strategy uses a model specifically for clustered data, which we believe fits the structure of the data better. From the complete-data analyses, no remarkable differences were found between the two imputation strategies.

Future work will explore dimension reduction strategies for multivariate outcomes using multivariate factor analysis. The development and examination of statistical strategies for analyzing incomplete data will be of great importance to researchers and policy makers seeking to appropriately interpret study results on complex data structures with missing observations.

Prevention, Health Services & Contexts of Health

Where Are the High-Risk Teenage Guys? An Analysis of Their Sexual Practices and Perceived Barriers to HIV Testing

Presenter: Branko Matich, Teen Access-Linda Vista Health Care Center

Principal Investigator: Branko Matich

Male adolescent youth from alternative schools lack adequate access to reproductive and sexual healthcare services. Very few studies have focused on the needs of this special population. The objective of this study was to explore the behavioral characteristics of these high-risk male youth.

The participants in this study were students from three court-mandated schools and four other alternative schools in San Diego. An anonymous 26-item survey was administered to assess the relationship between HIV/STD knowledge, reproductive health care access, communication skills, anxieties and utilization. Before health education classes or one-on-one counseling sessions, 103 surveys were collected from the male participants. The surveys for this study were collected beginning November 1, 2001 and ending January 31, 2002.

More than half of the male youth reported having sexual intercourse at 13 years of age or younger and 35% reported having 6 or more sexual partners during their life. Approximately 85% of the students in this study reported having sex at some point during their life. Even though the oldest participants in this study were 18, 60.0% of all Hispanics, 20.0% of blacks, and 5.7% whites reported having 6 or more partners during their lives.

Hispanic youth reported significantly higher anxiety levels about getting tested for HIV/STDs and lower health care utilization rates. Approximately 51% of Hispanic youth, 34.8% of blacks and only 25% of whites reported "very much" worry about getting tested for HIV and other STDs (p=.043). Only 48.8% of Hispanic males and as much as 78.8% of African Americans and 81.3% of whites reported being a patient in a clinic or doctors office in the past year (p=.038).

The data also indicate a significant negative relationship between the communication and anxiety measures. Males who expressed more trouble asking a medical provider a question or understanding the explanation of the provider were also more likely to report more anxiety regarding various sexual health issues.

The results from this study indicate that male adolescents, particularly Hispanic males, are likely to report fear about getting tested for HIV/STDs and unlikely to access reproductive health care services. High-risk male youth health disparities continue to be an issue in California. Future recommendations include: 1) Address assertive communication skills via one-on-one or group counseling sessions, 2) Involve females in their male partners health, 3) Involve and engage minority male youth as peer role models, 4) Have minority male youth work as health educators in a clinical and outreach setting, and 5) Use social marketing techniques to reach minority male youth.

Prevention, Health Services & Contexts of Health

Improving Measurement of HIV Risk among Adolescents in San Francisco

Presenter: Alexandra Minnis, UC-San Francisco

Authors: Alexandra Minnis, Mi-Suk Kang, Carla Rodas, Regina Otero-Sabogal, Nancy Padian

Principal Investigators: Regina Otero-Sabogal, Nancy Padian

UARP Award Number: M00-SF-056 & M00-SF-057A

Introduction: HIV behavioral epidemiological research relies on self-reports of risk behaviors. Methodological challenges emerge due to the lack of gold standard measures of risk and the existence of few and imperfect ways to assess reporting accuracy. Our aim is to identify accurate and acceptable ways to measure high-risk sexual and drug use behaviors that increase risk for STIs, including HIV, among adolescents. In particular, this study examines how the willingness to report sensitive information may vary between audio computer-assisted self-interviewing (ACASI) and interviewer-administered questionnaires.

Methods: We conducted a randomized, cross-over, longitudinal study to compare the prevalence of HIV risk behaviors reported through two survey administration modes. Between October 2001 and October 2002, we used a venue-based recruitment approach to enroll 556 adolescents aged 14-19 years from locations throughout San Francisco's Mission District. Participants were randomized to complete their baseline risk assessment interview using either ACASI or through interviewer-administered questionnaire. At two follow-up visits, six and twelve months after study enrollment, participants completed their interviews with the opposite mode from that used at the previous study visit. At the six-month follow-up visit, participants completed an anonymous evaluation questionnaire that assessed mode preference, comfort, and honesty in responding to sensitive questions. Analyses to date include comparisons of the proportions of reported behaviors at the baseline and first follow-up visits, including stratification by hypothesized effect modifiers. To assess the effects of interview mode on the prevalence of risk behaviors reported over time, we used a marginal models approach with GEE. Eighty-eight percent of participants completed the first follow-up visit; the final follow-up visits will be completed in December 2003.

Results: The majority of participants (76%) identified as Latino and the mean age was 16.4 years (SD=1.6). At baseline, 64% were sexually active and the median lifetime number of sexual partners was three (interquartile range: 1-6). Ninety percent of participants had used a computer prior to their interview. Reports of sexual activity and condom use did not vary by interview mode; however, in ACASI, participants were more likely to report having been treated for a sexually transmitted infection (OR=4.8; 95% CI=2.5, 9.1) and to have arranged for someone to have sex for money or drugs (OR=2.4; 95% CI=1.2, 4.8). At the first follow-up visit, ACASI respondents were more likely to report having had anal sex in the previous six months (OR=2.6; 95% CI=1.2, 5.6). Frequent alcohol and marijuana use over the previous six months (use at least weekly) were reported more often in ACASI compared to interviewer-administered questionnaire (from GEE: OR(alcohol)=1.8, 95% CI=1.4, 2.3; OR(marijuana)=2.6, 95% CI=1.2, 5.6). The evaluation questionnaire data suggest that more adolescents preferred ACASI to in-person interviews; though, many expressed no preference, and others highlighted the importance of developing rapport with an interviewer.

Conclusions: Preliminary analyses of the effects of interview mode on reports of sexual and drug use behaviors suggest that ACASI is associated with an increase in reports of high-risk behaviors. In addition, ACASI has been perceived as quite acceptable by adolescents participating in a longitudinal study sexual networks and STI/HIV and unintended pregnancy risk.

Prevention, Health Services & Contexts of Health

Build a Future Without AIDS

Presenter: James Mitchell, CSU-Hayward

California State University, Hayward was fortunate to receive a grant to implement AIDS Education within its Teacher Education program for academic year 2002-03 as part of the American Association of Colleges of Teacher Education's "Build a Future Without AIDS" initiative.

Students from two separate Teacher Education Department classes at CSUH, TED 5351 Psychological Foundations of Education, and TED 6901 Graduate Synthesis, were taught a conflict resolution and AIDS education curriculum. In Winter 2003, TED 5351 students participated by traveling in pairs to the two respective high school sites and teaching the AIDS Education curriculum in the Academic Controversy conflict resolution framework (www.co-operation.org). Spring semester Ted 6901 students traveled in three and four member-groups to visit the two separate sites with the Alameda County Office of Education (ACOE). In Winter Quarter, the CSU students were part of a fifth-year post baccalaureate teacher credential program and were predominantly Latino (47 %) and Asian (20%), with 17 % of the students being African American and 16% Caucasian. The Spring Quarter students from CSUH were pursuing a Master of Science in Education degree and were 67 % Caucasian, 20 % Latino, 10 % Asian and 3 % African American.

The high school students who received the curriculum were members of two schools and were part of the continuation day school population for the Alameda County Office of Education. Cultural demographics of this population were as follows: 77% African American, 15% Latino and 8 % Asian. The ACOE Community Day Center/School is a unique program that provides educational services for students ages 12 to 17 who are "at risk" of dropping out of school. The program is an alternative "regular" education program designed primarily to serve youth who are wards or dependents of the court or status offenders (incorrigible) and who are under the supervision of the Juvenile Court, Probation Department, or Social Services Agency. This program is a joint venture/partnership between ACOE and the School Districts. Courses offered include English, Math, Social Science, Science, and Health. Program provides group and individual counseling and mental health services. The program provides small classrooms staffed with credentialed teachers and instructional aides. Each student's academic educational needs are assessed and addressed through a self-paced, highly structured, individualized instructional program.

The students in the program receive supervision and counseling services from probation, social services, or community-based organizations. Referral to the program is through the Hayward (CA) District interagency discipline hearing committee that is chaired by the school district of residence. These ACOE students had been expelled from previous traditional assignments and many had served time in juvenile hall. TED 5351 students worked at site in Winter 2003 quarter, while TED 6901 students worked at site during Spring 2003 quarter.

The members of the ACOE classrooms demonstrated positive results related to achievement. Accordingly, members of the CSUH community participants demonstrated a gain in knowledge of the subject matter, a stronger liking for teaching and gratitude for having been requested to undertake this initiative.

Prevention, Health Services & Contexts of Health

Intervention for Children Aware of Mother's HIV+ Serostatus

Presenter: Debra A. Murphy, UC-Los Angeles

Principal Investigator: Debra A. Murphy

UARP Award Number: ID01-LA-019

Objectives: A randomized, controlled, small pilot trial of a support group intervention is being conducted with children age 7 – 14 (N = 50) whose mothers have disclosed their HIV status to the children. The three-session intervention, "Children United with Buddies," (CUB) is intended to: (1) foster peer interaction to promote normalization and validation of fears and concerns; (2) provide appropriate information regarding HIV transmission and treatment; and (3) teach concrete coping strategies. The aims of the study are to: (1) determine whether the CUB intervention improves children's knowledge about HIV; (2) determine if the CUB intervention reduces children's fears regarding stigma and the number of medications she takes; (3) determine if the intervention improves child/mother communication; and (4) investigate concerns and fears of the children through transcription of the audio-taped intervention sessions and thematic analysis of these tapes; and (5) investigate the concerns and fears of mothers with HIV/AIDS through transcription and analysis of audio-taped discussion sessions. The CUB intervention topics for the three sessions are: (1) communication between mother and child, particularly of feelings/concerns about her HIV, including guidance and practice to improve communication; (2) information about HIV, with an emphasis on ways that it cannot be transmitted; and (3) exploration of the impact of HIV/AIDS stigma on a family, including discussion of the degrees of secrecy practiced by participating families and the availability of "safe" people with whom children can share questions and feelings about their situation. The mothers' discussion groups are designed to parallel the CUB intervention. For example, mothers will be informed in the first session that their children are being taught to use communication as a coping skill, and that they will need the mothers' support and participation to be successful.

Progress to date: We enrolled 45 families in CUB; 30 have completed waves 1-3 of the intervention, and provided complete assessment data. In this group the mean age of the mothers is 37.6 (SD = 6.34, range 26 - 52); racial composition is 50% African-American, 23.5% Latina, 20.6 % white, 2.9% Asian American, and 2.9% are Native American/Alaskan native. Mean age of children is 10.6 (SD = 2.19, range 7 - 15); 47.1 % are male. The mean educational level of children is 4.85 (range K – 9th).

Future Plans: Complete implementation of intervention, and provide the intervention to the waiting list control group by end December 31, 2003. Transcribe/analyze audiotapes of children's and MWAs' groups, conduct quantitative analysis, and prepare final reports. As women continue to represent a growing population infected by HIV in California, with the attendant increase in children affected by the epidemic, this study will evaluate the impact of a child support group intervention in order to improve understanding of the mother-child relationship in families coping with a difficult and stigmatized disease throughout critical periods of children's development.

Prevention, Health Services & Contexts of Health

Drop-in Centers for High Risk Youth: Geomapping Outcomes and Implications for Outreach and Retention

Presenter: Audrey Shillington, San Diego State University

Collaborators: S. Lehman, J. Clapp, E. Blumberg, C. Sipan, M. Hovell

Principal Investigator: Audrey Shillington

UARP Award Number: PE00-SDSU-153

Background/Objectives: In the U.S., data indicates that youth and minorities account for a growing proportion of new HIV/AIDS cases. Given the extended latency period for demonstrable infection, it is likely that most young adults diagnosed with HIV or AIDS contracted the infection during adolescent years. AIDS is now the 9th leading cause of death for youth ages 15-24 and it has been estimated that at least half of all new HIV infections in the U.S. are among people under 25 (the majority of young people are infected sexually). Adolescence is a developmental stage known to be when people experiment with drug use and risky sexual behaviors. In a state-wide prevention effort, the California State Office of AIDS supported the creation of youth drop-in centers for HIV prevention. The purpose of this study is to examine the dispersion of drop-in center clientele across San Diego County for each center and how such dispersion may be associated with the ability to retain youth to the 3 month follow-up interview.

Methods: Youth were recruited into the CARRE Project (Centers for Adolescent Risk Reduction Evaluation Project) at three urban drop-in centers. An audio-computer assisted survey instrument (ACASI) was used to measure demographics, HIV-related risk, substance use, illegal behaviors, and other socio-emotional variables. Among other demographic variables, youth were asked to report the zip code of their current residence. These zip codes were loaded into MapInfo after the completion of all baseline and 3-month follow-up data were gathered and maps were created representing the geographic distribution of clients' zip code of residence for each center.

Results: A total of 286 youth were recruited into the 3 centers. At baseline there were 141 youth who participated from the LGBQ youth center, 97 who participated from the Hispanic Barrio location, and 48 who participated from the center for homeless youth. The overall retention rate at 3 month follow-up was vastly disparate, ranging from 30% (at the LGBTQ youth center) to 73% (at the center serving Hispanic youth). Geomapping revealed that the center with the highest retention rate also had the highest number of clientele living in close proximity to the agency (based on reported zip code of residence). In fact over half of those clientele reported living in the same zip code as the center.

Alternatively, with respect to the LGBQ drop-in center, geomapping revealed that the residence of the clientele ranged from the Mexican border region on the southern extreme to Orange County on the north side. For the LGBQ center, 8% were out of county or out of state, and only approximately 30% were within a 15 mile radius of the agency. The results are more difficult to understand for the drop-in center serving homeless youth. It was found that nearly 40% of homeless youth did not report a valid zip code. Our mapping revealed that, of those who did report a valid zip code, almost all were living within a 15-20 mile radius of the center.

Conclusions: Implications of this study are important for HIV prevention efforts with youth. Our data indicate that there is a great need for services that target LGBQ youth. It seems that these youth are willing to travel great distances to come to that particular center. However, the wide geographic range of clientele residence at that agency likely created difficulty in terms of project retention for longitudinal follow-up. In fact, retention rates were even lower than that at the agency for the homeless youth. In contrast, the agency that served youth within the agency's own physical location was the agency with the highest retention rate. Although we did not have the capabilities to map a fourth drop-in center in Imperial County, this agency also served the immediate local youth and had similar high retention rates at 3 month follow-up (75%). If a goal for an agency is to serve youth on multiple occasions, then our results would indicate that focusing on those who are nearby will result in higher numbers of contacts. Plans for future youth outreach should examine the issue of population based outreach vs. geographic catchment area based outreach.

Prevention, Health Services & Contexts of Health

Increasing the Accuracy of Self Reports of HIV-related Risk Behaviors: The Effects of Combining Audio-CASI with a Bogus Pipeline

Presenter: Jennifer Zellner, Center for Behavioral Epidemiology & Community Health, San Diego State University

Collaborators: Jennifer Zellner, Richard Gevirtz, Melbourne Hovell, Sharon Foster

Principal Investigator: Carol Sipan

UARP Award Number: IS02-CBECH-711

This project will evaluate youth's self-reports of HIV-related risk behaviors under conditions designed to increase the accuracy of these reports. The study aims to examine whether a combination of audio-computer assisted interviewing (audio-CASI) and the bogus pipeline (BPL) technique can provide more accurate reports than: 1) audio-CASI alone, 2) BPL alone, or 3) a standard paper and pencil interview alone. Participants will be 160 youth ages 14-22 attending two San Diego area Youth Drop-in Centers. Participants will be asked to complete a self-administered survey that includes measures assessing HIV-related risk behaviors, socially desirable responding, and demographic information. Half of the participants will be randomly assigned to complete these measures using a computer-administered survey, and the other half will be randomly assigned to complete identical paper-and-pencil measures. In addition, half of the total participants will be randomly assigned to complete these measures while attached to a physiological monitoring device, which they will be told can detect true reports of their lifestyle practices. Potential benefits of this project include the contribution of these data to epidemiological research aimed at identifying the HIV-related risk behaviors in which youth are engaging. This information can be subsequently used to design more effective prevention and intervention programs as well as to enhance the programs and services offered by the drop-in centers, which would benefit the high-risk population from which the sample will be drawn. In addition, data gathered in this study may make a contribution to methodological research aimed at identifying how the accuracy of self-reports of sensitive behaviors can be maximized, information that may then be used to inform the design of research assessing sensitive behaviors. Data collection will begin December 2003 and continue through April 2004.

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