PI: **Gandhi, Monica**	Title: Hair Extensions: Using Hair Levels to Interpret Adherence, Effectiveness and Pharmacokinetics with Real-World Oral PrEP, the Vaginal Ring, and Injectables	
Received: 09/02/2016	FOA: PA16-160	Council: 01/2017
Competition ID: FORMS-D	FOA Title: NIH Research Project Grant (Parent R01)	
2 R01 AI098472-06	Dual: HD	Accession Number: 3966039
IPF: 577508	Organization: UNIVERSITY OF CALIFORNIA, SAN FRANCISCO	
Former Number:	Department: Medicine	
IRG/SRG: BSCH	AIDS: N	Expedited: N
Subtotal Direct Costs (excludes consortium F&A) Year 6: Year 7: Year 8: Year 9: Year 10:	Animals: N Humans: Y Clinical Trial: N Current HS Code: 30 HESC: N	New Investigator: N Early Stage Investigator: N
Senior/Key Personnel:	*Organization:*	*Role Category:*
Monica Gandhi M.D.	The Regents of the University of California, San Francisco	PD/PI
Diane Havlir M.D.	The Regents of the University of California, San Francisco	Co-Investigator
Peter Bacchetti Ph.D	The Regents of the University of California, San Francisco	Co-Investigator
Jared Baeten M.D.	University of Washington	Co-Investigator
Jose Castillo-Mancilla M.D.	University of Colorado Denver	Co-Investigator
Leslie Benet Ph.D	The Regents of the University of California, San Francisco	Co-Investigator
Roy Roberto Gerona Ph.D	The Regents of the University of California, San Francisco	Co-Investigator
Elizabeth Brown Sc.D.	University of Washington	Other (Specify)-Other Significant Contributor

OMB Number: 4040-0001
Expiration Date: 06/30/2016

APPLICATION FOR FEDERAL ASSISTANCE
SF 424 (R&R)

3. DATE RECEIVED BY STATE	**State Application Identifier**

1. TYPE OF SUBMISSION*

❍ Pre-application ● Application ❍ Changed/Corrected Application

4.a. Federal Identifier
AI098472

b. Agency Routing Number

2. DATE SUBMITTED
2016-09-02

Application Identifier
P0513304

c. Previous Grants.gov Tracking Number

5. APPLICANT INFORMATION **Organizational DUNS*:** [redacted]

Legal Name*: The Regents of the University of California, San Francisco
Department:
Division:
Street1*: [redacted]
Street2: [redacted]
City*: [redacted]
County:
State*: [redacted]
Province:
Country*: [redacted]
ZIP / Postal Code*: [redacted]

Person to be contacted on matters involving this application
Prefix: Ms. First Name*: Julie Middle Name: C Last Name*: Tang Suffix:
Position/Title: Contracts and Grants Officer
Street1*: [redacted]
Street2:
City*: [redacted]
County: [redacted]
State*: [redacted]
Province:
Country*: [redacted]
ZIP / Postal Code*: [redacted]
Phone Number*: [redacted] Fax Number: [redacted] Email: [redacted]

6. EMPLOYER IDENTIFICATION NUMBER *(EIN) or (TIN)** [redacted]

7. TYPE OF APPLICANT* H: Public/State Controlled Institution of Higher Education

Other (Specify):
Small Business Organization Type ❍ Women Owned ❍ Socially and Economically Disadvantaged

8. TYPE OF APPLICATION*

❍ New ❍ Resubmission
● Renewal ❍ Continuation ❍ Revision

If Revision, mark appropriate box(es).
❍ A. Increase Award ❍ B. Decrease Award ❍ C. Increase Duration
❍ D. Decrease Duration ❍ E. Other *(specify)* :

Is this application being submitted to other agencies?* ❍ Yes ● No What other Agencies?

9. NAME OF FEDERAL AGENCY*
National Institutes of Health

10. CATALOG OF FEDERAL DOMESTIC ASSISTANCE NUMBER
TITLE:

11. DESCRIPTIVE TITLE OF APPLICANT'S PROJECT*
"Hair Extensions": Using Hair Levels to Interpret Adherence, Effectiveness and Pharmacokinetics with Real-World Oral PrEP, the Vaginal Ring, and Injectables

12. PROPOSED PROJECT
Start Date* Ending Date*
04/01/2017 03/31/2022

13. CONGRESSIONAL DISTRICTS OF APPLICANT
CA-012

SF 424 (R&R) APPLICATION FOR FEDERAL ASSISTANCE

14. PROJECT DIRECTOR/PRINCIPAL INVESTIGATOR CONTACT INFORMATION

Prefix: Dr. First Name*: Monica Middle Name: Last Name*: Gandhi Suffix: M.D.

Position/Title: Professor

Organization Name*: The Regents of the University of California, San Francisco

Department: Medicine

Division: School of Medicine

Street1*: [redacted]

Street2:

City*: [redacted]

County: [redacted]

State*: [redacted]

Province:

Country*: [redacted]

ZIP / Postal Code*: [redacted]

Phone Number*: [redacted] Fax Number: Email*: [redacted]

15. ESTIMATED PROJECT FUNDING

a. Total Federal Funds Requested* [redacted]

b. Total Non-Federal Funds* [redacted]

c. Total Federal & Non-Federal Funds* [redacted]

d. Estimated Program Income* [redacted]

16.IS APPLICATION SUBJECT TO REVIEW BY STATE EXECUTIVE ORDER 12372 PROCESS?*

a. YES ❍ THIS PREAPPLICATION/APPLICATION WAS MADE AVAILABLE TO THE STATE EXECUTIVE ORDER 12372 PROCESS FOR REVIEW ON:

DATE:

b. NO ● PROGRAM IS NOT COVERED BY E.O. 12372; OR

❍ PROGRAM HAS NOT BEEN SELECTED BY STATE FOR REVIEW

17. By signing this application, I certify (1) to the statements contained in the list of certifications* and (2) that the statements herein are true, complete and accurate to the best of my knowledge. I also provide the required assurances * and agree to comply with any resulting terms if I accept an award. I am aware that any false, fictitious, or fraudulent statements or claims may subject me to criminal, civil, or administrative penalties. (U.S. Code, Title 18, Section 1001)

● I agree*

** The list of certifications and assurances, or an Internet site where you may obtain this list, is contained in the announcement or agency specific instructions.*

18. SFLLL or OTHER EXPLANATORY DOCUMENTATION File Name:

19. AUTHORIZED REPRESENTATIVE

Prefix: Ms. First Name*: Julie Middle Name: C Last Name*: Tang Suffix:

Position/Title*: Contracts and Grants Officer

Organization Name*: The Regents of the University of California, San Francisco

Department: Research Management Services

Division: Office of Sponsored Research

Street1*: [redacted]

Street2: [redacted]

City*: [redacted]

County: [redacted]

State*: [redacted]

Province:

Country*: USA: UNITED STATES

ZIP / Postal Code*: [redacted]

Phone Number*: [redacted] Fax Number: [redacted] Email*: [redacted]

Signature of Authorized Representative*

[redacted]

Date Signed*

[redacted]

20. PRE-APPLICATION File Name:

21. COVER LETTER ATTACHMENT File Name:CoverLetter_Gandhi_R01renewal_083116.pdf

OMB Number: 4040-0010
Expiration Date: 06/30/2016

Project/Performance Site Location(s)

Project/Performance Site Primary Location

❍ I am submitting an application as an individual, and not on behalf of a company, state, local or tribal government, academia, or other type of organization.

Organization Name: The Regents of the University of California, San Francisco
Duns Number: [redacted]
Street1*: [redacted]
Street2:
City*: [redacted]
County: [redacted]
State*: [redacted]
Province:
Country*: [redacted]
Zip / Postal Code*: [redacted]
Project/Performance Site Congressional District*: CA-012

Project/Performance Site Location 1

❍ I am submitting an application as an individual, and not on behalf of a company, state, local or tribal government, academia, or other type of organization.

Organization Name: University of Washington
DUNS Number: [redacted]
Street1*: [redacted]
Street2:
City*: [redacted]
County:
State*: [redacted]
Province:
Country*: [redacted]
Zip / Postal Code*: [redacted]
Project/Performance Site Congressional District*: WA-007

Project/Performance Site Location 2

❍ I am submitting an application as an individual, and not on behalf of a company, state, local or tribal government, academia, or other type of organization.

Organization Name: University of Colorado Denver
DUNS Number: [redacted]
Street1*: [redacted]
Street2:
City*: [redacted]
County:
State*: [redacted]
Province:
Country*: [redacted]
Zip / Postal Code*: [redacted]
Project/Performance Site Congressional District*: CO-006

Funding Opportunity Number: PA-16-160. Received Date: 2016-09-02T14:18:25.000-04:00

OMB Number: 4040-0001
Expiration Date: 06/30/2016

RESEARCH & RELATED Other Project Information

1. Are Human Subjects Involved?* ● **Yes** ○ **No**

1.a. If YES to Human Subjects

Is the Project Exempt from Federal regulations? ○ Yes ● No

If YES, check appropriate exemption number: 1 __ 2 __ 3 __ 4 __ 5 __ 6 If

NO, is the IRB review Pending? ● **Yes** ○ **No**

IRB Approval Date:

Human Subject Assurance Number [redacted]

2. Are Vertebrate Animals Used?* ○ **Yes** ● **No**

2.a. If YES to Vertebrate Animals

Is the IACUC review Pending? ○ Yes ○ No

IACUC Approval Date:

Animal Welfare Assurance Number

3. Is proprietary/privileged information included in the application?* ○ **Yes** ● **No**

4.a. Does this project have an actual or potential impact - positive or negative - on the environment?* ○ **Yes** ● **No**

4.b. If yes, please explain:

4.c. If this project has an actual or potential impact on the environment, has an exemption been authorized or an environmental assessment (EA) or environmental impact statement (EIS) been performed? ○ Yes ○ No

4.d. If yes, please explain:

5. Is the research performance site designated, or eligible to be designated, as a historic place?* ○ **Yes** ● **No**

5.a. If yes, please explain:

6. Does this project involve activities outside the United States or partnership with international collaborators?* ○ **Yes** ● **No**

6.a. If yes, identify countries:

6.b. Optional Explanation:

	Filename
7. Project Summary/Abstract*	Abstract_R01Rnwl_Gandhi_Final08312016.pdf
8. Project Narrative*	ProjNarrative_R01Rnwl_Gandhi_Final083116.pdf
9. Bibliography & References Cited	Bibliography_GandhiR01rnwl_Final_090116.pdf
10.Facilities & Other Resources	FacilitiesResources_AllSites_09022016.pdf
11.Equipment	MajorEquipment_AllSites_08302016.pdf

Tracking Number: GRANT12240283
Funding Opportunity Number: PA-16-160. Received Date: 2016-09-02T14:18:25.000-04:00

PROJECT SUMMARY/ ABSTRACT

Three lessons of the PrEP (pre-exposure prophylaxis) clinical trials - that adherence is critical to effectiveness, that pharmacologic adherence measures are more reliable than self-report, and that daily pill-taking is difficult –must be applied to the next phase of HIV prevention research. This phase will investigate oral PrEP roll-out and optimization in high incidence settings, as well as novel long-acting methods for preventing HIV infection, such as injectables or vaginal rings. The vaginal ring prevented HIV acquisition in two recent trials, but poor adherence to consistent ring insertion dampened overall effectiveness. Injectable PrEP with long-acting cabotegravir is of interest, but will require adequate drug levels to be effective, especially at the end of dosing intervals and with missed visits. Pharmacologic metrics integrate biology (pharmacokinetics, PK) and behavior (adherence) and will be crucial to interpreting effectiveness with real-world oral PrEP, rings and injectables.

Our group has helped pioneer the use of small hair samples (which are easy to collect, store and ship) to monitor exposure (PK) and adherence to antiretrovirals (ARVs). During the first funding period of this R01, we made significant progress on our original aims, demonstrating that hair levels of ARVs, which monitor long-term exposure, are stronger predictors of treatment success than self-reported adherence (or plasma levels) in HIV-infected pregnant women, children, and adults. We have also shown preliminary utility of hair levels of tenofovir (TFV)/emtricitabine (FTC) to monitor adherence and toxicities with oral PrEP.

This proposal will leverage three important trials to explore key knowledge gaps that will arise in the next phase of HIV prevention work: The Sustainable East Africa Research in Community Health (SEARCH) trial (Dr. Havlir, chair and co-I) has just launched a large study providing oral PrEP to at-risk individuals in 16 communities in Africa. The HIV Open-Label Prevention Extension (HOPE) study in the Microbicide Trials Network (MTN) (Dr. Baeten, chair and co-I) will assess open-label use of the dapivirine vaginal ring. The Long-Acting Antiretroviral Therapy in Non-adherent HIV-Infected Individuals Trial (A5359, Dr. Castillo-Mancilla, co-chair and co-I)) in the AIDS Clinical Trials Group (ACTG) will examine long-acting injectables in HIV-infected patients with a history of poor adherence. All 3 trials will collect hair and plasma for drug levels, and track robust outcomes, to allow us to 1) investigate hair levels as metrics of adherence with the vaginal ring and oral PrEP in Africa and examine patterns of adherence (e.g. daily, around periods of risk, just prior to visits) by combining data in plasma and hair; and 2) examine hair levels as easy-to-collect metrics for PK monitoring with the use of injectables. The overarching goal of this renewal is to develop an integrated package of highly predictive biologic adherence and pharmacokinetic measures spanning PrEP delivery methods and optimization strategies. Defining predictors and patterns of adherence to oral PrEP and rings, as well as metrics to monitor PK with injectables, will inform public health interventions in HIV prevention.

PUBLIC HEALTH RELEVANCE/ PROJECT NARRATIVE

Pre-exposure prophylaxis (PrEP) with oral tenofovir (TFV) disoproxil fumarate/emtricitabine (TDF/FTC) works, but measuring PrEP drug levels to assess adherence in the PrEP trials helped us understand that 1) drug levels measure adherence better than self-report; and 2) it is difficult to take a pill every day. New ways to prevent HIV will involve testing a vaginal ring that is inserted monthly or injections of a long-acting antiretroviral (like cabotegravir), but we must examine drug levels in the human body when studying these novel tools to truly understand how well they work. This study will look at drug levels in small hair samples in three important trials (studying oral PrEP in Africa; the dapivirine vaginal ring in Africa under real-world conditions; and injectable agents in the U.S.) to see if hair measures can monitor the effectiveness of HIV prevention delivered via exciting new modalities and in high-incidence settings.

FACILITIES AND RESOURCES

SITE: University of California, San Francisco (UCSF)

UCSF: The University of California, San Francisco (UCSF), one of the ten campuses of the University of California, is devoted solely to graduate education and research in the health sciences. UCSF is one of the leading biomedical research and health science education centers in the world. The university is a major health care delivery center in northern California with a high volume of regional, national, and international patient referrals. UCSF is home to 16 research institutes, 1,500 laboratories, more than 5,000 ongoing research projects, and a library with a state-of-the-art computing and communications infrastructure. In 2006, UCSF applied for and was successfully awarded an NIH Center for Translational Sciences (CTSI), which is dedicated to research and education in clinical and translational science at UCSF, at affiliated institutions, and in participating communities. UCSF's four professional schools (Dentistry, Medicine, Nursing, and Pharmacy) are ranked in the top tier nationally and internationally (measured by academic quality, publication citations of faculty, and amount of extramural support for research and education). UCSF's graduate academic PhD programs are also ranked in the top tiers of programs in the biomedical and biopsychosocial disciplines. There are 35 academic departments, 17 multidisciplinary research centers, and many NIH-funded multidisciplinary research grants across campus.

UCSF is a world-renowned biomedical research center with an annual budget of over $5 billion to support its various research, teaching, and patient care activities. A large portion of the extramural funds received is allocated for biomedical research. Research funding is primarily obtained on a competitive basis from the federal government. Additional research funding is received annually from the State of California, the University of California Office of the President, private research foundations, state and local government agencies, private philanthropy, and industry. UCSF was awarded $560.4M in NIH funding in 2015, which was first among public institutions and second among all institutions nationwide. In 2015, the UCSF School of Medicine received $501.1M (ranked first), the UCSF School of Dentistry received $16.9M (ranked first), the School of Nursing received $14.0M (ranked first), and the School of Pharmacy received $27.0M (ranked first). Among faculty members are five Nobel laureates, 40 National Academy of Sciences members, 61 American Academy of Arts and Sciences members, 84 Institute of Medicine members, and 18 Howard Hughes Medical Institute investigators.

Over the past decade, UCSF's capacity for basic science and clinical research in the context of world-class graduate education has been increased by the construction of academic facilities at the new UCSF Mission Bay Campus. Research and clinical activities take place on the six main San Francisco campuses of UCSF: Parnassus, Mount Zion, Laurel Heights, San Francisco General Hospital (now known as ZSFG), San Francisco Veterans Administration Medical Center, and Mission Bay. A network of UCSF shuttle buses allows for efficient staff, reagent, and mail travel between all campus facilities.

SITE: Division of HIV, Infectious Diseases and Global Medicine, UCSF-ZSFG Campus

Dr. Monica Gandhi, Principal Investigator,
Dr. Diane Havlir, Co-investigator
Dr. Leslie Z. Benet (co-investigator), General Director of the Hair Analytical Laboratory
Dr. Roy Gerona (co-investigator), Laboratory director of the Hair Analytical Laboratory

OVERVIEW

Dr. Monica Gandhi is a Professor of Medicine and Associate Chief of the Division of HIV, Infectious Diseases, and Global Medicine at San Francisco General Hospital (now known as Zuckerberg San Francisco General or ZSFG). The HIV, ID and Global Medicine Division consists of a multidisciplinary HIV/AIDS clinic called Ward 86 (for which Dr. Gandhi serves as the Medical Director), an inpatient HIV-ID consultation service (which Dr. Gandhi co-directs), and a strong clinical and translational research program. The program has focused on

clinical, research and educational issues of HIV and HIV-associated illnesses (e.g., sexually transmitted and blood borne infections) for over 30 years. Academically, the Division holds weekly clinical grand rounds, monthly research forums and periodic seminars, which provide ample opportunity for peer review as well as dissemination of study information. The Division of HIV, ID and Global Medicine has become an internationally recognized center of clinical excellence and "standard-setter" for HIV care and research, pioneering a number of medical and scientific advances. The treatment model practiced at the UCSF-based “Ward 86” HIV Clinic, which Dr. Gandhi has directed since 2014, has been widely adopted around the world. The Division has also had a major presence in the developing world, training local providers and leading global research. For instance, Dr. Diane Havlir, who is Professor of Medicine and Chief of the Division of HIV, ID and Global Medicine (and co-I on this grant) has a very large research program in Uganda and Kenya called SEARCH, which is the study in which Aim 1 of this grant is embedded. The Division of HIV, ID and Global Medicine’s faculty is among the most cited in scientific publications and conducts work in all major areas of HIV science.

CLINICAL

The Ward 86 HIV Clinic occupies the entire 6th floor (Ward 86) of Building 80 at ZSFG and contains 15 patient examination rooms, a pharmacy, a clinical laboratory, a modern 7-bed treatment room for transfusions and drug administration, and conference and office space for both the non-physician staff and physician staff. The clinic currently follows approximately 2,700 HIV-infected individuals from the City of San Francisco. Dr. Gandhi is the Medical Director of Ward 86. Drs. Gandhi and Havlir see HIV-infected patients and patients on the HIV/ID consultation service in both the outpatient and inpatient setting at ZSFG.

COMPUTERS

See below general section on Computers for summary of UCSF Computer System.

The Division’s Research Group has 40 networked computer workstations with connections to the greater UCSF system and network file servers, and high-speed Internet access. A HIPPA-compliant server is dedicated to research data storage. Access to this server is restricted to persons on the UCSF network, and requires network log-on authentication for access. Access to digital research data is further restricted in particular folders to a small set of research staff and investigators working on the project, and access to research files is logged so that there is a record of which individuals have accessed files. Daily back-up is performed on network servers. Extensive information technology (IT) support is provided for all computer operations through the UCSF Dean’s office at ZSFG

OFFICE

The Division of HIV, ID and Global Medicine’s Research Group occupies approximately 15,000 sq. ft. of office space. This facility includes private offices and 63 workstations for investigators, administrators, finance and regulatory affairs staff, clinical research nurses, nurse practitioners, statisticians, data managers, research assistants, phlebotomists, pharmacy technicians, and computer support staff. This research facility also contains two conference rooms, a reception and patient waiting area, 7 exam rooms and 5 consult rooms, phlebotomy facilities, a room for processing laboratory specimens, and secured rooms for storing study medications and locked files for patient medical records. Dr. Gandhi’s and Dr. Havlir’s private offices are within the Division’s Research Group’s set of offices on the 4th floor of Building 80 at ZSFG.

ADMINISTRATIVE SUPPORT

The Division of HIV, ID and Global Medicine provides full supporting services that enable researchers to excel in clinical and translational research. Facilities, cleaning, and maintenance are professionally managed. Logistical support is provided by a skilled financial and administrative staff, including contracts and grants, financial controllers, human resources, and administrative management. The Finance Manager and Division Manager in the Division of HIV, Infectious Diseases and Global Medicine are administratively responsible for the HAL.

LABORATORY AND EQUIPMENT

The Analytical Division of the Drug Studies Unit (DSU) at UCSF was established in 1977 by the late Dr. Sid Riegelman, Dr. Leslie Benet, and Dr. Roger Williams. The Hair Analytical Laboratory (HAL) at UCSF was initially housed in the DSU and became its own independent Unit in 2012, with Dr. Leslie Benet (co-investigator on this grant) serving as its overall Director. Karen Kuncze, research associate on this grant application and Quality Assurance (QA) director of the HAL, has been working in the Unit and with Dr. Leslie Benet for the past 21 years. The Hair Analytical Laboratory (HAL) moved from the Department of Bioengineering and Therapeutic Sciences (BTS) to the Division of HIV, Infectious Diseases and Global Medicine (under Dr. Diane Havlir's overall leadership) in January 2016 although the site for the laboratory is still located at the UCSF-Parnassus campus (see Letter of Transfer signed by Drs. Gandhi, Benet and Havlir in "Letters of Support" section of grant, Letter 10). The HAL is in close proximity (same buildings and floors) to Dr. Gerona's laboratory housed within the Department of Obstetrics, Gynecology and Reproductive Sciences. Dr. Roy Gerona is now responsible for day-to-day operations of the HAL under the General Directorship of Dr. Leslie Benet and Dr. Gandhi (Clinical Director, HAL). The HAL applies Good Laboratory Practice (GLP) standards to meet the drug assay development requirements developed by the Food and Drug Administration and necessary for the DAIDS-supported Clinical Pharmacology and Quality Assurance Program (CPQA) to which all antiretroviral assays in biomatrices must be submitted prior to running assays from studies funded by the NIH clinical trials networks. Of note, the facilities for the HAL are described in more detail in a separate HAL description below since the analytical team for this grant application and the laboratory is located on a separate campus from the Division of HIV, IDand Global Medicine. Equipment for the HAL is described in the "Major Equipment" section.

SITE: Hair Analytical Laboratory (HAL), Medical Sciences Building, UCSF-Parnassus Campus

OVERVIEW

The joint HAL/Gerona laboratory is located on the Parnassus campus Medical Science Building. The HAL has completely equipped modern facilities and a highly trained staff to provide fully automated analysis for drugs and metabolites in biological matrices. Personnel include permanent staff and postdoctoral scholars. We have both the necessary expertise for the most challenging method-development projects and the capacity for rapid completion of high-volume routine assays, specifically directed towards the hair antiretroviral assays required for this research proposal (on which we have worked for over a decade) using methods we developed, validated and published (e.g. tenofovir and emtricitabine assays for Aim 1 already approved by CPQA; dapivirine and cabotegravir assays developed for this application – validation reports to be submitted to CPQA during this funding period prior to sample analyses). Hair specimens collected in the attached proposal will be analyzed for relevant antiretrovirals using LC-MS/MS-based methods and the first funding period of this grant has been highly productive with the HAL at UCSF (publishing 20 papers to date, with 2 currently in review).

The laboratory has four dedicated research assistants (one of whom –Anita Wen- will be fully funded and devoted to this R01 renewal project and one Quality Assurance Director -Karen Kuncze- who has been working on the hair antiretroviral assays since their inception at UCSF over a decade ago). Both are well-trained in running, operating, and maintaining LC-MS and GC-MS/MS instrumentation for method development, validation, and implementation. Karen Kuncze is well-versed on FDA regulations on bioanalytical method validation, safety-related policies and issues, and the analysis of data, including manual/automated computations and the recognition of irregularities and invalid results from the assays. She monitors and inspects all ongoing analytical studies to assure that equipment, personnel, methods, practices, records, and controls are in conformance with Good Laboratory Practice (GLP). Dr. Roy Gerona who has extensive experience in developing quantitative LC-MS methods for drugs and other small molecules in a variety of biological matrices, directs and runs the laboratory. Dr. Monica Gandhi who has over ten years of experience in HIV-AIDS adherence and exposure measurement (and over 15 years as an HIV doctor) works closely with the Gerona lab and oversees the hair antiretroviral analyses. Dr. Benet, who is a world-renowned pharmacologist, author of over 550 peer reviewed manuscript and book chapters, and has run a laboratory for over 45 years, is the General Director of the HAL and will also oversee the validation reports and hair analyses.

CLINICAL
NA

COMPUTERS
See below general section on Computers for summary of UCSF Computer System.
The laboratory has three high capacity computers dedicated to data analysis as well as eight laboratory computers for staff use, one of which is dedicated to sample inventory and data archiving. The laboratory has access to the university's electrical shop that can perform immediate repairs to minor equipment failure that would otherwise cause long work delays.

OFFICE SPACE
The HAL is located on the UCSF-Parnassus campus and has office space for the analytical team members housed there, including Dr. Roy Gerona, Dr. Leslie Benet, Distinguished Professor and Former Chairman of the Department of Bioengineering and Therapeutic Sciences, Anita Wen (staff research associate for this grant proposal) and Karen Kunze (staff research associate and QA director, HAL). The equipment for the LC-MS/MS methods in the HAL is described in the "Major Equipment" section.

SITE: Department of Epidemiology and Biostatistics, UCSF (Dr. Peter Bacchetti, co-investigator)

OVERVIEW
The Department of Epidemiology and Biostatistics (DEB) at UCSF carries out research on a broad range of applications of epidemiology and biostatistics from genes and cellular biology, to clinical care and population health and it provides postgraduate teaching and training. The major DEB programs located at Mission Bay include: Division of Biostatistics, Division of Clinical Epidemiology, Clinical and Translational Sciences Training, San Francisco Coordinating Center, and the Information Technology/Data management and administrative staff that support the academic mission. Other faculty and other UCSF facilities form the Divisions of Genetic and Cancer Epidemiology and of Preventive Medicine and Public Health. DEB faculty include 18 PhD biostatisticians and 33 MD and PhD epidemiologists engaged in a broad variety of clinical research activities. Multidisciplinary connections are enhanced by close collaborations with ~100 affiliated faculty whose primary appointments are in other departments of the Schools of Medicine, Pharmacy, Nursing and Dentistry.

COMPUTERS
See below general section on Computers for summary of UCSF Computer System.
The DEB contains approximately 300+ PC-compatibles (Windows and Linux) and 80 Macintosh computers. The computers share access to over 20 laser printers and over 145 print, file, and application servers, both physical and virtual. All research data reside in Microsoft SQL Server and MySQL databases. Databases are backed up three times daily including one backup which is routed off site to magnetic storage. All systems (i.e. network, servers, and environmental controls) are monitored 24 hours a day, seven days a week.

OFFICE
All personnel of the UCSF Biostatistical Consulting Unit, including Dr. Bacchetti, have office space within the area occupied by the Department of Epidemiology and Biostatistics at UCSF's Mission Bay campus, along with desktop computers and access to departmental "cloud" computing resources. The premises consist of approximately 40,000 square feet distributed among approximately 91 offices, 89 open work stations and other support facilities (server room, reception area/mail room, printer/photocopy areas, library, computer classroom, training classroom, conference rooms and kitchen areas).

COMPUTERS: University of California, San Francisco (UCSF)

UCSF VOICE AND DATA SERVICES

The UCSF Information Technology Services (ITS) hosts a centralized email server, and provides basic voice and data services in the support of the campus community. This includes planning, coordination, development of policies and procedures, implementation of new systems, and day-to-day operations. Enterprise Network Services (ENS), a department within ITS, supports academic, research and administrative activities across the UCSF campus network. Core services include network planning and implementation, voice and data network maintenance, remote access to UCSF networks, and internet access.

PREMIUM DESKTOP SUPPORT SERVICES

The Premium Desktop Support service (held by Drs. Gandhi, Bacchetti, Benet, and Gerona at UCSF) includes all services provided by the Basic Desktop Support service, with several differentiators that increase the overall scope, flexibility, quality, and responsiveness of the service. Premium Desktop Support is designed to address the needs of customers whose needs extend beyond what the Basic Desktop Support model provides. Examples of this include: customers who require extended support hours, faster response times, support of non-standard or out-of-warranty hardware configurations, enhanced training, special onsite support for presentations and events, and support for developer workstations. Standard productivity software, Microsoft Office and Adobe Acrobat pro are included.

Key differentiators of the Premium Desktop Support Services include:

- Hours of Support
- Response Times
- Hardware
- Software
- Storage
- Storage and Data backup
- User Training
- Project Management
- Presentation Support
- Administrative Rights

Hours of Support

Service Desk support is available 24/7/365. Onsite field support is available M-F 7-6. After-hours support is available through the Service Desk; field staff are available on-call and provide remote support. After-hours onsite support for UCSF locations is available with prior arrangement.

Response Times

For responses to incidents, the ITS goal is to assign and acknowledge ticket assignments from the Service Desk within 2 business hours of receipt. We will make every effort to respond to urgent issues in less time.

Hardware

Premium Desktop Support customers are encouraged to purchase Dell or Mac hardware based on the JACS standards. However, non-standard hardware models will be supported under Premium Desktop Support when a business justification exists. Support for out-of-warranty hardware and systems over 5 years old will also be provided to accommodate special situations when hardware upgrades are not feasible (e.g., lab computer equipment running legacy software) by special arrangement. Loaner laptops and projectors are available for reservation for up to 2 weeks.

Software

Clinical applications requiring a local installation and other applications out of manufacturer support will also be provided to accommodate special situations when software upgrades are not feasible by special arrangement.

Storage & Data Backup

- Clinical applications 10GB for individual file storage for specific folders, aggregated by department
- Unlimited UCSF Box storage

User Training

On-site training for application support including specialized expertise in productivity software including Office, Acrobat, and Endnote and other software by special arrangement.

Project Management

The Premium Desktop Support service includes project management for relocation coordination services for larger office and lab relocations (>3 people). Services include: network connectivity planning; coordinating requests for static IP addresses for printers/workstations; disconnecting/reconnecting computers, printers, and peripherals; configuring and confirming connectivity to required resources in the new location; and follow-up floor support in the days immediately following the move.

Presentation Support

Premium Desktop Support provides onsite presentation support at UCSF facility including connectivity to projectors, configuring/confirming wireless network access, and presentation troubleshooting.

ENHANCED DATA MANAGEMENT SYSTEMS

In addition to the desktop and computer support described above, UCSF Academic Research Services provides faculty and their research project teams with access to enhanced data management systems for the secure transfer, storage, and analysis of research data. These services are centralized within a firewalled system known as MyResearch, which users access through an encrypted portal. The MyResearch environment enables project to store large volumes of data. In addition, My Research houses a variety portal, which includes the statistical applications SAS, SPSS, Stata, and the data transfer utility Stat/Transfer.

MyResearch features the qualitative data analysis program Atlas.TI and the survey data collection program RedCap. Outside of the MyResearch environment, UCSF makes the Qualtrics survey data collection program available to UCSF researchers free of charge. Desktop licenses for the statistical programs SAS and SPSS (including the AMOS structural equation modeling module) are available for a modest annual fee (approximately $250) through the UCSF library's Research Software Licensing group.

FACILITIES AND RESOURCES

SITE: University of Washington (Dr. Jared Baeten, co-investigator; Dr. Elizabeth Brown, significant contributor)

OVERVIEW

The **University of Washington (UW),** one of the largest institutions of higher education in the West, and its affiliate institutions provide an excellent environment for training and research characterized by recent growth, diversity and excellence in all types of health-related research and education. Many of the approximately 3,900 teaching and research faculty are known nationally and internationally for their accomplishments. The University has among the top five universities, public and private, in federal funding since 1969. Of this, the largest share comes from the National Institutes of Health (NIH) and the Department of Health and Human Services (DHHS), indicating the depth and breadth of the University's health research program.

The University of Washington provides the only Schools of Medicine and Public Health for five states of the Pacific Northwest, with interdisciplinary collaborations facilitated by sharing of a contiguous campus with Schools of Pharmacy, Nursing, Social Work, and Dentistry, adjacent to Schools of Arts and Sciences, Business, Law, and Public Affairs. The UW and its affiliated institutions have developed interdisciplinary HIV/AIDS research, education, and service programs in most regions of the developing world. The Schools of Medicine and Public Health have jointly established a Department of Global Health (for which Dr. Baeten serves as Vice-Chair) providing the focal point for UW international health programs.

The UW research infrastructure offers a wide array of services to support researchers—including technology transfer, human subjects review, and grant and contract services. Faculty and staff have access to the UW library system, which is home to more than seven million volumes and 62,000 current serials. Each UW investigator and staff member has Ethernet access, and the UW mainframe computer is available to investigators and staff, which provides access to online reference services, websites, and databases.

The **International Clinical Research Center (ICRC; Dr. J. Baeten, Co-Director)** is a center within the Department of Global Health, University of Washington, dedicated to conducting high quality, high impact biomedical and implementation research and utilizing well-designed systems for research and clinical trial operations. The ICRC offices are located on the 12th floor of the Ninth & Jefferson building (NJB) located on the Harborview Medical Center campus. Approximately 6,000 sq. ft. is dedicated to ICRC office space for investigators and administrative staff in the NJB. The space provides for 30 faculty, including Dr. Baeten, visiting scientists, staff, and students. All offices and conference rooms are wired with T-100 Ethernet cabling and dual voice/data communication capabilities. Secure Wi-Fi access is available.

Eleven conference rooms on the 12th and 13th floors of NJB are available for use. All include data, phone, and projector connections; six include wall-mounted LCD monitors; four include Polycom videoconferencing capabilities; and one is a fully-equipped classroom for distance learning, including data connections, ceiling-hung projector and screen, lectern with data connections and in-room audio, a ceiling-mounted camera, press-to-talk boundary microphones, Polycom videoconferencing, and two-way audio from lectern to a control room with live webcasting, webinar, and lecture capture capability. One videoconferencing suite includes a dedicated Polycom videoconferencing system with 80-port hub, wall-mounted camera configured for enhanced telepresence, and two wall-mounted LCD monitors. This system enables video connections from up to 80 H.323-compliant videoconferencing clients as well as voice-only participants.

Faculty are provided with private, enclosed office spaces in close proximity to colleagues with similar research interests. Other staff are grouped together by function in a combination of enclosed offices and cubicles. Each team supervisor has a private enclosed office near other team members. These teams are divided into

operational focus including data, research, administration, and lab. There are two centrally-located administrative offices housing the main administrative staff including the administrative systems manager and grants operation manager as well as other key support staff.

The University of Washington is committed to the development of early stage investigators. The International Clinical Research Center conducts weekly work in progress meetings for early stage investigators to receive feedback on their research and has outstanding support for administration of study projects. The Department of Global Health, the University of Washington and Fred Hutchinson Cancer Research Center CFAR (Center for AIDS Research), and the University of Washington, conduct career enrichment workshops and seminars, facilitate formal peer groups and provide support and instruction for conducting research. These resources contribute to the support of early stage investigators, one of whom (a PhD candidate, biostatisician) will be supported in the subcontract to this R01 renewal to the University of Washington, and co-mentored by Drs. Baeten, Elizabeth Brown, Bacchetti and Gandhi.

Relevant Schools and Departments at the University of Washington

School of Public Health
The UW School of Public Health is ranked among the top ten public health schools in the U.S., and has had over 10,000 graduates in the past 40 years. The School houses the Departments of Epidemiology, Global Health, Biostatistics, Environmental and Occupational Health Sciences, and Health Services, and offers interdisciplinary programs in Health Administration, Maternal and Child Health, Nutritional Sciences, Pathobiology, and Public Health Genetics. More than 30 centers and institutes bring together faculty from throughout the School to collaborate and do research across disciplines. The School partners with a number of health organizations including the Bill & Melinda Gates Foundation, Fred Hutchinson Cancer Research Center, Group Health Research Institute, Seattle Children's Hospital, U.S. Department of Veterans Affairs, PATH, and local and regional health departments across a five-state region.

Division of Allergy and Infectious Diseases, Department of Medicine
The Division of Allergy and Infectious Diseases has over 75 full-time faculty members, 50 clinical faculty members, and 15 adjunct or affiliate faculty members. Faculty have been nationally and internationally recognized for their work in a variety of subspecialties, including phagocyte biology and function, HIV/AIDS and other sexually transmitted diseases and infections, viral diseases, immuno-compromised hosts, bacterial pathogenesis, geographic medicine, urinary tract infections, and the molecular biology of infectious diseases.

The Division offers two fellowship training programs which are closely integrated with a number of local hospitals, clinics, and research institutions to provide a wide variety of clinical and research experience. Research training is offered in 9 areas of special emphasis: Clinical Epidemiology of Infectious Diseases, Clinical Trials, Human Immunodeficiency Virus Infection, Immunocompromised Host, Infectious Disease Immunology, Leukocyte Biology and Function, Pathogenesis of Bacterial, Fungal, and Parasitic Diseases, Pathogenesis of Viral Diseases, and Sexually Transmitted Diseases. Affiliations include Fred Hutchinson Cancer Research Center, Harborview Medical Center, Seattle Cancer Care Alliance, Seattle Children's Hospital, University of Washington Medical Center, and VA Puget Sound Health Care System.

Department of Medicine
The University of Washington's Department of Medicine is one of the best-funded departments of medicine in the nation, ranking in the top 10 of most funded departments of medicine in the United States since 2006. The Department has more than 1,000 full-time faculty members who are active in all levels of training—medical school, four residency pathways, and subspecialty fellowship programs. The Department's residencies and fellowships are considered among the best programs in the country. Department of Medicine faculty members are leaders of major multidisciplinary and translational research centers at the University of Washington, including Center for AIDS and STD, Center for Lung Biology, Center for Research in Reproduction and

Contraception, Diabetes and Obesity Center of Excellence, Fred Hutchinson Cancer Research Center (FHCRC), Institute for Stem Cell and Regenerative Medicine, Institute of Translational Health Sciences, Kidney Research Institute, and affiliated with a number of research centers and projects including the AIDS Clinical Trials Unit, AIDS Vaccine Evaluation Unit, Center of Excellence in Women's Health, HIV Prevention Trials Unit, and Virology Research Clinic. Research partners include the Fred Hutchinson Cancer Research Center, Puget Sound Blood Center, Group Health Center for Health Studies, and other centers of advanced study, and research takes place in multidisciplinary centers affiliated with the Department, as well as laboratories at UW Medical Center, Harborview Medical Center, VA Puget Sound Health Care System, and Fred Hutchinson Cancer Research Center.

Department of Epidemiology
The Department of Epidemiology is consistently rated as one of the top epidemiology departments in the United States. The department offers MPH, MS, and PhD degrees in epidemiology, with approximately 165 graduate students at any one time. There is a wide range of faculty expertise, with 70 faculty and an additional ~100 health professionals and scientists holding adjunct and affiliate appointments in the department. Faculty research is highly interdisciplinary and encompasses a broad range of topics, including cancer, HIV/AIDS, sexually transmitted diseases, cardiovascular disease, maternal and child health, injury, trauma and violence, women's health, diseases of aging, and Alzheimer's disease. In addition to infectious agents, faculty research focuses on behavioral, nutritional, genetic, metabolic, environmental and medical factors associated with institutions and programs in the area, including Public Health Seattle-King County, the Fred Hutchinson Cancer Research Center, Group Health Research Institute, Harborview Injury Prevention and Research Center, the Veteran's Administration, and the University of Washington School of Medicine.

Department of Global Health (Vice Chair, Dr. Jared Baeten)
The Department of Global Health (DGH) was established in 2007 through a generous gift and endowment from the Bill & Melinda Gates Foundation, and complementary Washington State resources. UW DGH bridges the schools of Medicine and Public Health, with a mandate to harness the expertise and interdisciplinary power of all 16 UW schools and colleges. Currently, the department has more than 330 faculty representing 15 of 16 UW schools and colleges and 41 departments. It is the second largest department at the University in terms of funding for research and training programs, and includes more than 30 centers, programs, initiatives, and the Institute for Health Metrics and Evaluation (IHME). The Department offers a wide selection of programs, including MPH and PhD degrees, Health Metrics & Evaluation Fellowships, and Graduate Certificate Programs in Global Health, Global Health of Women, Adolescents, and Children (Global WACh), Global Injury and Violence Prevention, and HIV and STIs. A Global Health Minor is also open to students from across campus. Current and emerging focus areas include: health metrics and evaluation, infectious diseases, workforce development, health system strengthening and implementation science, climate change, global trauma and violence, global medicines safety, women, children and adolescent health, and a strong crosscutting focus on social justice and equity.

All of the **support services** at the University of Washington are available for the use of staff, trainees and faculty. These include a machine shop, electronics shop, computer graphics services, photographic services, and financial management services. There is daily courier service between the University of Washington, Fred Hutchinson Cancer Research Center, Harborview Medical Center, and several clinics and research sites to transport specimens and materials between clinics and laboratories.

COMPUTERS: University of Washington

The University of Washington leads the region in providing state-of-the-art access to networked information and innovative, cost-effective computing tools for a wide variety of applications. University-supported resources include Ethernet access and various databases including the Current Index to Statistics, Medline, the UW library catalog, and the Library of Congress. The University also negotiates group-discounted site licenses for

software that are widely used by the University community. UW Information Technology also offers Nebula Managed Desktop Services, which includes delivery and installation of the Nebula software suite, phone support, private and shared file server space, security (patching, anti-virus, hot fixes), power management, drive mappings, printer installs, file restores, and basic set-up and troubleshooting for Outlook email and calendaring. The UW Information Technology service has partnered with Google to provide "UW Google Apps", a service that provides access to many web-based applications that are integrated with UW email accounts, including Google Apps Email with over 7 GB of storage, Google Calendar, Google Talk, Google Docs, and other applications. UW Learning and Scholarly Technologies (LST) offers free workshops on software such as Adobe Creative Suite and Adobe Photoshop, and online curriculum in computing fundamentals, design and graphics, digital audio and video, document creation, spreadsheets and databases, and web publishing. UW LST also offers its own free online suite of web-based communication and collaboration applications for use in teaching, learning, research, and everyday work, including an online survey tool, file sharing, and shared work space.

All members of the ICRC team are supplied with robust computing technology, including laptops, desktops, printers, other peripherals and software; in many cases, these are available at discounted academic prices. Four faculty members use Apple laptops utilizing Bootcamp and Fusion to ensure compatibility with Windows-based programs. The remaining computers are equipped with Windows and Office. All computers are required to have Sophos anti-virus software. Other specialized software provided to personnel with demonstrated need include SAS, SPSS, Stata, Epi Info, R, S Plus, Endnote, Adobe Acrobat Professional, Adobe Photoshop and Illustrator, Microsoft Project and Visio.

The ICRC utilizes secure file servers managed and supported by University of Washington IT services. The servers have remote and local access capabilities, and are backed up daily with redundant backup storage off site. The file folders on the server are restricted to ICRC-specific user groups, the membership of which are regularly reviewed internally and maintained on an ongoing basis. In addition, the files within these directories are password-protected when deemed necessary. A restricted section of the server is reserved for the data team who have exclusive password-protected access. Changes to server access are carefully monitored and must be approved before implementation.

Primary IT support is provided in house. Services include on-demand software support, hardware troubleshooting, general technical support, computing services research, smartphone and A/V support. Travelling employees have access to this support and have redundant systems in place including remote backup, secure external hard drives and travel readiness sessions. Additional post-travel computer check-ups are performed to ensure continued stability of the equipment and programs. In conjunction with UW IT services, IT support is available 24 hours a day.

The ICRC Central Specimen Repository has 3 computers and 2 barcode scanners available for scanning incoming and outgoing specimens. The computers are linked to a dedicated in house server hosting the Repository Freezerworks database which is backed up nightly. Service is provided both in house and by the UW Health Sciences server group.

A Ricoh WorkCentre copier is available, with multifunction capability including copy, print, color and B&W scanning, and fax. Also available are an HP color laserjet printer and an HP B&W business size printer.

DATA MANAGEMENT

The ICRC contracts with DF/Net Research, Inc. to perform data management tasks (e.g. clinical database programming and maintenance). DF/Net uses DataFax, an off-the-shelf study and data management software package, that uses fax machines, bar codes, and intelligent character recognition (ICR) technologies to collect and monitor clinical study data. The DataFax system provides DF/Net data management staff with tools for data entry, data quality control, and overall study management. DataFax is considered a closed system with

centralized data management at DF/Net. The images of case report forms are received, processed by ICR software, and stored in a proprietary database on the DataFax server. All CRF images remain in an electronic form within DataFax throughout the data management process.

Security is included at the system, DataFax, and procedural level to limit data access to authorized individuals. All transactions are fully recorded in a secure audit trail.

In house data staff are provided with view-only access to a study's DataFax database via iDataFax. iDataFax is designed for users who need specific access to view subject case report forms (CRF), data, and data queries in a strictly defined role that does not allow for changing data. In addition, in house data staff are provided access to view and download study reports and/or CRFs for printing via the DF/Net web portal. Changes to access of this portal must be approved before implementation.

TELECONFERENCING CAPABILITIES

The ICRC regularly hosts logistically complex international conference calls utilizing either standard international long distance or a third-party teleconferencing service. Both options require a secure pin to use. Calls to African countries are often actively monitored in house to ensure call stability. The monitor is able to respond immediately to poor connections and dropped callers via an electronic activity panel provided by the teleconferencing service. The monitor and teleconferencing operator work in conjunction to ensure all parties have joined and remain on the call. A log of all calls is maintained and regularly reviewed.

Videoconferences are also periodically scheduled, most often utilizing Skype, Polycom or Adobe Connect. Two of four conference rooms are equipped with advanced videoconferencing equipment including high definition video cameras and projectors; all four rooms are equipped with webcams and LCD screens for use with Skype and other videoconferencing methods. A keypad-secured dedicated control room houses the Adobe Connect server. This server is also operable via an advanced remote control pad. All of these systems are supported in house.

CLINICAL: University of Washington

Clinical facilities of note of the UW and its affiliated institutions are detailed below.

Harborview Medical Center HIV Clinic

The Harborview Medical Center HIV clinic (where Dr. Baeten provides primary HIV care), called the Madison Clinic due to its previous location on Madison Avenue, is now located on the second floor of the West Clinic wing of the hospital and is under the direction of Dr. Robert Harrington. The Madison Clinic, a primary care clinic for HIV-seropositive persons in the Seattle area, is the single largest provider of AIDS care in King County. Approximately 1,300 patients are seen at the Madison Clinic each year, of whom one-fifth are female and one-third are ethnic/racial minorities. The clinic space includes a 12,000 square foot medical office with capacity for onsite services that include provision of inhalation therapy, intravenous treatments, and cancer chemotherapy. A pharmacy, a laboratory, and two conference rooms that are shared with the AIDS Clinical Trials Unit are located within the clinic. Madison Clinic is a nationally recognized outpatient teaching site for medical students, residents, and infectious disease fellows, many of whom follow their own panel of patients for one-half day per week throughout their fellowship.

University of Washington Virology Research Clinic (VRC)

The University of Washington Virology Research Clinic is located in the Ninth & Jefferson building (NJB) on the Harborview Medical Center (HMC) campus. Programs located on the HMC campus include clinical and research programs of the Division of the Infectious Diseases, including the Seattle King-County STD Clinic, HIV Clinic, Center for STD and AIDS Research, AIDS Clinical Trials Unit and the HPV research programs,

creating a unique setting that will facilitate referral of potential study subjects as well as exchange of ideas among faculty. The Virology Research Clinic contains 4,000 sq feet and includes 5 clinical exam rooms and 8 offices; 2 restrooms, a study coordinator suite along with a check in area, waiting room, laboratory, and secure areas for storage of charts, medication, supplies and specimens. IT support, laboratory, and courier services are part of the infrastructure support provided by the Department of Laboratory Medicine/Virology. The laboratory within the clinic includes a centrifuge, microscope, -20oC freezer, -70oC freezer, and a refrigerator for viral cultures. A full time courier transports research samples from clinic to the collaborating laboratories. There is ample locked cabinet space for patient record storage.

Seattle-King County Department of Public Health STD Clinic

Public Health – Seattle & King County operates a comprehensive, community-wide HIV/STD Control Program under the direction of Dr. Matthew Golden. The Program has a $17 million annual budget and a staff of approximately 80 persons. It is responsible for public health HIV/STD surveillance and prevention; administers the Ryan White program for King, Snohomish and Island counties; provides direct medical services related to sexually transmitted infections, and is the largest single diagnosing site for HIV infection in the Pacific Northwest quadrant of the U.S. The program's STD clinic is one of the few STD clinics in the US that is fully integrated into an academic medical center. It occupies 9,200 square feet of newly renovated space in Harborview Medical Center, with 24 examination/counseling rooms. Routine clinical services are provided primarily by nurse practitioners. The STD Clinic operates 50 hours per week and served patients during 12,346 visits in 2010. Approximately 31% of clinic patients are men who have sex with men, 25% are women, and 45% are heterosexual men; 40% of patients are racial/ethnic minorities. Treatment is provided on-site for all common STDs and genitourinary infections. Immediate consultation is routinely available from Harborview specialty services, such as gynecology, dermatology, and urology. The HIV/STD Program is an important clinical training site for medical students, residents, post-doctoral fellows, and AITRP trainees who rotate through the clinic. Training efforts are supported by the Seattle STD/HIV Prevention Training Center and a regional STD training program funded by the CDC. Since 1993, the HIV/STD Program has maintained a clinical database documenting demographic, clinical, epidemiologic, and behavioral data on all STD clinic patient visits; this database currently includes information on over 250,000 clinical evaluations. Additional databases include information collected through HIV/STD partner services and HIV/STD surveillance. All of these databases are available for research following review by PHSKC and removal of patient identifying information.

AIDS Clinical Trials Unit (ACTU)

The AIDS Clinical Trials Unit (ACTU) is one of 50 national AIDS Clinical Trials Group (ACTG) sites, and enrolls ~100 participants per year into clinical trials and natural history studies. The ACTU is located in the west wing of Harborview Medical Center in a 4,500 square foot medical office suite with eight exam rooms, a pharmacy, a laboratory, a waiting room and a medical records room.

FACILITIES AND RESOURCES

SITE: University of Colorado (Dr. Jose Castillo-Mancilla, co-investigator)

OVERVIEW

The University of Colorado-Anschutz Medical Campus (UC-AMC) in Aurora is the medical campus of the four-campus system of the University of Colorado. The Anschutz Medical Campus is a nationally recognized leader in the creation of new knowledge and innovative approaches to improving human health. With sponsored research awards totaling more than $400 million annually, CU Anschutz researchers collaborate with partner and affiliate hospitals, clinics and centers to bring research from the bench to the patient's bedside. It occupies at least 227 acres and is the largest redevelopment project for an academic health center currently in progress in the United States. The Division of Infectious Diseases of the Department of Medicine is housed on the 11th (top) floor of the Research Complex 2 (RC2) building and encompasses 19,518 sq. ft. of laboratory and office space.

CLINICAL

The Division of Infectious Diseases has a large HIV clinical program (in which Dr. Jose Castillo-Mancilla serves) which includes both in-patient and outpatient care at the University of Colorado Hospital (UCH) through the Infectious Diseases Group Practice (IDGP). The UCH is a private, not-for-profit entity with very strong ties and affiliations to UC-AMC. UCH has been consistently recognized as a leading academic medical center in the United States and is the major location for clinical care and research conducted by the faculty in the School of Medicine and the Skaggs School of Pharmacy and Pharmaceutical Sciences. The catchment area served by UCH includes the states of Colorado, Nebraska, Wyoming, Montana, New Mexico, North Dakota and South Dakota. The UCH has a large, centralized clinical laboratory, which includes hematology, chemistry, molecular virology and immunology.

Located in the 7th floor of the UCH Anschutz Outpatient Pavilion, the IDGP is the largest HIV/primary care clinic in the state of Colorado. It provides care for approximately 1,750 patients (17% women) of all racial backgrounds (White 70%, African American/Black African 21%, Asian 2% and Native American/Pacific Islander 2%, Other 5%; Hispanic 15%) and serves a patient population from the Denver Metro Area and remote locations within the states of Colorado and Wyoming. The IDGP is a Ryan White-funded multispecialty clinic staffed by 23 medical providers in the following specialties: infectious diseases/primary care, endocrinology, gynecology, hematology/oncology and psychiatry. It also provides support to patients through experienced nursing staff and social work and has the advantage of having an on-site pharmacy. The IDGP has strong, long-standing ties with all the research programs conducted in the Division of Infectious Diseases.

COMPUTERS

A completely networked computer system with hardware connections to the greater University of Colorado Denver system is available to all personnel for electronic mail, scientific writing, molecular analysis and information (including online journal subscription) access. UC-AMC servers are backed up every night.

OFFICES

Dr. Castillo-Mancilla maintains office space in the Research Complex 2 building. His office comprises 125 sq. ft. of space and is equipped with telephones, ethernet ports, wireless internet, FAX, scanner and photocopy machines. Dr. Castillo-Mancilla is supported by administrative assistants through the ID Division.

ADMINISTRATIVE RESOURCES

The Division of Infectious Diseases in the University of Colorado provides direct administrative support for all Human Resource issues, close monitoring and reporting on grant budgets, monitoring regulatory compliance and NIH-grant related regulations/deadlines, and assistance with grant submissions. Other services include telephone service, faxing capabilities, photocopying, information technology support, as well as proactive

research development (identification of new funding sources and local collaborations). Administrative assistance with clinical protocol development and regulatory submissions (IRB, CTRC) is provided as a Division core service.

MAJOR EQUIPMENT

SITE: University of California, San Francisco (UCSF)

EQUIPMENT

Our lab (Hair Analytical Laboratory -or HAL- at UCSF) has one state-of-the-art GC-MS/MS and two LC-MS instruments necessary to accomplish quantitative mass spectrometry analysis of small molecular targets including antiretrovirals and anti-TB drugs. The laboratory has an Agilent LC 1260- AB Sciex 5500 Triple Quadrupole mass spectrometer dedicated to quantitative targeted analysis. It also has an Agilent LC 1260- QTOF 6550 that is dedicated to non-targeted analysis. The lab recently acquired a Bruker Scion TQ GC-MS/MS ideal for the quantitative analysis of volatile non-polar compounds that are otherwise difficult to analyze using LC-MS. The laboratory has the necessary equipment accessories and additional instrument to support LC-MS/MS analysis, GC-MS/MS analysis and sample preparation. This includes a Peak Scientific 3C-AG high flow nitrogen gas generator, a Parker-Hannepin NitroFlow60 nitrogen generator, a Waters solid phase extraction manifold, a Biotage positive pressure extraction manifold, an Omni Bead Ruptor tissue homogenizer (used to grind hair samples), a Biotage rotavap evaporator, and a table top centrifuge and other additional necessary instrument to support lC-MS/MS analysis, GC-MS/MS analysis and sample preparation. The lab maintains two -80 freezers (12ft^3), a -20 freezer (10 ft^3), three 3ft^3 freezers, and two 3ft^3 refrigerators. The laboratory also shares a fully equipped tissue culture room with laminar flow hoods with its adjacent laboratory.

The laboratory is well-equipped to tackle the three aims of the proposed study. The two LC-MS instruments in the lab that will be used in the study are state-of-the-art equipment and are currently among the most sensitive and technically adept of all commercially available LC-MS instruments. The primary instrument that will be used in the proposed study, the Agilent LC1260- AB Sciex 5500 Triple Quadrupole MS, is ideal for quantitative analysis. This platform remains one of the most sensitive of commercially available tandem mass spectrometers achieving fg/mL-ng/mL (ppq-ppb) sensitivity for most drug analytes with typical linear dynamic ranges of five orders of magnitude making it ideal for the quantitation of very low level drugs that may be extracted in challenging matrices like hair. The targeted analyses of various antiretrovirals and anti-TB drugs are currently being developed and validated in this instrument. The current R01 renewal proposal has apportioned leasing and equipment maintenance contract costs on this machine proportionate to the work proposed here for the 3 Aims. The other LC-MS instrument, Agilent LC 1260- QTOF 6550, is the latest and most sensitive QTOF platform commercially available from Agilent. It is capable of routinely achieving mass resolutions between 25,000- 40,000, currently the highest among QTOF platforms. Its accompanying software, the Agilent MassHunter Qualitative Analysis, Quantitative Analysis, Personal Compound Database and Library, Mass Profiler and Mass Structure Correlator are the most advanced and user-friendly software available for non-targeted analysis. This instrument will be used in a supportive capacity to investigate potential interferences and other analytical issues in sample analysis that may require non-targeted testing.

MAJOR EQUIPMENT

SITE: University of Washington (Dr. Jared Baeten, co-investigator; Dr. Elizabeth Brown, significant contributor)

EQUIPMENT: University of Washington

Not applicable for this application.

MAJOR EQUIPMENT

SITE: University of Colorado (Dr. Jose Castillo-Mancilla, co-investigator)

EQUIPMENT: University of Colorado

Not applicable for this application.

OMB Number: 4040-0001
Expiration Date: 06/30/2016

RESEARCH & RELATED Senior/Key Person Profile (Expanded)

PROFILE - Project Director/Principal Investigator

Prefix: Dr. First Name*: Monica Middle Name Last Name*: Gandhi Suffix: M.D.

Position/Title*: Professor
Organization Name*: The Regents of the University of California, San Francisco
Department: Medicine
Division: School of Medicine
Street1*: [redacted]
Street2:
City*: [redacted]
County:
State*:
Province:
Country*: [redacted]
Zip / Postal Code*:

Phone Number*: [redacted] Fax Number:

E-Mail*: [redacted]

Credential, e.g., agency login: [redacted]

Project Role*: PD/PI Other Project Role Category:

Degree Type: MD, MPH Degree Year: 1996

Attach Biographical Sketch*: File Name: NIH_Biosketch_MGandhi_R01renewal083016.pdf

Attach Current & Pending Support: File Name:

Funding Opportunity Number: PA-16-160 . Received Date: 2016-09-02T14:18:25.000-04:00

PROFILE - Senior/Key Person

Prefix: MD First Name*: Diane Middle Name V Last Name*: Havlir Suffix: M.D.

Position/Title*: Professor
Organization Name*: The Regents of the University of California, San Francisco
Department: Medicine
Division: School of Medicine
Street1*: [redacted]
Street2:
City*: [redacted]
County:
State*:
Province:
Country*: [redacted]
Zip / Postal Code*:

Phone Number*: [redacted] Fax Number: [redacted]

E-Mail*: [redacted]

Credential, e.g., agency login:

Project Role*: Co-Investigator Other Project Role Category:

Degree Type: MD Degree Year: 1984

Attach Biographical Sketch*: File Name: NIH_Bios_DHavlir_Gandhi_R01rnwl082016.pdf

Attach Current & Pending Support: File Name:

PROFILE - Senior/Key Person

Prefix: Dr. First Name*: Peter Middle Name Last Name*: Bacchetti Suffix: Ph.D

Position/Title*: Professor
Organization Name*: The Regents of the University of California, San Francisco
Department: Epidemiology and Biostatistics
Division: School of Medicine
Street1*: [redacted]
Street2:
City*: [redacted]
County:
State*: [redacted]
Province:
Country*: [redacted]
Zip / Postal Code*:

Phone Number*: [redacted] Fax Number: [redacted]

E-Mail*: [redacted]

Credential, e.g., agency login:

Project Role*: Co-Investigator Other Project Role Category:

Degree Type: PhD Degree Year: 1987

Attach Biographical Sketch*: File Name: NIH_Biosketch_PBacchetti_Gandhi_R01rnwl.pdf

Attach Current & Pending Support: File Name:

PROFILE - Senior/Key Person

Prefix: Dr. First Name*: Jared Middle Name Last Name*: Baeten Suffix: M.D.

Position/Title*: Professor
Organization Name*: University of Washington
Department: Global Health
Division: International Clinical Re Ctr
Street1*: [redacted]
Street2:
City*: [redacted]
County:
State*: [redacted]
Province:
Country*: [redacted]
Zip / Postal Code*:

Phone Number*: [redacted] Fax Number: [redacted]

E-Mail*: [redacted]

Credential, e.g., agency login:

Project Role*: Co-Investigator Other Project Role Category:

Degree Type: MD Degree Year: 2003

Attach Biographical Sketch*: File Name: NIH_Biosketch_JBaeten_Gandhi_R01renewal.pdf

Attach Current & Pending Support: File Name:

PROFILE - Senior/Key Person

Prefix: Dr. First Name*: Jose Middle Name Last Name*: Castillo-Mancilla Suffix: M.D.

Position/Title*: Associate Professor
Organization Name*: University of Colorado Denver
Department: Medicine
Division: School of Medicine
Street1*: [redacted]
Street2:
City*: [redacted]
County:
State*: [redacted]
Province:
Country*: [redacted]
Zip / Postal Code*:

Phone Number*: [redacted] Fax Number: [redacted]

E-Mail*: [redacted]

Credential, e.g., agency login:

Project Role*: Co-Investigator Other Project Role Category:

Degree Type: MD Degree Year: 1999

Attach Biographical Sketch*: File Name: NIH_Bios_JCastillo_Mancilla_Gandhi_R01rnwl.pdf

Attach Current & Pending Support: File Name:

PROFILE - Senior/Key Person

Prefix: Dr. First Name*: Leslie Middle Name Z Last Name*: Benet Suffix: Ph.D

Position/Title*: Professor
Organization Name*: The Regents of the University of California, San Francisco
Department: Bioengineering and Therapeutic
Division: School of Pharmacy
Street1*: [redacted]
Street2:
City*:
County:
State*:
Province:
Country*:
Zip / Postal Code*:

Phone Number*: [redacted] Fax Number: [redacted]

E-Mail*: [redacted]

Credential, e.g., agency login:

Project Role*: Co-Investigator Other Project Role Category:

Degree Type: Ph.D Degree Year: 1965

Attach Biographical Sketch*: File Name: NIH_Biosketch_LBenet_Gandhi_R01renewal.pdf

Attach Current & Pending Support: File Name:

PROFILE - Senior/Key Person

Prefix: Dr. First Name*: Roy Roberto Middle Name L Last Name*: Gerona Suffix: Ph.D

Position/Title*: Assistant Professor
Organization Name*: The Regents of the University of California, San Francisco
Department: Obstetrics and Gynecology
Division: School of Medicine
Street1*: [redacted]
Street2:
City*:
County:
State*:
Province:
Country*:
Zip / Postal Code*:

Phone Number*: [redacted] Fax Number:

E-Mail*: [redacted]

Credential, e.g., agency login:

Project Role*: Co-Investigator Other Project Role Category:

Degree Type: PhD Degree Year: 2008

Attach Biographical Sketch*: File Name: NIH_Biosketch_RGerona_Gandhi_R01rnwl.pdf

Attach Current & Pending Support: File Name:

PROFILE - Senior/Key Person

Prefix: Dr. First Name*: Elizabeth Middle Name R. Last Name*: Brown Suffix: Sc.D

Position/Title*: Professor
Organization Name*: University of Washington
Department: Biostatistics
Division: School of Public Health
Street1*: [redacted]
Street2:
City*: [redacted]
County:
State*: [redacted]
Province:
Country*: [redacted]
Zip / Postal Code*:

Phone Number*: [redacted] Fax Number:

E-Mail*: [redacted]

Credential, e.g., agency login: [redacted]

Project Role*: Other (Specify) Other Project Role Category: Other Significant Contributor

Degree Type: Sc.D. Degree Year: 2002

Attach Biographical Sketch*: File Name: NIH_Biosketch_EBrown_Gandhi_R01rnwl0816.pdf

Attach Current & Pending Support: File Name:

OMB No. 0925-0001 and 0925-0002 (Rev. 10/15 Approved Through 10/31/2018)

BIOGRAPHICAL SKETCH
DO NOT EXCEED FIVE PAGES.

NAME: **Monica Gandhi**

eRA COMMONS USER NAME (credential, e.g., agency login): [redacted]

POSITION TITLE: Professor of Medicine and Associate Division Chief

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
University of Utah	B.S.	06/1991	Molecular Biology
Harvard Medical School	M.D.	06/1996	Medicine
University of California, San Francisco		07/1999	Internal Medicine Residency
University of California, San Francisco		04/2003	Infectious Diseases Fellowship
University of California, San Francisco		04/2003	Center for AIDS Prevention Studies Postdoctoral Fellowship
University of California, Berkeley	M.P.H.	06/2001	Epidemiology/Biostatistics

A. Personal Statement

I am a Professor of Medicine and Associate Chief in the Division of HIV, Infectious Diseases and Global Medicine at the University of California, San Francisco (UCSF). I have worked on clinical research studies investigating adherence to antiretrovirals (ARVs) and their pharmacokinetics (PK) in domestic and global populations for over a decade. This research platform started with an NIAID/NIH-awarded K23 Career Development Award (K23 AI06065) from 2005-2010, with Dr. Leslie Z. Benet (co-investigator on this application and General Director of the Hair Analytical Laboratory (HAL) at UCSF) serving as primary mentor. Using the Women's Interagency HIV Study (WIHS) as a platform, we showed that pharmacokinetic parameters of antiretrovirals in diverse populations with multiple comorbidities can differ substantially from parameters modelled in small, early phase studies. I served as the Chair of the Pharmacology Working Group in the multisite WIHS cohort from 2003-2014 and, in that role, helped pioneer the measurement of ARV concentrations in small hair samples at UCSF as measures of both adherence and pharmacokinetic variability.

We received an R01 from NIAID/NIH (R01 AI098472) in 2011 to further investigate these hair measures within the NIH-funded clinical trials networks, studying multiple applications of this innovative measure for assessing both adherence and PK. The initial funding period of this R01 award was productive, generating 20 papers demonstrating important uses for hair measures in treatment and with tenofovir disoproxil fumarate/ emtricitabine-based PrEP. **We now seek a renewal of this productive R01 grant,** with new aims extending the use of hair measures to investigate innovative and exciting long-acting methods for preventing HIV infection, such as the dapivirine vaginal ring and long-acting injectables. We continue our collaborations with the networks (e.g. MTN and ACTG; Aims 2 and 3, respectively) in this proposal and forge a new collaboration with a large study examining novel mechanisms to deliver oral PrEP on a population level in Africa (SEARCH, Aim 1). The UCSF HAL – whose infrastructure is supported by this R01 – is now working collaboratively with multiple HIV clinical trials to extend the use of this novel metric into a variety of applications.

I am a member of the Advisory Council for the NIH Office of AIDS Research and serve on the Executive Committee of the Adult AIDS Clinical Trials Group (ACTG). I am also the medical director of Ward 86, one of the largest and oldest HIV clinics in the country, which is based at San Francisco General Hospital (SFGH). Ward 86 recently instituted a PrEP clinic and I am interested in studying the real-world application of findings from the aims proposed here. I have an additional interest in teaching and mentorship in HIV and serve as the co-Director of the UCSF Center for AIDS Research (CFAR) Mentorship Program. I also co-direct the Mentoring Program in the CFAR Network of Integrated Clinical Systems (CNICS), which integrates data from 8 centers of HIV care nationwide, and have developed a yearly "Mentoring the Mentors" workshop at UCSF which trains mid-level and senior HIV researchers in specialized skills and techniques to fostering early career scholars from underrepresented groups (funded by R24). I serve as Assistant Program Director of Clinical Research for

the Infectious Diseases fellowship at UCSF with a special interest in increasing diversity in the biomedical research workforce. I and other collaborators on this renewal (Drs. Diane Havlir, Jared Baeten, Les Benet, Jose Castillo-Mancilla) have a keen interest in mentorship and hope to use this R01 award, if funded, as an additional platform to train early career scholars in adherence measurement and pharmacokinetics.

I have co-authored 26 publications on the use of hair measures in the context of HIV treatment or prevention (20 funded by this R01 on hair levels and PK), many with my collaborators on this application (Bacchetti, Benet, Havlir, Gerona or with mentees*), with key publications related to PrEP listed below:

a. [redacted]
b. **Gandhi M**, Glidden DV, Liu A, et al. Concentrations of TFV-DP/FTC-TP in dried blood spots and TFV/FTC in hair are strongly correlated in iPrEx OLE: Implications for PrEP adherence monitoring. *Journal of Infectious Diseases* Nov 1;212(9):1402-6. PMCID: PMC4601920
c. Baxi SM*, Liu A, Bacchetti P, Mutua G, Sanders EJ, Kibengo FM, Haberer JE, Rooney J, Hendrix CW, Anderson PL, Huang Y, Priddy F, **Gandhi M**. Comparing the Novel Method of Assessing PrEP Adherence/Exposure using Hair Samples to other Pharmacologic and Traditional Measures. *JAIDS* 2015 Jan 1;68(1):13-20. PMCID: PMC4262724
d. Liu AY, Yang Q, Huang Y, Bacchetti P, Anderson PL, Jin C, Goggin K, Stojanovski K, Grant R, Buchbinder SP, Greenblatt RM, **Gandhi M**. Strong Relationship between Oral Dose and Tenofovir Hair Levels in a Randomized Trial: Hair as a Potential Adherence Measure for Pre-Exposure Prophylaxis (PrEP). *PLoS One.* 2014;9(1):e83736. PMCID: PMC3885443

B. Positions and Honors

Positions and Employment

1996-2002	Resident, Internal Medicine and Fellow, Infectious Diseases, UCSF
2000-2003	Postdoctoral fellow, TAPS program, Center for AIDS Prevention, UCSF
2003-2009	Assistant Professor, Department of Medicine, Division of Infectious Diseases, UCSF
2008-now	Director, San Francisco General Hospital (SFGH) HIV Consult Service
2009-2013	Associate Professor, Division of HIV/AIDS, UCSF
2008-2015	Core faculty, Master of Science Degree in Global Health Sciences, UCSF
2009-2015	Education Director, HIV/AIDS Division
2010-now	Program Director, UCSF Building Interdisciplinary Careers in Women's Health Research (BIRCWH) K12 scholarship 2010-2014; Chair of Advisory Committee 2015-on
2013-now	Professor, Division of HIV, Infectious Diseases, and Global Medicine, UCSF
2013-now	Co-Director for UCSF Center for AIDS Research (CFAR)'s Mentoring Program
2014-now	Medical Director, HIV Clinic at SFGH ("Ward 86")
2015-now	Associate Division Chief for Clinical Operations/Education, Division of HIV, ID and Global Medicine
2016-now	Assistant Program Director for Clinical Research, Infectious Diseases Fellowship, UCSF

Other Experience and Professional Memberships

2000-now	Infectious Diseases Society of America (membership number 009532)
2006-now	HIV specialist, American Academy of HIV Medicine (AAHIVM ID# 16272)
2014-now	Member, Clinical Pharmacology Adherence Group (CPAG), Adult AIDS Trials Group (ACTG)
2014-now	Member, NIH Office of AIDS Research Advisory Council (OARAC)
2016-now	Member, ACTG Executive Committee (Investigator-at-Large)

Honors and Awards

2000	Housestaff Teaching Award from UCSF School of Medicine, 2000
2003-2005	Awarded UCSF BIRCWH K12 Scholarship
2004-2005	Hellman Family Award for Early Career Faculty, UCSF
2008	Essential Core Teaching Award (Excellence in Small Group Instruction), UCSF
2011	Sarlo Award for Excellence in Teaching, AIDS Research Institute, UCSF
2012	Meg Newman Teaching Award, Positive Health Practice, SFGH
2013	John L. Ziegler Annual Award for Outstanding Mentoring, Global Health Sciences Masters' Program

2015 Nominated for Chancellor's Award for the Advancement of Women
2015 "Defender of *Patient Humanity Award" from UCSF Infectious Diseases Division*
2016 Vince Pons Award for Teaching in Clinical Infectious Diseases, ID Division, UCSF

C. Contribution to Science

1. **Monitoring treatment outcomes in HIV and TB:** Pharmacologic measures of adherence have proven useful in the context of HIV prevention, where HIV viral loads cannot be used as a surrogate for adherence, and for monitoring the toxicities of PrEP. Hair levels also have a role in monitoring HIV treatment outcomes, predicting virologic response better than self-reported adherence or single plasma ARV concentrations; monitoring mother to infant ARV transfer in the context of pregnancy and breastfeeding; and measuring responses to adherence interventions. Moreover, in the last year of the first funding period of this R01, we extended the use of these measures to the fields of latent and active TB infection. Four key publications are noted below:
    a. Gerona R*, Wen A, Chin AT, Koss CA, Bacchetti P, Metcalfe J, **Gandhi M**. Quantifying Isoniazid Levels in Small Hair Samples: A Novel Method for Assessing Adherence during the Treatment of Latent and Active Tuberculosis. *PLoS One.* 2016;11(5):e0155887. PMCID: PMC4871544
    b. Koss C*, Natureeba P, Mwesigwa J, Cohan D, Nzarubara B, Bacchetti P, Horng H, Clark TD, Plenty A, Ruel TD, Achan J, Charlebois ED, Kamya MR, Havlir DV, **Gandhi M**. Hair Concentrations of Antiretrovirals Predict Viral Suppression in HIV-Infected Pregnant and Breastfeeding Ugandan Women. *AIDS* 2015 Apr 29(7): 825-830 PMCID: PMC4438773
    c. Hickey MD*, Salmen CR, Tessler RA, Omollo D, Bacchetti P, Magerenge R, Mattah B, Salmen MR, Zoughbie D, Fiorella KJ, Geng E, Njoroge B, Jin C, Huang Y, Bukusi EA, Cohen CR, **Gandhi M**. Antiretroviral concentrations in small hair samples as a feasible marker of adherence in rural Kenya. *JAIDS* 2014;66(3):311-315. PMCID:PMC4146734
    d. **Gandhi M,** Ameli N, Bacchetti P, et al. Atazanavir Concentrations in Hair Samples are the Strongest Predictor of Outcomes in HIV Infection. *Clinical Infectious Diseases* 2011 May 15; 52(10): 1267-1275. PMCID: PMC3079399

2. **Pharmacokinetic variability in real-world populations**: My K23 award was focused on assessing pharmacokinetic variability in diverse populations, including women, minorities, and those with comorbidities or substance use. We were also interested in the impact of pharmacogenomics on short and long-term antiretroviral exposure. Key publications on ARV pharmacokinetics stemming from this work, **and relevant to Aim 3 of the current application,** are listed below:
    a. **Gandhi M**, Greenblatt RM, Bacchetti P, et al. A Single Nucleotide Polymorphism in CYP2B6 Leads to >3-fold Increases in Efavirenz Concentrations in Intensive PK Curves and Hair Samples in HIV-infected Women. *Journal of Infectious Diseases* 2012 Nov;206(9):1453-1461.PMCID: PMC3466997
    b. Baxi SM*, Greenblatt RM, Bacchetti P, Scherzer R, Minkoff H, Huang Y, Anastos K, Cohen M, Gange SJ, Young M, Shlipak MG, **Gandhi M**. Common clinical conditions - age, low BMI, ritonavir use, mild renal impairment - affect tenofovir pharmacokinetics in a large cohort of HIV-infected women. *AIDS.* 2014;28(1):59-66. PMCID: PMC3956315
    c. **Gandhi M**, Benet LZ, Bacchetti P, et al. Nonnucleoside reverse transcriptase inhibitor pharmacokinetics in a large unselected cohort of HIV-infected women. *JAIDS* 2009;50(5):482-491.PMCID: PMC2700138
    d. **Gandhi M**, Aweeka F, Greenblatt RM, Blaschke TF. Sex differences in pharmacokinetics and pharmacodynamics. *Annu Rev Pharmacol Toxicol.* 2004;44:499-523. PMID: 14744256

3. **HIV infection in women**: Much of my additional research has focused on sex differences in HIV infection, with an emphasis on viral load differences in men and women early on in infection, sex differences in pharmacokinetics and ARV levels in pregnancy, barriers to participation in clinical trials of new therapies for HIV-positive women, factors that contribute to differential outcomes for HIV-infected women in the United States, and interactions between antiretrovirals and hormonal contraceptives. **This interest in relevant to Aim 2 of this application** which seeks to help maximize the effectiveness of the dapivirine vaginal ring to prevent HIV acquisition in women.
    a. Patel R*, Maricianah O, **Gandhi M**, et al.. Comparison of pregnancy rates among HIV-positive women using contraceptives and efavirenz- or nevirapine-based antiretroviral therapy in Kenya. *Lancet HIV* 2015 Nov; 2(11): e474-e48. PMCID: PMC4632202

b. **Gandhi M**, Mwesigwa J, Aweeka F, et al. Hair and Plasma Data Show That Lopinavir, Ritonavir, and Efavirenz All Transfer From Mother to Infant In Utero, But Only Efavirenz Transfers via Breastfeeding. *JAIDS.* 2013;63(5):578-584. PMCID: PMC3800282
c. **Gandhi M**, Ameli N, Bacchetti P, et al. Eligibility criteria for HIV clinical trials and generalizability of results: the gap between published reports and study protocols. *AIDS* 2005 Nov;19(16):1885-1896. PMID: 16227797
d. **Gandhi M**, Bacchetti P, Miotti P, et al. Does patient sex affect human immunodeficiency virus levels? *Clinical Infectious Diseases* 2002 Aug;35:313-22. PMID: 12115098

4. **Mentoring in HIV research**: I also have a particular interest in HIV teaching and mentorship, especially focused on mentoring women and early career investigators of diversity, as well as working on programs to provide specialized training to mid-and-senior level HIV researchers to become more effective mentors (funded initially by a NIMH R24 on which I served as PI). I co-direct the UCSF CFAR Mentorship program and the national CNICS Mentoring Program. Through support from a Fogarty International Training Grant, I directed four "Mentoring the Mentors" workshops for global health researchers internationally (Peru in May 2013; Kenya June 2013; India November 2014; South Africa March 2016). Consistent with the high-priority areas for AIDS research in training **we hope to continue to use this R01 as a platform for mentoring**. Key publications in HIV mentoring and teaching listed:
    a. **Gandhi M,** Johnson MO. Creating more effective mentors: Mentoring the mentor. *AIDS and Behavior* 22016 Sep;20 Suppl 2:294-303. PMCID: PMC4995126
    b. Johnson, MO and **Gandhi M.** A mentor training program improves mentoring competency for researchers working with early-career investigators from underrepresented backgrounds. *Advances in Health Sciences Education* 2015 Aug;20(3):683-9. PMCID: PMC438373
    c. **Gandhi M**, Fernandez A, Stoff DM,et al. Development and implementation of a workshop to enhance the effectiveness of mentors working with diverse mentees in HIV research. *AIDS Research and Human Retroviruses* 2014 Aug;30(8):730-7. PMCID: PMC4118696
    d. **Gandhi M** and Gandhi RT. Single pill combination therapy for HIV-1 infection. *New England Journal of Medicine* 2014 July;371:248-59. PMID: 25014689. DOI 0.1056/NEJMct1215532

*Indicates first-author is a mentee

Complete List of Published Work in MyBibliography:
http://www.ncbi.nlm.nih.gov/sites/myncbi/monica.gandhi.1/bibliography/44803451/public/?sort=date&direction=descending

D. Research Support

R01 AI098472 (Gandhi) – seeking renewal 12/15/11-11/30/16
NIH/NIAID
Plugging Hair ARV Levels as Adherence Biomarkers into HIV Prevention Trials
This proposal extends our novel approach to assess antiretroviral (ARV) adherence and exposure using ARV measurements in small hair samples to the clinical trial setting. We will insert hair measures as objective biomarkers of adherence to antiretrovirals in HIV-infected pregnant and breastfeeding women and in a PrEP trial in African women.
Role: PI

R01 AI123024 (Gandhi, Metcalfe) 12/01/15-11/30/20
NIAID/NIH
Novel methods of pharmacologic monitoring for multidrug resistant tuberculosis treatment in the setting of HIV infection
This proposal extends the use of measuring drug concentrations in small hair samples as a measure of adherence/exposure from the HIV setting to the MDR-TB setting, leveraging two South African clinical trials studying optimal treatments for MDR-TB in the new era of anti-TB therapy.
Role: Co-PI

R21 AI112362-01 (Gandhi) 04/1/14-3/30/16, in NCE

NIAID/NIH
Hair measures to assess adherence and explain outcomes in an HIV treatment trial
This proposal seeks to extend the approach of using hair antiretrovirals levels to monitor adherence and exposure in a treamtne trial of naïve patients, partnering with the AIDS Clinical Trials Group (ACTG) to further test our methodology in a clinical trial which randomized patients to 3 NNRTI-sparing regimens (A5257).
Role: PI

2P30 AI027763 (Volberding) 07/01/12-08/31/17
NIH/NIAID
UCSF-GIVI Center for AIDS Research (CFAR)
I serve as the Co-Director of the CFAR-Gladstone Institute of Virology and Immunology (GIVI) mentoring program at UCSF. In this role, I am responsible for developing and innovating for the robust mentorship program in HIV research through CFAR at UCSF and developing “Mentoring the Mentors” training programs for HIV researchers nationwide. I also serve on the CFAR Advisory Board and the Scientific Council.
Role: Co-Investigator

R24AI067039 (Saag) 07/01/10 – 8/31/16
NIH/NIAID
The CFAR (Center for AIDS Research) Network of Integrated Clinical Systems (CNICS).
CNICS is a clinic-based research network that reflects the outcomes of clinical decisions and management options used in the care of HIV infected individuals at 8 CFAR sites. I serve as the Co-Director of the national CNICS Mentoring Program.
Role: Co-Investigator

K12HD052163 (Brindis) 07/31/16 – 07/31/20
NICHD/NIH
UCSF-Kaiser/DOR Building Interdisciplinary Research Careers in Women’s Health Program (BIRCWH)
This grant supports a training program for junior faculty who plan to pursue a clinical or translational research career in women’s health. After serving as Program Director of the UCSF BIRCWH from 2010-2014, I transitioned to the Chair of the Advisory Board in 2015
Role: Chair of the UCSF BIRCWH Advisory Board

Completed (partial)

R24MH094274 (Gandhi) 07/11/11 - 07/30/13
NIMH/NIH
Developing a Mentoring Network of Diverse Health Professionals
The main goal of this grant was to develop a mentoring network for early career investigators from diverse backgrounds. The mentoring was tied closely to data available from the CNICS platform. The project included the development of the “Mentoring the Mentors" workshop series.
Role: PI

K23 AI067065 (Gandhi) 10/1/05-7/31/10
NIAID/NIH
Assessing antiretroviral exposure in diverse populations. This K23 Mentored Patient-Oriented Research Career Development Award provided support for my primary research project of assessing a variety of measures, including population pharmacokinetics modellng, to assess exposure to antiretroviral medications in diverse HIV-infected populations.
Role: PI

R21 MH085598 (Liu, P.I. 01/01/09-01/01/11
NIMH/NIH
Hair as a Biomarker of Tenofovir Prophylactic Exposure. This project aimed to develop the use of hair levels as a novel biological marker of patient adherence and drug exposure to oral tenofovir with an ultimate application in HIV pre-exposure prophylaxis trials
Role: Co-investigator

OMB No. 0925-0001 and 0925-0002 (Rev. 10/15 Approved Through 10/31/2018)

BIOGRAPHICAL SKETCH
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NAME: **Diane V. Havlir**

eRA COMMONS USER NAME: [redacted]

POSITION TITLE: Professor of Medicine and Division Chief, University of California, San Francisco

EDUCATION/TRAINING (Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)

INSTITUTION AND LOCATION	DEGREE (if applicable)	Completion Date MM/YYY	FIELD OF STUDY
St. Olaf College, Northfield, MN	BA	1980	Chemistry/Biology
Duke University Medical School, Durham, NC	MD	1984	Medicine
University of California, San Francisco (UCSF)	Residency	1987	Internal Medicine
Case Western Reserve University	Fellowship	1990	Infectious Diseases

A. Personal Statement

My research over the last two decades has been focused on prevention, treatment and pathogenesis studies of HIV and associated co-infections. I am currently the principal investigator (along with Dr. Moses Kamya in Uganda, see letter of support for this application) for the Sustainable East Africa Research in Community Health (SEARCH) study and am extremely enthusiastic to serve as a co-investigator on Dr. Gandhi's proposal to use innovative biomedical approaches (via hair sampling) to measure adherence to ART for prevention during the next phase of our study. Aim 1 of the proposed grant application ("Hair Extensions": Using Hair Levels to Interpret Adherence, Effectiveness and Pharmacokinetics with Real-World Oral PrEP, the Vaginal Ring, and Injectables) will leverage the SEARCH study. The SEARCH study (NCT 01864603) has successfully enrolled over 320,000 persons in 32 communities. This community cluster randomized study is testing the hypothesis in the first phase that that universal HIV test and treatment in a multi-disease, streamlined care setting will reduce new HIV infections and preserve community health. In the second phase of SEARCH - relevant to the current proposal - the 32 communities are re-randomized to targeted PREP and targeted cascade enhancements versus a test and treat strategy only. Dr. Gandhi and I have worked together on a number of projects (with 8 co-authored publications) and the objectives she proposes here to advance adherence measurement in our novel study will allow us to interpret the effectiveness of PrEP.
Below is a sampling of some SEARCH publications.

1. Chamie G, Kwarisiima D, Clark TD, Kabami J, Jain V, Geng E, Balzer LB, Petersen ML, Thirumurthy H, Charlebois ED, Kamya MR, **Havlir DV**; the SEARCH Collaboration. Uptake of Community-Based HIV Testing during a Multi-Disease Health Campaign in Rural Uganda. PLoS One. 2014 Jan 2;9(1):e84317. eCollection 2014. PMID: 24392124; PMCID: 3879307.
2. Jain V, Byonanebye DM, Liegler T, Kwarisiima D, Chamie G, Kabami J, Petersen ML, Balzer LB, Clark TD, Black D, Thirumurthy H, Geng EH, Charlebois ED, Amanyire G, Kamya MR, **Havlir DV;** SEARCH Collaboration. Changes in Population HIV RNA Levels in Mbarara, Uganda During Scale-Up of HIV Antiretroviral Therapy Access. *J Acquir Immune Defic Syndr*.2014 Mar 1;65(3):327-32. PMID: 24146022; PMCID: PMC4172444
3. Jain V, Byonanebye DM, Amanyire G, Kwarisiima D, Black D, Kabami J, Chamie G, Clark TD, Rooney JF, Charlebois ED, Kamya MR, **Havlir DV**; the SEARCH Collaboration. Successful antiretroviral therapy delivery and retention in care among asymptomatic individuals with high CD4+ T-cell counts at least 350 cells/μl in Rural Uganda. AIDS. Sep 24;28(15):2241-9.PMID: 25022596. PMCID:PMC4894849
4. Chamie G, Clark TD, Kabami J, Kadede K, Ssemmondo E, Steinfeld R, Lavoy G, Kwarisiima D, Sang N, Jain V, Thirumurthy H, Liegler T, Balzer LB, Petersen ML, Cohen CR, Bukusi EA, Kamya MR, **Havlir DV**,

Charlebois ED. A hybrid mobile approach for population-wide HIV testing in rural east Africa: an observational study. *Lancet HIV*. 2016 Mar;3(3):e111-9. PMID: 26939734; PMCID: PMC4780220.

B. Positions and Honors

Positions

1984-1987 Internal Medicine Resident, University of California, San Francisco

1987-1988 Chief, Veterans Administration Home Based Health Care Program

1988-1990 Infectious Diseases Fellow, Case Western Reserve University

1990-1996 Assistant Professor, University of California, San Diego

1999-2002 Associate Professor, University of California, San Diego

2002-present Professor of Medicine, University of California, San Francisco

2002-2015 Chief, HIV/AIDS Division, San Francisco General Hospital

2015-present Chief, HIV, Infectious Diseases and Global Medicine Division, San Francisco General Hospital

Service and Professional memberships

2014-present: Chair, WHO Global HIV Drug Resistance Surveillance Network; 2008-present, Scientific Advisory Committee for the Infectious Diseases Center for Global Health and Policy; 2010-2012: Co-Chair, International AIDS Conference, Washington; 2008-2010: Scientific Chair, International AIDS Conference, Vienna, Austria; 2006-2014: Chair, HIV/TB working group of the WHO /STOP TB partnership; 2006-2014: Member, Board of Directors of the STOP TB partnership; 2002-2010: International AIDS Society Governing Council and Executive Committee; 2002-present: Member and author, World Health Organization, WHO Care Committee for Antiretroviral Treatment Guidelines for Resource Limited Settings; Member, International AIDS Society and Infectious Diseases.

Honors

2016 Visiting Professor, Columbia University; 2015 Heroes and Hearts Award, San Francisco General Hospital; 2014 Project Inform Thomas M Kelley Leadership Award; 2014 Chancellors Award for the Advancement of Women, UCSF; 2014 Pathways Mentorship Award, UCSF; 2013 St. Olaf College Alumni Achievement Award; 2012 Joseph E. Smadel Infectious Diseases Society of America Award; 2012 United States Co-Chair for XIX International AIDS Conference; 2012, Vanity Fair Hall of Fame, “Pioneering leader in the fight against AIDS”; 2010 ARI (AIDS Research Institute) Award for Outstanding Mentoring; 2010 Scientific Chair for XVIII International AIDS Conference, Vienna; 2009 UCSF Pediatric Mentorship Award.

C. Contributions to Science

HIV treatment Strategies

My research career for the last two decades has been focused on advancing HIV treatment and prevention and treatment of co-infections. Early trials shed light on HIV reservoir and viral dynamics, established azithromycin for M. avium prophylaxis, provided key evidence for global guidelines on the dose and combinations of optimal antiretroviral therapy, and have advanced optimal antiretroviral management strategies. Highlights of early studies are shown:

1. **Havlir D V**, Dube MP, Sattler FR, Forthal DN, Kemper CA, Dunne MW, Parenti DM, Lavelle JP, White AC, Jr., Witt MD, Bozzette SA, McCutchan JA. Prophylaxis against disseminated Mycobacterium avium complex with weekly azithromycin, daily rifabutin, or both. California Collaborative Treatment Group. N Engl J Med. 1996;335(6): 392-8. PMID: 8676932.
2. **Havlir DV**, Marschner IC, Hirsch MS, Collier AC, Tebas P, Bassett RL, Ioannidis JP, Holohan MK, Leavitt R, Boone G, Richman DD. Maintenance antiretroviral therapies in HIV infected patients with undetectable plasma HIV RNA after triple-drug therapy. AIDS Clinical Trials Group Study 343 Team. N Engl J Med. 1998 Oct 29;339(18):1261-8. PMID: 9791141.

3. **Havlir DV**, Hellmann NS, Petropoulos CJ, Whitcomb JM, Collier AC, Hirsch MS, Tebas P, Sommadossi JP, Richman DD. Drug susceptibility in HIV infection after viral rebound in patients receiving indinavir-containing regimens. JAMA. 2000 Jan 12;283(2): 229-34. PMID: 10634339.
4. **Havlir DV**, Bassett R, Levitan D, Gilbert P, Tebas P, Collier AC, Hirsch MS, Ignacio C, Condra J, Gunthard HF, Richman DD and Wong. Prevalence and predictive value of intermittent viremia with combination HIV therapy JK. JAMA. 2001 Jul 11;286(2): 171-9. PMID: 11448280.

HIV and Tuberculosis

My research in this area has focused on epidemiology, implementation science and clinical trials for co-treatment of HIV and TB. Our randomized study of timing of ART in HIV + adults with TB helped formed the basis for the World Health Organization Global Treatment Guidelines.

1. **Havlir DV**, Getahun H, Sanne I and Nunn P. Opportunities and challenges for HIV care in overlapping HIV and TB epidemics. JAMA. 2008 Jul 23;300(4): 423-30. PMID: 18647985.
2. Chamie G, Charlebois ED, Srikantiah P, Walusimbi-Nanteza M, Mugerwa RD, Mayanja H, Okwera A, Whalen CC, **Havlir DV.** Mycobacterium tuberculosis Microbiologic and Clinical Treatment Outcomes in a Randomized Trial of Immediate versus CD4(+)-Initiated Antiretroviral Therapy in HIV-Infected Adults with a High CD4(+) Cell Count. Clin Infect Dis. 2010 Aug 1;51(3):359-62. PMID: 20569064; PMCID: PMC2919368.
3. **Havlir DV**, Kendall MA, Ive P, Kumwenda J, Swindells S, Qasba SS, Luetkemeyer AF, Hogg E, Rooney JF, Wu X, Hosseinipour MC, Lalloo U, Veloso VG, Some FF, Kumarasamy N, Padayatchi N, Santos BR, Reid S, Hakim J, Mohapi L, Mugyenyi P, Sanchez J, Lama JR, Pape JW, Sanchez A, Asmelash A, Moko E, Sawe F, Andersen J, Sanne I. Timing of antiretroviral therapy for HIV-1infection and tuberculosis. N Engl J Med. 2011 Oct 20;365(16):1482-91. PMCID: PMC3327101.
4. Marquez C, Chamie G, Achan J, Luetkemeyer AF, Kyohere M, Okiring J, Dorsey G, Kamya MR, Charlebois ED, **Havlir DV**. Tuberculosis Infection in Early Childhood and the Association with HIV-Exposure in HIV-Uninfected Children in rural Uganda. *Pediatr Infect Dis J*. 2016 May;35(5):524-9; PMID: 26771662; PMCID: PMC4829461

HIV and co-infection epidemiology, prevention and treatment in the international setting

In 2000, I began working in a research collaboration in east Africa, Uganda and Kenya, to help define the natural history and optimal treatment of HIV and related co-infections in resource limited settings. I lead a grant looking at the interface between malaria and HIV in East Africa and optimal ART strategies during pregnancy. These studies have shed key insights into HIV and co-infections and contributed to global guidelines for HIV and co-infection treatment.

1. Charlebois ED, Ruel TD, Gasasira AF, Achan J, Kateera F, Akello C, Cao H, Dorsey G, Rosenthal PJ, Ssewanyana I, Kamya MR, **Havlir DV**. Short-Term Risk of HIV Disease Progression and Death in Ugandan Children Not Eligible for Antiretroviral Therapy. J Acquir Immune Defic Syndr. 2010 Nov;55(3):330-5. PMCID: PMC302513.
2. Achan J, Kakuru A, Ikilezi G, Ruel T, Clark TD, Nsanzabana C, Charlebois E, Aweeka F, Dorsey G, Rosenthal PJ, **Havlir D**, Kamya MR. Antiretroviral Agents and Prevention of Malaria in HIV-Infected Ugandan Children. N Engl J Med. 2012 Nov 29;367(22):2110-18. PMCID: PMC3664297
3. Jain V, Byonanebye DM, Amanyire G, Kwarisiima D, Black D, Kabami J, Chamie G, Clark TD, Rooney JF, Charlebois ED, Kamya MR, **Havlir DV**; the SEARCH Collaboration. Successful antiretroviral therapy delivery and retention in care among asymptomatic individuals with high CD4+ T-cell counts at least 350 cells/μl in Rural Uganda. AIDS. Sep 24;28(15):2241-9.PMID: 25022596. PMCID: PMC4894849
4. Cohan D, Natureeba P, Koss CA, Plenty A, Luwedde F, Mwesigwa J, Ades V, Charlebois ED, Gandhi M, Clark TD, Nzarubara B, Achan J, Ruel T, Kamya MR, **Havlir DV.** Efficacy and safety of lopinavir/ritonavir versus efavirenz-based antiretroviral therapy in HIV-infected pregnant Ugandan women. AIDS. 2015 Jan 14;29(2):183-91. PMCID: PMC4428759

Complete list of published work (>250 publications):

http://www.ncbi.nlm.nih.gov/pubmed/?term=havlir+D

D. Research Support

ONGOING

UM1AI069496 (Buchbinder, Havlir) 12/01/2013 – 11/30/2020
NIH/NIAID
San Francisco Bay CTU
The major goal of this project is to advance HIV prevention and treatment science forward and being major contributors to the HVTN, HPTN, MTN and ACTG.
Role: Co-Principal Investigator

[redacted]

P01 HD059454 (Havlir) 08/1/2008-06/30/2018
NIH-NICHD
Novel Strategies to Prevent Malaria and Improve HIV Outcomes in Africa
The primary goal will be to build on current knowledge to establish new approaches to reduce HIV and malaria burden in sub-Saharan Africa, and to advance the public health approach to both diseases.
Role: Principal Investigator

U01AI099959 SEARCH Supplement (Havlir) 01/01/2014 – 06/30/2018
NIH/NIAID
Sustainable East Africa Research on Community Health
Overall goal: Evaluate health, economic, education outcomes of CD4 independent ART delivered in multi-disease diagnosis and care government sponsored system in rural East Africa. SEARCH is deploying a population level intervention (PRECEDE framework) to reduce new HIV infections and improve overall community health.
Role: Principal Investigator

T32 AI060530 (Havlir) 09/05/2005 – 07/31/2021
NIH/NIAID
Training in HIV Translational Research
The aim of this program is to train patient-based physician scientists in HIV translational research under the careful supervision of a small and carefully selected group of clinical and laboratory scientists.

U01AI099959 (Havlir) 06/01/2012 – 06/30/2017
NIH/NIAID
Reducing Failure-to-Initiate ART: Streamlined ART Start Strategy (START)
The major goal of this project is to test our Streamlined ART Start Strategy (START) in a randomized, trial in 24 clinics in Uganda.
Role: Principal Investigator

PAST (selected)

K24 AI051982 (Havlir) 2002-2012
NIH/NIAID
Therapeutic Strategies for HIV Disease

The purpose of this grant was to help work ideal and feasible antiretroviral regimens in under-resourced settings after designing clinical trials of HIV therapies in the domestic setting. The additional focus was on mentoring using an innovative platform of translational patient-based research.
Role: Principal Investigator

U01AI062677 (Havlir) 2004-2008
NIAID/NIH
Clinical Studies of Interactions Between HIV and Malaria
We propose to investigate the epidemiology of HIV and malaria co-infection through a series of studies in Kampala, Uganda. These studies will be conducted at a time of rapid expansion of antiretroviral (ARV) therapy in Uganda, both allowing us to study the effects of ARV therapy on malaria/HIV co-infection, and ensuring that our findings will be relevant for future HIV care in sub-Saharan Africa.

OMB No. 0925-0001 and 0925-0002 (Rev. 10/15 Approved Through 10/31/2018)

BIOGRAPHICAL SKETCH

DO NOT EXCEED FIVE PAGES.

NAME: **Peter Bacchetti**

eRA COMMONS USER NAME (credential, e.g., agency login): [redacted]

POSITION TITLE: Professor In Residence

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
Univ. of Calif., Berkeley, CA	B.A.	06/80	Philosophy & Statistics
Stanford Univ., Stanford, CA	M.S.	06/82	Statistics
Univ. of Calif., Berkeley, CA	Ph.D.	06/87	Biostatistics

A. Personal Statement

I have worked on HIV-related research since 1982 and have served as principal investigator of six grants developing new statistical methods for application to research on HIV and other infectious diseases. I have worked with Dr. Monica Gandhi (PI on this application), WIHS, and the NIAID-supported clinical trial networks since the inception of measurement of antiretroviral levels in hair as a marker of adherence and exposure. I helped plan and am a co-investigator on Dr. Gandhi's current R01 grant (NIAID/NIH R01 A1098472) that this application seeks to renew. I have guided the statistical analyses for a number of projects related to the use of hair levels of ARVs with Dr. Gandhi in both the WIHS study (where she chaired the Pharmacology Working Group 2003-14) and on independent projects. I have also collaborated with Dr. Gandhi on other investigations on a number of other topics related to HIV infection in women. I will serve as the primary biostatistician on this RO1 renewal with Dr. Gandhi entitled *"Hair Extensions": Using Hair Levels to Interpret Adherence, Effectiveness and Pharmacokinetics with Real-World Oral PrEP, the Vaginal Ring, and Injectable PrEP.*

I have extensive experience analyzing research data and handling statistical issues that arise in studies such as the one proposed. As Director of Biostatistical Consulting for UCSF for over 20 years and a collaborator on a wide variety of studies, I have guided the design, statistical analysis, interpretation, and presentation of hundreds of studies. I believe that my focus on promoting statistical best practices and avoiding common pitfalls will also contribute to the success of this important proposal. Dr. Gandhi and I have co-authored multiple publications (23 total) on various HIV-related topics, including the use of hair concentrations in the setting of HIV and TB:

1. Baxi SM, Greenblatt RM, **Bacchetti P**, Jin C, French AL, Keller MJ, Augenbraun MH, Gange SJ, Liu C, Mack WJ, *Gandhi M*. Nevirapine Concentration in Hair Samples is a Strong Predictor of Virologic Suppression in a Prospective Cohort of HIV-Infected Patients. *PLOS One* 2015 Jun 8;10(6):e0129100. PMCID: PMC4460031
2. Koss C, Natureeba P, Mwesigwa J, Cohan D, Nzarubara B, **Bacchetti P**, Horng H, Clark TD, Plenty A, Ruel TD, Achan J, Charlebois ED, Kamya MR, Havlir DV, *Gandhi M*. Hair Concentrations of Antiretrovirals Predict Viral Suppression in HIV-Infected Pregnant and Breastfeeding Ugandan Women. *AIDS* 2015 Apr 29(7): 825-830 PMCID: PMC4438773
3. Hickey M, Salmen CR, Tessler RA, Omollo D, **Bacchetti P**, Magerenge R, Mattah B, Salmen MR, Zoughbie D, Fiorella KJ, Geng E, Njoroge B, Jin C, Huang Y, Bukusi EA, Cohen CR, *Gandhi M*. Antiretroviral concentrations in small hair samples as a feasible marker of adherence in rural Kenya. *JAIDS* 2014 Jul 1;66(3):311-5. PMCID: PMC4146734
4. *Gandhi M***,** Ameli N, **Bacchetti P**, Anastos K, Young M, Cohen M, Minkoff H, Gange SJ, Greenblatt RM. Atazanavir Concentrations in Hair Samples are the Strongest Predictor of Outcomes in HIV Infection. *Clinical Infectious Diseases* 2011 May 15; 52(10): 1267-1275. PMCID: PMC3079399

B. Positions and Honors

Positions and Employment

1982-1985 Statistician, Epidemiology and Biostatistics, University of California, San Francisco
1985-1987 Senior Statistician, Epidemiology and Biostatistics, University of California, San Francisco
1988-1993 Adjunct Assistant Professor, Epidemiology and Biostatistics, University of California, San Francisco
1993-1999 Adjunct Associate Professor, Epidemiology and Biostatistics, University of California, San Francisco
1993-2014 Leader, Biostatistical Consulting, University of California, San Francisco
1999-2005 Adjunct Professor, Epidemiology and Biostatistics, University of California, San Francisco
2005-present Professor In Residence, Epidemiology and Biostatistics, University of California, San Francisco

Other Experience and Professional Memberships

1987-present International Biometric Society, Western North American Region
1987-present American Statistical Association
2007-2007 Speaker at informational meeting, NIH Peer Review Task Force
2008-2008 Grant reviewer, Special Study Section, NIH
2009-2009 Challenge grant reviewer, NIH
2009-2014 Active participant, Clinical and Translational Science Award national consortium, Biostatistics, Epidemiology, and Research Design, Online Resources Task Force
2010-2010 Ad hoc review panel member, NIH
2010-2010 Grant reviewer, Special Study Section, NIH
2010-2011 Chair, Clinical and Translational Science Award national consortium, Biostatistics, Epidemiology, and Research Design, Online Resources Task Force
2010-present College of CSR reviewers, NIH
2012-2012 Grant Reviewer, Special Emphasis Panel, NIH
2012-2013 Organizer , presenter, and session chair, Clinical and Translational Science Award national consortium, Biostatistics, Epidemiology, and Research Design, Online Journal Club
2013-2013 Grant Reviewer, Clinical Trials Unit proposals, NIAID
2013-2014 Active Participant, and invited session proposal co-organizer for 2014 Joint Statistical Meetings, Clinical and Translational Science Award national consortium, Biostatistics, Epidemiology, and Research Design, Ethical Practice of Biostatistics in Clinical and Translational Research Working Group

Honors

1980 Phi Beta Kappa, University of California, Berkeley
1980 Statistics Departmental Citation (outstanding graduating senior), University of California, Berkeley
1988 First place, student paper competition
, Biometric Society, Western North American Region
1998 Mortimer Spiegelman Award for outstanding contributions to health statistics, American Public Health Association
2004 Fellow of the American Statistical Association, American Statistical Association
2009 Award for Excellence in Faculty Advising in the Master's Degree in Clinical Research Program, University of California, San Francisco

C. Contribution to Science

1. I have participated in many other studies, many in conjunction with Dr. Gandhi, examining levels of anti-retroviral medication in hair to measure long-term drug exposure. Self-reported adherence, pill counts, electronic counting of bottle openings, and snapshot plasma drug levels all have drawbacks that make measurement of hair levels a useful complement or alternative for understanding and predicting success in treating or preventing HIV infection. Publications have shown associations with treatment success that are stronger for hair levels than for other predictors, and have found good acceptability of hair collection in many resource-limited settings. Hair collection has become more common in HIV-related clinical trials,

including pre-exposure prophylaxis studies. I have advised on study designs and guided the statistical analyses and interpretation of results for these studies.

a. *Gandhi M*, Ameli N, **Bacchetti P**, Gange SJ, Anastos K, Levine A, Hyman CL, Cohen M, Young M, Huang Y, Greenblatt RM; Women's Interagency HIV Study (WIHS). Protease inhibitor levels in hair strongly predict virologic response to treatment. *AIDS*, **23**:471-8, 2009. PMCID: PMC2654235.
b. Liu AY, Yang Q, Huang Y, **Bacchetti P**, Anderson PL, Jin C, Goggin K, Stojanovski K, Grant R, Buchbinder SP, Greenblatt RM, *Gandhi M*. Strong Relationship between Oral Dose and Tenofovir Hair Levels in a Randomized Trial: Hair as a Potential Adherence Measure for Pre-Exposure Prophylaxis (PrEP). *PLoS ONE*, **9**:e83736, 2014. PMCID: PMC3885443
c. Baxi SM, Liu A, **Bacchetti P**, Mutua G, Sanders EJ, Kibengo FM, Haberer JE, Rooney J, Hendrix CW, Anderson PL, Huang Y, Priddy F, *Gandhi M*. Comparing the Novel Method of Assessing PrEP Adherence/Exposure using Hair Samples to other Pharmacologic and Traditional Measures. *J Acquir Immune Defic Syndr* 2015 Jan 1;68(1):13-20. PMCID: PMC4262724
d. Prasitsuebsai W,Kerr SJ, Truong KH, Ananworanich J, Do VC, Nguyen LV, Kurniati N, Kosalaraksa P, Sudjaritruk T, Chokephaibulkit K, Thammajaruk N, Singtoroj T, Teeraananchai S, Horng H, **Bacchetti P**, *Gandhi M*, Sohn AH. Using lopinavir concentrations in hair samples to assess treatment outcomes on second-line regimens among Asian children. *AIDS Research and Human Retroviruses* 2015 Oct;31(10):1009-14. PMCID:PMC4576945

2. I have participated in many studies of biological aspects of HIV infection, with emphasis on transmission and early infection and on persistence of infection during effective long-term treatment. These have improved understanding of aspects that include transmitted drug resistance mutations, which types of cells and tissues harbor how much latent HIV, possible latency reversing strategies, and the value of early or intensified anti-retroviral treatment. These studies have influenced emerging improvements in treatment strategies and formulation of further studies aiming toward functional cure of HIV infection, although much work in these areas remains in an early, pre-clinical stage. I have guided the statistical analysis and interpretation of these studies and have developed and performed customized analyses for several, with careful documentation and example computer programs provided in online appendices of publications.

a. Jain V, Sucupira MC, **Bacchetti P,** Hartogensis W, Diaz RS, Kallas EG, Janini LM, Liegler T, Pilcher CD, Grant RM, Cortes R, Deeks SG, Hecht FM. Differential Persistence of Transmitted HIV-1 Drug Resistance Mutation Classes. *J Infect Dis*, **203**:1174-118, 2011. PMCID: PMC3107558.
b. Josefsson L, Eriksson S, Sinclair E, Ho T, Killian M, Epling L, Shao W, Lewis B, **Bacchetti P**, Loeb L, Custer J, Poole L, Hecht FM, Palmer S. Hematopoietic Precursor Cells Isolated From Patients on Long-term Suppressive HIV Therapy Did Not Contain HIV-1 DNA. *J Infect Dis*, **206**:28-34, 2012. PMCID: PMC3415927.
c. Jain V, Hartogensis W, **Bacchetti P**, Hunt PW, Hatano H, Sinclair E, Epling L, Lee TH, Busch MP, McCune JM, Pilcher CD, Hecht FM, Deeks SG. Antiretroviral Therapy Initiated Within 6 Months of HIV Infection Is Associated With Lower T-Cell Activation and Smaller HIV Reservoir Size. *J Infect Dis*. **208**(8):1202-11, 2013. PMCID: PMC3778965.
d. Hatano H, Yukl SA, Ferre AL, Graf EH, Somsouk M, Sinclair E, Abdel-Mohsen M, Liegler T, Harvill K, Hoh R, Palmer S, **Bacchetti P**, Hunt PW, Martin JN, McCune JM, Tracy RP, Busch MP, O'Doherty U, Shacklett BL, Wong JK, Deeks SG. Prospective Antiretroviral Treatment of Asymptomatic, HIV-1 Infected Controllers. *PLoS Pathog*., **9**(10):e1003691, 2013. PMCID: PMC3795031.

3. I have been sole or lead author of a number of publications addressing sample size planning. Although traditional power-based approaches are deeply entrenched, these publications have elucidated problems with both its theory and practice, including false presumptions, harmful consequences, and the lack of any valid rationale for ignoring costs when choosing sample size. Many researchers around the country and the world have contacted me praising this work, but it appears to have had little impact on the day to day practice of peer review. I developed the main ideas and led the writing for all these publications.

a. **Bacchetti P**, McCulloch CE, Segal MR. Simple, defensible sample sizes based on cost efficiency (with Discussion and Rejoinder). *Biometrics*, **64**: 577-594, 2008. PMCID: 2769573.
b. **Bacchetti P**. Current sample size conventions: flaws, harms, and alternatives. *BMC Medicine*, **8**:17, 2010. PMCID: PMC2856520.
c. **Bacchetti P**, Deeks SG, McCune JM. Breaking free of sample size dogma to perform innovative translational research. *Science Translational Medicine*, **3**: 87ps24, 2011. PMCID: PMC3134305.

d. www.ctspedia.org/EthicsSampleSize.

4. I led a number of investigations of fundamental aspects of the early AIDS epidemic in the United States. These included showing that survival after AIDS diagnosis was shorter than previously reported, that incubation time from HIV infection to AIDS diagnosis was longer than previously reported, and that uncertainty about incubation times had a strong influence on reconstructions of past HIV infection rates and projections of future AIDS incidence. These helped improve understanding of and response to the AIDS epidemic, until effective treatments changed the nature of the epidemic.
   a. **Bacchetti P**, Moss AR. Incubation period of AIDS in San Francisco. *Nature*, **338**: 251-253, 1989.
   b. **Bacchetti P**, Segal MR, and Jewell NP. Backcalculation of HIV Infection Rates. *Statistical Science*, **8**: 82-119, 1993.
   c. **Bacchetti P**. Historical assessment of some specific methods for projecting the AIDS epidemic. *American Journal of Epidemiology*, **141**: 776-781, 1995.
   d. **Bacchetti P**. Incidence of HIV-related Deaths in the United States: Seasonality and Trend. *Statistics in Medicine*, **16**: 645-652, 1997.

5. I have developed and applied a number of novel statistical methods to address issues in infectious disease research that could not be optimally examined with standard methods. A deconvolution method for estimating the incubation time from HIV infection to AIDS diagnosis provided strong evidence for longer times than had been previously believed, and applying similar methods to the outbreak of variant Creutzfeldt-Jakob disease in the United Kingdom showed that evidence favored a role of patient age in the risk of developing disease once infected rather than in risk of initial infection, as had been believed. Novel analyses showed that assuming hepatitis C infection at the time of first reported risk behavior, a nearly universal practice in the field, was likely to be inaccurate in many cases, that liver biopsy had poor accuracy for measuring fibrosis, and that Markov (memoryless) assumptions that had been used for modeling fibrosis progression were likely to be inaccurate. These results added evidence in favor of developing and using non-invasive measures of liver fibrosis. I developed the main ideas and led the writing of publications.
   a. **Bacchetti P**. Estimating the Incubation Period of AIDS by Comparing Population Infection and Diagnosis Patterns. *Journal of the American Statistical Association*, **85**: 1002-1008, 1990.
   b. **Bacchetti P**. Age and variant Creutzfeldt-Jakob disease. *Emerging Infectious Diseases*, **9**:1611-12, 2003.
   c. **Bacchetti P**, Tien PC, Seaberg EC, O'Brien TR, Augenbraun MH, Kral AH, Busch MP, Edlin BR. Estimating past hepatitis C infection risk from reported risk factor histories: implications for imputing age of infection and modeling fibrosis progression. *BMC Inf Dis*, **7**:145, 2007. PMCID: 2238758.
   d. **Bacchetti P**, Boylan R, Astemborski J, Shen H, Mehta SH, Thomas DL, Terrault NA, Monto A. Progression of Biopsy-Measured Liver Fibrosis in Untreated Patients with Hepatitis C Infection: Non-Markov Multistate Model Analysis. *PLoS ONE*, **6**(5): e20104, 2011. PMCID: PMC3103523.

Complete List of Published Work (>270 publications):
http://www.ncbi.nlm.nih.gov/sites/myncbi/1BaTkg44jxzAu/bibliography/50823555/public/?sort=date&direction=ascending.

D. Research Support (selected)

R01AI098472 Gandhi (PI) 12/01/2011-11/30/2016
NIH/NIAID Plugging Hair as a Biomarker of Adherence into Ongoing HIV Prevention Trials
This studies hair levels of antiretrovirals as an objective biomarker of medication exposure in a number of different studies. Dr. Bacchetti advises on design and sampling issues and oversees statistical analyses.
Role: Co-Investigator

R21 AI112362 Gandhi (PI) 04/01/2014-02/28/2017 in NCE
NIH/NIAID Hair measures to assess adherence and explain outcomes in an HIV clinical trial
This proposal seeks to extend the approach of using hair antiretrovirals levels to monitor adherence and exposure to the HIV treatment trial setting, partnering with the AIDS Clinical Trials Group (ACTG) to further test our methodology in a clinical trial. By incorporating hair measures into A5257, which randomized participants to fixed treatment regimens and performed frequent viral load monitoring, we hope to harness hair levels to predict impending virologic failure, providing algorithms for adherence interventions in the real-world.

Role: Co-Investigator

R01 AI123024 Gandhi, Metcalfe (co-PIs) 12/01/2015-11/30/2020
NIH-NIAID Novel methods of pharmacologic monitoring for multidrug resistant tuberculosis treatment in the setting of HIV infection
This proposal extends the use of measuring drug concentrations in small hair samples as a measure of adherence/exposure from the HIV setting to the MDR-TB setting, leveraging two South African clinical trials studying optimal treatments for MDR-TB in the new era of anti-TB therapy. Dr. Bacchetti advises on design and implementation issues and guides statistical analysis and interpretation.
Role: Co-Investigator

U01 AI-034989 Greenblatt (PI) 08/01/1993-12/31/2017
NIH/NIAID The Connie Wofsy Women's HIV Study
This investigates the natural and treated history of HIV in women, with special attention to the effect of HIV therapy and reproductive aging on metabolic and functional outcomes. Dr. Bacchetti advises on design issues and guides statistical analyses and interpretation for various projects.
Role: Co-Investigator

U19 AI096109 Deeks, Picker (co-PIs) 07/01/2016-06/30/2021
NIH/NIAID Delaney AIDS Research Enterprise to Cure HIV
The major goals of this project are to: (1) to characterize and then therapeutically overcome the barriers to CD8+ T cell-mediated clearance and/or control of SIV/HIV during and after ART, (2) determine the location and burden of HIV in lymphoid tissues during ART, (3) determine the impact of immune checkpoint blockers on HIV/SIV-specific immunity and reservoir during ART, and (4) determine the safety and immunogenicity of a human CMV/HIV vector. Dr. Bacchetti provides statistical guidance for all projects.
Role: Co-Investigator

R01HD074511 Pilcher (PI) 07/25/2012-05/31/2017
NIH/NIAID Host Factors Influencing HIV Viral Load and Infectivity in Semen
The aims to extend our understanding of how HIV is sexually transmitted, by determining how HIV is efficiently amplified to high levels in the genital tracts of some men, but not in other men. By focusing on the specific mechanism that HIV uses to amplify itself in the male genital tract, we hope to identify new ways that drugs or vaccines could be used to interrupt the cycle of sexual HIV transmission and reduce spread of HIV infection. Dr. Bacchetti guides and oversees statistical analyses and contributes their interpretation.
Role: Co-Investigator

OMB No. 0925-0001 and 0925-0002 (Rev. 10/15 Approved Through 10/31/2018)

BIOGRAPHICAL SKETCH
DO NOT EXCEED FIVE PAGES.

NAME: **Jared Murray Baeten**

eRA COMMONS USER NAME (credential, e.g., agency login): [redacted]

POSITION TITLE: Professor and Vice Chair

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
Washington University, St. Louis, MO	B.A.	05/1995	Chemistry & Religious Studies
University of Washington, Seattle, WA	Ph.D.	08/2001	Epidemiology
University of Washington, Seattle, WA	M.D.	06/2003	Medicine
Massachusetts General Hospital, Boston, MA	Internship & Residency	06/2006	Primary Care Internal Medicine
University of Washington, Seattle, WA	Fellowship	06/2008	Infectious Diseases

A. Personal Statement

Since 1997, I have worked on large-scale prospective studies of HIV-1 and other sexually transmitted infections among populations of high-risk African women and men. My research focuses on the prevention of HIV-1 and other sexually transmitted infections, including clinical trials of novel prevention interventions, epidemiologic studies of risk factors for HIV-1 transmission, and behavioral and implementation science research aimed at optimizing prevention delivery. My work is highly multidisciplinary and collaborative in nature, as reflected in the breadth of research questions and methods, diversity of funding sources (within the past five years: NIH institutes NIAID, NICHD, NIDDK, NIMH, NINR, FIC, CDC, USAID, Bill & Melinda Gates Foundation), and number of collaborators (more than four dozen in the past five years). I was co-PI for the Partners PrEP Study, the phase III, placebo-controlled trial of oral tenofovir-based pre-exposure prophylaxis (PrEP) for HIV-1 prevention among HIV-1 seronegative members of HIV-1 serodiscordant couples in Kenya and Uganda, which in 2011 demonstrated definitive HIV-1 protection of PrEP in heterosexual populations. We have followed the Partners PrEP Study with a multidisciplinary, implementation science study of PrEP and antiretroviral therapy (ART) for HIV-1 prevention among East African HIV-1 serodiscordant couples (the Partners Demonstration Project; role: PI) and new projects to deliver PrEP to young women at risk. Additional work has explored social and behavioral factors that support or undermine adherence to PrEP and ART, innate and acquired immunologic characteristics related to HIV-1 protection, and the clinical safety of PrEP.

Microbicides hold substantial promise as an HIV-1 prevention strategy and I served as chair of MTN-020/ASPIRE, a multisite phase III trial that demonstrated the efficacy and safety of the dapivirine vaginal ring for HIV-1 prevention in women (published NEJM 2016). **I will also chair the follow-up study – MTN-025 or the HIV Open-Label Prevention Extension (HOPE) trial**- that will evaluate how to optimize adherence to and delivery of the dapivirine vaginal ring via an open-label design. I am thrilled to serve as co-investigator on Dr. Monica Gandhi's R01 renewal application entitled "*Hair Extensions": Using Hair Levels to Interpret Adherence, Effectiveness and Pharmacokinetics with Real-World Oral PrEP, the Vaginal Ring, and Injectables* to explore the utility of an additional metric of adherence to the dapivirine vaginal ring in the HOPE study using hair concentrations. Dr. Gandhi's initial funding period for this R01 has been productive and I am delighted to join the team of investigators for this renewal studying new applications for the hair measures. For the present grant, I will work with Dr. Gandhi and other collaborators (see my and other MTN leaders' letters of support) to help implement the study within MTN-025 and participate in the analyses and interpretation of results.

B. Positions and Honors

Positions and Employment

07/2008-06/2011 Assistant Professor, Departments of Global Health and Medicine

Adjunct Assistant Professor, Department of Epidemiology
University of Washington, Seattle, WA
07/2011-06/2014 Associate Professor, Departments of Global Health and Medicine
Adjunct Associate Professor, Department of Epidemiology
University of Washington, Seattle, WA
07/2014-present Professor, with tenure, Departments of Global Health, Medicine, and Epidemiology
Vice Chair, Department of Global Health (since 07/2015)
University of Washington, Seattle, WA

Honors

1994, 1995	Sigma Xi, Phi Beta Kappa
2001	Outstanding Student Award, Department of Epidemiology
2002	Alpha Omega Alpha
2010	American Sexually Transmitted Diseases Association Young Investigator Award
2012	*POZ Magazine* 100 Leaders in HIV
2013	Outstanding Mentor Award, University of Washington School of Public Health
2013	Association of Schools of Public Health Award for Distinguished Research in Public Health
2015	University of Washington School of Medicine Alumni Association Early Achievement Award

Other

Editorial Board, *AIDS* (2008-present); Editorial Board, *AIDS & Behavior* (2012-present)
NIH standing study section member: AIDS Clinical Studies and Epidemiology (ACE) (2015-present)
NIH implementation science study sections (ZAI1 BP-A J2 1, ZRG1 AARR-F [90] S) (2011-present)

C. Contribution to Science

1. **Pre-exposure prophylaxis (PrEP) for HIV-1 prevention.** PrEP, in which an HIV-1 uninfected person uses an antiretroviral medication as chemoprophylaxis to prevention HIV-1 acquisition, is a new, proven prevention strategy. Our Partners PrEP Study demonstrated that PrEP was efficacious for HIV-1 protection in heterosexual populations and the results of the Partners PrEP Study contributed directly to US FDA approval of PrEP for HIV-1 prevention and normative guidance from CDC and WHO to make PrEP part of HIV-1 prevention worldwide. We have published more than three dozen manuscripts from the Partners PrEP Study, addressing key questions for this new prevention strategy: adherence, the relationship between adherence and effectiveness, clinical safety, and antiretroviral resistance. I have led this work, along with a large, multinational and multidisciplinary team, and I have participated in national and international discussions to develop guidelines for PrEP clinical provision and implementation. Moreover, I recently chaired the MTN-020 or ASPIRE study, which (along with the RING trial), showed the efficacy of the dapivirine vaginal ring in reducing rates of HIV-1 acquisition in young women for the first time and am chairing the open-label phase of this study (MTN-025) now (relevant to Aim 2 of this R01 renewal).
   a. [redacted]
   b. **Baeten JM**, Donnell D, Ndase P, et al. Antiretroviral prophylaxis for HIV prevention in heterosexual men and women. N Engl J Med. 2012;367:399-410. PMCID: 3770474.
   c. Mugo NR, Hong T, Celum C, Donnell D, Bukusi EA, John-Stewart G, Wangisi J, Were E, Heffron R, Matthews L, Morrison S, Ngure K, **Baeten JM**; Partners PrEP Study Team. Pregnancy incidence and outcomes among women receiving preexposure prophylaxis for HIV prevention: a randomized, placebo-controlled trial. JAMA. 2014;312:362-71. PMCID: 25038355.
   d. Mugwanya KK, Wyatt C, Celum C, Donnell D, Mugo NR, Tappero J, Kiarie J, Ronald A, **Baeten JM**; Partners PrEP Study Team. Changes in glomerular kidney function among HIV-1 uninfected men and women receiving emtricitabine-tenofovir disoproxil fumarate preexposure prophylaxis: a randomized clinical trial. JAMA Int Med. 2015;175:245-54. PMCID: 4354899.
2. **Implementation science to optimize HIV-1 prevention delivery.** Achieving public health impact with HIV-1 prevention interventions will require implementation science to efficiently and effectively deliver these strategies. We are currently conducting a multidisciplinary, implementation science study of PrEP and antiretroviral therapy (ART) for HIV-1 prevention among East African HIV-1 serodiscordant couples (the Partners Demonstration Project; role: PI); we recently reported that the integrated delivery of PrEP and

ART in this population reduced incident HIV-1 by 96% (Baeten, CROI 2015). I have led or co-led multiple studies to define optimized prevention delivery, including epidemiologic analyses, mathematical modeling, delivery science, and cost-estimation studies. I serve as Vice Chair of the Department of Global Health at the University of Washington, the first program in the world to offer a PhD in Implementation Science.

a. [redacted]

b. Hallett T, **Baeten JM**, Heffron R, et al. Optimal uses of antiretrovirals for prevention in HIV-1 serodiscordant heterosexual couples in South Africa: a modelling study. PLoS Med. 2011;8:e1001123. doi: 10.1371/journal.pmed.1001123. PMCID: 3217021.

c. Kahle E, Hughes J, Lingappa J, John-Stewart G, Celum C, Nakku-Joloba E, Njuguna S, Mugo N, Bukusi E, Manongi R, **Baeten JM**; Partners in Prevention HSV/HIV Transmission Study and the Partners PrEP Study Teams. An empiric risk scoring tool for identifying high-risk heterosexual HIV-1-serodiscordant couples for targeted HIV-1 prevention. J Acquir Immune Defic Syndr. 2013;62:339-47. PMCID: 3620695.

d. Ying R, Sharma M, Heffron R, Celum C, **Baeten JM**, et al. Cost-effectiveness of pre-exposure prophylaxis targeted to high-risk serodiscordant couples as a bridge to sustained ART use in Kampala, Uganda. J Int AIDS Soc. 2015;18:20013. doi: 10.7448/IAS.18.4.20013. PMCID: 4509901.

3. **Behavioral and social science to understand use of PrEP and ART for HIV-1 prevention.** The development of PrEP and ART as novel HIV-1 prevention interventions has revealed that these strategies operate within a complex behavioral context. Working with a multidisciplinary group of collaborators, we have explored adherence to these interventions and drivers of adherence/nonadherence, sexual behavior (including risk compensation), and the individual, dyadic, and societal factors that influence prevention use. These studies have used multiple methods: intensive adherence monitoring, quantitative and qualitative data collection, and mHealth approaches. This work is integral to understanding how to develop new prevention tools and how to deliver effective ones for the greatest impact.

   a. Haberer JE, **Baeten JM**, Campbell J, et al. Adherence to antiretroviral prophylaxis for HIV prevention: a substudy cohort within a clinical trial of serodiscordant couples in East Africa. PLoS Med. 2013;10:e1001511. doi: 10.1371/journal.pmed.1001511. PMCID: 3769210.

   b. Curran K, Mugo NR, Kurth A, Ngure K, Heffron R, Donnell D, Celum C, **Baeten JM**. Daily short message service surveys to measure sexual behavior and pre-exposure prophylaxis use among Kenyan men and women. AIDS Behav. 2013;17:2977-85. PMCID: 3812384.

   c. Mugwanya K, Donnell D, Celum C, Thomas KK, Ndase P, Mugo N, Katabira E, Ngure K, **Baeten JM**; Partners PrEP Study Team. Sexual behaviour of heterosexual men and women receiving antiretroviral pre-exposure prophylaxis for HIV prevention. Lancet Infect Dis. 2013;13:1021-8. PMCID: 3920826.

   d. Curran K, Ngure K, Shell-Duncan B, Vusha S, Mugo NR, Heffron R, Celum C, **Baeten JM**. "If I am given antiretrovirals I will think I am nearing the grave": Kenyan HIV serodiscordant couples' attitudes regarding early initiation of antiretroviral therapy. AIDS. 2014;28:227-33. PMCID: 4040408.

4. **Hormonal contraception as a risk factor for HIV-1 acquisition and transmission.** For more than 15 years, I have led studies to understand the relationship between use of hormonal forms of contraception and acquisition and transmission of HIV-1 and other sexually transmitted infections. In 2012, we published the results of a prospective, observational study among HIV-1 serodiscordant couples from seven African countries that found that use of the injectable contraceptive depot medroxyprogesterone acetate (DMPA, or Depo-Provera®) was associated with a doubling of the risk of HIV-1 acquisition by women; these results received considerable international attention, including an immediate statement by WHO. I am a member of the WHO Task Force on Contraception and HIV and along with a consortium of partners co-lead a randomized trial (the ECHO study) evaluating HIV-1 risk related to different contraceptive methods.

   a. **Baeten JM**, Nyange PM, Richardson BA, et al. Hormonal contraception and risk of sexually transmitted disease acquisition: results from a prospective study. Am J Obstet Gynecol. 2001;185:380-5. PMID: 11518896.

   b. **Baeten JM**, Benki S, Chohan V, Lavreys L et al. Hormonal contraceptive use, herpes simplex virus

infection, and risk of HIV-1 acquisition among Kenyan women. AIDS. 2007;21:1771-7. PMID: 17690576.

c. Heffron R, Donnell D, Rees H, Celum C, Mugo N, Were E, de Bruyn G, Nakku-Joloba E, Ngure K, Kiarie J, Coombs RW, **Baeten JM**; Partners in Prevention HSV/HIV Transmission Study Team. Use of hormonal contraceptives and risk of HIV-1 transmission: a prospective cohort study. Lancet Infect Dis. 2012;12:19-26. PMCID: 3266951.

d. Morrison CS, Chen P-L, Kwok C, **Baeten JM**, et al. Hormonal contraception and the risk of HIV acquisition: an individual participant data meta-analysis. PLoS Med. 2015;12:e1001778. doi: 10.1371/journal.pmed.1001778. PMCID: 4303292.

5. **Novel risk factors for HIV-1 acquisition and transmission.** Epidemiologic studies exploring behavioral and biologic factors that facilitate HIV-1 spread have been central to the development of new prevention interventions. Throughout my career, I have led work to describe novel risk factors for HIV-1 acquisition and transmission, including clinical, behavioral, and biologic correlates.

a. Donnell D, **Baeten JM**, Kiarie J, et al. Heterosexual HIV-1 transmission after initiation of antiretroviral therapy: a prospective cohort analysis. Lancet. 2010;375: 2092-8. PMCID: 2922041.

b. **Baeten JM**, Donnell D, Kapiga S, Ronald A, et al. Male circumcision and risk of male-to-female HIV-1 transmission: a multinational prospective study in African HIV-1 serodiscordant couples. AIDS. 2010;24:737-44. PMCID: 2919808.

c. **Baeten JM**, Kahle E, Lingappa JR, Coombs RW, et al. Genital HIV-1 RNA predicts risk of heterosexual HIV-1 transmission. Sci Transl Med. 2011;3:77ra29. PMCID: 3087186.

d. Kahle E, Campbell M, Lingappa J, Donnell D, Celum C, Kapiga S, Ondondo R, Mugo N, Mujugira A, Fife K, Mullins J, **Baeten JM**; Partners in Prevention HSV/HIV Transmission Study Team. HIV-1 subtype C is not associated with higher risk of heterosexual HIV-1 transmission: a multinational study among HIV-1 serodiscordant couples. AIDS. 2014;28:235-43. PMCID: 4090091.

Complete List of Published Work in MyBibliography (from >160 peer-reviewed publications):
http://www.ncbi.nlm.nih.gov/myncbi/browse/collection/41428984/

D. Research Support

Ongoing Research Support (selected)

NIH/NIMH R01 MH095507 **Baeten (PI)** **08/10/11 – 07/31/21**
Optimizing antiretroviral-based HIV prevention for HIV serodiscordant couples
We proposed a series of integrated studies to optimize targeted delivery and sustained use of antiretroviral HIV-1 prevention in African HIV-1 serodiscordant couples.
Role: Principal Investigator

NIH/NIAID R01 AI096968 **Baeten, Lund (PIs)** **04/01/12 – 03/31/17**
PrEP and protective immune responses against HIV-1
We propose to explore anti-HIV-1 responses in HIV-1 exposed but uninfected persons receiving PrEP, evaluate the relationship between anti-HIV-1 immune responses and protection against HIV-1 acquisition, and test mucosal samples from persons on PrEP to evaluate immune responses at the site of HIV-1 exposure.
Role: Co-Principal Investigator (multiple PI mechanism)

[redacted]

USAID APS-OAA-14-000076 **Baeten, Celum (PIs)** **07/01/15 – 06/30/20**

Scaleable, effective delivery of microbicides and PrEP for young women in Kenya and South Africa
We propose to develop and evaluate effective, scalable strategies that are context-specific and gender responsive for closing critical gaps in microbicide and PrEP delivery for African women in high HIV incidence settings.
Role: Co-Principal Investigator

CDC U48 DP 005013 **Harris (PI)** **09/03/14 – 09/29/19**
SIP 14-023 project: Health promotion and disease prevention research centers: special interest project competitive supplements (SIPs)
The project will conduct series of innovative clinical and biologic studies to understand the effect of progestin-based contraception on HIV-1 transmission and disease.
Role: Project Co-Principal Investigator (for SIP 14-023)

NIH/NIMH MH098744 **Haberer (PI)** **06/04/13 – 05/31/18**
Real-world adherence to HIV PrEP in serodiscordant African couples
The goal of this project is to determine if people can and will adhere adequately enough to PrEP in the “real world” to be protected against HIV seroconversion.
Role: Co-Investigator, Subcontract Principal Investigator

[redacted]

NIH/NIAID/NICHD/NIMH UO1 AI068633 **Hillier (PI)** **06/29/06 – 11/30/20**
Microbicide Trials Network
The mission of the MTN is to reduce the sexual transmission of HIV through the development and evaluation of products, which reduce the transmission of HIV when applied topically to mucosal surfaces.
Role: Co-Investigator and MTN-020/ASPIRE & MTN-025/HOPE Protocol Chair

NIH/NIDDK R01 DK100272 **Wyatt (PI)** **08/01/14 – 07/31/17**
Incidence and implications of subclinical kidney injury with tenofovir based PrEP
The goal of the proposed research is to better understand the risk of kidney and bone toxicity with the use of TDF/FTC in healthy, HIV-uninfected individuals.
Role: Co-Investigator, Subcontract Principal Investigator

[redacted]

NIH/NIMH R01 MH107251 **Bekker (PI)** **04/01/15 – 03/31/19**
Design and delivery of combination HIV prevention in young South African women
The major goal of this project is to explore whether partners can be engaged in HIV testing and prevention to inform development of a pilot intervention in a cohort of 100 HIV-negative women to improve communication about risk and integrate social motivators to facilitate uptake of combination prevention and PrEP adherence
Role: Co-Investigator

USAID AID-OAA-A-15-00032 **Montgomery (PI)** **10/01/15 – 09/30/20**
CHARISMA
Proposes to improve measurement of the beneficial impacts and harmful social effects of microbicide use through data analysis from primary and secondary sources and development of a novel scale. Role: Co-I

OMB No. 0925-0001 and 0925-0002 (Rev. 10/15 Approved Through 10/31/2018)

BIOGRAPHICAL SKETCH
DO NOT EXCEED FIVE PAGES.

NAME: **Castillo-Mancilla, Jose Ramon**

eRA COMMONS USER NAME (credential, e.g., agency login): [redacted]

POSITION TITLE: Associate Professor of Medicine

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable.)*

INSTITUTION AND LOCATION	DEGREE (if applicable)	Completion Date MM/YYYY	FIELD OF STUDY
La Salle del Pedregal, Mexico City, Mexico City	BS	06/1992	Biology/Pre-Med
La Salle University Medical School, Mexico City, Mexico City	MD	01/1999	Medicine
Instituto Nacional de Ciencias Medicas "Salvador Zubiran", Mexico City, Mexico City	Resident	03/2000	Internal Medicine
Mount Sinai Medical Center, Miami, FL	Resident	06/2003	Internal Medicine
The Cleveland Clinic, Cleveland, OH	Fellow	06/2005	Infectious Diseases

A. Personal Statement

I am an Associate Professor of Medicine in the Division of Infectious Diseases at the University of Colorado School of Medicine. I am a translational researcher focused on applied clinical pharmacology with a special emphasis on antiretroviral drug adherence, optimization of current antiretroviral therapies, pharmacogenomics, and pre-exposure prophylaxis (PrEP). I am currently funded by the NIH/NIAID through a K23 Career Development Award aimed at investigating a novel pharmacological biomarker of drug adherence in HIV-infected individuals using nucleoside analog anabolites in dried blood spots. I am a core investigator in the Colorado Antiviral Pharmacology Laboratory (which has a diverse research portfolio in the U.S. and around the world) and have several ongoing research collaborations on antiretroviral adherence and clinical pharmacology. In addition, I am an investigator in the AIDS Clinical Trials Group (ACTG) where I am the **Co-Chair of A5359,** a multi-site study aiming to evaluate the efficacy of long-acting antiretrovirals in non-adherent individuals. Moreover, I am the **Vice-Chair of the ACTG Underrepresented Populations Committee**, which aims at expanding the inclusion of minorities (including non-adherent individuals) in HIV clinical trials. I am also funded through an R21 Exploratory Research Award aimed at investigating the biological consequences of antiretroviral adherence variations beyond virologic suppression in HIV-infected individuals.

I am delighted to serve as a co-investigator on Dr. Monica Gandhi's R01 renewal grant ("Hair Extensions": Using Hair Levels to Interpret Adherence, Effectiveness and Pharmacokinetics with Real-World Oral PrEP, the Vaginal Ring, and Injectable PrEP). Dr. Gandhi and I have presented together at recent meetings (see my letter of support) and have worked together in the relatively small world of ARV pharmacology for many years. In my role as Co-Chair of A5359, I supported the inclusion of hair collection into the protocol (along with Dr. Adriana Andrade, core pharmacologist on the protocol, as well as ACTG leadership). My role in the R01 will be to ensure hair collection proceeds smoothly in A5359 once the study starts enrolling in 2017, to help in data analysis and interpretation of drug levels for the PK work proposed in Aim 3, and contribute to publications. Dr. Gandhi and I have a shared interest in mentoring early career investigators of diversity and hope to use this grant, if re-funded, as a platform for mentoring in the areas of adherence and pharmacology.

A few key publications related to my work in ARV pharmacology are listed below:

a) Zheng JH, Rower C, McAllister K, **Castillo-Mancilla J**, Klein B, Meditz A, Guida LA, Kiser JJ, Bushman LR, Anderson PL. Application of an intracellular assay for determination of tenofovir-diphosphate and emtricitabine-triphosphate from erythrocytes using dried blood spots. J Pharm Biomed Anal. 2016 Apr 15;122:16-20. PubMed PMID: 26829517; PubMed Central PMCID: PMC4764437.

b) Chai PR, **Castillo-Mancilla J**, Buffkin E, Darling C, Rosen RK, Horvath KJ, Boudreaux ED, Robbins GK, Hibberd PL, Boyer EW. Utilizing an Ingestible Biosensor to Assess Real-Time Medication Adherence. J Med Toxicol. 2015 Dec;11(4):439-44. PubMed PMID: 26245878; PubMed Central PMCID: PMC4675608.

c) **Castillo-Mancilla JR**, Searls K, Caraway P, Zheng JH, Gardner EM, Predhomme J, Bushman LR, Anderson PL, Meditz AL. Short communication: Tenofovir diphosphate in dried blood spots as an objective measure of adherence in HIV-infected women. AIDS Res Hum Retroviruses. 2015 Apr;31(4):428-32. PubMed PMID: 25328112; PubMed Central PMCID: PMC4378663.

d) **Castillo-Mancilla JR**, Zheng JH, Rower JE, Meditz A, Gardner EM, Predhomme J, Fernandez C, Langness J, Kiser JJ, Bushman LR, Anderson PL. Tenofovir, emtricitabine, and tenofovir diphosphate in dried blood spots for determining recent and cumulative drug exposure. AIDS Res Hum Retroviruses. 2013 Feb;29(2):384-90. PubMed PMID: 22935078; PubMed Central PMCID: PMC3552442.

B. Positions and Honors

Positions and Employment

1999 - 2000	Resident in Internal Medicine, INCMNSZ, Mexico City
2000 - 2003	Intern/Resident in Internal Medicine, Mount Sinai Medical Center, Miami, FL
2003 - 2005	Fellow in Infectious Diseases, The Cleveland Clinic, OH
2005 - 2008	Attending Physician, Rio Grande Medical Group, Las Cruces, NM
2008 - 2015	Assistant Professor of Medicine, University of Colorado-AMC, Aurora, CO
2015 -	Associate Professor of Medicine, University of Colorado-AMC, Aurora, CO

Other Experience and Professional Memberships

2003 -	Member, Infectious Diseases Society of America
2003 -	Member, HIV Medical Association
2005 - 2008	Member, New Mexico Medical Society
2006 - 2011	Member, Southern Medical Association
2008 -	Member, International AIDS Society
2008 -	Member, Colorado IDSA Chapter
2009 -	Member, National Hispanic Medical Association
2012 -	Member, International Association of Physicians in AIDS Care
2012 -	Member, American College of Physicians

Honors

1996	Medical School Representative to the National Academy of Medicine, Academia Nacional de Medicina, Mexico
1999	Suma Cum Laude, La Salle University Medical School, Mexico
2000	Intern of the Year, Mount Sinai Medical Center, Miami, FL
2001	Florida State Champion, American College of Physicians
2003	Resident of the Year, Mount Sinai Medical Center, Miami, FL
2003	Inpatient Student Teaching Award, University of Miami School of Medicine, Miami, FL
2005	Fellow of the Year, The Cleveland Clinic, Cleveland, OH
2008	Esperanza Award, Camino de Vida Center for HIV Services, Las Cruces, New Mexico
2016	Rising Star, University of Colorado-AMC/Department of Medicine, Aurora, Colorado

C. Contribution to Science

1. Development of New Measures of Antiretroviral Adherence

Our group discovered that tenofovir-diphosphate in red blood cells and dried blood spots has a 17-day half-life and high accumulation from first-dose to steady state, which make this measure suitable to assess

cumulative drug adherence and exposure (PMID:22935078). Based on this unique pharmacology, we developed a pharmacokinetic model that is highly informative of tenofovir dosing over a prolonged period of time, analogous to hemoglobin A1c measurements in patients with diabetes mellitus. This adherence measure has been found to strongly correlate and outperform other measures of antiretroviral adherence in HIV-infected individuals (PMID:25328112) and to be highly predictive of efficacy to pre-exposure prophylaxis (PrEP) in a large, randomized clinical trial (PMID: 25065857). Similar work from our group has focused on the quantification of parent antiretrovirals in dried blood spots (PMID:26829517) to quantify drug adherence. We have also contributed to a better understanding on the use of ingestible biosensors to objectively measure drug adherence and drug intake (PMID:26245878)

a. **Castillo-Mancilla JR**, Zheng JH, Rower JE, Meditz A, Gardner EM, Predhomme J, Fernandez C, Langness J, Kiser JJ, Bushman LR, Anderson PL. Tenofovir, emtricitabine, and tenofovir diphosphate in dried blood spots for determining recent and cumulative drug exposure. AIDS Res Hum Retroviruses. 2013 Feb;29(2):384-90. PubMed PMID: 22935078; PubMed Central PMCID: PMC3552442.
b. **Castillo-Mancilla JR**, Searls K, Caraway P, Zheng JH, Gardner EM, Predhomme J, Bushman LR, Anderson PL, Meditz AL. Short communication: Tenofovir diphosphate in dried blood spots as an objective measure of adherence in HIV-infected women. AIDS Res Hum Retroviruses. 2015 Apr;31(4):428-32. PubMed PMID: 25328112; PubMed Central PMCID: PMC4378663.
c. Zheng JH, Rower C, McAllister K, **Castillo-Mancilla J**, Klein B, Meditz A, Guida LA, Kiser JJ, Bushman LR, Anderson PL. Application of an intracellular assay for determination of tenofovir-diphosphate and emtricitabine-triphosphate from erythrocytes using dried blood spots. J Pharm Biomed Anal. 2016 Apr 15;122:16-20. PubMed PMID: 26829517; PubMed Central PMCID: PMC4764437.
d. Chai PR, **Castillo-Mancilla J**, Buffkin E, Darling C, Rosen RK, Horvath KJ, Boudreaux ED, Robbins GK, Hibberd PL, Boyer EW. Utilizing an Ingestible Biosensor to Assess Real-Time Medication Adherence. J Med Toxicol. 2015 Dec;11(4):439-44. PubMed PMID: 26245878; PubMed Central PMCID: PMC4675608.

2. Immunopharmacology and optimal dosing of pre-exposure prophylaxis (PrEP)

Tenofovir has immunomodulatory effects in vitro. We have identified specific in vivo immunomodulatory effects of tenofovir-emtricitabine, the only regimen approved for HIV Pre-Exposure prophylaxis (PrEP), in at-risk individuals (PMID:25763783). These additional pharmacodynamic effects could contribute to the known antiviral activity of this PrEP regimen in high-risk individuals. Additionally, we have also focused our research on the optimization of PrEP dosing based on pharmacokinetic data and have contributed to research aimed at understanding the PrEP dosing patterns that provide protection against HIV acquisition (PMID:25409469). Furthermore, we have evaluated the effect of TDF/FTC exposure on the endogenous nucleotide pool to better understand their relationships in the context of pharmacologic efficacy and toxicity (PMID:27353267).

a. **Castillo-Mancilla JR**, Meditz A, Wilson C, Zheng JH, Palmer BE, Lee EJ, Gardner EM, Seifert S, Kerr B, Bushman LR, MaWhinney S, Anderson PL. Reduced immune activation during tenofovir-emtricitabine therapy in HIV-negative individuals. J Acquir Immune Defic Syndr. 2015 Apr 15;68(5):495-501. PubMed PMID: 25763783; PubMed Central PMCID: PMC4358752.
b. Seifert SM, Glidden DV, Meditz AL, **Castillo-Mancilla JR**, Gardner EM, Predhomme JA, Rower C, Klein B, Kerr BJ, Guida LA, Zheng JH, Bushman LR, Anderson PL. Dose response for starting and stopping HIV preexposure prophylaxis for men who have sex with men. Clin Infect Dis. 2015 Mar 1;60(5):804-10. PubMed PMID: 25409469; PubMed Central PMCID: PMC4402345.
c. [redacted]

d. Anderson PL, Reirden D, **Castillo-Mancilla J**. Pharmacologic Considerations for Preexposure Prophylaxis in Transgender Women. J Acquir Immune Defic Syndr. 2016 Aug 15;72 Suppl 3:S230-4. PubMed PMID: 27429188; PubMed Central PMCID: PMC4955879

3. Optimization of Antiretroviral Therapy

We have contributed to the optimization of antiretroviral therapy through a better understanding of the pharmacogenomics of atazanavir. Our research identified a unique pharmacogenetic profile of unboosted atazanavir according to CYP3A5 expression status and discovered new interactions with drug transporter polymorphisms (PMID:26892777, PMID:22394315). We also demonstrated in a meta-analysis that efavirenz is a better first-line therapy option for HIV-1 infection in resource-limited settings compared to nevirapine and protease inhibitors (PMID:22707879).

a. **Castillo-Mancilla JR**, Aquilante CL, Wempe MF, et al. Pharmacogenetics of unboosted atazanavir in HIV-infected individuals in resource-limited settings: a sub-study of the AIDS Clinical Trials Group (ACTG) PEARLS study (NWCS 342). J Antimicrob Chemother. 2016 Jun;71(6):1609-18. PubMed PMID: 26892777; PubMed Central PMCID: PMC4867099.

b. Kile DA, MaWhinney S, Aquilante CL, Rower JE, **Castillo-Mancilla JR**, Anderson PL. A population pharmacokinetic-pharmacogenetic analysis of atazanavir. AIDS Res Hum Retroviruses. 2012 Oct;28(10):1227-34. PubMed PMID: 22394315. Publicly available: http://online.liebertpub.com/doi/pdf/10.1089/aid.2011.0378

c. **Castillo-Mancilla JR**, Campbell TB. Comparative effectiveness of efavirenz-based antiretroviral regimens in resource-limited settings. J Comp Eff Res. 2012 Mar;1(2):157-170. PubMed PMID: 22707879; PubMed Central PMCID: PMC3374961.

4. HIV Epidemic in Foreign-Born and Minority Individuals

One focus of my research is on the HIV epidemic in individuals born outside of the United States in an attempt to understand the unique clinical and social aspects of this vulnerable population (PMID:22562621). We have also investigated sexual risk behaviors that are unique to Hispanics in the U.S. (PMID:21932002). Lastly, we have worked in conjunction with the AIDS Clinical Trials Group-Underrepresented Populations Committee to better characterize the barriers to clinical research participation in minority individuals in the U.S. (PMID:24518211, PMID:25688896).

a. Carten ML, **Castillo-Mancilla JR**, Allshouse AA, Johnson SC. Characteristics of foreign-born HIV infected individuals and differences by region of origin and gender. J Immigr Minor Health. 2013 Aug;15(4):667-72. PubMed PMID: 22562621.

b. **Castillo-Mancilla J**, Allshouse A, Collins C, et al. Differences in sexual risk behavior and HIV/AIDS risk factors among foreign-born and US-born Hispanic women. J Immigr Minor Health. 2012 Feb;14(1):89-99. PubMed PMID: 21932002; PubMed Central PMCID: PMC4504232.

c. **Castillo-Mancilla JR**, Cohn SE, Krishnan S, Cespedes M, Floris-Moore M, Schulte G, Pavlov G, Mildvan D, Smith KY, ACTG Underrepresented Populations Survey Group. Minorities remain underrepresented in HIV/AIDS research despite access to clinical trials. HIV Clin Trials. 2014 Jan-Feb;15(1):14-26. PubMed PMID: 24518211; PubMed Central PMCID: PMC4031907.

d. Heumann C, Cohn SE, Krishnan S, **Castillo-Mancilla JR**, Cespedes M, Floris-Moore M, Smith KY. Regional variation in HIV clinical trials participation in the United States. South Med J. 2015 Feb;108(2):107-16. PubMed PMID: 25688896; PubMed Central PMCID: PMC4356522.

D. Research Support

Ongoing Research Support

K23 AI104315-03

Castillo-Mancilla, Jose Ramon (PI)

06/20/13-05/31/18

Quantifying Drug Adherence and Drug Exposure to Antiretroviral Therapy

The proposed research will develop a new pharmacologic approach to quantify drug exposure and drug adherence to antiretroviral therapy, which could lead to more efficacious HIV treatment and prevention strategies. The PI in this K23 award is under the mentorship of Peter Anderson, PharmD
Role: PI

R21 AI124859-01
Castillo-Mancilla, Jose Ramon/Li, Jonathan (PI)
03/15/16-02/28/18
Impact of ART Adherence on HIV Persistence and Inflammation
The goal of this project is to evaluate the relationship between drug exposure/adherence and the HIV reservoir and chronic inflammation.
Role: PI

R01 AI122300, NIH/NIAID
Remien, Robert/Orrel, Catherine (PI)
12/01/15-11/30/20
Use of ARV Drug Levels in DBS to Assess and Manage ART Adherence in South Africa
The goal of this project is to document the utility of a dried blood spot assay of tenofovir-diphosphate to assess and manage ART adherence in a low-resource, real-world setting in South Africa. Role: Co-Investigator
Role: Co-Investigator

R01 DA040499, NIH/NIDA
Kiser, Jenifer (PI)
07/15/15-05/31/20
Antiviral pharmacology and adherence in drug users.
The proposed research will define the pharmacokinetics of direct acting agents (DAA) in HIV/HCV co-infected drug users, determine the DAA concentrations associated with gradients of adherence and establish the adherence-efficacy relationship for DAA.
Role: Co-Investigator

Completed Research Support

UL1 RR025780, NIH, NCRR
Castillo-Mancilla, Jose Ramon (PI)
04/01/11-04/30/12
Effects of CYP3A5, ABCB1, PXR and SLCO1B1 polymorphisms on the metabolism of atazanavir in HIV-infected patients
The purpose of this study is to evaluate the association of genetic variations on the pharmacokinetics and the metabolism of unboosted atazanavir in HIV-infected, treatment-naive patients in multiple regions.
Role: PI

UM1 AI068636, NIH, AIDS Clinical Trials Group
Castillo-Mancilla, Jose Ramon (PI)
06/01/10-05/31/11
Minority HIV Investigator Mentoring Program
The purpose of this award is to foster the inclusion of underrepresented minorities in HIV clinical research and allow new minority investigators to become involved in AIDS Clinical Trials Group-related research and activities.
Role: PI

OMB No. 0925-0001 and 0925-0002 (Rev. 10/15 Approved Through 10/31/2018)

BIOGRAPHICAL SKETCH
DO NOT EXCEED FIVE PAGES.

NAME: **Leslie Zachary Benet**

eRA COMMONS USER NAME (credential, e.g., agency login): [redacted]

POSITION TITLE: Professor of Bioengineering & Therapeutic Sciences, Prof. of Pharmaceutical Chemistry

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
University of Michigan, Ann Arbor, MI	A.B.	1959	English
University of Michigan, Ann Arbor, MI	B.S.	1960	Pharmacy
University of Michigan, Ann Arbor, MI	M.S.	1962	Pharm Chemistry
University of California, San Francisco, CA	PhD.	1965	Pharm Chemistry

A. Personal Statement

Dr. Benet is a pioneer in the pharmacokinetics/pharmacodynamics (PKPD) field serving as the Director of the NIH funded program project grant "Pharmacokinetics-Pharmacodynamics" at UCSF for 19 years, and the author of significant breakthrough papers in the field as indicated in section C. Dr. Benet is a Professor and former Chairman (1978-1998) of the Department of Bioengineering and Therapeutic Sciences of the University of California, San Francisco (UCSF). He has published more than 550 peer-reviewed papers and book chapters and is listed among Thompson Reuter's Most Highly Cited Pharmacologists, worldwide, with his peer reviewed publications having been cited on more than 24,000 occasions. His H-factor of 74 (Thompson Reuters) and 85 (Google Scholar) is the highest among PKPD scientists. Dr. Benet is a committed mentor having served as the thesis advisor for 55 PhD graduates and trained an additional 122 postdoctoral fellows and visiting scientists in his laboratory at UCSF, including 17 MD Clinical Pharmacology fellows and 16 PharmD Research Fellows. He served as the primary mentor for Dr. Monica Gandhi's K23 award from NIAID/MIH (K23 AI067065) from 2005-2010, entitled Asessing Antiretroviral Exposure in Diverse Populations, which generated findings relevant to Aim 3 of this proposal. He is the recipient of 9 honorary doctorate degrees, 5 from European universities and 4 from U.S. institutions. In 2000 and 2016, he was selected as the recipient of the UCSF Graduate Division Faculty Mentorship Award and in 2007 was selected as the 7th UCSF Distinguished Clinical Lecturer.

Dr. Benet's leadership of the Hair Analytical Laboratory at UCSF contributed substantially to the productivity of the first funding period of Dr. Gandhi's R01 and HAL will continue to support the hair assays relevant to this renewal application *(*"Hair Extensions": Using Hair Levels to Interpret Adherence, Effectiveness and Pharmacokinetics with Real-World Oral PrEP, the Vaginal Ring, and Injectables). Dr. Benet and Dr. Gandhi have been working together since 2001 and the productivity of the HAL has thrived under their dual leadership since the start of this R01 (Dr. Gandhi serves as Clinical Director of the HAL). Dr. Benet will serve as co-investigator on the renewal, receiving support all five years for his leadership role of the HAL and to contribute to the PK analyses proposed for Aim 3 (PK analyses of long-acting cabotegravir using plasma and hair levels).

B. Positions and Honors

Positions and Employment

1965-69 Assistant Professor of Pharmacy, Washington State University, Pullman, Washington
1969-71 1971-76 Assistant and Associate Professor of Pharmacy and Pharmaceutical Chemistry, UCSF
1975-97 Editor, *Journal of Pharmacokinetics & Biopharmaceutics*

1976- Professor, Departments of Bioengineering & Therapeutic Sciences and Pharmaceutical Chemistry, UCSF (Dept of Pharmacy until 1996; Biopharmaceutical Sciences from 1996 to May 2009)
1978-98 Chairman, Dept of Biopharmaceutical Sciences (Pharmacy until 1996), UCSF
1979-98 Director, Center for Drug Kinetics & Dynamics Research, UCSF

Honors

1977-81 Member, Pharmacology Study Section, NIH; Chairman, 1979-81
1978 Elected Fellow, American Association for the Advancement of Science
1984-88 Member, Pharmacological Sciences Review Committee, NIH; Chairman, 1986-88
1985-86 President, Academy of Pharmaceutical Sciences; Elected Fellow 1973
1986 President, American Association of Pharmaceutical Scientists; Elected Fellow
1987 Elected Member, Institute of Medicine of the National Academy of Sciences
Awarded Honorary Doctor of Pharmacy degree, University of Uppsala, Sweden
1988 Distinguished Service Award, American College of Clinical Pharmacology; Elected Fellow
1989 First Distinguished Scientist Award, American Association of Pharmaceutical Scientists
1990-94 Member, Generic Drugs Advisory Committee, FDA
1991 Volwiler Research Achievement Award, American Association of Colleges of Pharmacy
1993-94 President, American Association of Colleges of Pharmacy
1993-98 Member, Science Board, FDA
1995 Awarded Honorary Doctor of Philosophy, Leiden University, The Netherlands;
Rawls Palmer Progress in Medicine Award, American Society for Clinical Pharmacology and Therapeutics;
Therapeutics Frontiers Lecturer, American College of Clinical Pharmacy
1997 Awarded Honorary Doctor of Science degrees, University of Illinois at Chicago, and Philadelphia College of Pharmacy and Science
1999 Awarded Honorary Doctor of Science degree, Long Island University
2000 Higuchi Research Prize, American Pharmaceutical Association
Wurster Research Award in Pharmaceutics, American Association of Pharmaceutical Scientists
2001 Høst-Madsen Medal, International Pharmaceutical Federation
2002 Honorary Member, Academia de Ciencias Farmaceuticas de Chile
2003 Listed by ISI among the Most Highly Cited Pharmacologists World Wide
Member of Honour, Romanian Academy of Medical Sciences
2004 Career Achievement in Oral Drug Delivery Award, Controlled Release Society; Elected Fellow
Research Achievement Award, 2nd Pharmaceutical Sciences World Congress
2005 Awarded Honorary Doctor of Philosophy degree, University of Athens, Greece
2007 Distinguished Clinical Research Lecturer – UCSF
International Honorary Member – Japanese Society for the Study of Xenobiotics
2008 Paul Ehrlich Magic-Bullet Lifetime Achievement Award
2010 Awarded Honorary Doctor of Philosophy Degree, Catholic University of Leuven, Belgium
Oscar B. Hunter Memorial Award in Experimental Therapeutics, American Society of Clinical Pharmacology and Therapeutics
2011 Distinguished Investigator Award, American College of Clinical Pharmacology
Awarded Honorary Doctor of Science Degree, University of Michigan.
2012 Awarded Honorary Membership, International Pharmaceutical Federation
Pharmaceutical Research, September 2012 issue dedicated in Dr. Benet's honor under the title, "Fifty Years of Scientific Excellence and Still Going Strong"
2013 Ebert Prize, American Pharmacist Association
Journal of Pharmaceutical Sciences, September 2013 issue dedicated in Dr. Benet's honor
AAPS Journal Outstanding Manuscript Award
2014 Guest Professorship, Sichuan University, Sichuan Province, China (May 2014-April 2019)
Invited Plenary Lecture, 17th International Pharmaceutical Technology Symposium – IPTS 2014, Antalya, Turkey
Invited Keynote Speech, American Conference on Pharmacometrics, ACOP 2014, Las Vegas, NV
2015 Listed among the "25 Top Pharmacy Professors" in the U.S.A. by Medical Technology Schools

William B. Abrams Lectureship, Food and Drug Administration/Center for Drug Evaluation and Research (FDA/CDER) and the American Society for Clinical Pharmacology and Therapeutics (ASCPT) (April 29)
ISSX (International Society for the Study of Xenobiotics) North American Scientific Achievement Award.
Thompson Reuters Highly Cited Researcher. One of 9 pharmacologists worldwide to be listed in the 2001, 2014 and 2015 compilations.

2016 Remington Honor Medal, American Pharmacists Association (March 7)
Awarded Honorary Doctor of Philosophy Degree, University of Lisbon, Portugal

C. Contributions to Science

In the September 2013 issue of the Journal of Pharmaceutical Sciences, dedicated in Professor Benet's honor, Dean Emeritus James Doluisio, University of Texas and past president of both the American Pharmacist's Association and the American Association of Pharmaceutical Scientists characterized Dr. Benet as "The most important pharmaceutical scientist world-wide over the past 50 years. Through his original research and leadership, he has influenced the quality and, importantly, the culture of the pharmaceutical sciences throughout the world!" In the September 2012 issue of Pharmaceutical Research, also dedicated to Professor Benet, we find "Driven by science as few of us are, his contributions to the pharmaceutical and biomedical fields have been major leaps in our understanding of key concepts."

1. Clinical Pharmacokinetics

In the early 1970s Dr. Benet and coworkers introduced the concept of "drug clearance", a key to understanding how much drug is active in the body at a time and hence the most effective dose for a patient. The introduction of clearance concepts transformed the quantitative assessment of drug disposition from a series of differential equations to parameters that reflected changes in pathology and physiology and allowed prediction of drug dosing. This early work, together with Dr. Benet's second most highly cited publication related to the determination of the space available in the body in which drug may distribute and the introduction of mean residence times provide the framework for modern pharmacokinetics and the ability to correlate drug disposition with pharmacodynamics. These early papers, together with the invitation to Dr. Benet to provide detailed descriptions of pharmacokinetics beginning with the 1980 edition of Goodman & Gilman, the "bible of pharmacology", has transformed and made relevant the field of pharmacokinetics to clinical medicine. Continuing work on basic pharmacokinetic principles, for example, the clinical relevance of changes in protein binding, have further contributed to understanding the clinical relevance of pharmacokinetics and pharmacodynamics. (citations numbered from Dr. Benet's publication list; citation statistics from Thomson Reuters Web of Science, All Databases)

14. General Treatment of Linear Mammilary Models with Elimination from Any Compartment as Used in Pharmacokinetics. L.Z. Benet. J. Pharm. Sci., 61, 536-541 (1972). Cited 186 times
19. Clearance Concepts in Pharmacokinetics. M. Rowland, L.Z. Benet and G.G. Graham. J. Pharmacokinet. Biopharm., 1, 123-135 (1973). Cited 678 times
60. Noncompartmental Determination of the Volume of Distribution Steady-State. L.Z. Benet and R.L. Galeazzi. J. Pharm. Sci., 68, 1071-1074 (1979). Cited 950 times
427. Changes in Plasma Protein Binding Have Little Clinical Relevance. L.Z. Benet and B-a. Hoener. Clin. Pharmacol. Ther. 71, 115-121 (2002). Cited 332 times

2. Transporter Enzyme Interplay

Dr. Benet's third most cited publication in Molecular Carcinogenesis in 1995 described for the first time the overlap/interplay of metabolic enzymes and drug transporters, which continues today to lead to new approaches and concepts in understanding and defining drug-drug interactions and the predictability of the importance of pharmacogenomics in characterizing drug disposition.

327. Overlapping Substrate Specificities and Tissue Distribution of Cytochrome P450 3A and P-Glycoprotein: Implications for Drug Delivery and Activity in Cancer Chemotherapy. V.J. Wacher, C.Y. Wu and L.Z. Benet. Mol. Carcinog., 13, 129-134 (1995). Cited 687 times
378. Role of P-glycoprotein and Cytochrome P450 3A in Limiting Oral Absorption of Peptides and Peptidomimetics. V. J. Wacher, J. A. Silverman, Y. Zhang and L. Z. Benet. J. Pharm. Sci., 87, 1322-1330 (1998). Cited 320 times

423. Unmasking the Dynamic Interplay between Intestinal P-Glycoprotein and CYP3A4. C.L. Cummins, W. Jacobsen and L.Z. Benet. J. Pharmacol. Exp. Ther. 300, 1036-1045 (2002). Cited 221 times
486. Predicting Drug Disposition, Absorption/Elimination/Transporter Interplay and the Role of Food on Drug Absorption. J.M. Custodio, C.-Y. Wu and L. Z. Benet. Adv. Drug Deliv. Rev. 60, 717-733 (2008). PMCID: PMC2292816. Cited 196 times

3. The Recognition of the Importance of Intestinal Metabolism

Until Dr. Benet's 1992-1995 series of publications in Clinical Pharmacology and Therapeutics, no one believed that intestinal metabolism was a major player in the decreased bioavailability of many important drugs, especially the immunosuppressive agents. And that the outcome could be explained in terms of transporter-enzyme interplay. His introduction of this concept was confirmed by his ability to obtain patents for inhibiting intestinal metabolism and intestinal drug transport to increase bioavailability, since licensed to Eastman Chemical Company.

275. Bioavailability of Cyclosporine with Concomitant Rifampin Administration is Markedly Less Than Predicted By Hepatic Enzyme Induction. M.F. Hebert, J.P. Roberts, T. Prueksaritanont and L.Z. Benet. Clin. Pharmacol. Ther., 52, 453-457 (1992). Cited 267 times
333. Differentiation of Absorption and First-Pass Gut and Hepatic Metabolism in Humans: Studies with Cyclosporine. C-Y. Wu, L.Z. Benet, M.F. Hebert, S.K. Gupta, M. Rowland, D.Y. Gomez and V.J. Wacher. Clin. Pharmacol. Ther., 58, 492-497 (1995). Cited 284 times
362. Role of Intestinal P-glycoprotein (mdr1) in Interpatient Variation in the Oral Bioavailability of Cyclosporine. K.S. Lown, R.R. Mayo, A.B. Leichtman, H. Hsiao, D.K. Turgeon, P. Schmiedlin-Ren, M.B. Brown, W. Guo, S.J. Rossi, L.Z. Benet and P.B. Watkins. Clin. Pharmacol. Ther. 62 , 248-260 (1997). Cited 564 times
408. The Gut as a Barrier to Drug Absorption. Y. Zhang and L.Z. Benet. Clin. Pharmacokinet., 40, 159-168 (2001). Cited 373 times

4. Acyl Glucuronides

Dr. Benet's laboratory was the first to identify in vivo in humans that a metabolic process, acyl glucuronidation, previously thought only to be a detoxifying mechanism could in fact be an activating mechanism leading to immunologic toxicity of carboxylic acid drugs.

170. Irreversible Binding of Zomepirac to Plasma Protein In Vitro and In Vivo. P.C. Smith, A.F. McDonagh and L.Z. Benet. J. Clin. Invest., 77, 934-939 (1986). Cited 173 times
260. Acyl Glucuronides Revisited: Is the Glucuronidation Process a Toxification as Well as a Detoxification Mechanism? H. Spahn-Langguth and L.Z. Benet. Drug Metab. Rev., 24, 5-48 (1992). Cited 359 times
281. Evidence for Covalent Binding of Acyl Glucuronides to Serum Albumin Via an Imine Mechanism as Revealed by Tandem Mass Spectrometry. A. Ding, J.C. Ojingwa, A.F. McDonagh, A.L. Burlingame and L.Z. Benet. Proc. Natl. Acad. Sci. USA, 90, 3797-3801 (1993). Cited 130 times
374. Identification of the Hepatic Protein Targets of Reactive Metabolites of Acetaminophen in Vivo in Mice Using Two-dimensional Gel Electrophoresis and Mass Spectrometry. Y. Qiu, L. Z. Benet and A. L. Burlingame. J. Biol. Chem., 273, 17940-17953 (1998). Cited 183 times

5. Biopharmaceutics Drug Disposition Classification System (BDDCS)

In 2005, we noted that a Biopharmaceutics Drug Disposition Classification System (BDDCS) could serve as the basis for predicting the influence of transporters in determining drug bioavailability and disposition. We suggested that BDDCS may be useful in predicting overall drug disposition including: routes of drug elimination; the effects of efflux and absorptive transporters on oral drug absorption; when transporter-enzyme interplay will yield clinically significant effects (e.g., low bioavailability and drug-drug interactions); the direction, mechanism and importance of food effects; the potential for flip-flop kinetics; and transporter effects on post-absorptive systemic drug concentrations following oral and intravenous dosing. We reasoned that poorly permeable compounds will not be readily reabsorbed from the kidney lumen or from the bile duct and thus, be more amenable to elimination from the systemic circulation in an unchanged form. Thus, high permeability rate Class 1 and 2 compounds should be primarily eliminated in humans by metabolism, while the poor permeability rate Class 3 and 4 compounds would be preferentially eliminated unchanged in the urine and bile. The recognition of the correlation between intestinal permeability rate and extent of metabolism allows prediction of BDDCS class for an NME to be based on passive membrane permeability.

461. Predicting Drug Disposition via Application of BCS: Transport/Absorption/Elimination Interplay and Development of a Biopharmaceutics Drug Disposition Classification System. C-Y. Wu and L.Z. Benet.

Pharm. Res. 22, 11-23 (2005). Cited 615 times
519. BDDCS Applied to Over 900 Drugs. L.Z. Benet, F. Broccatelli and T.I. Oprea. AAPS J. 13, 519-547 (2011). PMCID: PMC3231854. Cited 147 times
521. Improving the Prediction of the Brain Disposition for Orally Administered Drugs Using BDDCS. F. Broccatelli, C.A. Larregieu, G. Cruciani, T.I. Oprea and L.Z. Benet. Adv. Drug Deliv. Rev. 64, 95-109 (2012). PMCID: PMC3496430. Cited 31 times
540. Predicting when Biliary Excretion of Parent Drug is a Major Route of Elimination in Humans. C. M. Hosey, F. Broccatelli and L. Z. Benet. AAPS J. 16, 1085-1096 (2014). PMCID: PMC4147063 Cited 4 times

Complete List of Published Work
http://www.ncbi.nlm.nih.gov/sites/myncbi/leslie z.benet.1/bibliography/43840166/public/?sort=date&direction=ascending

D. Research Support
Although Dr. Benet continues to submit and receive NIH support, the primary source of funds to run his laboratory over the past decade comes from his consultation fees and Board of Directors remunerations all of which are made payable to the Regents of the University of California to support the research studies in Dr. Benet's laboratory. This results in approximately $350-$500 thousand per year that may be used for innovative and new research projects.

Ongoing Research Support
1 U01 AI 118594 Stock (PI) 7/1/15-6/30/20 1.2 Calendar
NIH/NIAID
Impact of CCR5 Blockade in HIV+ Kidney Transplant Recipients
Role: Co-Investigator
Dr. Benet's laboratory analyzes blood samples for maraviroc-based antiretroviral regimens and immunosuppressive agents in the patients in this multi-site study.

Completed Research Support

R43 RR031474 Benet (Co-PI) 7/23/10-11/15/11 1.2 calendar
NIH/NIGMS
Development of Transporter-Based Predictive ADME Platform
Using transfected cellular systems predict transported-enzyme interplay in drug disposition of new molecular entities.

1 U01 GM61390 Giacomini (PI) 4/1/00-6/30/15 0.6 Calendar
NIH/NIGMS
Pharmacogenetics of Membrane Transporters
Role: Co-Investigator
Dr. Benet examined the effects of transporter polymorphism on drug disposition and develops phenotypic parameters for evaluating transporter-enzyme interplay that can be modified by genotypic differences.

1 R43 GM1135917 Huang, Benet (Co-PIs) 1/15/15-10/14/15 0.9 Calendar
NIH/NIGMS
A novel mechanistic modeling platform for predicting drug clearance and disposition mediated by transporters and enzyme
Role: PI UCSF
Dr. Benet led the UCSF component of this SBIR grant to develop new predictive mechanisms.

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BIOGRAPHICAL SKETCH
DO NOT EXCEED FIVE PAGES.

NAME **Roy R. Gerona**

eRA COMMONS USER NAME (credential, e.g., agency login): [redacted]

POSITION TITLE: Assistant Professor

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
University of the Philippines	B.S.	10/90	Chemistry (*cum laude*)
University of the Philippines	M.S.	05/98	Biochemistry
University of Wisconsin, Madison	Ph.D.	06/08	Biochemistry
University of California, San Francisco	Postdoctoral	07/11	Clinical Chemistry and Pharmacogenomics

A. Personal Statement

Dr. Gerona is currently an Assistant Professor in the Department of Obstetrics, Gynecology and Reproductive Sciences at UCSF. Dr. Gerona has extensive experience in analytical chemistry and in developing quantitative methods for analyzing small molecules in a variety of biological matrices. Before pursuing his Ph.D. in Biochemistry at the University of Wisconsin, Madison, Dr. Gerona was a faculty member at the University of the Philippines, where he taught analytical chemistry, organic chemistry, and biochemistry. After earning his PhD, he joined UCSF for a postdoctoral and Clinical Chemistry fellowship. During his postdoctoral fellowship and as faculty, he has developed extensive expertise in the applications of high resolution and tandem mass spectrometry in clinical toxicology and environmental biomonitoring. For instance, during his Clinical Chemistry fellowship, he successfully developed and implemented a workflow for non-targeted analysis of small molecules that is used in identifying and quantifying drugs and toxic substances involved in emergency intoxications referred to the California Poison Control Center. He remains active in toxicology and has developed and validated methods to analyze a number of novel designer drugs. He has also expanded this work to environmental biomonitoring, pioneering an approach to the identification of novel chemicals that he has extended to other fields.

In the four years since Dr. Gerona established his own laboratory at UCSF, he has successfully implemented methods for the quantitative analysis of several drug panels including those for designer drugs, drugs of abuse, endocrine disrupting compounds such as Bisphenol A (BPA) and its metabolites, BPA replacements, environmental phenols, phthalate metabolites, perfluorinated compounds; and, recently endogenous metabolites such as those relevant in glycolysis, urea cycle and oxidative stress. Given his impressive record, Drs. Les Benet and Monica Gandhi approached him to be part of the UCSF Hair Analytical Laboratory (HAL) team in 2014. He contributed to a successful R01 application (NIAID/NIH R01 AI123024 Gandhi, Metcalfe) to analyze anti-TB drugs in hair, for which he now serves as the primary analytic chemist. Dr. Gerona is currently developing methods of analysis for other additional small molecule targets in hair, including novel antiretrovirals, endogenous metabolites, and environmental chemicals.

Dr. Gerona's broad experience in using LC-MS platforms to measure pharmaceutical drugs in various biological matrices aligns well with the expertise required to achieve the goals of the three Specific Aims of Dr. Gandhi's proposed R01 renewal ("Hair Extensions": Using Hair Levels to Interpret Adherence, Effectiveness and Pharmacokinetics with Real-World Oral PrEP, the Vaginal Ring, and Injectable PrEP).

Over the past few months alone, Drs. Gerona, Gandhi and Peter Bacchetti (primary biostatistician on this R01 renewal) have published two papers on analyzing anti-TB drugs in hair and their abstract on a multi-analyte panel for TB drugs in hair (selected from over 6700 abstracts submitted to AIDS 2016) was awarded the prestigious TB/HIV Research Prize at the International AIDS Conference in Durban, South Africa (July 2016). Dr. Gerona has developed methods to analyze isoniazid, a number of MDR-TB drugs, and new antiretrovirals in small hair samples, with two papers under review. Relevant publications with Dr. Gandhi are below:

1. **Gerona R**, Wen A, Koss C, *Bacchetti P, Gandhi M*, Metcalfe J. A multi-analyte panel for non-invasive pharmacokinetic monitoring of second-line anti-tuberculosis drugs. The International Journal of Tuberculosis and Lung Disease. 2016; 20(7): 991-2. **PMID: 27191185**; **PMCID in progress**
2. **Gerona R**, Wen A, Chin AT, Koss CA, *Bacchetti P*, Metcalfe J, *Gandhi M*. Quantifying Isoniazid Levels in Small Hair Samples: A Novel Method for Assessing Adherence during the Treatment of Latent and Active Tuberculosis. PLoS One. 2016; 11(5):e0155887**. PMCID: PMC4871544**

B. Positions and Honors

Positions and Employment

1998-2001 Assistant Professor, Institute of Chemistry, University of the Philippines
2008-2009 Post-Doctoral Researcher, Department of Biochemistry, University of Wisconsin, Madison
2009-2014 Post-Doctoral Fellow, Department of Laboratory Medicine, UC San Francisco

Honors

2002 Wharton Scholarship, Department of Biochemistry, University of Wisconsin, Madison
2013 Young Investigator Award, Mass Spectrometry Applications to the Clinical Laboratory Annual Conference.
2016 International AIDS Society's TB/HIV Research Prize

C. Contributions to Science

Besides my recent work in the development of mass spectrometry methods for monitoring antiretrovirals and TB drugs in small hair samples with Dr. Monica Gandhi, I have a number of other areas of significant expertise in analytic chemistry, all relevant to the measurement of small molecules in biologic matrices.

1. **Development of mass spectrometry methods for monitoring environmental toxins in biological matrices.**
   My laboratory has applied mass spectrometry methods to environmental biomonitoring. My laboratory serves as the analytical core for the Program on Reproductive Health and the Environment (PRHE) at UCSF and has existing collaborations with leading researchers in environmental exposure science. Along with PRHE, my laboratory is pioneering the application of general suspect screening in environmental biomonitoring with the aim of identifying novel environmental chemicals that should be monitored in pregnant women including those associated with specific clinical markers of endocrine disruption and reproductive abnormalities. My laboratory's initial work in general suspect screening has recently been submitted for publication but the laboratory has representative publications on the targeted LC-MS methods we have developed for environmental biomonitoring, including for BPA.
   a. **Gerona, RR**, Woodruff T, Dickenson CA, Pan J, Schwartz JM, Sen S, Friesen M, Fujimoto VY, Hunt PA. BPA, BPA glucuronide, and BPA sulfate in mid-gestation umbilical cord serum in a northern California cohort. Environ Sci Technol. 2013. 47(21); 12477-85. PMID: 23941471**, PMCID: PMC3881559**
   b. **Gerona RR**, Pan J, Zota AR, Schwartz JM, Friesen M, Taylor JA, Hunt PA, Woodruff T. Direct measurement of Bisphenol A (BPA), BPA glucuronide and BPA sulfate in a diverse and low-income population of pregnant women reveals high exposure, with potential implications for previous exposure estimates: a cross-sectional study. Environ Health. 2016. 15(1):50. PMID: 27071747, **PMCID PMC4828888**
   c. MacIsaac, J, **RR Gerona**, P Blanc, L Apatira, M Friesen, M Coppolino, S Janssen. Healthcare Worker Exposures to the Antibacterial Agent Triclosan. J Occup Environ Med. 2014. 56(8): 834-9. PMID: 25099409**, PMCID: PMC4133120**
2. **Non-targeted testing of drugs of abuse in emergency intoxications using high resolution mass spectrometry.**
   During my post-doctoral training at San Francisco General Hospital, I pioneered the application of high-resolution mass spectrometry in Clinical Toxicology. I developed a general unknown screening workflow process for the identification of drugs and toxic substances involved in emergency intoxication cases referred to the California Poison Control Center. Numerous cases that were solved through this workflow have been published by my group, along with the general description of the analytical methods we developed. This work continues to be actively pursued in my laboratory with particular emphasis on designer drugs intoxication through collaborations with the Drug Enforcement Administration (DEA), the

Department of Homeland Security and various Poison Centers across the country. Our work has been instrumental in assisting the DEA in identifying novel intoxicating drugs to help establish safety and treatment protocols. The following are representative publications from this work:

a. Wu AH, **Gerona R**, Armenian P, French D, Petrie M, Lynch KL. Role of liquid chromatography-high-resolution mass spectrometry (LC-HR/MS) in clinical toxicology. Clin Toxicol. 2012. 50(8): 733-42. **PMID: 22888997,** Publicly available: http://www.tandfonline.com/doi/full/10.3109/15563650.2012.713108
b. Thornton SL, Lo J, Clark RF, Wu AH, and **Gerona RR.** Simultaneous detection of multiple designer drugs in serum, urine, and CSF in a patient with prolonged psychosis. Clinical Toxicol. 2013. 50(10): 1165-8. **PMID: 23163617**, Publicly available: http://www.tandfonline.com/doi/full/10.3109/15563650.2012.744996
c. Trecki J, **Gerona R**, Schwartz M. Synthetic Cannabinoid-Related Illnesses and Deaths. New England Journal of Medicine. 2015. 373:103-107. **PMID: 26154784**, Publicly available: http://www.nejm.org/doi/full/10.1056/NEJMp1505328

3. **Targeted quantitative analysis of drugs and toxic substances using high resolution tandem mass spectrometry.**
In confirming the suspect drugs identified through general unknown screening, I have developed several panels for testing substances and designer drugs in illicit drug matrices and biological matrices. The targeted methods I developed are among the first targeted drug methods developed using high-resolution mass spectrometry. These panels have been used in emergency intoxication testing as well as several collaborative projects aimed at identifying and quantifying drugs in pharmaceuticals and illicit drug products. The following are representative publications that have come out of this work:

a. Cantrell L, J Suchard, A Wu and **RR Gerona**. Stability of active ingredients in long-expired prescription medications. Archives of Internal Medicine. 2012. 172(21): 1685-7. **PMID: 23045150**, Publicly available: http://archinte.jamanetwork.com/article.aspx?articleid=1377417
b. Schneir A, Ly BT, Casagrande K, Darracq M, Offerman SR, Thornton S, Smollin C, Vohra R, Rangun C, Tomaszewski C, **Gerona RR**. Comprehensive analysis of “bath salts” purchased from California stores and the internet. Clin Toxicol. 2014. 52(7): 651-8. **PMID: 25089721**, Publicly available: http://www.tandfonline.com/doi/full/10.3109/15563650.2014.933231
c. [redacted]

4. **Development of mass spectrometry methods for the identification and monitoring of drug metabolites and endogenous metabolic intermediates.**
More recently, my laboratory has started exploring and utilizing mass spectrometry in targeted metabolomics. Through collaborations with various research groups at UCSF we have started developing LC-MS methods for the quantitative analysis of metabolic intermediates and drug metabolites in cell extracts and various animal and human biological matrices. The laboratory has recently developed LC-MS/MS methods for the analysis of urea cycle metabolites, glycolytic metabolites and oxidative stress markers. This work is currently being expanded to cover other key metabolic pathways prioritizing those that are most relevant to our collaborators. Manuscripts for publication from this work are currently being written; however, our first work on a drug metabolite has been published:

a. Spiller HA, Russell JL, Casavant MJ, Ho RY, **Gerona RR.** Identification of N-Hydroxy-para-aminobenzoic acid in a cyanotic child after benzocaine exposure. Clin Toxicol (Phila). 2014. 52(9):976-9. **PMID: 25211007,** Publicly available: http://www.tandfonline.com/doi/full/10.3109/15563650.2014.958615

Complete List of Published Work:
http://www.ncbi.nlm.nih.gov/sites/myncbi/1VgHz2XMaCFkv/bibliography/47877056/public/?sort=date&direction=ascending

D. Research Support

Ongoing Research Support (selected)

R01 AI098472, NIH/NIAID Gandhi (PI) 12/15/11-11/30/16
Plugging hair ARV levels as adherence biomarkers into HIV prevention trials
The study extends initial work on using hair ARV measures in observational cohorts to the NIH-funded clinical trial networks. We use validated hair assays (and work with the Division of AIDS Clinical Pharmacology and Quality Assurance program) to measures ARVs in a number of different trials.
Role: Co-Investigator

R01 AI123024-01, NIH/NIAID Gandhi/Metcalfe (PI) 01/01/16-12/31/20
Novel methods of pharmacologic monitoring for multidrug resistant tuberculosis treatment in the setting of HIV infection
The goal of the study is to evaluate the use of anti-TB drug analysis in hair in monitoring adherence to anti-TB drug medication among HIV-infected patients with multidrug resistant tuberculosis. The utility of hair anti-TB drug levels will then be assessed in predicting treatment outcomes. I serve as the primary analytic chemist for this work.
Role: Co-Investigator

R01 HD31544, NIH/NIEHS Hunt (PI) 07/01/08-08/31/16
Meiotic Studies of Chemicals with Estrogenic Activity in Human Female Gametes
The goal of the study is to characterize and define association between maternal bisphenol A exposure and the earliest events of oocyte development in the developing fetus.
Role: Collaborator

P01 ES022841-01, NIH/NIEHS/USEPA Woodruff (PI) 06/15/13-05/31/18
The UCSF Pregnancy Exposures to Environmental Chemicals (PEEC) Children's Center
The PEEC Children's Center will advance our understanding of how exposure to environmental chemicals affects early development using an innovative multidisciplinary approach that integrates research on sources and exposures to environmental chemicals during pregnancy with basic biological research, and translates these scientific findings to healthcare providers, policy makers and community groups in order to improve clinical care and promote policies that prevent prenatal exposures to harmful chemicals.
Role: Co-Investigator

EPA-STAR, USEPA Woodruff (PI) 10/01/14-09/30/18
A Non-targeted Method for Measuring Multiple Chemical Exposures Among a Demographically Diverse Population of Pregnant Women in Northern California
The study aims to apply an innovative non-targeted biomonitoring method using liquid chromatography-quadrupole time-of-flight mass spectrometry (LC-QTOF/MS) to profile the presence and co-occurrence of over 700 chemicals classified as Environmental Organic Acids among a diverse group of pregnant women.
Role: Co-Investigator

11-E0022, CalEPA Woodruff (PI) 06/15/12 - 12/31/16
Evaluating Background and Cumulative Exposures to Environmental Chemicals

The goal of the study is to evaluate samples collected from pregnant women using a non-targeted LC-MS approach to determine their chemical exposures profiles and scientifically inform efforts to characterize cumulative exposures. **Role: Co-Investigator**

OMB No. 0925-0001 and 0925-0002 (Rev. 10/15 Approved Through 10/31/2018)

BIOGRAPHICAL SKETCH
DO NOT EXCEED FIVE PAGES.

NAME: **Elizabeth R. Brown**

eRA COMMONS USER NAME (credential, e.g., agency login): [redacted]

POSITION TITLE: Research Professor in Biostatistics

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
University of Virginia, Charlottesville, VA	B.S.	05/94	Mechanical Engineering
University of Colorado, Denver	M.S.	06/98	Biometrics
Harvard University, Cambridge, MA	Sc.D.	07/02	Biostatistics

A. Personal Statement

Dr. Brown is a Research Professor in the University of Washington's Department of Biostatistics and a Member in the Vaccine and Infectious Disease and Public Health Science Divisions at the Fred Hutchinson Cancer Research Center. Dr. Brown has worked in HIV research, collaborating with scientists and developing novel statistical methods and approaches, for over 15 years. Dr. Brown has contributed to HIV prevention research as Principal Investigator (PI) of the Microbicide Trials Network Statistical and Data Management Center since June of 2011 and prior to that as the lead statistician on two phase 3 and one phase 1 clinical trials for prevention of mother to child transmission of HIV.

Since Dr. Brown is fully funded by the MTN, she will serve as a significant contributor on Dr. Monica Gandhi's R01 renewal entitled "Hair Extensions": Using Hair Levels to Interpret Adherence, Effectiveness and Pharmacokinetics with Real-World Oral PrEP, the Vaginal Ring, and Injectable PrEP (see letter of support). She performed the primary analyses for the NEJM paper on the MTN-020 (or ASPIRE) trial and was also responsible for the main adherence analysis to come out of this study (presented at the International AIDS Conference (AIDS 2016) in Durban, South Africa in July 2016). She is the main protocol statistician for MTN-025, which is the HIV Open-Label Prevention Extension (HOPE) trial in which Aim 2 of this application is embedded. The importance of objective measures of adherence when assessing the effectiveness of oral or vaginal-based PrEP has been demonstrated by Dr. Brown in the earlier trial and she will lend her statistical expertise to the analyses of data from this grant with Drs. Gandhi, Bacchetti, and Baeten.

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B. Positions and Honors

Employment

2002-2009 Research Assistant Professor, Department of Biostatistics, University of Washington, WA
2004-2009 Assistant Member, Fred Hutchinson Cancer Research Center, Seattle, WA
2009-present Research Associate Professor, Department of Biostatistics, University of Washington, WA
2009-2013 Associate Member, Fred Hutchinson Cancer Research Center, Seattle, WA
2014-present Member, Fred Hutchinson Cancer Research Center, Seattle, WA

Honors

1997 University of Colorado Health Sciences Center Master's Fellowship
1998 Statistical Graphics Section of the ASA Student Paper Competition Winner
1998 Maurice Davies Award as the Outstanding Master's Student of the Year, University of Colorado Health Sciences Center
1998 – 2002 National Research Service Award (NRSA) Training Grant, National Institute of Allergic and Infectious Diseases, NIH

2002 Student Award Winner, Eastern North American Region/International Biometric Society (ENAR) Student Award Winner
2006 NIH Travel Award, ENAR Young Investigators Meeting, Tampa, FL

Other Experience and Professional Memberships

1998 – present Member, American Statistical Association
1998 – present Member, International Biometric Society
2002 – present Referee for: American Journal of Epidemiology, Annals of Applied Statistics, Applied Statistics (JRSS-C), Biometrics, Biostatistics, BMC Medical Research Methodology, Circulation, International Journal of Biostatistics, Journal of Computational and Graphical Statistics, Journal of the American Medical Association, Journal of the American Statistical Association, Lifetime Data Analysis, Statistics in Medicine, Radiology, The Lancet Infectious Diseases
2012-Present Associate Editor, Journal of the American Statistical Association, Case Studies and Applications
June 2012 Program Chair for the Western North American Region of the International Biometrics Society meeting, Fort Collins, CO
2013 President-Elect, Western North American Region of the International Biometrics Society (WNAR)
2013 – 2015 Member, Council of Presidents of Statistical Societies
2014 President, Western North American Region of the International Biometrics Society (WNAR)
2014 – 2016 Member, Local Organizing Committee of 2016 International Biometrics Society Conference
2015 - 2017 American Statistical Association (ASA) Council of Sections Representative, Biometrics Section
2015 Past President, Western North American Region of the International Biometrics Society (WNAR)

C. Contribution to Science

Dapivirine ring for HIV prevention

Women in sub-Saharan Africa remain at risk for HIV infection with few options for HIV prevention. Although pre-exposure prophylactics containing tenofovir have been proven to be an effective prevention tool, adherence to these products in women was low and HIV protection was not shown in two large trials. A vaginal ring containing dapivirine designed to be worn 28 days straight could overcome this adherence barrier. I was the protocol statistician for MTN-020, the first study showing effectiveness of a vaginal ring containing dapivirine against HIV infection. Secondary analyses, presented in the primary paper, illustrated the potential relationship between adherence and efficacy in the ring, suggesting that effectiveness may in fact be much higher than the primary analysis estimate of 27%. At the 2016 AIDS conference, I shared further results from the study estimating that the observed risk reduction in adherent women compared to placebo was at least 56%. Comparisons of high adherence to placebo increased this estimate to 75% or greater. The vaginal ring containing dapivirine has the potential to offer women at risk a discreet, self-controlled tool to protect themselves against HIV infection. Study of feasible metrics of long-term adherence, such as those offered by hair levels, in the next phase of the study (MTN-025) will be essential as proposed in this renewal application.

1. Baeten JM, Palanee-Phillips T, **Brown ER**, Schwartz K, Soto-Torres LE, Govender V, Mgodi NM, Matovu Kiweewa F, Nair G, Mhlanga F, Siva S, Bekker LG, Jeenarain N, Gaffoor Z, Martinson F, Makanani B, Pather A, Naidoo L, Husnik M, Richardson BA, Parikh UM, Mellors JW, Marzinke MA, Hendrix CW, van der Straten A, Ramjee G, Chirenje ZM, Nakabiito C, Taha TE, Jones J, Mayo A, Scheckter R, Berthiaume J, Livant E, Jacobson C, Ndase P, White R, Patterson K, Germuga D, Galaska B, Bunge K, Singh D, Szydlo DW, Montgomery ET, Mensch BS, Torjesen K, Grossman CI, Chakhtoura N, Nel A, Rosenberg Z, McGowan I and Hillier S for the MTN-020–ASPIRE Study Team. Use of a Vaginal Ring Containing Dapivirine for HIV-1 Prevention in Women. N Engl J Med. 2016 Feb 22;DOI: 10.1056/NEJMoa1506110: 26900902.
2. [redacted]

Risk prediction for HIV

Prediction of outcomes in HIV research typically examines correlation between potential markers and surrogate outcomes. In this paper, I introduced time-varying ROC curves to HIV prognostic research with a hard outcome, mortality. In this paper, we examined the usefulness of the CD4 cell count, CD4 cell percentage (CD4%), human immunodeficiency virus type 1 (HIV-1) load, total lymphocyte count (TLC), body mass index (BMI), and hemoglobin measured at 32 weeks' gestation as predictors of mortality in a cohort of HIV-1–infected women in Nairobi, Kenya. Of particular interest was determining if WHO guidelines for initiation of antiretroviral therapy were relevant for pregnant women. The CD4 cell count and CD4% measured during pregnancy were both useful predictors of mortality among pregnant women. TLC, BMI, and hemoglobin had a limited predictive value, and the HIV-1 load did not predict mortality any better than the CD4 cell count alone. As well as contributing to clinical literature, this manuscript introduced new approaches for evaluating potential biomarkers to HIV disease progression research. To my knowledge this approach was completely novel in studies of HIV disease progression. This paper was also selected for full Editorial Commentary in the same issue by Mary Glenn Fowler and Maxensia Owor.

1. **Brown ER**, Otieno P, Mbori-Ngacha DA, Farquhar C, Obimbo EM, Nduati R, Overbaugh J, John-Stewart GC. Comparison of CD4 cell count, viral load, and other markers for the prediction of mortality among HIV-1-infected Kenyan pregnant women. J Infect Dis. 2009;199(9):1292-300 PMCID: 2758232.

Analysis of HIV prevention studies

It is well known that enrolling a population where a significant proportion are not at risk for the endpoint of interest can result in bias and inefficiency in effectiveness estimates and therefore has implications for the design and interpretation of HIV prevention trials and biomarker studies. My team built stochastic models to estimate the proportion of participants in an HIV prevention trial exposed to HIV at any point during follow-up, finding that, in fact, observed incidence rates may actually correspond to low to moderate exposure rates. To address this issue, we have also developed novel models for estimating effectiveness in HIV prevention trials when a proportion of the population is never exposed to HIV and therefore not at risk.

1. Dimitrov D, Donnell D, **Brown ER**. High incidence is not high exposure: What proportion of prevention trial participants are exposed to HIV? PLoS ONE. 2015;10(1):e0115528; PMCID: 4287619.
2. Zhang J, **Brown ER**. Estimating the effectiveness in HIV prevention trials by incorporating the exposure process: Application to HPTN 035 data. Biometrics. 2014;70(3):742-750. PMCID: 4239192.
3. Coley RY, **Brown ER**. Estimating effectiveness in HIV prevention trials with a Bayesian hierarchical compound Poisson frailty model. Statistics in Medicine. 2016;35(15):2609-34. PMCID: 26869051.
4. [redacted]

Complete List of Published Work in MyBibliography:
http://www.ncbi.nlm.nih.gov/sites/myncbi/elizabeth.brown.1/bibliography/41144571/public/?sort=date&direction=ascending

D. Research Support

ONGOING
U01 AI068615-10
(E Brown)
6/29/2006-11/30/2020
Agency: NIH/NIAID
Title: *SDMC: Microbicide Trials Network*
The MTN SDMC scientific agenda includes the following aims: 1. Ensure the collection of complete, high quality data by providing state-of-the-art secure data management systems and training according to best data and clinical management practices. 2. Provide statistical and epidemiologic leadership and support throughout the protocol development and implementation process, including study design, monitoring and analysis and

reporting. 3. Develop and implement innovative statistical and epidemiological approaches to improve the scientific understanding of HIV risk, how microbicides reduce this risk and how this reduction may be modified or influenced by biological and behavioral factors.
Role: Principal Investigator

UM1 AI068633
(Hillier)
06/29/2006–11/3/2020
Agency: NIH/NIAID
Title: *LOC: Microbicide Trials Network, The Leadership Group for a clinical research network on microbicides to prevent HIV (leadership and operational group).*
The objectives of the Microbicide work is to reduce the sexual transmission of HIV through the development and evaluation of products, which reduce the transmission of HIV when applied topically to mucosal surfaces.
Role: Consortium Principal Investigator

R01 AI029168
(Hughes)
5/1/2014 - 4/30/2019
Agency: NIH/NIAID (University of Washington Sub Award [Self])
Title: *Statistical Issues in AIDS Research*
In this application, we outline plans for the development of statistical methods that will be directly applicable to current problems in the field of HIV/AIDS research. In particular, we propose to develop methods for the analysis of data from stepped wedge randomized trials, trials to prevent mother to child transmission of HIV, discordant partner studies, and trials or studies which utilize two-phase or other complex sampling designs. Since two test dates, we continue work on methods for interval censored data and focus on issues related to competing risks and correlated interval censored data and focus on issues related to competing risks and correlated interval censored data and focus on issues related to competing risks and correlated interval censored data. Finally, as the search for an effective HIV vaccine presents ever greater challenges, the investigators on this proposal are uniquely positioned to develop novel statistical methods for analyzing data from studies of T-cell based vaccines as well as approaches designed to elicit neutralizing antibodies.
Role: Co-investigator

R03MH106352
(Balkus)
12/15/2014-11/30/2016
Agency: NIH/NIMH
Development and Validation of an HIV Risk Assessment Tool for African Women
This proposal will utilize data collected in the course of several recently completed large-scale clinical trials for HIV prevention in African women in order to develop and validate an HIV risk assessment tool to predict HIV risk within one year.
Role: Co-Investigator

COMPLETED RESEARCH SUPPORT
R01HL103729-03

(McClelland)
09/16/11 – 5/31/14
Agency: NIH/NHLBI (Sub from University of Washington)
Title: *Longitudinal Methods for Cardiovascular Disease Research*
This research will extend and develop statistical methods tailored to CVD research. The aims are 1) to develop improved methods for estimation of biomarker associations in the presence of extensive medication use; and 2) to develop improved measures and models of coronary artery calcium, its relationship with risk factors and its impact on disease progression.
Role: Co-investigator

U01 AI068632-07
(D Donnell)
6/29/2006 -12/31/2013
Agency: NIH/DAIDS (Sub from Johns Hopkins University)
Title: *International Maternal Pediatric Adolescent AIDS Clinical Trials (IMPAACT)*
The aim of this study is to provide statistical leadership and data management support for a network of field sites that will conduct Phase I-III trials of promising mother-to-child transmission HIV prevention methods.
Role: Statistician

R01HL095126
(E Brown and R Kronmal)
9/25/2008 – 06/30/2013
Agency: NIH/NHLBI
Title: *CVD and Metabolic Complications of HIV/AIDS Data Coordinating Center*
The purpose of the project is to foster collaborative research to elucidate the underlying mechanisms of metabolic and anthropometric abnormalities seen in HIV infection and highly active antiretroviral therapy and their relationship to cardiovascular disease risk.
Role: Co-Principal Investigator (Contact PI)

R01 HL106800-01
(S Bennett)
9/01/2010 - 8/31/2013
Agency: NIH/NHLBI
Title: *Data Coordinating Center for Systems Biology Approach to Mechanisms of TB*
This application proposes a data coordinating center to coordinate the collaborative activities of four studies of the mechanisms of reactivation of latent tuberculosis.
Role: Co-investigator

Budget justification

Timeline for proposed research	
Year 1	• Continue hair collection in SEARCH (Aim 1) and MTN-025 (Aim 2) – both started Aug 2016 • Start hair collection for ACTG A5339 (Aim 3) • Perform final validation experiments for the dapivirine (Aim 2) hair assay using initial samples and submit assay validation reports/ standard operating procedures to DAIDS CPQA program
Year 2	• MTN-025 (Aim 2) finishes enrollment and hair analyses begins • Continue to collect hair in SEARCH (Aim 1) and A5359 (Aim 3) • Manuscript generation of methods for dapivirine hair assay • Perform final validation experiments for the CAB (Aim 3) hair assay using initial samples and submit AVR/SOP to DAIDS CPQA program for peer review and approval
Year 3	• Finish MTN-025 hair assays and initiate data analyses – correlations, triangulation, outcomes • Finish up hair collection in SEARCH (Aim 1) and start analyzing samples • Continue to collect hair in A5359 (Aim 3) • Manuscript generation of methods for cabotegravir hair assay
Year 4	• Finish SEARCH hair assays and initiate data analyses - correlations, triangulations, outcomes • Start analyzing hair samples for A5359 (Aim 3) • Complete data analyses for MTN-025 (Aim 2) • Manuscript generation for acceptability, feasibility papers, correlation analyses for Aims 1, 2
Year 5	• Complete hair assays for A5359 (Aim 3) • Manuscript generation of final hair levels and outcomes papers for Aims 1, 2 and 3 • Laboratory collaborations for work on transferring hair assay technology to African settings

PERSONNEL

UCSF Academic Personnel

Monica Gandhi MD MPH, Principal Investigator (1.2 calendar months years 1-3; 1.8 calendar months years 4-5). Dr. Gandhi is a Professor of Medicine and Associate Chief in the Division of HIV, Infectious Diseases and Global Medicine at UCSF. She also serves as the Medical Director of the Division's large HIV Clinic ("Ward 86") at San Francisco General Hospital. She will be responsible for the overall design and implementation of the research plan over all 5 years of this proposed renewal of NIAID/NIH R01 AI098472.

Dr. Gandhi has extensive experience in the pharmacoepidemiology of HIV infection. She has worked on studies to investigate pharmacokinetic parameters to antiretrovirals in "real world" populations using the Women's Interagency HIV Study (WIHS) as a platform. She served as the Chair of the Pharmacology Working Group of the multi-site WIHS study from 2003-2014 before focusing her work on investigating hair concentrations of ARVs in various international HIV treatment and prevention trials during the first funding period of this R01. She serves as an elected member of the Office of AIDS Research Advisory Council (OARAC) and the ACTG Executive Committee. In Years 1and 2 of the grant, she will work with Drs. Havlir, Baeten and Castillo-Mancilla to oversee hair collection in the three clinical trials (Aim – SEARCH; Aim 2- MTN-025 and Aim 3- ACTG A5359, respectively). She serves as the Clinical Director of the Hair Analytical Laboratory (HAL) at UCSF with Dr. Les Benet serving as General Director. Dr. Gandhi, along with Drs. Gerona and Benet, will ensure that the validation of the hair assays for Aim 2 (dapivirine) and Aim 3

(cabotegravir) is completed, with submission of the analytic validation reports/standard operating procedures (AVR/SOP) to CPQA for peer review and approval. In Year 3-5 of the grant, she will oversee the hair analyses for all three studies with Dr. Gerona and work with her co-investigators and consultants on data analyses, data interpretation, presentation and publication.
Note: Current annual institutional salary exceeds the current Federal Executive Level II Salary Cap of $185,100.

Diane Havlir MD, Co-investigator (0.6 calendar months years 1-5). Dr. Havlir is a Professor of Medicine and Chief of the Division of HIV, Infectious Diseases, and Global Medicine at UCSF. She has led many productive and influential research programs to work on strategies to reduce the HIV burden on an individual and population level. She is currently the co-Principal Investigator (along with Moses Kamya MBChB, MPH, PhD, Dean of the School of Medicine, Makerere University) of the SEARCH trial, which has successfully enrolled ~340,000 individuals in 32 communities in Kenya and Uganda. Aim 1 of the current proposal will investigate hair and plasma measures of tenofovir and emtricitabine in the PrEP trial being launched in the second phase of SEARCH as biomarkers of adherence (which will be assessed in relationship to effectiveness) and exposure (which will be assessed in relationship to toxicities). Drs. Havlir and Gandhi (along with consultant Dr. Moses Kamya) will be responsible for overseeing hair collection among PrEP participants over the first 3 years of the study. They will then work with the other investigators and Dr. Kamya on the proposed analyses and manuscript generation. With their mutual commitment to mentorship, Drs. Havlir and Gandhi will use Aim 1 of the proposed study as a platform for mentoring junior investigators, both U.S. and Africa-based.
Note: Current annual institutional salary exceeds the current Federal Executive Level II Salary Cap of $185,100.

Peter Bacchetti PhD, Co-investigator (1.2 calendar months years 1-2; 1.8 calendar months years 3- 5). Dr. Bacchetti is Professor of Epidemiology and Biostatistics at UCSF. Dr. Bacchetti served as the primary biostatistician during the first funding period of this R01 we are hoping to renew. He is an internationally recognized expert in HIV biostatistics and will provide statistical consultation and guide analyses for the proposed study throughout all five years of the award. He has co-authored 23 publications with Dr. Gandhi and has served as the lead statistician on all projects within the multicenter WIHS study and Dr. Gandhi's independent studies that involve using antiretroviral concentrations in hair as markers of adherence and exposure. Increased effort is requested for Years 3-5 when the majority of the statistical analyses for Aims 1-3 will be performed in conjunction with co-investigators, collaborators (including significant contributor Dr. Elizabeth Brown, lead biostatistician of the MTN, and the PhD student at U of Washington), and consultants.
Note: Current annual institutional salary exceeds the current Federal Executive Level II Salary Cap of $185,100.

Leslie Z. Benet PhD, Co-investigator (0.6 calendar months years 1-4; 1.2 calendar months year 5). Dr. Benet is Professor of Bioengineering and Therapeutic Sciences and Professor of Pharmaceutical Chemistry at UCSF. He is a world-renowned expert in pharmacokinetics (PK) and one of the most highly-cited pharmacologists in the world with over 550 publications and book chapters. He is the General Director of the Hair Analytical Laboratory (HAL) at UCSF and will be responsible for general oversight of the hair work during all 5 years of this application, with Dr. Gerona serving as the laboratory director. He will ensure, along with Drs. Gandhi and Gerona, that the dapivirine and cabotegravir hair assays for Aims 2 and 3, respectively, are validated and submitted to the CPQA program for peer review and approval prior to sample analysis (the assays relevant to Aim 1 have already been approved by CPQA). During year 5 of the grant, he will inform the data analyses for Aim 3, which involves modelling the pharmacokinetics of cabotegravir in ACTG A5359 via hair and plasma levels. With the co-investigators and consultants, he will aid in disseminating the findings of this proposal,

including methods reports and PK implications.
Note: Current annual institutional salary exceeds the current Federal Executive Level II Salary Cap of $185,100.

Roy R. Gerona PhD, Co-investigator (2.4 calendar months years 1-5). Dr. Gerona is an Assistant Professor in the Department of Obstetrics, Gynecology and Reproductive Sciences at UCSF. Dr. Gerona runs a Clinical Toxicology and Environmental Biomonitoring Laboratory (CTEBL) that specializes in developing mass spectrometry assays for the quantitative analysis of small organic molecules in biological matrices. He was brought into the Hair Analytical Laboratory at UCSF during the first funding period of this R01 by General Director Dr. Les Benet and Clinical Director Dr. Monica Gandhi based on his vast expertise in developing and validating assays in a variety of biomatrices for novel drugs and molecules. He will serve as the principal analytic chemist for the proposed study and developed the assays for dapivirine and cabotegravir in small hair samples for this application (Approach, Preliminary Data, Section 3C3). He will direct the validation of the assays for dapivirine and cabotegravir in years 1 and 2 of the grant and, along with Drs. Benet and Gandhi, submit the AVR/SOP reports to the CPQA for peer review and approval. He will serve as the first author on the hair assay methods papers generated from this grant. During Years 2-5 of the grant, he will be responsible for guiding the staff research associate and quality assurance (QA) director in the lab in performing the analyses of hair specimens collected in the HOPE/MTN-025, SEARCH, and ACTG 5359 trials. Dr. Gerona will contribute to data interpretation of drug levels in hair for all three studies and to manuscript generation. Dr. Gerona will also aid in laboratory communications between the UCSF HAL and Africa-based laboratories during the phase of technology transfer in year 5 of the grant.

UCSF staff

Anita Wen, Staff Research Associate I (12.0 calendar months years 1-5). Ms. Wen, a Staff Research Associate in the UCSF CTEBL and Hair Analytical Laboratory, will help coordinate the research activities for the study relevant to the analytic assays. She will lead the experiments under Dr. Gerona's guidance during years 1 and 2 of the award to validate the LC-MS/MS assays to quantitatively measure dapivirine and cabotegravir in hair. She will, along with the QA director (Karen Kuncze) and Dr. Gerona (with oversight from Drs. Benet and Gandhi) help generate the AVR/SOP reports for the CPQA program for peer review and approval. During years 2-5, she will serve as the lead technician running the analyses of dapivirine, tenofovir/ emtricitabine, and cabotegravir levels in hair for the HOPE/MTN-025, SEARCH, and ACTG 5359 trials, respectively, using the validated LC-MS/MS assays. Ms. Wen will also facilitate laboratory communications between the UCSF HAL and Africa-based laboratories during the phase of technology transfer in year 5 of the grant.

Karen Kuncze, Staff Research Associate II and Quality Assurance Director (12.0 calendar months years 1-5). Karen Kuncze has been working with the Hair Analytical Laboratory at UCSF for the past 10 years (and with Dr. Les Benet in the Drug Studies Unit for the past 21 years) as a research associate and quality assurance director. She has expertise in project management, analytical theory and techniques of analyzing drugs in a variety of biomatrices, especially hair samples. She is well-versed on FDA regulations on bioanalytical method validation, safety-related policies and issues, and the analysis of data, including manual/automated computations and the recognition of irregularities and invalid results from the assays. She monitors and inspects all ongoing analytical studies to assure that equipment, personnel, methods, practices, records, and controls are in conformance with Good Laboratory Practice (GLP). In addition to her QA duties, she will assist Ms. Wen in the validation experiments for the dapivirine and cabotegravir hair assays and in running the levels for the large number of samples to be collected in the three trials. Ms. Kuncze will also aid with

laboratory communications related to quality assurance protocols between the UCSF HAL and Africa-based laboratories during the phase of technology transfer in year 5 of the grant.

Stephen May, Project Coordinator (1.8 calendar months years 1-5). Under the direction of Dr. Gandhi, Mr. May will be responsible for study coordination and communication with all collaborators and sites, data management and gathering information for project reports and statistics for all three Aims. Mr. May was the study coordinator during the first funding period for this R01 and is familiar with IRB submissions, coordination of hair sample shipments, establishing material transfer agreements, etc., for related projects.

Katherine (Katie) Sausen Snyman MPH, Uganda-based Quality Assurance Laboratory Coordinator for SEARCH (1.8 calendar months years 1-5). The proper collection, transfer, processing, and storage of specimens from the community health campaigns and the health clinics in the 32 communities randomized to the SEARCH interventions are critical to the success of this large research program. Ms. Snyman has been responsible for the coordination of the laboratory specimens collected in Uganda and Kenya for the SEARCH study since 2013. Given the complexity of this trial and the need for a designated associate in SEARCH to coordinate the hair and plasma collection for adherence measurement in Aim 1 of this R01 renewal, Ms. Snyman will be funded all 5 years of this grant. Ms. Snyman will work in-country with the key persons involved in specimen collection and processing for both Uganda and Kenya. She will ensure that collection of hair and plasma specimens follow proper QC monitored procedures and set up a specimen tracking system for movement and storage of specimens. She will also oversee both IRB and national requirements and the process for specimen shipments. In the last year of the grant, she will be working with the laboratory personnel in the HAL, along with Drs. Gandhi, Gerona and Benet, on technology transfer for the hair assays in Uganda and Kenya.

Pursuant to University of California policy, the salaries in the initial budget are based on current published UC salary scales and include University mandated range adjustments and merit increases scheduled to occur before the proposed project start date. Merit increases for faculty, other academic appointments, and staff on step-based pay plans are included at the time they are due according to UC guidelines for the normal length of time at each step. Projections for salaries, fringe benefits, and merit increases have been prorated to conform to the grant years of this proposal.

Fringe Benefit Rates:

UCSF's Office of Research published fringe benefit rates:

Benefit Rate	07/01/16-06/30/17	07/01/17-06/30/18	07/01/18-06/30/19, until amended
Academic Benefits	33.90%	34.15%	34.35%
Staff Benefits	41.90%	42.15%	42.35%

MATERIALS AND SUPPLIES

Computers, software and printer: In Year 2, two computers, a printer and software is requested for documentation and communicating of study activities at an estimated cost of $9,800. A replacement computer in year four is requested at a cost of [redacted].

Hair collection and other general supplies are estimated at [redacted] in year 1 of the study (when all three studies will be collecting hair), then [redacted] per year for years 2-3 when hair collection for two studies will continue, then $1000 in year 4 when only hair for A5359 will be collected. Total [redacted] across all years.

Laboratory supplies for Hair Analytical Laboratory: In Year 1, the Gerona Lab is requesting [redacted] in laboratory supplies for the validation of the antiretroviral drug assays in hair. These costs are for the purchase of reference and internal drug standards and blank human hair; supplies for standard curve, quality assurance and quality control sample preparation; as well as for liquid chromatography columns, laboratory solvents and reagents, test tubes, pipettes, gloves, and other basic supplies utilized for sample processing and analysis.

In Years 2-5, funding is requested for laboratory supplies needed to run the assays of antiretroviral drug levels in ~8000 hair samples ([redacted] per year in Years 2-3; [redacted] in Year 5). This is for the purchase of liquid chromatography columns, guard columns, drug standards, blank matrices, organic solvents for sample extraction and mobile phase runs, reagents, bead ruptor tubes, pH meter probes, solid phase cartridges, test tubes, micro centrifuge tubes, volumetric flasks, graduate cylinders, pipettes, syringes, pipette tips, spare parts for liquid chromatography pumps and auto samplers, gloves, cleaning agents, and other basic supplies utilized for sample processing, analysis, storage and data processing.

TRAVEL

International trips

Travel to Uganda, Kenya, South Africa and Zimbabwe: Dr. Gandhi will travel to Uganda and Kenya to work with Katie Snyman (QA lab coordinator of SEARCH) on overseeing quality sample collection of hair and plasma at selected sites in the SEARCH study (Aim 1) in Year 1. She will travel to South Africa and Zimbabwe the first year of the grant to oversee hair collection and ensure sample quality collection in the MTN-025 (Aim 2) study in Year 1. Attendance at the annual SEARCH retreat at Makerere University is requested for years 2-5 for Dr. Gandhi to present to study collaborators and participate in data analysis discussions with Uganda and Kenya-based colleagues. Each trip will last for 10 days and is estimated at [redacted] per trip including airfare, lodging, meals and local transportation. These study trips are budgeted at [redacted] during Year 1 and [redacted] during Years 2-5. Attendance at the International AIDS Conference is scheduled in years 2-5 for Drs. Gandhi and Gerona at a cost of [redacted] including registration, airfare, hotel, meals and local transportation. The cost per year for these two trips is [redacted]. International travel is therefore budgeted at $9,200 in Year 1 and [redacted] per year in Years 2-5.

Domestic trips

[redacted] is requested per year for all 5 years to send the principal investigator and/or co-investigators to domestic conferences to present the findings from this research project, including to a) the Conference on Retroviruses and Opportunistic Infections; b) the yearly Microbicide Trials Network (MTN) meetings, sponsor of the MTN-025 trial; and c) the yearly ACTG meeting, sponsor of the A5359 trial. All travel will be domestic. Study trips are budgeted at [redacted] per year.

The total cost per year for all trips is [redacted] during the 1st year and then [redacted] per year for Years 2-5.

OTHER DIRECT COSTS

Publication: Publication costs are budgeted at [redacted] per year in years 2- 4, and [redacted] for year 5. A total cost

of [redacted] over the project period is requested.

Specimen shipping: The cost of shipping specimens back to UCSF at the end of each study is estimated at [redacted] per year for the Years 1-3, [redacted] during Year 4 (just for A5359), and no costs during the 5th year of analyses. Total shipping costs [redacted]

Equipment Lease and Service Agreement:
LC-MS/MS Equipment Lease – The lease of the LC-MS/MS equipment that will be used for assay validation and sample analyses in Dr. Gerona's laboratory costs [redacted] per year. Costs proportionate to the time that the LC/MS-MS equipment will be used for the Aims of this grant have been apportioned for each year ([redacted] during Year 1 of validation; [redacted] Years 2 and 3; [redacted] Years 4 and 5)

LC/MS/MS Service Agreement – The service contract for the LC-MS/MS equipment used for assay validation and sample analyses in Dr. Gerona's laboratory cost [redacted] per year. Costs proportionate to the time that the LC/MS-MS equipment will be used for the Aims of this grant have been apportioned for each year ([redacted] during Year 1 of validation; [redacted] Years 2 and 3; [redacted] Years 4 and 5).

UCSF Data & Network recharge ([redacted] all years): UCSF has installed a high quality network for transmission of information and data at the campus level. The network directly supports numerous campus systems for support of research, training and patient care, and is widely utilized by all UCSF personnel. The costs for this network are being distributed campus-wide to all employees, and are based on effort provided for each project. Per review and agreement by our cognizant federal agency, UCSF data network costs are an allowable direct expense. Questions from the sponsoring agency regarding this charge should be directed to the Department of Health and Human Services -Division of Cost Allocation, San Francisco CA. Effective 7/1/14-6/30/16, the funding model for data network service includes a UCSF-wide per capita recharge of [redacted]/month/FTE. The rate increases in future years, as follows:

7/1/2016 - 6/30/17	[redacted]/month/FTE
7/1/2017 - 6/30/18	[redacted]/month/FTE
7/1/2018 and beyond:	[redacted]/month/FTE

Computing and Communication Device Support Services ([redacted] all years): Computing and communication device support services (CCDSS) provides integral support to campus voice and data technology functions. CCDSS includes software installation/updates, internet security, hardware setup/configuration, and centrally managed patching, storage and backup. The recharge rates are provided for under our approved DS-2, will be computed in accordance with applicable OMB requirements, including 2 CFR Part 220 (formerly Circular A-21), and will be reviewed and adjusted annually. Effective 7/1/15-6/30/16, the funding model for data network service includes a UCSF-wide per capita recharge of $86/month/FTE. The rate increases:

7/1/2015-6/30/2016	[redacted]/month/FTE
7/1/2016-6/30/2017	[redacted]/month/FTE
7/1/2017-6/30/2018 and beyond	[redacted]/month/FTE

CONSULTANT COSTS

and triangulated. For instance, a dapivirine plasma level which is always ≥ 95pg/ml at a visit in combination with a low dapivirine hair level suggests ring insertion just prior to visits, but not steady use. Consistently and simultaneously high plasma and hair dapivirine levels at each visit, with low levels in the ring, suggest good adherence over the month. High levels of dapivirine in the segment of hair closest to the scalp indicate good recent adherence, whereas undetectable levels in the more distal segment can indicate a multiweek holiday.

In a recent analysis, we showed that over half of VOICE participants had detectable TFV concentrations in hair, whereas fewer than one-quarter had detectable TFV levels in plasma, suggesting that many women took study product at least once weekly in the preceding 4 to 6 weeks.[48] This analysis argued against "white coat adherence" patterns in the study and suggested more complex patterns of non-adherence. Our data were consistent with a qualitative study in VOICE where women reported taking study drug intermittently or not as directed, rather than not taking it at all,[110] possibly suggesting women may have been trying to use oral study product "on demand" at the time of sexual exposure. **Assessing patterns of exposure to oral PrEP or the vaginal ring among specific groups in high-incidence settings can inform the development of subsequent adherence interventions tailored to different patterns of drug-taking.**

3A6. Embedding hair measures in three important trials will provide insight on adherence and exposure, and thereby effectiveness, with "PrEP 2.0"

SEARCH PrEP study: The **Sustainable East Africa Research in Community Health (SEARCH)** study is a collaboration conducting community-based research in East Africa (principal investigators Diane Havlir MD (*co-I on this proposal*), Maya Petersen MD, PhD, Moses Kamya MBChB, MPH, PhD).[49,50,111-118] The original study randomized 32 communities in Uganda and Kenya (~340,000 individuals) to receive universal HIV testing and treatment versus standard of care. **In the second phase, the study will evaluate how to deliver PrEP on a population level, targeting high-risk individuals and investigating novel delivery mechanisms.** In phase 2, the 32 communities will all receive universal HIV treatment via streamlined care and will be re-randomized to the next intervention, the provision of targeted PrEP to individuals with high-risk profiles. Plasma and hair samples for drug levels, as well as self-assessments of risk and self-reported adherence, will be collected at each visit. HIV incidence at 3 years (the primary outcome) will be compared among intervention and control communities.

MTN-025 or HOPE study: **The HIV Open-Label Prevention Extension (HOPE) study** (chaired by Jared Baeten MD, PhD, *co-I on this application*) in the Microbicide Trials Network (MTN-025) will examine the dapivirine vaginal ring in an open-label trial for safety, adherence and efficacy in preventing HIV acquisition. Participants will receive a vaginal ring containing 25mg of dapivirine to be replaced each month over a total period of 12 months. Hair, plasma and used rings will be collected at each visit and analyzed for dapivirine levels. Safety, tolerability, and HIV incidence will be monitored.

ACTG A5359 study: **The Long-Acting Antiretroviral Therapy in Non-adherent HIV-Infected Individuals Trial** in the AIDS Clinical Trials Group (ACTG A5359, co-chaired by Jose Castillo-Mancilla MD, *co-I on this renewal*) will randomize patients with a history of poor adherence (with virologic suppression after an oral lead-in phase) to a LA cabotegravir plus LA rilpivirine-based regimen administered every 4 weeks. Hair and plasma concentrations of CAB, HIV viral loads, and factors associated with PK variability will be collected during this phase. The purpose of **Aim 3** is to investigate the utility of hair levels for exposure monitoring in the context of injectable PrEP.

3B. INNOVATION

This application proposes four major innovations (**Figure 3**) with the already novel technique of analyzing ARV concentrations in hair samples to advance this methodology into the next phase of HIV prevention work. We propose to "extend" hair levels to **novel and exciting modalities of antiretroviral delivery, such as vaginal rings and injectables, for the first time** (I). We propose to incorporate this measure into a large-scale PrEP study in East Africa which aims to **establish practice paradigms for the roll-out of oral PrEP** in a variety of high-risk populations (young women, mobile populations, fisherfolk, etc.) (II). Although rarely employed to date, the incorporation of both short and long-term measures of adherence into oral PrEP and vaginal PrEP trials, **and the triangulation of these measures during study analysis,** as proposed here, should help assess patterns of adherence to PrEP (oral or rings) in Africa (e.g. daily, at time of risk, multiweek holidays),[48] which will be necessary to understand[69] when designing precision public health interventions for HIV prevention (III). Finally, although hair concentrations and other pharmacologic measures assess adherence, they also serve as **measures of pharmacokinetics,** which will be essential to incorporate during the investigation and roll-out of injectable ARVs**, especially at the end of the dosing interval and in the context of prevention**. We propose to study hair levels as a metric for drug exposure to LA-CAB in a study for the first time (IV).

emphasis on adherence, optimization of current antiretroviral therapies, PrEP and pharmacogenomics. Dr. Castillo-Mancilla is an investigator in the Adult AIDS Clinical Trials Group (ACTG) and the Co-Chair of the Long-Acting Antiretroviral Therapy in Non-adherent HIV-Infected Individuals Trial (A5359), in which Aim 3 will be based. He is the Vice-Chair of the ACTG Underrepresented Populations Committee, which aims at expanding the inclusion of minorities (including non-adherent individuals) in HIV clinical trials. Dr. Gandhi and Dr. Jose Castillo-Mancilla have a shared interest in mentoring early career investigators of diversity and hope to use this grant, if re-funded, as a platform for mentoring in the areas of adherence and pharmacology. Dr. Castillo-Mancilla's role in this proposal will be to ensure hair collection proceeds smoothly in A5359 once the study starts enrolling in 2017, to help in data analysis and interpretation of drug levels for the pharmacokinetics work proposed in Aim 3, and contribute to publications.
This collaboration with University of Colorado is budgeted at [redacted] direct costs and [redacted] indirect cost for a total of [redacted] over the entire proposed project period.

Summary of Direct Costs (DC) from all sites:

Description	Year 1	Year 2	Year 3	Year 4	Year 5	TOTAL
UCSF - DC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
University of Washington – DC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
UC Denver – DC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Subtotal DC from All Sites	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Summary of Direct and F&A costs:

Description	Year 1	Year 2	Year 3	Year 4	Year 5	TOTAL
UCSF - Direct Costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
University of Washington - total costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
UC Denver - total costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Subtotal UCSF's DC (inclusive of subs' total costs)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
UCSF - F&A Costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total Costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Budget Justification
University of Washington

Personnel

Jared Baeten, MD, PhD, Co-Investigator (0.60 Calendar Months, years 1 – 5). Dr. Baeten is Professor and Vice Chair in the Department of Global Health with additional full appointments in the Departments of Medicine and Epidemiology at the University of Washington. He is an infectious disease physician with extensive experience in clinical epidemiology research in resource-limited settings. He has worked for the past 17 years on epidemiologic studies defining risk factors for HIV-1 acquisition and transmission using data from large prospective African cohort studies. His work bridges biomedical intervention studies (particularly large-scale clinical trials), observational epidemiology (of risk factors for HIV-1 acquisition, correlates of genital HIV-1 shedding, and the interaction between sexually transmitted infections and HIV-1), implementation science (to deliver effective HIV-1 prevention interventions), studies at the interface between laboratory science and HIV-1 epidemiology (particularly studies of virologic and immunologic factors that influence of HIV-1 pathogenesis), and behavioral epidemiology (particularly of sexual behavior and adherence to HIV-1 prevention). He has received funding from diverse sources (four institutes at the National Institutes of Health [NIAID, NICHD, NIMH, NINR], other governmental funding [USAID], and private funding [the Bill & Melinda Gates Foundation]), attesting to the multidisciplinary and multifaceted nature of his work. He has extensive experience with studies of HIV-1 serodiscordant couples, including co- and lead investigator roles in the Partners in Prevention HSV/HIV Transmission Study (co-investigator), Couples Observational Study (project director), Partners PrEP Study (co-chair), and Partners Demonstration Project (chair). In addition, he has led or collaborated on complimentary research about factors that influence uptake and use of HIV-1 prevention in couples, including fertility intentions, HIV-1 risk perceptions and preferences, and adherence. Additional work focuses on the development of new HIV-1 prevention strategies for women, including topical microbicides (through the NIH-funded Microbicides Trials Network, in which he serves as Protocol Chair for MTN-020/ASPIRE, a phase III trial of the dapivirine vaginal ring for HIV-1 prevention), and studies exploring the relationship between hormonal contraceptive use and HIV-1 risk. He is a member of the leadership team for the ECHO trial, a randomized trial of contraceptives to compare HIV incidence in 12 sites in East and southern Africa. He will bring his extensive experience in designing, implementing, and analyzing complex multi-center international HIV-1 prevention research to this study. As co-Investigator, Dr. Baeten will commit effort during all years of the project to work with the team intensively in the design of the project, advise on implementation, and participate in the analysis and results interpretation.

TBN, Graduate Research Assistant, (6.0 Calendar Months in Years 2 – 5)
A doctoral graduate student from the departments of Epidemiology or Biostatistics will be brought onto the project to work with Dr. Baeten on routine operations reports and epidemiologic analyses. As is standard for doctoral students at the University of Washington, 25% effort will be dedicated each year to ensure that statistical analysis plans and data analysis, interpretation and dissemination are robust and of high quality. The student will be provided workspace and computing facilities within the International Clinical Research Center.

Benjamin Browning-Roberts, Program Operations Specialist (0.60 calendar months in years 2-5). Mr. Browning-Roberts will provide overall budget and grants management support for the study. He will monitor and review invoices according to the terms of the agreement and will oversee all financial aspects of the project, including preparation of monthly budget summary reports, and preparation of noncompetitive renewal budgets. He will devote 5% effort in all years.

Tuition for the graduate student is estimated to be [redacted] for 1.5 quarters in year 2, and then [redacted] for 3 quarters in years 3, [redacted] in year 4 and [redacted] in year 5.

Fringe benefits are calculated as follows: [redacted] for Faculty; [redacted] for Professional staff and [redacted] for Graduate Students.

The **indirect cost rate** at the University of Washington for research is [redacted] MTDC for year 1. Per the DHHS negotiated rate agreement dated 4/29/2016, the F&A rate is scheduled to increase to [redacted] in Year 2 and to [redacted] in Years 3 through 5. Tuition is excluded from the IDC base.

Budget Justification

University of Colorado Denver

Personnel:
Dr. Jose R. Castillo-Mancilla, MD, Co-Investigator, will devote 0.6 calendar months with support requested. He will provide direct scientific input for the study implementation in relation with study design, adherence and data interpretation. In addition, he will support the team with the development of research abstract and presentations in scientific conferences and collaborate with manuscript preparation for submission.

Fringe Benefit Rates:
We applied the following rates to our fringe benefits calculations.
Years 01-02: [redacted]
Years 03-05: [redacted]

Other Expenses:
None.

F&A Rate:
We have applied our F&A rate of [redacted] on Modified Total Direct Costs (MTDC) per our Department of Health and Human Services' Facilities and Administrative Cost Rates Agreement dated 03/08/2016.

PHS 398 Cover Page Supplement

OMB Number: 0925-0001

Expiration Date: 10/31/2018

1. Human Subjects Section

Clinical Trial? ❍ Yes ● No

*Agency-Defined Phase III Clinical Trial? ❍ Yes ❍ No

2. Vertebrate Animals Section

Are vertebrate animals euthanized? ❍ Yes ● No

If "Yes" to euthanasia

Is the method consistent with American Veterinary Medical Association (AVMA) guidelines?

❍ Yes ❍ No

If "No" to AVMA guidelines, describe method and proved scientific justification

3. *Program Income Section

*Is program income anticipated during the periods for which the grant support is requested?

❍ Yes ● No

If you checked "yes" above (indicating that program income is anticipated), then use the format below to reflect the amount and source(s). Otherwise, leave this section blank.

*Budget Period	*Anticipated Amount ($)	*Source(s)

PHS 398 Cover Page Supplement

4. Human Embryonic Stem Cells Section

*Does the proposed project involve human embryonic stem cells? ❍ Yes ● No

If the proposed project involves human embryonic stem cells, list below the registration number of the specific cell line(s) from the following list: http://grants.nih.gov/stem_cells/registry/current.htm. Or, if a specific stem cell line cannot be referenced at this time, please check the box indicating that one from the registry will be used:

Specific stem cell line cannot be referenced at this time. One from the registry will be used.

Cell Line(s) (Example: 0004):

5. Inventions and Patents Section (RENEWAL)

*Inventions and Patents: ❍ Yes ● No

If the answer is "Yes" then please answer the following:

*Previously Reported: ❍ Yes ❍ No

6. Change of Investigator / Change of Institution Section

❑ Change of Project Director / Principal Investigator

Name of former Project Director / Principal Investigator

Prefix:

*First Name:

Middle Name:

*Last Name:

Suffix:

❑ Change of Grantee Institution

*Name of former institution:

PHS 398 Research Plan

OMB Number: 0925-0001
Expiration Date: 10/31/2018

Introduction	
1. Introduction to Application (Resubmission and Revision)	
Research Plan Section	
2. Specific Aims	SpecificAims_GandhiR01rnwl_Final_090116.pdf
3. Research Strategy*	ResStrategy_Final_GandhiR01rnwl_090216.pdf
4. Progress Report Publication List	First_R01_Progress_Report_Pub_List.pdf
Human Subjects Section	
5. Protection of Human Subjects	ProtectionOfHumanSubjects_Final083016.pdf
6. Data Safety Monitoring Plan	DataSafetyMonitoringPlan_Final083161.pdf
7. Inclusion of Women and Minorities	InclusionWomenMinorities_Gandhi_FINAL_090116.pdf
8. Inclusion of Children	InclusionOfChildren_Gandhi_Final_090116.pdf
Other Research Plan Section	
9. Vertebrate Animals	
10. Select Agent Research	
11. Multiple PD/PI Leadership Plan	
12. Consortium/Contractual Arrangements	ConsortiumArrangementsFinal083116.pdf
13. Letters of Support	LettersOfSupport_All_082916.pdf
14. Resource Sharing Plan(s)	ResourceSharingPlan_Final083116.pdf
15. Authentication of Key Biological and/or Chemical Resources	AuthenticationKeyBiolChemicalRes.pdf
Appendix	
16. Appendix	Appendices_Gandhi_R01rnwl.pdf

Tracking Number: GRANT12240283
Funding Opportunity Number: PA-16-160 . Received Date: 2016-09-02T14:18:25.000-04:00

2. SPECIFIC AIMS

After the efficacy of oral pre-exposure prophylaxis (PrEP) was demonstrated in multiple trials,[1-5] the World Health Organization cited broad indications for global roll-out.[6] Three lessons of the PrEP clinical trials - that adherence is critical to effectiveness,[7,8] that objective adherence measures are more reliable than self-report,[9] and that daily pill-taking is challenging[10] –must be applied to the next phase of prevention research. This phase will investigate best practices for **oral PrEP roll-out and optimization in high incidence settings**, as well as **novel long-acting methods for preventing HIV infection**, such as injectables or vaginal rings. The dapivirine vaginal ring reduced rates of HIV acquisition in two recent trials,[11,12] **but poor adherence to consistent ring use** dampened overall effectiveness.[13] Injectable PrEP with long-acting cabotegravir is of great interest,[14,15] but will require **adequate drug levels to be effective**,[16] especially at the end of dosing intervals[17] and when visits are missed. Pharmacologic measures that integrate behavior (adherence) and biology (pharmacokinetics [PK]) will be crucial to interpreting and optimizing effectiveness during PrEP roll-out and with long-acting modalities.

Pharmacologic assays monitor adherence and exposure by measuring drug levels in a biologic matrix. **Our group at UCSF has advanced the field of antiretroviral (ARV) monitoring via hair levels**.[18-44] The concentration of a medication in hair, which is easy to collect, store and ship[29], reflects drug uptake from the systemic circulation over weeks to months.[18] Moreover, combining different pharmacologic measures (e.g. levels in plasma, hair, or vaginal rings) can help assess **patterns of adherence**.[45-48] This **R01 renewal, which addresses key knowledge gaps for the roll-out of oral PrEP, vaginal rings and injectables, builds on the productivity, infrastructure, and investment in its predecessor**. We have published 20 papers from the first grant[25-44] demonstrating important uses for hair measures in treatment -where hair levels are stronger predictors of outcomes[22-27] than self-reported adherence[22,23,25] or plasma levels[24,27]- and with oral PrEP.[39-43]

We will leverage **three important trials** in this proposal (with chairs as co-investigators) to explore **crucial unanswered questions on adherence to and effectiveness of oral PrEP in Africa and extend the investigation of hair measures to vaginal rings and long-acting injectables**. The Sustainable East Africa Research in Community Health (**SEARCH**) trial[49,50] has just launched a large study providing PrEP to at-risk individuals in 16 communities in Africa. The HIV Open-Label Prevention Extension (**HOPE/Microbicide Trials Network-025**) study will assess open-label use of the dapivirine vaginal ring.[11,12] The Long-Acting Antiretroviral Therapy in Non-adherent HIV-Infected Individuals Trial (**A5359**) in the AIDS Clinical Trials Group (ACTG) will examine long-acting (LA) injectables in HIV-infected patients with a history of poor adherence. **All 3 trials will collect hair and plasma,** and track robust outcomes, to allow investigation of our key hypotheses and aims.

We hypothesize that hair concentrations, coupled with shorter-term measures, in large studies of PrEP (both oral and the dapivirine vaginal ring) will allow us to better predict effectiveness and assess **patterns of adherence**[45] (e.g. daily, around periods of risk, just prior to visits, drug holidays) to these agents among **key subgroups in Africa**.. We further hypothesize that examining both hair and plasma metrics for long-acting cabotegravir (CAB) will provide insight for real-world **pharmacokinetic monitoring** with the use of injectables.

AIM 1: To evaluate concentrations of PrEP drugs in hair and plasma as biomarkers of adherence and predictors of effectiveness in a large community cluster randomized trial (SEARCH). We will analyze hair and plasma tenofovir and emtricitabine levels among participants on PrEP in SEARCH, evaluating each metric individually and in combination, as predictors of HIV seroconversion and toxicity in multivariate models. Predictors and patterns of adherence (assessed via the objective measures) among key subgroups (e.g. young women, fishermen, PrEP via home vs clinic delivery, those with HIV-positive partners) will be examined.

AIM 2: To investigate the use of hair levels as a long-term measure of dapivirine exposure in the open-label trial of the dapivirine vaginal ring (MTN-025). Hair levels with use of the dapivirine ring will be analyzed as predictors of seroconversion in multivariate models in HOPE, comparing this metric to self-reported adherence, plasma and residual ring dapivirine levels. Concordance and discordance of drug levels in the three matrices will assess patterns of adherence among key subgroups (e.g. women < 25 years). A threshold for dapivirine exposure in hair associated with a low risk of HIV acquisition will be determined.

AIM 3: To examine the utility of hair levels for PK monitoring of LA cabotegravir in a diverse population (A5359). We will assess real-world factors associated with PK variability to CAB, examine hair levels between injections via segmental analysis, and examine correlations between CAB levels in hair and plasma at the end of dosing intervals, all to provide evidence for exposure monitoring using hair levels with injectable PrEP.

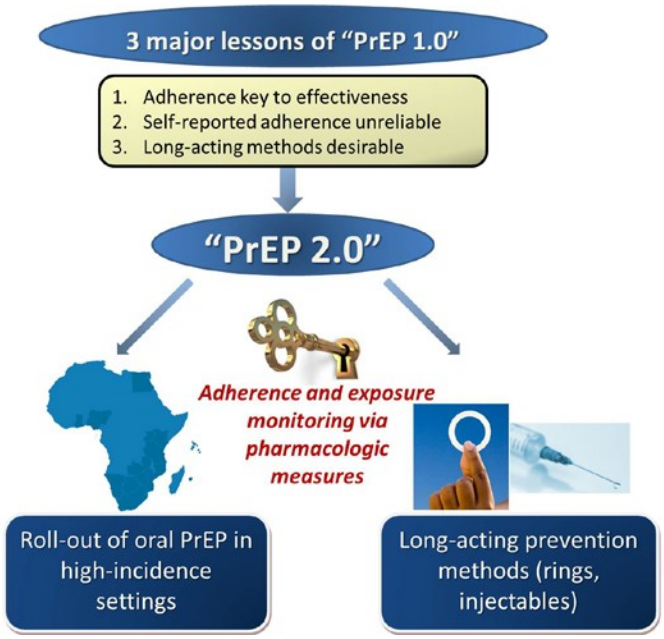
The overarching goal of this proposal, harnessing work from the first R01, is to **develop an integrated package of highly predictive biologic adherence measures spanning PrEP delivery methods and optimization strategies.** Defining predictors and patterns of adherence to oral PrEP and rings, as well as **metrics to monitor PK with injectables**, will inform precision public health interventions in HIV prevention.

3. RESEARCH STRATEGY

3A. SIGNIFICANCE

3A1. The PrEP clinical trials revealed the critical importance of evaluating adherence using pharmacologic measures: Massive advances in HIV prevention have been demonstrated over the past 5 years. Pre-exposure prophylaxis (PrEP) with oral tenofovir disoproxil fumarate/emtricitabine (TDF/FTC) was effective in placebo-controlled trials at preventing HIV acquisition among at-risk individuals, including men who have sex with men (MSM)[1,4] and transgender women, heterosexual men and women,[2,3] and intravenous drug users.[5] PrEP, now broadly recommended by the Centers for Disease Control and Prevention (CDC)[51] and the World Health Organization (WHO),[6] is entering an exciting phase of global expansion.

Figure 1: The **key** to interpreting "PrEP 2.0" will be to incorporate robust metrics of pharmacologic adherence and exposure during the evaluation phase



The oral TDF/FTC-based PrEP trials highlighted three major lessons (**Figure 1**): 1) there is a profound relationship between adherence and effectiveness;[52] 2) self-reported adherence can be a poor predictor of actual use;[7,8,53] and 3) daily pill-taking can be difficult, making long-acting methods desirable.[10] The second wave of evaluation for oral PrEP and next-generation prevention modalities must incorporate these lessons of "PrEP 1.0".

Pharmacologic measures, which integrate both behavior (adherence) and exposure (pharmacokinetics), assess drug concentrations in a biomatrix such as plasma, peripheral blood mononuclear cells (PBMCs), dried blood spots (DBS) or hair. Substantial discordance between self-reported measures of adherence and drug detection in trials, such as the global iPrEx study,[1,54] the FEM-PrEP study,[7] Partners PrEP,[2,55,56] and VOICE,[8,57] **have highlighted the critical importance of incorporating objective pharmacologic measures of exposure when interpreting PrEP effectiveness**.[54,55,58,59] For instance, the efficacy of TDF/FTC in the global iPrEx trial rose from 44% overall to an estimated 92% among those with detectable blood drug levels.[1] Despite high rates of self-reported adherence to study product in FEM-PrEP[7] and VOICE[8] (two trials in young, sexually active women in Africa), these trials demonstrated no efficacy of daily TDF/FTC in reducing HIV acquisition. Crucial to interpretation, random plasma tenofovir (TFV) levels among women on active drug were detectable in fewer than 30% of participants. **As the global focus on oral PrEP shifts from the clinical trial phase to open-label studies, demonstration projects, and real-world roll-out, incorporating objective measures to assess adherence will be important.**

3A2. The first phase of what could be known as "PrEP 2.0" (Figure 1) must address knowledge gaps on how to optimize PrEP in high-incidence settings*:* PrEP with oral TDF/FTC works. Now is the time to investigate PrEP delivery in real-world settings[60] and how to optimize adherence, and thereby effectiveness, in high incidence regions[61] and among high-risk groups.[62] Although some predictors of adherence to PrEP in placebo-controlled trials have been defined,[54,63-66] more limited data[67,68] exists on predictors and patterns of adherence[69] to PrEP in the real-world,[70] especially in relevant African settings. Many of the open-label trials or demonstration projects of PrEP to date (e.g. iPrEx open label extension [OLE],[71] PROUD,[72] PrEP Demo[73]) have focused on MSM in resource-rich settings and cannot provide insight for how PrEP will be taken among key subgroups (e.g. young women[74], those in serodiscordant couples, men, mobile populations[75]) in high incidence areas with mainly heterosexual risk. Incorporating robust adherence metrics into studies seeking to establish practice paradigms for PrEP in Africa, such as the SEARCH PrEP trial (**Section 3A6**), is essential.

3A3. The second phase of what could be dubbed "PrEP 2.0" (Figure 1) will study the use of long-acting sustained-release prevention methods: Daily pill-taking has proven challenging with oral TDF/FTC-based PrEP, a challenge that was most prominent in the trials performed exclusively in women.[7,8,10] The second generation of PrEP will involve the use of sustained-release compounds delivered either locally or systemically.

Dapivirine vaginal ring: With 50% of the 36.7 million infected persons worldwide being female and a disproportionate incidence of new infections both globally and in sub-Saharan Africa occurring in adolescent

girls and young women,[74,76] a woman-controlled method of prevention is poignantly needed. The pericoital use of 1% TFV gel showed initial promise in the CAPRISA 004 Phase IIb trial,[77] although two subsequent large trials examining daily dosing (VOICE)[8] and peri-coital dosing (FACTS-001)[78] failed to demonstrate protective efficacy. In VOICE and FACTS-001, adherence to the prescribed schedule of the gel was low, raising interest in longer-acting approaches independent of coital or daily use. **Vaginal rings can provide sustained release of drugs, such as ARVs, in a controlled manner and are part of the armamentarium of "PrEP 2.0".**

Two recently-presented Phase III trials[11,12] (**Table 1**) examined the safety and efficacy of a silicone vaginal ring containing dapivirine, a nonnucleoside reverse transcriptase inhibitor (NNRTI), compared to a placebo ring (each self-inserted monthly) in preventing HIV acquisition. The MTN-020 or ASPIRE trial and the International Partnership for Microbicides (IPM) RING trial each enrolled African women between 18-45 years. Because rings are self-inserted and removable, the effectiveness of this strategy depends on adherence. Based on limited phase I/II PK data,[79,80] two objective measures of adherence were employed: 1) a plasma dapivirine level of >95 picograms (pg)/milliliter (mL) indicated short-term adherence (~8 hours use); 2) a residual dapivirine level[81] in the used ring of <22 milligrams (mg) served as an indicator of good adherence over a longer period.[13] The overall reduction in HIV-1 incidence was 27% in ASPIRE and 31% in the RING trial, but the protective efficacy in both was higher in older women. The vaginal ring was not effective for women < 21 years in either trial, with inadequate adherence a contributing factor, as adjudicated by the objective measures. As with oral PrEP, the efficacy of the vaginal ring in preventing HIV rose with higher adherence as assessed objectively. In MTN-020, the risk reduction for HIV acquisition rose from 31% to 65% when residual ring levels (a long-term measure) indicated high adherence (e.g. <22mg).[13] Given that plasma levels reflect a snapshot of exposure (**Figure 2**) and that residual ring levels exhibit substantial intra-individual, environmental and analytic variability,[81] **investigating hair levels in the open-label phase of the dapivirine ring trial will provide evidence whether a more feasible and accurate long-term adherence metric** can be employed to monitor ring use in the real-world.

Table 1: Results of two recently-presented Phase III trials of the dapivirine vaginal ring (ASPIRE (MTN020) and RING)

	ASPIRE study (N=2629)	RING study (n=1959)
HIV incidence per 100 py (DPV ring vs placebo)	3.3 vs. 4.5	4.1 vs 6.1
Overall reduction in HIV-1 incidence	27% (1-46), p 0.05	31% (1-52), p 0.04
Remove data from 2 low-adhering sites	37% (12-56), p 0.007	---
Women >21 years	56% (31-71), p <0.001	37% (3-59), p 0.07
Women 18-21 years	-27% (-133, 31), p 0.45	15% (-60, 55), p 0.43

Long-acting injectables for prevention: Given the challenges with daily oral PrEP use,[15] the use of long-acting injectable ARVs for HIV prevention in at-risk individuals is a thrilling, albeit nascent, field of investigation.[14] The most promising agent developed to date for long-acting (LA) PrEP is cabotegravir, an integrase strand transfer inhibitor (INSTI) formulated into nanocrystals to allow for monthly or less frequent intramuscular dosing.[82] The combination of LA cabotegravir and LA rilpivirine is effective in maintaining virologic suppression in HIV-infected patients after induction with orally-administered regimens.[83-85] Ongoing trials will evaluate the efficacy of LA cabotegravir for protection against HIV acquisition among high-risk individuals.

In any study involving LA agents, despite injection occurring in the clinic, adequate exposure to the medication (e.g. drug levels above a certain threshold) must be maintained throughout and at the end of the dosing period.[16] Indeed, given the possibility of missed or delayed injection visits in the real-world, especially in populations most at risk of low adherence (where injectables will be used[15]), **the "pharmacokinetic tail", or exposure at the end of the dosing interval, must leave a comfortable margin for protective or treatment efficacy**. Therefore, PK monitoring with the use of injectables, whether for HIV treatment or prevention, will be important. **Indeed, PK monitoring may be most crucial with injectable PrEP,** where there is no easy surrogate for assessing adequate drug exposure (such as viral suppression in the context of treatment).

Initial PK evaluations of any new drug, including LA CAB,[82] are often performed in small numbers of "ideal" patients without concomitant conditions that could influence the PK of the medication under actual-use conditions. **Our group**[21,44,86,87] and others have shown that the **PK parameters of ARVs in real-world, diverse populations** can differ significantly from parameters modeled in small, early phase studies. To this point, in a recent phase 2a safety and pharmacokinetic study (ÉCLAIR study)[17] of high-dose long-acting cabotegravir delivered every 12 weeks, **plasma levels at the end of the dosing interval were lower in 70% of participants than had been predicted by early phase 1 PK models.**[82] We will examine factors that influence PK variability to CAB, as well as the utility of hair levels (and their combination with plasma levels) for PK monitoring with injectable cabotegravir. **Aim 3** is meant to be "**forward thinking**". If PK metrics will be essential to monitor with LA CAB, especially in the context of prevention, studies to define those metrics will

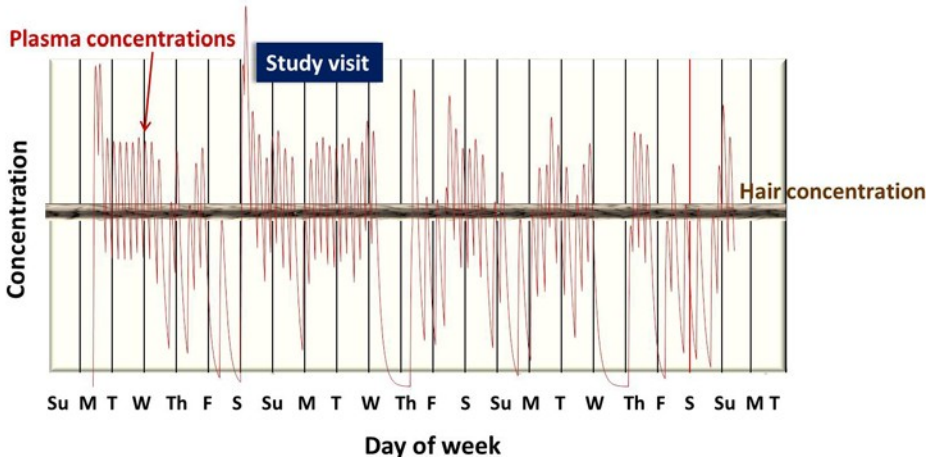
facilitate roll-out, with monitoring tools in place, once results from the clinical trials are finalized.

3A4. Hair levels have advantages as a tool for monitoring adherence and exposure to "PrEP 2.0"

The limitations of more "subjective" methods to monitor antiretroviral adherence in HIV treatment and prevention settings, such as self-report and pill counts, are well-described.[9,40,53,88-94] Self-report is subject to social desirability[93] and recall bias, pill counts are subject to manipulation,[8,95-97] and medication electronic monitoring systems (MEMS), like the other measures, cannot measure actual drug ingestion or exposure.[98] Pharmacologic adherence monitoring, especially for PrEP[40] and other disease states (e.g. latent tuberculosis infection treatment[36,37]) where a surrogate biomarker of adherence or response (e.g. HIV viral loads) cannot be measured, is therefore crucial.

Plasma drug levels, although frequently incorporated in the clinical trials of oral PrEP[1,5,7,8] represent only the most recent doses taken,[55,99-101] and are susceptible to significant intra-individual (day-to-day) variability (**Figure 2**).[99] Moreover, a plasma level on a single day may not reflect typical patterns of use. For instance, a plasma level may be high at a study visit (**Figure 2, *Study visit***) because drug was taken in anticipation of that visit e.g. "white coat adherence".[102]

Figure 2: Plasma levels show day-to-day variability. At the study visit, "white coat adherence" can result in a high plasma level. Hair concentrations provides cumulative measures. Combinations of short and long-term measures can demonstrate adherence patterns



Metrics that provide information on drug exposure over relatively long periods may be advantageous for agents released over time (e.g. dapivirine from vaginal rings) or with long half-lives (e.g. long-acting cabotegravir). For medications phosphorylated and trapped intracellularly, such as the active moieties of TFV or FTC, concentrations of intracellular anabolites in PBMC[1,59] or DBS[103,104] relay information on exposure over longer dosing periods.[41,104] The measurement of TFV/FTC anabolites in DBS has proven useful for adherence monitoring during oral PrEP.[45,71] Moreover, hair and DBS measures of TFV and FTC (and their anabolites TFV-DP and FTC-TP) are strongly correlated.[41] However, **because INSTIs (e.g. cabotegravir) and NNRTIs (e.g. dapivirine) do not exhibit intracellular phosphorylation, measurement of intracellular concentrations in DBS do not offer any additional advantage to plasma levels with these ARVs.** Further, all of these matrices (plasma, PBMCs, DBS, as well as urine) require a cold chain and biohazard precautions. Residual levels of dapivirine in vaginal rings were associated with effectiveness in MTN-020 (ASPIRE).[13] Residual ring concentrations, however, can vary by site of insertion, method of insertion, ring washing, use of other vaginal products, active menses or intercourse.[81]

Many drugs are incorporated from the systemic circulation into hair as it grows[18,105] and hair concentrations serve as long-term measures of exposure.[21] Moreover, hair reliably grows in the occipital portion of the scalp at a rate of approximately 1 centimeter per month,[106,107] so that distance from the scalp along the cut hair strand serves as a marker of time.[108] **Hair collection does not require phlebotomy and hair is stored and shipped at room temperature without the need for biohazardous precautions, leading to feasibility advantages in resource-limited settings.**[29] Our group has shown the pharmacodynamic relevance of hair measures in multiple settings.[18-42] In previous studies, where hair collection is incorporated from the beginning of the protocol with field staff and participant education, as will happen in our three partnering trials, **high rates of acceptability of hair collection (>95%) have been documented**.[25,27,29,32,40] **Demonstrating that hair measures can serve as an important monitoring tool in the context of "PrEP 2.0" will have feasibility and logistical advantages for real-world, and especially low-income, settings.**

3A5. Combining pharmacologic measures can detect patterns of adherence

Pill-taking patterns are highly associated with PrEP efficacy.[69] Combining short- and long-term pharmacologic measures of adherence, a strategy infrequently employed to date, can provide insight on patterns of adherence[45-48] e.g., taking drug just prior to clinic visits,[102] daily dosing, taking drug only around sex or during "seasons of risk"[109] (**Figure 2**). Other patterns of PrEP taking (e.g. delayed initiation, frequently missed doses, multiweek holidays, early discontinuation)[69] can be modeled **if objective adherence measures are collected**

and triangulated. For instance, a dapivirine plasma level which is always ≥ 95pg/ml at a visit in combination with a low dapivirine hair level suggests ring insertion just prior to visits, but not steady use. Consistently and simultaneously high plasma and hair dapivirine levels at each visit, with low levels in the ring, suggest good adherence over the month. High levels of dapivirine in the segment of hair closest to the scalp indicate good recent adherence, whereas undetectable levels in the more distal segment can indicate a multiweek holiday.

In a recent analysis, we showed that over half of VOICE participants had detectable TFV concentrations in hair, whereas fewer than one-quarter had detectable TFV levels in plasma, suggesting that many women took study product at least once weekly in the preceding 4 to 6 weeks.[48] This analysis argued against "white coat adherence" patterns in the study and suggested more complex patterns of non-adherence. Our data were consistent with a qualitative study in VOICE where women reported taking study drug intermittently or not as directed, rather than not taking it at all,[110] possibly suggesting women may have been trying to use oral study product "on demand" at the time of sexual exposure. **Assessing patterns of exposure to oral PrEP or the vaginal ring among specific groups in high-incidence settings can inform the development of subsequent adherence interventions tailored to different patterns of drug-taking.**

3A6. Embedding hair measures in three important trials will provide insight on adherence and exposure, and thereby effectiveness, with "PrEP 2.0"

SEARCH PrEP study: The **Sustainable East Africa Research in Community Health (SEARCH)** study is a collaboration conducting community-based research in East Africa (principal investigators Diane Havlir MD (*co-I on this proposal*), Maya Petersen MD, PhD, Moses Kamya MBChB, MPH, PhD).[49,50,111-118] The original study randomized 32 communities in Uganda and Kenya (~340,000 individuals) to receive universal HIV testing and treatment versus standard of care. **In the second phase, the study will evaluate how to deliver PrEP on a population level, targeting high-risk individuals and investigating novel delivery mechanisms.** In phase 2, the 32 communities will all receive universal HIV treatment via streamlined care and will be re-randomized to the next intervention, the provision of targeted PrEP to individuals with high-risk profiles. Plasma and hair samples for drug levels, as well as self-assessments of risk and self-reported adherence, will be collected at each visit. HIV incidence at 3 years (the primary outcome) will be compared among intervention and control communities.

MTN-025 or HOPE study: **The HIV Open-Label Prevention Extension (HOPE) study** (chaired by Jared Baeten MD, PhD, *co-I on this application*) in the Microbicide Trials Network (MTN-025) will examine the dapivirine vaginal ring in an open-label trial for safety, adherence and efficacy in preventing HIV acquisition. Participants will receive a vaginal ring containing 25mg of dapivirine to be replaced each month over a total period of 12 months. Hair, plasma and used rings will be collected at each visit and analyzed for dapivirine levels. Safety, tolerability, and HIV incidence will be monitored.

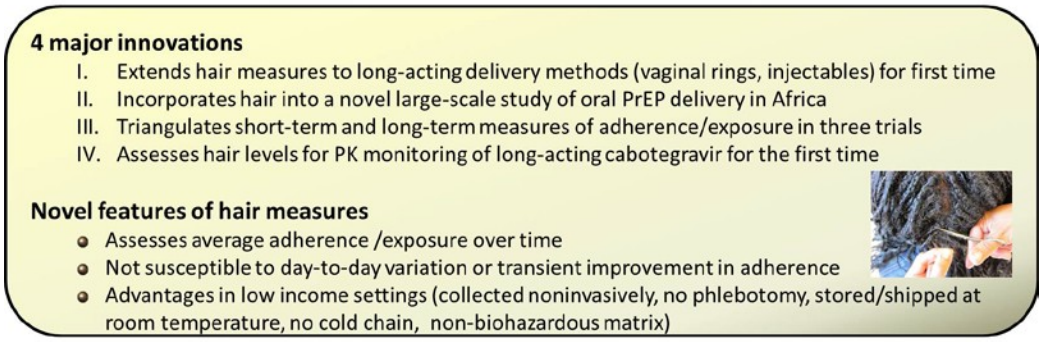
ACTG A5359 study: **The Long-Acting Antiretroviral Therapy in Non-adherent HIV-Infected Individuals Trial** in the AIDS Clinical Trials Group (ACTG A5359, co-chaired by Jose Castillo-Mancilla MD, *co-I on this renewal*) will randomize patients with a history of poor adherence (with virologic suppression after an oral lead-in phase) to a LA cabotegravir plus LA rilpivirine-based regimen administered every 4 weeks. Hair and plasma concentrations of CAB, HIV viral loads, and factors associated with PK variability will be collected during this phase. The purpose of **Aim 3** is to investigate the utility of hair levels for exposure monitoring in the context of injectable PrEP.

3B. INNOVATION

This application proposes four major innovations (**Figure 3**) with the already novel technique of analyzing ARV concentrations in hair samples to advance this methodology into the next phase of HIV prevention work. We propose to "extend" hair levels to **novel and exciting modalities of antiretroviral delivery, such as vaginal rings and injectables, for the first time** (I). We propose to incorporate this measure into a large-scale PrEP study in East Africa which aims to **establish practice paradigms for the roll-out of oral PrEP** in a variety of high-risk populations (young women, mobile populations, fisherfolk, etc.) (II). Although rarely employed to date, the incorporation of both short and long-term measures of adherence into oral PrEP and vaginal PrEP trials, **and the triangulation of these measures during study analysis,** as proposed here, should help assess patterns of adherence to PrEP (oral or rings) in Africa (e.g. daily, at time of risk, multiweek holidays),[48] which will be necessary to understand[69] when designing precision public health interventions for HIV prevention (III). Finally, although hair concentrations and other pharmacologic measures assess adherence, they also serve as **measures of pharmacokinetics,** which will be essential to incorporate during the investigation and roll-out of injectable ARVs**, especially at the end of the dosing interval and in the context of prevention**. We propose to study hair levels as a metric for drug exposure to LA-CAB in a study for the first time (IV).

The ease of collection and hair's ability to be stored and shipped at room temperature without biohazard provide feasibility advantages to this measure. This R01 renewal builds on the productivity[25-44] and foundational work of its predecessor, including important collaborations built with the NIH-funded clinical trial networks during the original funding period. Overall, this application is highly innovative in leveraging three large funded HIV trials to extend our novel approach of assessing adherence and pharmacokinetics via hair levels to the next phase of HIV prevention research in a cost-effective manner.

Figure 3: Innovative Features of "Hair Extensions" (RO1 renewal)



3C. APPROACH

PROGRESS REPORT: NIAID/NIH R01 AI098472 (15-Dec-11 to 30-Nov-16); **See publication list file**
3C1. Our group has been productive during the first funding period of this R01, making substantial progress on all original aims and publishing 20 papers.[25-44] We demonstrated the preliminary utility of hair levels to monitor PrEP adherence and toxicities in VOICE and other PrEP studies (Aim 1); we published findings relevant to the hypotheses of Aim 2 in several studies (of note, the PROMISE study launched later than anticipated, so we are analyzing samples now); and we developed a low-cost hair assay (Aim 3).

1st R01 Aim 1: Hair concentrations with oral PrEP: In a formative study, in which TDF was given to HIV-uninfected volunteers via directly observed dosing of 2, 4 and 7 doses/week (with wash-out periods), we found a strong linear relationship between TDF dose and TFV hair concentrations.[39] This study enables us to estimate TDF dosing patterns from hair concentrations in various studies.[42] We examined factors contributing to TDF exposure in women.[44] We have also evaluated relationships between hair levels and other metrics of adherence in the phase II International AIDS Vaccine Initiative (IAVI) PrEP trials.[40] In iPrEx OLE, a large PrEP demonstration project,[71] we showed strong correlations between hair levels of TFV/FTC and DBS levels of TFV-diphosphate /FTC-triphosphate.[41] Recently, we showed a strong association between higher levels of TFV/FTC in hair and greater declines in renal function in iPrEx OLE (Gandhi et al, *Lancet HIV* paper in press, **Appendix A**)[42], **showing for the first time that hair levels can monitor for toxicities on PrEP**. Finally, we examined patterns of adherence to oral TDF/FTC by combining both hair and plasma measures in VOICE.[48]

1st R01 Aims 2, 3: Hair levels in treatment and maternal-child patterns: We have shown that hair levels are strong independent predictors of virologic suppression in HIV treatment,[22-27] providing pharmacodynamic relevance for the longitudinal exposure data provided by hair samples. Hair levels predict outcomes better than self-reported adherence[22,23,25] or single plasma ARV levels[24,27] in children and adults. Hair ARV levels in HIV-positive women strongly predict virologic outcomes during pregnancy and breastfeeding.[25] Moreover, hair levels in neonates reflect exposure to maternal ARVs *in utero* and hair levels in infants reflect exposure to maternal ARVs during breastfeeding.[28,30] **We further demonstrated that hair levels of ARVs increase following adherence interventions in both the U.S.[34] and Kenya.**[35] We developed low-cost ARV assays in hair.[33] Finally, we have extended our hair methods to monitor adherence/exposure to TB treatment.[36-38]

PRELIMINARY DATA FOR THIS RENEWAL APPLICATION:

3C2. Acceptability of hair collection in SEARCH

As of this proposal date, SEARCH phase 2 (**Aim 1**) has launched and PrEP initiated in the community Nsiika in western Uganda. Persons at high risk (via self-identification or the SEARCH risk score), were offered PrEP. To date, 113 persons were initiated on PrEP (60 female; 65% <35 years) and **all but one provided hair for PK analysis at the 1 month visit**. In a separate study in SEARCH communities (*The Mobility in SEARCH Study*, PI Carol Camlin, R01MH104132; co-I Gandhi), hair samples have been collected from 837 participants as of August 2016; 95.8% (837/874) of those enrolled consented to hair collection and 94.6% of those contacted (837/885) consented, **leading to an overall acceptability rate of ~95% for hair collection in SEARCH**. MTN-025 (**Aim 2**) has just launched (end August 2016) and enrollment for A5359 (**Aim 3**) will begin in 2017.

[redacted]

[redacted]

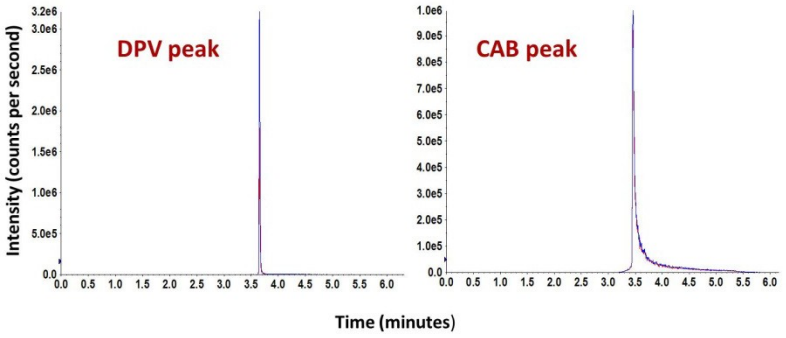


Figure 4: Representative extracted ion chromatograms for dapivirine (DPV) and cabotegravir (CAB) spiked in hair.

[redacted]

RESEARCH DESIGN AND METHODS:

3C4. Study overview and team: The three aims of this study are embedded in three trials, each detailed below. We have assembled a talented interdisciplinary team for this grant composed of the chairs of the three trials, as well as experts in pharmacokinetics and analytic chemistry. **Dr. Diane Havlir** (co-I) has conducted extensive research on HIV internationally and co-leads the Makerere University (MU)-UCSF collaboration and SEARCH study with **Dr. Moses Kamya** (*see letter of support (LOS) from Drs. Havlir and Kamya and approval letter from MU-UCSF collaboration*). **Dr. Jared Baeten** (co-I, *see LOS*) is an expert in PrEP, served as the PI

of the Partners PrEP study,[2] and led the original MTN-020 (ASPIRE trial).[11] His protocol co-chairs in MTN-025 (**Dr. Thesla Palanee** from South Africa and **Dr. Nyaradzo Mgodi** from Zimbabwe) will serve as consultants (*see both LOS)*. **Dr. Sharon Hillie**r, the PI of the overall MTN, strongly endorses this proposal (*see LOS*) and **Dr. Elizabeth Brown**, PI of the MTN Statistical Center, will serve as a significant contributor (*see LOS).* **Dr. Jose Castillo-Mancilla** (co-I and co-chair of A5359, *see LOS on behalf of ACTG*) is an emerging leader on drug levels, ARV pharmacology and ART in diverse populations. **Dr. Leslie Benet** (co-I, *see LOS*) is a world-renowned expert on pharmacokinetics and the overall Director of the Hair Analytical Laboratory at UCSF and **Dr. Roy Gerona** (co-I) is an analytic chemist with vast expertise in developing and validating assays for novel drugs. Finally, **Dr. Peter Bacchetti** (co-I) has been an HIV biostatistician since the beginning of the epidemic and has worked on hair and PK studies at UCSF with Dr. Gandhi (co-authoring 23 papers) for over a decade.

3C5. Aim 1: To evaluate concentrations of PrEP drugs in hair and plasma as biomarkers of adherence and predictors of effectiveness in a large community cluster randomized trial (SEARCH)

Study population for Aim 1: The study population for this Aim will be composed of HIV-uninfected men and women receiving PrEP in the second phase of SEARCH study. SEARCH (NCT01864603) is a community cluster randomized study that randomized 32 communities (20 in Uganda and 12 in Kenya) to either a universal HIV test and treat strategy versus the country standard of care at the time. Each community contains roughly 10,000 persons and ~340,000 individuals were enrolled during the first phase by holding community-wide health fairs which tested and referred patients for multiple diseases (e.g. HIV, malaria, TB, diabetes, hypertension) in the rural community sites.[49,116,117] During its first phase, the intervention arm of SEARCH exceeded the UNAIDS “90-90-90” targets for testing, receipt of ART, and virologic suppression.[50,118]

In the second phase, the same 32 communities are re-randomized to either an intervention arm, consisting of targeted PrEP to at-risk individuals (on top of universal streamlined ART for HIV-infected) or to a control arm (only universal streamlined ART). HIV seroconversions will be measured after 3 years. In each intervention community, persons at high risk for HIV seroconversion based on one of three categories will be provided PrEP: 1) those with a high-risk profile based on a set of factors associated with seroconversion in the first phase of SEARCH (age, gender, region, marital status, occupation, polygamy status, education, alcohol use, circumcision status); 2) those who self-identify as being at risk; and 3) those in serodiscordant couples. Participants will receive PrEP at a clinic or outside the clinic and multiple covariates collected and assessed in relation to adherence (**Table 2**, last row). Approximately 400 individuals per intervention community, or **6400 total participants in 16 communities, are estimated to eventually be on PrEP. A major strength of this large trial is that it will enroll individuals with a variety of risks**, including fisherfolk around Lake Victoria,[121] mobile populations,[75] men and women in polygamous relationships, young women, etc., allowing predictors and patterns of adherence to be determined in a number of important groups.

Table 2: Schedule of evaluations for SEARCH PrEP trial (**Aim 1**)

Evaluation (SEARCH)	Baseline visit	4 week visit	12 week visit	Every 12 weeks	144 weeks
Provision of oral PrEP	●	●	●	●	
Self-reported adherence		●	●	●	●
HIV testing	●	●	●	●	●
Personal risk assessment	●	●	●	●	●
Creatinine / STD screen	●		●	●	●
Hair and plasma for PK		●	●	●	●
Covariates*	●	●	●	●	●

**Covariates in models of hair levels vs seroconversion and in adherence models:* *Age, gender, site, marital status, occupation, polygamy status, education level, circumcision status, alcohol use, presence of an STD, self-assessment of risk, stigma*

Data collection for Aim 1: Table 2 summarizes the schedule of evaluations in SEARCH PrEP. After the baseline visit, participants have a follow-up visit at 4 weeks and then quarterly up to 144 weeks. HIV rapid serology is performed at baseline and every visit. Signs or symptoms of acute HIV infection and of toxicity are assessed. PrEP is dispensed at each visit, **either at the study clinic or offsite** based on patient preference, or a randomization scheme if no preference. Demographic information, including age, sex and residence, is collected at baseline, and a stigma survey administered.

Once the participant is on PrEP, self-reported adherence is assessed at every visit via a 3-day adherence recall survey. Participants are asked about self-perception of risk at baseline and every visit on PrEP, with specific questions on whether he/she a) is currently at risk for HIV infection; b) anticipates being at risk in the next 3 months; c) is in a serodiscordant relationship; and d) knows anyone at risk for HIV infection. Creatinine is measured at baseline and the estimated creatinine clearance (eCrCl) by the Cockcroft Gault equation[122] and the glomerular filtration rate (eGFR) by the Modification of Diet in Renal Disease (MDRD) formula[123] calculated.

Hair collection*:* At the 4 week follow-up visit and every 12 weeks, plasma and hair are collected for drug levels. The procedure for hair collection (**all 3 Aims**) has been outlined previously (**Figure 5**).[22,23,29,40] Briefly, the steps

are as follows: 1. Clean the blades of a pair of scissors with an alcohol pad and allow blades to dry; 2. Lift up the top layer of hair from the occipital region of the scalp. Isolate a small thatch (50-100 strands) from underneath this layer; 3. Cut the small hair sample as close to the scalp as possible; 4. Place the thatch inside an unfolded piece of foil; 5. Place a narrow label over the distal end (the side furthest from the scalp) to denote directionality if strands long enough; 6. Refold the foil to enclose the sample; 7. Place a study ID label on the folded piece of foil; 8. Place the foil inside the plastic (e.g. Ziploc) bag, each containing a desiccant pellet, and seal. We provide pictures and videos of the hair collection process to sites for a variety of hair styles (short, cropped, curly, weaves, braids) (**Appendix B**). Samples are kept at room temperature prior to batch shipment without biohazard precautions.

Figure 5: Hair collection process for all Aims

Laboratory methods for Aim 1: The assays for measuring TFV and FTC in hair samples in the UCSF HAL[39] have been peer-reviewed and approved by the DAIDS CPQA program.[119] Briefly, the proximal section of the thatch of hair (generally about 1-2cm, depending on duration of exposure to be assessed) is cut down and chopped to 1-2 mm length segments and 5 mg is weighed and processed. TFV and FTC in the cut hair sample are extracted with 50% methanol/water containing 1% trifluoroacetic acid, 0.5% hydrazine dihydrochloride, and internal standard in a 37°C shaking water bath overnight (>12 hours) and then analyzed by LC-MS/MS. The relative error (%) and precision (coefficients of variation) for spiked quality control hair samples at low, medium and high concentrations are all <15%. The method to analyze TFV in hair is validated from 0.002 nanograms (ng)/mg to 0.400 ng/mg hair[39] and the method to analyze FTC in hair is validated from 0.02 to 4.0 ng/mg.[40]

Study methods for Aim 1:

Hair levels as predictors of effectiveness

1) Study design**:** With 6400 participants on PrEP in SEARCH and with hair collected at the 4 week visit and then quarterly, a total of 6400 x 13 = ~83,200 hair samples should be collected. We will employ a sampling strategy similar to a case-control design at the time of the trial's completion and the subsequent availability of outcome data to select which hair samples will be analyzed by our laboratory. Specifically, hair levels will be measured **for every visit from all seroconverters** and from a simple random sample of controls who did not acquire HIV. We plan three times as many controls as seroconverters, based on balancing the need to obtain ample information about the controls (and leverage all the other information that will already be available) against the diminishing marginal returns when the number of controls is vastly larger than that of the seroconverters. **Random sampling of a small fraction of non-seroconverters will provide nearly as much information and be more cost efficient and feasible than testing specimens from all participants.** Our design will be more informative than a classic case-control study because it will take advantage of having a single known sampling fraction from the well-defined pool of potential controls. We will therefore be able to use sampling fraction weights to properly combine data from seroconverters (sampled with certainty) and controls in order to obtain accurate estimates for the entire study population. Such weighting methods are readily available in standard software packages e.g. the *svyset* and *svy:* prefix in Stata or the *SurveyReg* and *SurveyLogistic* procedures in SAS. In addition, these methods will remain valid with additional participants sampled with certainty to better address the association between drug exposure and renal toxicity (see below).

2) Statistical methods: We will fit a discrete-time Cox model using the pooled logistic regression approach[124] to estimate the association of hair TFV and FTC levels with the primary outcome of seroconversion in the entire sample, controlling for factors associated with incidence in the first phase of SEARCH (**Table 2**, last row), as well as stigma, having an STD, and self-identified risk. We will examine the associations of plasma TFV and FTC levels and self-reported adherence with seroconversion, comparing their explanatory utility to that of hair levels and assessing the potential value of using two or all three measures together. Using survey-weighting to account for the sampling fraction of control subjects will enable meaningful estimates of intercepts and rate estimates. Fitted model parameters will **calculate levels of TFV or FTC in hair associated with high levels of protection from HIV.** Hair levels will be examined both as categorical (e.g. quartiles) – which are easier for clinicians/researchers to interpret- and continuous predictors. Based on experience, we expect log transformed

hair levels to predict outcomes better than raw levels and to more closely meet the linearity assumption.

3) Sample size: Assumptions in the SEARCH PrEP trial imply a total of 100 HIV seroconversions among persons on PrEP over follow-up within the intervention communities. We will therefore be analyzing hair samples from 100 cases and hair from a random sample of 300 controls, so 400 x 13 visits= 5200 samples from 5200 person-visits (along with the 1300 additional samples measured to assess renal toxicity; see below). **This is a highly cost-efficient sample size choice, which we believe makes this innovative study worth performing**.[125-130] To estimate power, we considered the simplified situation of a single observation per person, with analysis comparing the bottom quartile of hair levels to the top 3 quartiles. In this case, the power is ≥80% for an odds ratio of ≥2.1. This corresponds to a seroconversion rate by the end of follow up of ~ 2.6% among those with hair levels in the bottom quartile versus ~1.2% or less among those with hair levels in the top three quartiles. Having multiple observations per person will improve power and precision, as will the inclusion of hair concentration data from participants who are selected based on renal toxicities (next section).

Hair levels as predictors of renal toxicity

Renal toxicity is the most frequent adverse effect observed on TDF/FTC-based treatment or PrEP.[42,131-142] The CDC Clinical Practice Guidelines for PrEP define an eCrCl of 60ml/min as the threshold at which PrEP should be discontinued.[51] We will examine the association of **hair levels with renal toxicity** using the above samples measured for the study of effectiveness, supplemented with data from participants likely to be most informative concerning toxicity. This will include up to 100 persons who reach an eCrCl ≤60 ml/min *or* whose CrCl declines by >15% at any point (100 x 13 visits =1300 person-visits). We will also include samples where renal function is defined by eGFR. We note that these participants' data will also contribute to the effectiveness analysis, just as the seroconverters contribute to this toxicity analysis. Both analyses will account for the sampling fraction of controls and the certain sampling of both the seroconverters and those with the greatest renal toxicity, so that our overall sample accurately reflects the entire study population. We anticipate few participants will meet renal criteria for certain sampling, likely associated with high TDF exposure, and also seroconvert, likely associated with low TDF exposure. Nevertheless, overlap, if it occurs, will not detract from the validity of our design.

1) Statistical methods: The mean percent change in eCrCl from baseline at each visit will be estimated for all participants in SEARCH PrEP from a linear mixed effects model, adjusted for age, sex, baseline CrCl, hypertension and diabetes, concomitant drugs (e.g. NSAIDs), and site. Multivariate logistic regression models will assess predictors of renal decline (eCrCl falling to ≤60 ml/min *or* a decline of ≥15%). The probability of eCrCl falling to ≤60 ml/min (and then ≤70 ml/min[42,143]) at least once over the study will be calculated among participants whose baseline eCrCl was above that level. Analyses will be repeated using eGFR.

For all participants on PrEP in whom hair levels will be analyzed (total ~5200 + 1300 =6500 person-visits),we will assess the relationship between hair concentrations and % change in eCrCl (or eGFR) from baseline.[42] As in our *in press* paper (*Lancet HIV*, **Appendix A**),[42] data from STRAND[39] will provide estimates for dosing patterns based on TFV levels in hair. Using data from these same person-visits, the multivariate logistic regression models for predictors of renal decline will be repeated, **but adding hair level data**, with levels categorized into quartiles and assessed as continuous measures. We will also examine the associations of self-reported adherence and plasma TFV/FTC levels with renal outcomes, comparing their explanatory utility to that of hair levels and assessing the potential value of using two or all three measures together. Unassayed hair samples in SEARCH PrEP will be available for simultaneous or future analyses by proposing investigators.

Correlations, predictors and patterns of adherence:

1) Correlations: We will examine scatterplots and Spearman correlation coefficients between hair and plasma concentrations of TFV/FTC, as well as with self-reported adherence measures.

2) Predictors of adherence; We will perform univariate linear mixed effects regression models using hair levels of TFV/FTC assessed as continuous outcomes **with a number of candidate predictor variables that may influence adherence** (**Table 2,** last row), as well as plasma levels, self-reported adherence, self-assessment of risk either at the study visit or estimated over the prior 3 months (as determined by the self-assessment data from the prior visit). We will then build multivariate models by forward stepwise selection to assess how associations with self-reported adherence and plasma levels change when controlled for other factors, and to explore independent associations of the other factors with hair levels. We will use log transformed hair levels, with estimated coefficients back-transformed into fold-effects. Because detection limits for TFV and FTC in hair are low, we will treat undetectable levels as equal to the detection limit. We will further reduce the influence of small differences between very low hair levels by adding the detection limit to all values before transformation.

3) Patterns of adherence: Concordance and discordance between hair and plasma concentrations of TFV/FTC

will provide information on patterns of adherence. For instance, taking medication only shortly before visits[102] will produce high plasma levels, but low or undetectable hair levels. Detectable hair levels despite undetectable plasma levels[48] could indicate ongoing intermittent use, perhaps with episodes of higher anticipated risk.

3C6. Aim 2: To investigate the use of hair levels as a long-term measure of dapivirine exposure in the open-label trial of the dapivirine vaginal ring (MTN-025).

Study population for Aim 2: The study population for this Aim will be composed of HIV-negative women enrolled in MTN-025. The primary objectives of this study are to evaluate safety, tolerability, HIV incidence, and HIV-1 viral resistance among women who acquire HIV infection under relatively real-world conditions. The study population of MTN-025 will include former participants of the placebo-controlled phase 3 MTN-020 trial[11] (ASPIRE; **Section 3A3**) who remained HIV-noninfected, are not pregnant, and wish to enroll. Of 2629 women enrolled in ASPIRE from Malawi, South Africa, Uganda and Zimbabwe, 2452 were alive and remained HIV-noninfected by the end of the trial. We anticipate 70-85% of the women in ASPIRE, ~1800 participants, will enroll into MTN-025.

Table 3: Schedule of evaluations for MTN-025 dapivirine ring trial (**Aim 2**)

Evaluation (MTN microbicide trials network)	Baseline visit	Months 1 and 2	Months 3, 6 and 9	Month 12 (product end)	1 month after product end
Provision of DPV ring	●	●	●		
Self-reported adherence		●	●	●	
HIV testing	●	●	●	●	●
Hair and plasma for PK		●	●	●	●
Collection of used ring		●	●	●	
STDs, pregnancy, safety labs, covariates*	●	●	●	●	●

***Covariates in models of hair levels vs seroconversion and in adherence models:** Age, region, marital status, attitudes toward and understanding of the efficacy of the vaginal ring, alcohol and drug use, anxiety/depression, sexual activity, condom use, vaginal practices, circumcision status of the partner(s) and his/their knowledge of the participant's participation in the study, presence of an STD

Data collection for Aim 2: The schedule of evaluations in MTN-025 is summarized in **Table 3**. All participants will receive a vaginal ring containing 25mg of dapivirine to be replaced monthly over 12 months. Rings are self-inserted. Hair, plasma and used rings will be collected at each visit (monthly for the first 3 months, then quarterly) where a ring was used and at the exit visit (one month after product end) for the analysis of dapivirine levels. The survey on self-reported adherence asks about days that the ring was out over the past month and requests participants to rate overall use.

Laboratory methods for Aim 2: Hair will be collected as described in **Section 3C5**. See **Section 3C3** for the methods we have developed for analyzing dapivirine in small hair samples. As in ASPIRE, the plasma levels of dapivirine will be analyzed (at Johns Hopkins University) using a validated ultra-performance LC-MS/MS-based assay with a lower limit of quantification of 20pg/mL.[11,144] The method for acetone extraction of dapivirine from used rings and analysis of concentrations via high pressure liquid chromatography has also been described.[11,81]

Study methods for Aim 2:

Hair levels as predictors of effectiveness (see methods under Aim 1 for details on sampling strategy)

1) Study design**:** With ~1800 participants provided the vaginal dapivirine ring and hair samples collected at months 1, 2, 3, 6, 9, and 12, as well as the post-study visit (**Table 3**), ~1800 x 7 visits = 12,600 hair samples should be collected. We will employ a similar sampling strategy as proposed in the **Aim 1** methods (**Section 3C5**) and analyze hair levels from all visits in all seroconverters and from visits of randomly sampled controls (3:1) who remain HIV-noninfected. Unassayed hair samples will be available for other studies and researchers.

2) Statistical methods: As in **Aim 1**, a pooled logistic regression approach[124] will estimate the association of dapivirine levels in hair with the primary outcome of HIV seroconversion in the entire sample, controlling for covariates that could be associated with HIV risk already collected in MTN-025 (**Table 3,** last row)**,** such as age, region, marital status, attitudes toward and understanding of the efficacy of the vaginal ring, alcohol and drug use, anxiety/depression, sexual activity, condom use, vaginal practices, and presence of an STD. We will also examine the association of self-reported adherence, plasma dapivirine concentrations, and residual ring levels with seroconversion, comparing their explanatory utility to that of hair levels and assessing the potential value of using two, three, or all four measures together. Fitted model parameters will be used to **calculate levels of dapivirine in hair from use of the vaginal ring associated with high levels of protection from HIV.** Hair levels will be examined as described for **Aim 1**. Of note, the dapivirine ring has little systemic toxicity, but 10-18% of participants who seroconverted in either the placebo or ring arms of the two phase 3 studies[11,12] had NNRTI resistance (with no difference in resistance rates by arm). **In MTN-025, hair levels of dapivirine in seroconverters will be examined via logistic regression to predict the presence of NNRTI resistance.**

3) Sample size: Based on the seroconversion rate of 3.3 per 100 person years among participants in the vaginal ring arm in ASPIRE,[11] we estimate ~60 HIV seroconversions among persons in MTN-025 over the duration of the study. We will therefore be analyzing hair samples over 7 visits from 60 cases and over visits from a random sample of 180 controls, so 240 x 7 visits= 1680 samples. Calculations using the framework described for **Aim 1** indicate power ≥80% if the relative risk in the lowest quartile of hair levels versus the top 3 quartiles is ≥2.9, corresponding to a seroconversion rate of 6.6% in the lowest quartile of hair levels and 2.3% in the others. Having multiple observations per person (n=7) will improve power and precision.

Correlations, predictors and patterns of adherence:

1) Correlations: We will examine scatterplots and Spearman correlation coefficients between hair, plasma and residual ring concentrations of dapivirine, as well as with self-reported adherence measures.

2) Predictors of adherence: We will perform univariate linear mixed effects regression models using hair levels of dapivirine assessed as a continuous outcome, paralleling those described for **Aim 1**, but with covariates now including residual ring levels and the candidate predictors that could influence adherence collected in MTN-025 (noted in **Table 3,** last row). We will then build multivariate models by forward stepwise selection to assess independent associations. We will also examine the associations of plasma levels, residual ring levels, and self-reported adherence with hair levels, and how these change when controlled for other factors.

3) Patterns of adherence: Concordance and discordance between hair, plasma and residual ring levels of dapivirine will provide information on patterns of adherence at each visit (see **Section 3A5** for examples).

3C7. Aim 3: To examine the utility of hair levels for pharmacokinetic (PK) monitoring of long-acting cabotegravir in a diverse population (A5359).

Study population for Aim 3: The study population for this Aim will be composed of individuals on long-acting CAB in ACTG A5359. The primary objective of A5359 (a phase III study) is to compare treatment outcomes with long-acting injectable agents versus the standard of care in diverse HIV-infected individuals with a previous history of non-adherence. In step 1 of the study, participants will be initiated on an oral induction ART regimen with financial incentives provided at weeks 4, 8, 12, 16 and 20 when benchmarks of virologic control are achieved. Participants achieving virologic suppression will then be randomized (in step 2) to staying on the oral regimen or switching to a combination of long-acting CAB and rilpivirine administered every 4 weeks to complete 76 weeks. Since the purpose of **Aim 3** is to explore the utility of hair concentrations for PK monitoring with LA CAB, **only participants in the long-acting arm of A5359 will be investigated in this proposal.**

Data collection for Aim 3: The schedule of evaluations in step 2 for participants in the long-acting arm of A5359 is shown in **Table 4**. After receiving 4 weeks of oral CAB (30mg) and oral rilpivirine daily from weeks 20 to 24 (following the oral ART lead-in phase from weeks 0 to 20), participants will receive intramuscular injections of LA CAB and rilpivirine every 4 weeks in the clinic up to 76 weeks. **Any missed or delayed visits are carefully noted** and, in this non-adherent population, are not unexpected. HIV RNA levels will be measured every 4-8 weeks and hair/plasma samples collected quarterly for PK monitoring. Weights, heights, CD4 counts, urine toxicology screens, alcohol/drug use, concomitant conditions, symptom screens and safety labs will be assessed every 4-8 weeks.

Table 4: Schedule of evaluations for long-acting arm of A5359 (**Aim 3**)

Evaluation (ACTG AIDS Clinical Trials Group)	Oral ART lead in (weeks 0-20)	Baseline visit	Every 4 weeks	~Every 8 weeks	Every 12 weeks	Week 76 (product end)
Provision of oral CAB + RPV		●				
Provision of IM LA CAB + RPV			●			
Hair and plasma for PK		●			●	●
HIV RNA level, factors*		●		●		●

*Factors (that can influence PK) assessed in relationship to hair and plasma levels of CAB: Age, sex, BMI, urine toxicology assays, alcohol and drug use, concomitant conditions or medications, renal and hepatic function

Laboratory methods for Aim 3: Hair collection is described (**Section 3C5**). **Section 3C3** outlines our methods for analyzing CAB in small hair samples. Plasma levels of CAB will be run centrally by ACTG.

Study methods for Aim 3: Given the importance of PK monitoring with injectables (whether used in treatment or prevention), these analyses will assess the use of hair levels for such monitoring in a diverse population.

Assessment of pharmacokinetics of LA cabotegravir using hair and plasma measures

1) Correlations between plasma and hair levels: Hair levels may have feasibility advantages over plasma levels for PK monitoring of injectable CAB if the two metrics correlate strongly. Scatterplots and correlation coefficients between hair and plasma concentrations of CAB will be examined every 12 weeks. In addition, we

will use mixed effects linear models for repeated measures to assess how well hair levels can predict trough plasma levels, using the 7 measurements performed per participant (weeks 20, 24, 36, 48, 60, 72, 76) during the injectable phase and evaluating CAB levels in each hair segment (see below), as well as the average level.

2) Modeling factors associated with CAB exposure: In this diverse population, sex, race/ethnicity, body mass index (BMI), age, renal and hepatic function, drug and alcohol use (**Table 4,** last row) will be examined in relationship to hair and plasma concentrations at the end of the dosing interval to assess factors associated with different exposure patterns. Protective efficacy for LA CAB is modeled to be achieved throughout the dosing interval if plasma levels are in excess of 4x the protein-adjusted 90% inhibitory concentration against the virus.[120] **The estimated 4x PA-IC_{90} in plasma is 0.66 µg/ml, which corresponds to an estimated drug concentration of 66ng/mg in hair**. We will therefore examine factors associated with trough levels modeled both as continuous outcomes and when categorized per these potential thresholds.

3) Segmental analysis of hair samples: One of the advantages of hair is that distance from the scalp along the cut strand serves as a marker of time, based on growth rates of ~1 cm every 4 weeks (**Section 3A4**).[106-108] Segmental analysis is most often employed to assess use of substances over time.[145-148] In A5359, we will use segmental analysis to determine concentrations of LA CAB from the time of injection to the end of the dosing interval by segmenting the hair into 0.25cm sections. Each segment will reflect the average systemic CAB concentration over the time it grew, so these segments will reflect CAB exposure over the 1st week, 2nd week, 3rd week and 4th week after injection for those who do not miss visits. **In this non-adherent group of patients, missed or delayed visits are expected, and segmental analysis of 2 or even 3 cm of hair will be particularly helpful to perform after such delays to explore the PK impact of such lapses.** We will examine factors (**Table 4,** last row) - such as sex, race/ethnicity, BMI - associated with a more rapid decay in CAB levels, as indicated by the difference in levels in the last 2 or 3 segments. Finally, we will examine patterns of hair levels over each week since the last injection to examine how low concentrations, e.g. < 4x PA-IC_{90} of the virus, occur (e.g., lower than typical over all weeks vs rapid decline following good initial levels).

4) Sample size: Sample size is necessarily limited to that of the LA CAB arm of A5359 (N at least 150, likely larger). The additional expense of obtaining and analyzing hair drug levels for this proposal is relatively low, making this a highly cost-efficient proposal.[125-130] This aim is necessarily exploratory because injectables are new, but we can calculate the likely precision of estimated correlations between hair and plasma levels. Using just one time point, an observed correlation of 0.8 among N=150 participants would have a 95% confidence interval from 0.73 to 0.85. This is already reasonably precise, and the models using repeated measures will utilize all data to provide a good assessment of how well hair levels can predict trough plasma levels.

Exploratory analyses will examine hair levels as predictors of virologic suppression with treatment

Since hair levels could be used to monitor LA CAB during real-world treatment as well as PrEP, and because the levels expected to achieve protective efficacy are likely to parallel those required for treatment efficacy, an exploratory analysis for **Aim 3** will examine virologic suppression. Multivariate random effects logistic regression models for repeated measures will estimate the association of CAB hair and plasma levels (and using both in combination) with the dichotomous outcome of virologic suppression (<50 copies/mL). We will evaluate levels in each of the 4 segments (most recent week, 8-14 days ago, 15-21 days ago, 22-28 days ago, longer with missed visits) separately, along with their average (including other factors that could influence PK).

We will examine possible thresholds of CAB levels as predictors of loss of viral suppression. *A priori* cutoffs can be based on the hair and plasma levels expected to exceed the 4x PA-IC_{90} against the virus. We will assess these dichotomizations in plasma and hair as predictors of suppression, comparing their performance to modeling them in continuous or multi-category models. If we identify thresholds that perform well, we will also use them as outcomes, modeling factors associated with achieving these thresholds.

CONCLUSION: The completion of these aims should allow us to **develop an integrated package of highly predictive biologic adherence and pharmacokinetic measures spanning PrEP delivery methods and optimization strategies** during the next phase of biomedical HIV prevention implementation. These findings should advance real-world strategies to 1) monitor adherence to oral PrEP among key groups in high-incidence settings to interpret effectiveness; 2) monitor adherence to the dapivirine vaginal ring to thereby expand its protective potential in women; and 3) monitor the “PK tail” during actual use of injectable ARVs to ensure protective efficacy between doses. **Future studies** that could stem from this work include designing adherence interventions based on the patterns of drug-taking or ring use demonstrated in this proposal or determining the frequency of PK monitoring needed (**or the possibility of less frequent injections for some individuals based on PK characteristics** with the use of injectables. Our proposal to extend the funding for this R01, which has been productive to date,[25-44] will help extend hair measures into the era of “PrEP 2.0”.

PROGRESS REPORT PUBLICATION LIST

Our group has been productive during the first funding period of this NIAID/NIH R01 AI098472 (PI: Gandhi; 15-Dec-11 to 30-Nov-16), performing foundational work and publishing 20 papers. We made substantial progress on all original aims. We published on the use of hair levels to monitor oral PrEP in VOICE and other findings relevant to PrEP studies (Aim 1); we published findings relevant to the hypotheses of Aim 2 regarding hair levels in the context of treatment and maternal-child transmission in several studies (the PROMISE study, in which Aim 1 was originally embedded, launched later than anticipated, so we are analyzing samples now); and we published a low-cost assay (Aim 3). We have used this first R01 as a platform for mentoring (* indicates first-author is a mentee), given the commitment of all investigators on the grant to mentoring early stage investigators. We now seek renewal for a new set of aims.

20 papers published during the first funding period of R01

1. **Gandhi M**, Mwesigwa J, Aweeka F, Plenty A, Charlebois E, Ruel TD, Huang Y, Clark T, Ades V, Natureeba P, Luwedde FA, Achan J, Kamya MR, Havlir DV, Cohan D. Hair and Plasma Data Show That Lopinavir, Ritonavir, and Efavirenz All Transfer From Mother to Infant In Utero, But Only Efavirenz Transfers via Breastfeeding. *J Acquir Immune Defic Syndr.* 2013;63(5):578-584. PMCID: PMC3800282. **(Aim 2 of first funding period)**

2. Liu AY, Yang Q, Huang Y, Bacchetti P, Anderson PL, Jin C, Goggin K, Stojanovski K, Grant R, Buchbinder SP, Greenblatt RM, **Gandhi M**. Strong Relationship between Oral Dose and Tenofovir Hair Levels in a Randomized Trial: Hair as a Potential Adherence Measure for Pre-Exposure Prophylaxis (PrEP). *PLoS One*. 2014;9(1):e83736. PMCID: PMC3885443. **(Aim 1 of first funding period)**

3. **Gandhi M**, Yang Q, Bacchetti P, Huang Y. A low-cost method for analyzing nevirapine levels in hair as a marker of adherence in resource-limited settings. *AIDS Res Hum Retroviruses.* 2014;30(1):25-28. PMCID: PMC3887402. **(Aim 3 of first funding period)**

4. Hickey MD*, Salmen CR, Tessler RA, Omollo D, Bacchetti P, Magerenge R, Mattah B, Salmen MR, Zoughbie D, Fiorella KJ, Geng E, Njoroge B, Jin C, Huang Y, Bukusi EA, Cohen CR, **Gandhi M**. Antiretroviral concentrations in small hair samples as a feasible marker of adherence in rural Kenya. *J Acquir Immune Defic Syndr.* 2014;66(3):311-315. PMCID: PMC4146734. **(Aim 2)**

5. Bartelink IH, Savic RM, Mwesigwa J, Achan J, Clark T, Plenty A, Charlebois E, Kamya M, Young SL, **Gandhi M**, Havlir D, Cohan D, Aweeka F. Pharmacokinetics of lopinavir/ritonavir and efavirenz in food insecure HIV-infected pregnant and breastfeeding women in Tororo, Uganda. *Journal of Clinical Pharmacology.* 2014;54(2):121-132. PMCID: PMC3933454. **(Aim 2)**

6. Baxi SM*, Greenblatt RM, Bacchetti P, Scherzer R, Minkoff H, Huang Y, Anastos K, Cohen M, Gange SJ, Young M, Shlipak MG, **Gandhi M**. Common clinical conditions - age, low BMI, ritonavir use, mild renal impairment - affect tenofovir pharmacokinetics in a large cohort of HIV-infected women. *AIDS.* 2014;28(1):59-66. PMCID: PMC3956315. **(Aim 1)**

7. Prasitsuebsai W, Kerr SJ, Truong KH, Ananworanich J, Do VC, Nguyen LV, Kurniati N, Kosalaraksa P, Sudjaritruk T, Chokephaibulkit K, Thammajaruk N, Singtoroj T, Teeraananchai S, Horng H, Bacchetti P, **Gandhi M**, Sohn AH. Using Lopinavir Concentrations in Hair Samples to Assess Treatment

Outcomes on Second-Line Regimens Among Asian Children. *AIDS Res Hum Retroviruses.* 2015;31(10):1009-1014. PMCID: PMC4576945. **(Aim 2)**

8. Koss C*, Natureeba P, Mwesigwa J, Cohan D, Nzarubara B, Bacchetti P, Horng H, Clark TD, Plenty A, Ruel TD, Achan J, Charlebois ED, Kamya MR, Havlir DV, **Gandhi M**. Hair Concentrations of Antiretrovirals Predict Viral Suppression in HIV-Infected Pregnant and Breastfeeding Ugandan Women. *AIDS*. 2015;29(7):825-830. PMCID: PMC4438773. **(Aim 2)**

9. Baxi SM*, Greenblatt RM, Bacchetti P, Jin C, French AL, Keller MJ, Augenbraun MH, Gange SJ, Liu C, Mack WJ, **Gandhi M**. Nevirapine Concentration in Hair Samples Is a Strong Predictor of Virologic Suppression in a Prospective Cohort of HIV-Infected Patients. *PLoS One*. 2015; Jun 8;10(6):e0129100. PMCID: PMCID: PMC4460031. **(Aim 2)**

10. Olds PK, Kiwanuka JP, Nansera D, Huang Y, Bacchetti P, Jin C, **Gandhi M**, Haberer JE. Assessment of HIV antiretroviral therapy adherence by measuring drug concentrations in hair among children in rural Uganda. *AIDS Care.* 2015;27(3):327-332. PMCID: PMC4305465. **(Aim 2)**

11. Cohan D, Natureeba P, Koss CA, Plenty A, Luwedde F, Mwesigwa J, Ades V, Charlebois ED, **Gandhi M**, Clark TD, Nzarubara B, Achan J, Ruel T, Kamya MR, Havlir DV. Efficacy and safety of lopinavir/ritonavir versus efavirenz-based antiretroviral therapy in HIV-infected pregnant Ugandan women. *AIDS*. 2015;29(2):183-191. PMCID: PMC4428759. **(Aim 2)**

12. Gwadz M, Cleland CM, Applegate E, Belkin M, **Gandhi M**, Salomon N, Banfield A, Leonard N, Riedel M, Wolfe H, Pickens I, Bolger K, Bowens D, Perlman D, Mildvan D, Heart to Heart Collaborative Research T. Behavioral Intervention Improves Treatment Outcomes Among HIV-Infected Individuals Who Have Delayed, Declined, or Discontinued Antiretroviral Therapy: A Randomized Controlled Trial of a Novel Intervention. *AIDS Behav*. 2015. Oct;19(10):1801-17. PMCID: PMC4567451. **(Aim 2)**

13. Hickey MD*, Salmen CR, Omollo D, Mattah B, Fiorella KJ, Geng EH, Bacchetti P, Blat C, Ouma GB, Zoughbie D, Tessler RA, Salmen MR, Campbell H, **Gandhi M**, Shade S, Njoroge B, Bukusi EA, Cohen CR. Pulling the network together: quasi-experimental trial of a patient-defined support network intervention for promoting engagement in HIV care and medication adherence on Mfangano Island, Kenya. *J Acquir Immune Defic Syndr*. 2015. Aug 1;69(4):e127-34. PMCID: PMC4485532. **(Aim 2)**

14. Baxi SM*, Liu A, Bacchetti P, Mutua G, Sanders EJ, Kibengo FM, Haberer JE, Rooney J, Hendrix CW, Anderson PL, Huang Y, Priddy F, **Gandhi M**. Comparing the Novel Method of Assessing PrEP Adherence/Exposure Using Hair Samples to Other Pharmacologic and Traditional Measures. *J Acquir Immune Defic Syndr*. 2015;68(1):13-20. PMCID: PMC4262724. **(Aim 1)**

15. **Gandhi M**, Glidden DV, Liu A, Anderson PL, Horng H, Defechereux P, Guanira JV, Grinsztejn B, Chariyalertsak S, Bekker LG, Grant RM, iPrEx Study T. Strong Correlation Between Concentrations of Tenofovir (TFV) Emtricitabine (FTC) in Hair and TFV Diphosphate and FTC Triphosphate in Dried Blood Spots in the iPrEx Open Label Extension: Implications for Pre-exposure Prophylaxis Adherence Monitoring. *J Infect Dis.* 2015;212(9):1402-1406. PMCID: PMC4601920. **(Aim 1)**

16. [redacted]

[redacted]

17. Sheth AN*, Rolle CP, **Gandhi M**. HIV pre-exposure prophylaxis for women. *J Virus Erad*. 2016;2(3):149-155. PMCID: PMC4967966. **(Aim 1)**

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19. Mave V*, Chandanwale A, Kinikar A, Khadse S, Kagal A, Gupte N, Suryavanshi N, Nimkar S, Koli H, Khwaja S, Bharadwaj R, Joshi S, Horng H, Benet LZ, Ramachandran G, Dooley KE, Gupta A, **Gandhi M**. Isoniazid hair concentrations in children with tuberculosis: a proof of concept study. *Int J Tuberc Lung Dis.* 2016;20(6):844-847. PMCID: PMC4889729. **(Aim 2)**

20. Gerona R*, Wen A, Koss C, Bacchetti P, **Gandhi M**, Metcalfe J. A multi-analyte panel for non-invasive pharmacokinetic monitoring of second-line anti-tuberculosis drugs. *Int J Tuberc Lung Dis.* 2016;20(7):991-992. PMID: 27287660. PMCID in progress. **(Aim 2)**

*Indicates first-author is a mentee of PI

5. PROTECTION OF HUMAN SUBJECTS

This study involves the analysis of small hair samples already to be collected in the SEARCH PrEP trial (Aim 1, collection ongoing), Microbicide Trials Network (MTN)-025 (HOPE) trial (Aim 2, collection starting late August 2016), and the Adult Clinical Trials Group (ACTG) A5359 trial (Aim 3, collection to start 2017). The SEARCH PrEP and the MTN-025 trials have Data and Safety Monitoring Boards (DSMB) already in place, Institutional Review Board (IRB)/Ethics Committee (EC) approvals from all participating sites, and IRB-approved consent forms with information about hair collection. The DSMB and IRB approvals for A5359 are currently being established. The SEARCH trial has been registered at Clinical Trials.Gov under number NCT01864603 and the MTN-025 trial is registered under number NCT02858037. As per ACTG guidelines, A5359 will also be registered on ClinicalTrials.gov. This R01 renewal proposal adds on hair collection to procedures already planned and approved in the three partnering trials, so the risk to human subjects section for this grant will be restricted to the risks of hair collection.

RISKS TO HUMAN SUBJECTS

Hair collection methods have been outlined in previous papers by our group and are described in detail in **Section 3C5** of the Research Strategy (see also **Figure 5** of the Research Strategy and **Appendix B**). Of note, the entire hair collection process takes approximately 90 seconds, which minimizes discomfort to participants.

Although usually painless, there is a small risk of a cut to the skin from the scissors. The NIH-funded Women's Interagency Study has been collecting small hair samples from HIV-positive participants on antiretroviral therapy every six months since 2002 using the hair collection procedure outlined above. No injury or any other adverse event has ever been reported from the collection process. During the first funding period of this R01, hair was collected from HIV-infected women and their infants in Uganda (the PROMOTE trial), HIV infected pregnant women and their infants in the IMPAACT 1077 PROMISE trial, HIV-infected children in Uganda, and participants of several PrEP trials, along with several other studies. There have been no reported cases of scalp nicking or other injury from hair collection in any of these studies.

One other question raised by study staff and participants can be whether the collection of small hair specimens (approximately 50-100 strands for all Aims of this R01 renewal) would be disruptive to hair styles or could be accomplished from participants with male-pattern baldness. The human scalp loses an average of 100 strands of hair per day so the amount of hair we propose to collect for this project is less than this amount. Moreover, the size of the hair sample collected for the antiretroviral assays is small and collection is usually easily accomplished from participants with short or limited amounts of hair (e.g. with male-pattern baldness). Hair cannot be collected from a completely bald scalp and we do not analyze pubic or axillary hair for our studies to minimize variability. Over the past 12 years of collecting hair from participants in the WIHS cohort, the study has never registered any complaints that the process has been disruptive to hair styles. **In previous studies, where hair collection is incorporated from the beginning of the protocol with field staff and participant education, as will happen in our three partnering trials, high rates of acceptability of hair collection (>95%) have been documented**.[25,27,29,32,40] Therefore, the risks to human subjects from this study in our three partnering trials are minimal.

6. DATA SAFETY AND MONITORING PLAN

This study involves the analysis of small hair samples already to be collected in the SEARCH PrEP trial (Aim 1, NCT01864603), Microbicide Trials Network (MTN)-025 (HOPE) trial (Aim 2, NCT02858037), and the Adult Clinical Trials Group (ACTG) A5359 trial (Aim 3, ClinicalTrials.Gov registration in progress). The SEARCH PrEP and the MTN-025 trials have Data and Safety Monitoring Boards (DSMB) already in place and the DSMB for the A5359 trial is being established.

Data monitoring and quality assurance will be performed on an ongoing basis for the hair collection component of all three studies. The project coordinators and statisticians will monitor study data every month to ensure the accuracy and completeness of consent forms, study questionnaires, and the rates of hair collection. In order to ensure patient safety, data and safety monitoring for each study will include review of all adverse events, enrollment, and protocol deviations. All project staff will be responsible for reporting adverse events, including breach of confidentiality, to the site project managers who will, in turn report the to the protocol chairs and co-chairs.

In terms of quality assurance for the hair collection, we will work with the research coordinators at each site to troubleshoot any barriers to hair collection. Dr. Gandhi will present to the field staff of the multi-site SEARCH study in the first year of this award and to the MTN-025 study coordinators at the MTN Network meeting to help train field staff on the procedures of hair collection. Of note, the SEARCH team has been collecting hair for another study embedded in the communities of SEARCH and the rates of acceptability of hair collection are over 95% (see **Section 3C2**, Research Strategy). Pictures (**Appendix B**) and videos are provided to sites to instruct field staff on the process of hair collection from heads with a variety of hair styles. Finally, to ensure that we receive hair samples of sufficient quantity from research sties, we will enact a process of quality control in each study to reduce pre-analytic variation in sample quality. We will screen hair sample collection in real-time (either from pictures or from samples shipped to the laboratory) to ensure that hair is being collected and labeled properly. For the NIH-funded clinical trial network studies (MTN-025 and ACTG A5359), we will enlist the aid of the Frontier Sciences Laboratory Data Management System (LDMS) to help ensure quality in hair collection for trials within the NIH-funded clinical trials networks. Sites that do not collect hair in adequate quantities for the proposed study will be re-trained in real-time on proper methods of hair collection (and be subject to the usual regulations involving quality control at NIH CTU sites)

INCLUSION OF WOMEN AND MINORITIES

This proposal is based in three studies, the SEARCH PrEP trial, the MTN-025 dapivirine ring open-label extension trial and the ACTG A5359 trial. Each of these trials will enroll both women and minorities

Aim 1 (SEARCH PrEP): Of 6400 participants anticipated to be on PrEP in this large trial, all will be from Africa and approximately half (3200) will be women. Of note, women in the SEARCH trial access HIV care more frequently when HIV-infected and women might be more likely to access PrEP than men in the SEARCH PrEP trial, which may lead to a higher proportion of SEARCH PrEP participants being women.

Aim 2 (MTN-025): The study population of MTN-025 (which aims to evaluate the dapivirine vaginal ring under relatively real-world conditions) is composed entirely of women from four sites in Africa (Malawi, South Africa, Uganda and Zimbabwe).

Aim 3 (A5359): The population of ACTG A5359 is composed of participants with a history of poor adherence to antiretroviral therapy in the past. This population is expected to be diverse in terms of gender and race/ethnicity. We estimate 30% African Americans/ up to 20% Latino/ and ~25% women. The final sample size of this step in the study (participants randomized to long-acting agents) has not been completely determined but is expected to be larger than N=150 (will use latter as estimate for now).

PHS Inclusion Enrollment Report

This report format should NOT be used for collecting data from study participants.

OMB Number:0925-0001 and 0925-0002
Expiration Date: 10/31/2018

***Study Title:** "Hair Extensions": Using Hair Levels to Interpret Adherence, Effectiveness and Pharmacokinetics with Real-World Oral PrEP, the Vaginal Ring, and Injectables (Foreign sites)

***Delayed Onset Study?** ❑ Yes ☑ No

If study is not delayed onset, the following selections are required:

Enrollment Type ☑ Planned ❑ Cumulative (Actual)

Using an Existing Dataset or Resource ❑ Yes ☑ No

Enrollment Location ❑ Domestic ☑ Foreign

Clinical Trial ❑ Yes ☑ No

NIH-Defined Phase III Clinical Trial ❑ Yes ☑ No

Comments: Foreign sites (Clinical trials already registered - we are inserting a new measure): SEARCH PrEP study Aim 1: 6400 participants from East Africa (Uganda and Kenya)on PrEP in SEARCH, estimate half male, half female; MTN-025 study Aim 2: 1800 women using the dapivirine vaginal ring in African sites (Malawi, South Africa, Uganda and Zimbabwe) in MTN-025

Racial Categories	Ethnic Categories									Total
	Not Hispanic or Latino			Hispanic or Latino			Unknown/Not Reported Ethnicity			
	Female	Male	Unknown/ Not Reported	Female	Male	Unknown/ Not Reported	Female	Male	Unknown/ Not Reported	
American Indian/Alaska Native	0	0		0	0					**0**
Asian	0	0		0	0					**0**
Native Hawaiian or Other Pacific Islander	0	0		0	0					**0**
Black or African American	5000	3200		0	0					**8200**
White	0	0		0	0					**0**
More than One Race	0	0		0	0					**0**
Unknown or Not Reported										
Total	**5000**	**3200**		**0**	**0**					**8200**

PHS Inclusion Enrollment Report

This report format should NOT be used for collecting data from study participants.

OMB Number:0925-0001 and 0925-0002
Expiration Date: 10/31/2018

***Study Title:** "Hair Extensions": Using Hair Levels to Interpret Adherence, Effectiveness and Pharmacokinetics with Real-World Oral PrEP, the Vaginal Ring, and Injectables (Domestic sites)

***Delayed Onset Study?** ❑ Yes ☑ No

If study is not delayed onset, the following selections are required:

Enrollment Type ☑ Planned ❑ Cumulative (Actual)

Using an Existing Dataset or Resource ❑ Yes ☑ No

Enrollment Location ☑ Domestic ❑ Foreign

Clinical Trial ❑ Yes ☑ No

NIH-Defined Phase III Clinical Trial ❑ Yes ☑ No

Comments: Domestic site (Clinical trial will be registered and funded elsewhere- this proposal will insert a new measure): More than 150 participants in the long-acting arm of ACTG A5359, estimate 110 male (40 female) and 30 percent African American, 20 percent Hispanic or Latino.

Racial Categories	Ethnic Categories									Total
	Not Hispanic or Latino			Hispanic or Latino			Unknown/Not Reported Ethnicity			
	Female	Male	Unknown/ Not Reported	Female	Male	Unknown/ Not Reported	Female	Male	Unknown/ Not Reported	
American Indian/Alaska Native	0	0		0	0					**0**
Asian	0	0		0	0					**0**
Native Hawaiian or Other Pacific Islander	0	0		0	0					**0**
Black or African American	12	36		0	0					**48**
White	20	52		0	0					**72**
More than One Race	0	0		8	22					**30**
Unknown or Not Reported										
Total	**32**	**88**		**8**	**22**					**150**

INCLUSION OF CHILDREN

This proposal is based in three studies, the SEARCH PrEP trial, the MTN-025 dapivirine ring open-label extension trial and the ACTG A5359 trial.

Aim 1 (SEARCH PrEP): The inclusion criteria for the SEARCH PrEP trial allows for participants ≥15 years of age to enroll. Therefore, this trial may enroll children between the ages of 15 and 17 years who self-identify at being at risk for HIV infection. Potential participants in this particular age group (age 15-17 years) can only start PrEP with parental co-consent. Of note, the Adolescent Trials Network (ATN) 113 study evaluated the safety and tolerability of oral tenofovir disoproxil fumarate (TDF)/ emtricitabine in young men between the ages of 15 and 17 years and found the medication to be safe in this age range.

As per the Preliminary data section in this grant application (**Section 3C2**), the SEARCH PrEP trial has launched in the intervention community Nsiika in western Uganda. Of the 113 participants started on PrEP to date, 30% were aged 18-25, 35% aged 26-35, 19% aged 36-45, 11% aged 46-55, and 4% aged >55. No children between the ages of 15-17 years were enrolled, likely to the requirement of parental co-consent. During the conduct of this study, there is a rigorous system of adverse event reporting (along with a DSMB) and children will be closely followed if enrolled in any of the intervention communities.

Aim 2 (MTN-025): The study population of MTN-025 includes former participants of the placebo-controlled phase 3 MTN-020 trial of the dapivirine vaginal ring (ASPIRE; **Section 3A3**). Former ASPIRE participants who remained HIV-noninfected, are not pregnant, and wish to enroll in MTN-025 will be enrolled. The MTN-020 only enrolled women between 18-45 years of age and none of the women in MTN-025, therefore, will be less than 18 years old.

Aim 3 (A5359): The inclusion criteria of the ACTG A5359 trial state that only individuals who are ≥18 years of age can enroll, so no children will be enrolled in this particular study.

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CONSORTIUM/CONTRACTUAL ARRANGEMENTS

Sub-contracts will be established with the University of Washington (UW) and the University of Colorado, Denver (Anschutz Medical Campus) for this R01 renewal.

The subcontract with UW (co-I: Jared Baeten MD, PhD) will support work on a) ensuring hair collection proceeds as planned in the MTN-025 study (in which Aim 2 of this proposal is embedded), and monitoring acceptability rates; b) helping the MTN data management team put hair level data together with covariate and outcome data from the parent MTN-025 study for the purposes of data analyses; c) contributing to the analyses outlined in the proposal for Aim 2; d) participating in abstract and manuscript generation from this study; and e) communicating with senior levels of leadership in the Microbicide Trials Network (MTN) on data findings.

The subcontract with UCD (co-I: Jose Castillo-Mancilla MD) will support work on a) ensuring hair collection proceeds as planned in the ACTG A5359 study (in which Aim 2 of this proposal is embedded) with monitoring of acceptability rates; b) helping the ACTG data management team put hair level data together with covariate and outcome data from the parent A5359 study for the purposes of data analyses; c) contribute to the pharmacokinetic analyses outlined in the proposal for Aim 3 given his expertise; d) participating in abstract and manuscript generation from this study; and e) communicating with senior levels of leadership in the Adult AIDS Clinical Trials Group (ACTG) on data findings.

RESOURCE SHARING PLAN

Data from this project will be shared through collaborative publications in the scientific literature, with article repository into the NIH database as well as through national, regional and international conference presentations. We will also share our findings in a prompt manner with local and regional stakeholders and policy makers to ensure that these strategies to measure drug adherence/exposure for oral tenofovir disoproxil fumarate (TDF)/emtricitabine in high-incidence settings (Aim 1), dapivirine with use of the dapivirine vaginal ring (Aim 2), and injectable cabotegravir (Aim 3) can be quickly scaled up when appropriate scientifically. We will also provide regular updates on the study through emails and informal presentations to our collaborators and the Community Advisory Board (CAB) members of all three studies. We have also budgeted funds to publish some of our findings in open-source journals to make them immediately accessible to researchers in resource-limited settings who may not have access to library subscriptions or journals requiring payment for online content. During the final year of the proposal, our laboratory-based investigators and staff will work with Africa-based laboratories (from sites associated with the SEARCH trial and MTN-025) to help develop local capacity for hair assay development. Finally, we will provide public access to the blinded data sets of hair concentration data in SEARCH PrEP, MTN-025 and ACTG A5359 once the research teams have completed project analyses, presentations, and publications.

AUTHENTICATION OF KEY BIOLOGICAL AND/OR CHEMICAL RESOURCES

Not applicable for this project