Connecting Resources for Urban Sexual Health (CRUSH)

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CRUSH: Connecting Resources for Urban Sexual Health

A Demonstration Project

For

Expanding Access to

Sexual Health Services for Young Men who have Sex with Men (Y/MSM)

Including provision of

HIV Pre-exposure Prophylaxis

with Truvada®

CRUSH Protocol

Version 1.0

A collaboration of

East Bay AIDS Center,

UCSF- Center for AIDS Prevention Studies,

Gladstone Institutes

Sponsored by

California HIV Research Program

I. Introduction

The East Bay AIDS Center (EBAC) in Oakland, California has been providing comprehensive primary care including case management, inpatient clinical care, and pharmacy services to patients living with HIV for over 25 years. The Downtown Youth Clinic (DYC), a division of EBAC, has developed innovative approaches to the care of young people with HIV, including open access, structured transition from pediatric settings, and extensive peer involvement in care. The clinicians and staff of EBAC/DYC have considerable expertise in the management of antiretroviral medications and the clinical care of populations infected with HIV, including young men who have sex with men (MSM) of color, and have a strong interest in applying those skills to the prevention of HIV infection. With the assistance of researchers from the UCSF Center for AIDS Prevention Studies and the Gladstone Institute of Virology and Immunology, we propose to broaden the scope of EBAC/DYC's services to include comprehensive HIV prevention and sexual health services for HIV-negative participants, including the provision of pre-exposure prophylaxis (PrEP).

The overall project, CRUSH (Connecting Resources for Urban Sexual Health), includes enhanced treatment and linkage to care (TLC+) for HIV seropositives, and comprehensive sexual health services for both HIV-positives and young adults who are HIV-negative but at high risk of HIV acquisition. One component of CRUSH will be to offer PrEP to eligible high risk HIV-negatives. This new and expanded protocol application addresses the expanded research and program evaluation activities which will constitute the CRUSH Project, including the implementation of pre-exposure prophylactics (PrEP) for eligible HIV negative individuals.

PrEP with Truvada® (FTC/TDF) has been demonstrated in clinical trials to reduce rates of new HIV infections,[1–3] and has recently been approved by the FDA for use in MSM and other high-risk populations.[4] The CDC has issued interim guidance on the use of PrEP, emphasizing the importance of parallel interventions to reduce risk for other sexually transmitted infections (STIs), frequent HIV testing, and adherence support to maximize the benefits and minimize the risks of PrEP.[5,6] Additional concerns

regarding implementation include the limited known demand for PrEP, particularly among the population of young MSM of color currently at highest risk in the United States; lack of overall clinical capacity; and potential challenges of fitting the intervention into current clinical models.[7]

II. Study Goal and Aims

The overall goal of the CRUSH project is to enhance and extend a response to the local HIV/AIDS epidemic in Alameda County with a set of innovative, evidence-based interventions across the continuum of HIV prevention and care, targeting individuals and communities most vulnerable to HIV. The East Bay AIDS Center, in partnership with the University of California San Francisco's Center for AIDS Prevention Studies, the Gladstone Institutes, and several key community-based organizations, are engaging in a participatory partnership to enhance and implement HIV services which target the East Bay's highest risk population- young men who have sex with men (Y/MSM). Specifically, the CRUSH Project is designed to evaluate a combination of program approaches to address the sexual health care needs of young gay men of color and their sexual partners by enhancing the current program activities of the Downtown Youth Clinic. By enhancing this existing model program for HIV-infected youth, and adapting/tailoring a number of intervention elements to address the prevention needs of HIV negative youth, we will enhance linkage to and retention in comprehensive care for HIV positive youth, and meanwhile reduce the likelihood of HIV acquisition in those who are negative. Figure 1 presents a schematic of the overall project plan, including three overarching demonstration aims.

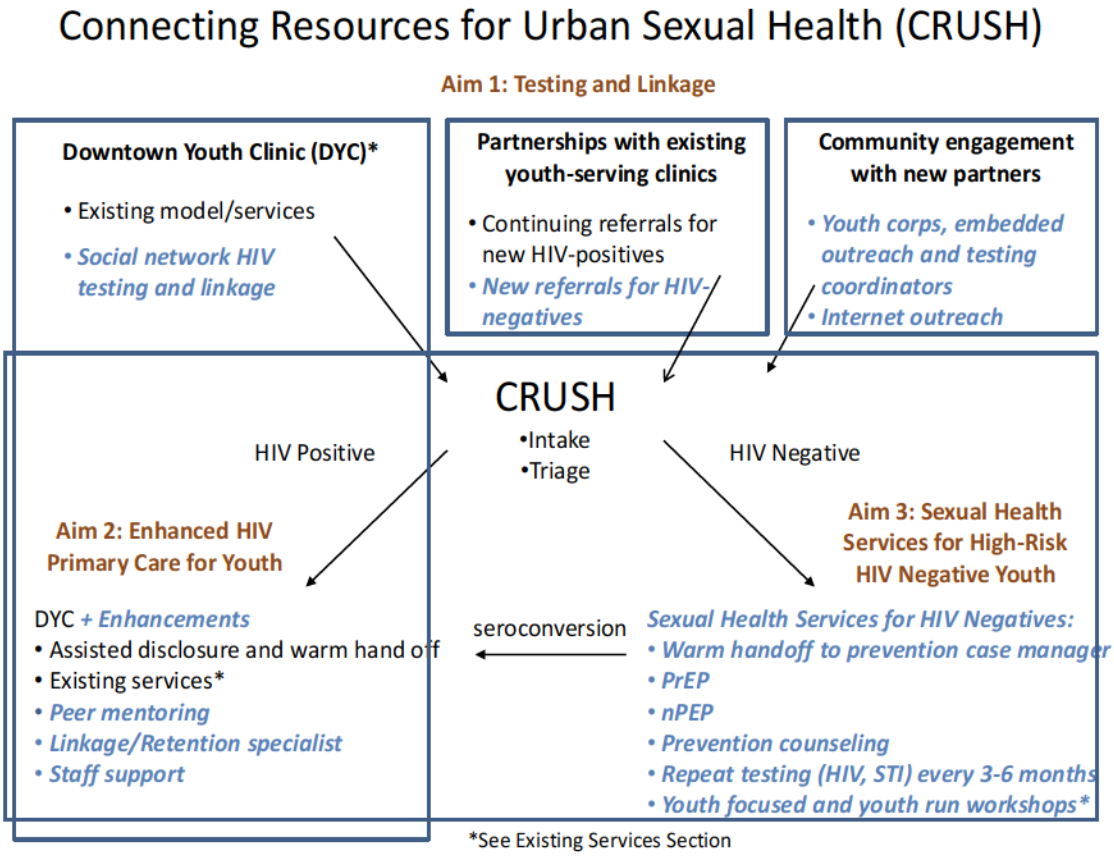
The primary aims of this demonstration project and associated interventions are as follows**:**

Aim 1: Test and link young MSM of color to sexual health services: We will expand our currently successful HIV testing strategy—***collaborations and systems of referral of new cases of HIV from existing partners***—so that referrals are also received for high risk negatives to receive sexual health services. We will also implement two new strategies: an enhancement we have used successfully in prior

projects—***social network testing***; and an innovative strategy derived from evidence from our pilot study—a ***youth outreach corps working with existing and new community partner agencies***.

Aim 2: Enhance and evaluate engagement and retention strategies for young MSM of color infected with HIV: We will plan to optimize the current HIV care and treatment services at DYC by adding three new components: a ***patient peer mentoring component***; ***a linkage and retention specialist;*** and ***psychosocial support for program staff***.

Aim 3: Engage and retain HIV-uninfected young MSM of color in sexual health services, including PrEP: Finally, at the heart of the CRUSH project is our plan to build a highly innovative and much needed model of sexual healthcare that integrates sexual health services for HIV-uninfected young MSM of color into an HIV care setting. These services will replicate the developmentally appropriate, culturally sensitive aspects of the DYC model to offer a highly effective combination HIV prevention strategy, including PrEP, and also: ***warm-hand offs for high risk***



negatives; non-occupational post-exposure prophylaxis (nPEP) when indicated; risk reduction counseling; frequent HIV and STI testing, including testing a highly sensitive method of detecting early HIV infection; and youth-focused programming.

III. Study Population

We propose to target young MSM of color in the East Bay for a comprehensive intervention, which builds on our experience and includes culturally-competent HIV testing, sexual health services including pre-exposure prophylaxis (PrEP), and an integrated linkage and retention program into sexual health services for both high-risk HIV-negative men and HIV-positive men. More specifically **we will focus on African American, Chicano/Latino, and Asian/Pacific Islander MSM** under 30 in the most highly affected cities of western Contra Costa County and northern Alameda County including Oakland, San Pablo, Berkeley, Richmond, and San Leandro.

III.1 Eligibility of HIV Positive Individuals

- HIV positive individuals between the ages of 18-29.

Seropositives outside the target CRUSH age range will be referred for clinical care as appropriate at DYC, EBAC, or elsewhere.

III.2 Eligibility of HIV Negative Individuals

Among those who are HIV negative, we specifically aim to recruit the following most highly impacted communities in the East Bay:

- Men between the ages of 18-29 who are ever sexually active with men;
- Transgender females (M2F) between the ages of 18-29 who are sexually active with men; Transgender males (F2M) between the ages of 18-29 who are sexually active with men; and

- Any HIV negative person aged 18-29, male or female, who has at least one known HIV positive (i.e. serodiscordant) sexual partner;

.

All HIV positives and negatives who meet the eligibility above and present at the clinic will be offered a voluntary opportunity to consent for participation. Participants must meet eligibility criteria and must be willing and able to provide informed consent, utilizing English or Spanish language.

IV Specific Research Activities

We hypothesize that we can reduce the impact of HIV among young MSM by expanding the current DYC services structure in two ways. We intend to expand HIV testing, and linkage to and retention in care for youth who test HIV+, providing them with intensive risk reduction counseling and antiretroviral treatment, and thereby ultimately reducing the risk of further HIV transmission. And we intend for the first time to offer a comprehensive combination package of preventive services to HIV negative youth, including routine accesses to HIV/STI screening and treatment, and access to HIV pre-exposure prophylaxis (PrEP).

In order to demonstrate and evaluate the efficacy of the CRUSH project, we have identified specific program elements and research activities which will be further explained as part of this protocol:

- Audio-computer-assisted self-administered interviewing (ACASI)
- Peer-to-Peer Mentoring
- Social Networking HIV Testing
- Qualitative Interview Methods: key informant and focus groups
- Clinical supervision and evaluation for staff and community partners

All HIV positive and negative participants eligible to participate in CRUSH will be asked to voluntarily consent to participate in the above activities, with the exception of 'Clinical supervision and evaluation for staff and community partners', which is an intervention aimed at CRUSH staff and community partner personnel who work directly with the CRUSH study, and 'Peer to peer mentoring, which will be particularly focused on HIV positive participants.

In addition to the above research elements, this protocol outlines the clinical procedures of:

- Nucleic acid testing (NAT) to detect early infection with HIV, HCV, or HBV
- nPEP, for HIV negative individuals who have had a recent high risk exposure;
- PrEP implementation, for eligible HIV negatives; and for those receiving PrEP:
- Testing dried blood spots for drugs levels (tenofovir and emtricitabine); and
- For participants who become infected with HIV while receiving PrEP, allele-specific PCR-based minor variant drug resistance testing

V. Recruitment

The CRUSH Project will employ 3 main outreach and recruitment strategies to potential study participants:

Community Based Outreach via a **Youth Outreach Corps**: We will be collaborating with community partners to provide venue and street based outreach to recruit study participants. Our formative evaluation provided insight into the need to reach out to youth in non-traditional settings in order to provide access to testing and linkage to care. We will assemble a small group of outreach workers by providing funds for staff in 3 community based agencies: RYSE Youth Center in Richmond, the HIV Education and Prevention Project of Alameda County (HEPPAC), and Asian Health Services (AHS). Each organization will assign a part-time outreach worker, who will be supervised through their respective agency program manager. Program managers and outreach workers work as a team and will

attend monthly outreach meetings for the CRUSH Project, where outreach strategies, venues, and events and locations frequented by the target populations can be mapped and shared, and plans for outreach can be established jointly. Outreach and promotional materials for the CRUSH Project will be developed jointly with partners, and reviewed by a community advisory board. While no specific data will be collected from outreach activities for purposes of research, outreach staff will document weekly contacts made for CRUSH recruitment, and potential participants, upon arrival, will be asked at check-in where they learned about the CRUSH study.

Clinic based outreach: EBAC/DYC is currently a referral center for MSM who test positive at local HIV testing centers. Under the CRUSH project, EBAC/DYC will collaborate with these local programs, and others, to implement a parallel referral system for high risk individuals who test HIV-negative and meet CRUSH eligibility criteria. In addition, current HIV-positive DYC patients will be informed of CRUSH study activities by DYC staff members, and if eligible, may also participate in the study. In addition, identified HIV-negative partners of current EBAC/DYC clients , who are between the ages of 18 and 29 and otherwise meet study eligibility criteria as described in section V, will be called to determine whether they are interested in participating in CRUSH.

On-line and Internet Outreach: We will create an on-line presence for the CRUSH Project, utilizing websites and social media programs which are popular with the target population. All messaging and use of on line sites will be monitored by the CRUSH Project Director, and implemented through the Youth Outreach Corps.

We will develop and place banner adds which have links to eligibility information about the CRUSH study on websites which are frequented by the target population. These include: *Black Gay Chat, Adam4Adam*, and *Men4Now*, *Grinder,* and *Jacked.* We will employ search engine optimization tools to ensure that our website is ranked highly for searches such as "Oakland HIV" or "East Bay STD Testing" as research in our area has shown that many youth use websites like Google and Yahoo to find sexual health information.

We will develop a page on Facebook. The Facebook page will be solely maintained by CRUSH staff, and monitored by the Project Director. No identifying information about patients or participants will be published, and we will maintain strict privacy settings. Only pictures and quotes from CRUSH staff members at DYC, links to the website, links to other trusted sources of health information, information about how to text or call to make an appointment, and CRUSH eligibility criteria will be allowed on the page.

EBAC/DYC will continue to provide clinically appropriate sexual health services to people who either are ineligible for enrollment in the CRUSH project, or choose not to participate. If individuals receiving services at EBAC/DYC who are not enrolled in CRUSH become eligible and interested in participating, they can be enrolled in the study. Likewise, participants in CRUSH can choose to continue to receive sexual health services, but decline or be ineligible for PrEP. Any HIV negative CRUSH participant can opt at any time to be evaluated for the appropriateness of PrEP; and any HIV positive individual currently or newly accessing services at DYC/EBAC may opt in to the CRUSH study.

Figure 1 demonstrates the flow of the CRUSH study participation and clinical services for HIV-negative and HIV-positive participants who do or do not choose to enroll as CRUSH research participants.

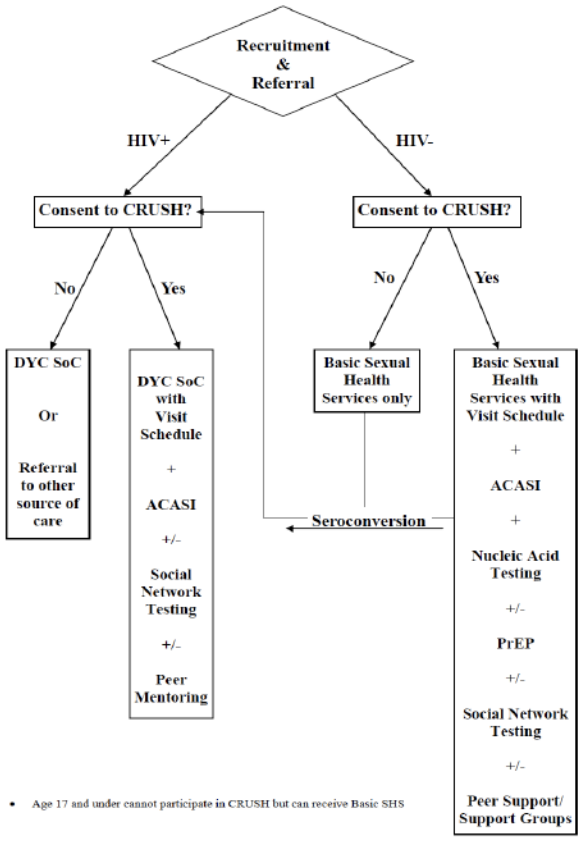


Figure 1: CRUSH Study Design

VI. Study Procedures

VI.1 Consent Procedures

All consent procedures and activities linked to the study will take place at the East Bay AIDS Center. All potential study participants will have the opportunity to meet with study staff one-on-one to learn about the study and ask

questions for clarification. All interviews will be held in a one-on-one fashion in a private setting. Participants will be told that they are being offered the opportunity to voluntarily participate in a confidential study about understanding the best ways to help young people in the East Bay access sexual health care and stay healthier.

Individuals who voluntarily chose to participate in study activities will be asked to sign a consent form. A study coordinator will explain the purpose and objectives of the study, and the various activities it involves. Persons who are HIV-positive will have a separate consent procedure from those who are HIV-negative, to ensure clarity in the procedures that are specific to serostatus. Participants will be told clearly that participation is completely voluntary, and that they can decline to answer any questions that they do not want to answer. Persons at high risk for HIV infection who decline research participation can nonetheless receive sexual health services at CRUSH, with referrals as appropriate for clinical care. The informed consent process will also include a medical records release authorization.

If the individual is eligible and agrees to participate, study staff will explain the terms of the study's consent form. The names and telephone numbers of the interviewer and principal investigator/project director will be given verbally to all participants, and summarized on the consent form, a copy of which will be provided.

Once the consent form is completed and signed, activities described for the initial study visit will commence. A $40 incentive will be given upon completion of the initial study interview and ACASI. Participants will receive $25 for each additional scheduled study follow up visit and interview. There will be no compensation for as-needed or drop-in clinical visits.

All study personnel who will have direct contact with participants (the Project Director, Project Coordinator, Retention Specialist, Medical Assistants, clinicians, and Downtown Youth Clinic youth advocates staff) will be trained in consent procedures. All staff will have obtained CITI human subjects training certificates prior to study start.

VI.2 Audio-computer-assisted self-administered interviewing (ACASI)

Once a participant has been deemed eligible and has completed the consent process, audio computer assisted self-interviewing (ACASI) software will be used to collect information at baseline and at 1, 6 and 12 months after enrollment. ACASI will be administered in a private space on a laptop or tablet computer. Study staff will be available to answer questions or offer assistance should the participants have difficulty with the software. ACASI interviews will be identified by a study number only. ACASI interviews will be backed up at the end of every day to a secure server with backup recording capabilities. The ACASI will have a branch assessments built into its programming structure, leading participants into the set of questions adapted for sero-status (HIV-negative or HIV-positive). A draft questionnaire is included, appendix 5.

V1.3 Peer-to-Peer Mentoring for HIV Positives

A Peer to Peer Mentoring strategy will be offered to newly diagnosed HIV-positive participants of CRUSH, as well as to those current DYC patients at risk of falling out of care (defined as not having seen a provider or picked up medications in the previous 6 months), and to out-of-care patients being re-linked to care. The CRUSH LCSW will lead the monitoring of this strategy, including training and supervision of peers. "Peer readiness" of potential peer mentors will be assessed based on the following criteria:

- Stably in care: on and adherent to treatment, attendance at routine medical appointments (at least 3 in a row);
- Comfortable with their sexual identity, out about their sexual identity;
- Good interpersonal skills and have established relationships with DYC program staff.

The staff will nominate up to 10 potential peer mentors. These patients will be approached with the idea of becoming a mentor and asked to participate. Once a minimum of 3 mentors are secured, training will be scheduled. The mentoring training will be developed by the CRUSH LCSW and based in part on components of diabetes self-management mentor programs, as well as the Big Brother/Big Sister programs. Mentors will be asked to participate for a minimum of 6 months, and may participate for the duration of the project. Responsibilities include a willingness to meet face to face, online or in a group situation with mentees. Mentors will gain practice in providing guidance and listening skills by co-facilitating group workshops or support groups with the clinical supervisor. An ethics of confidentiality will be a key component of each training.

Trained peers will be matched with an HIV-positive client. Both peer and mentees will have completed initial consent to participate in the peer program.

The LCSW will establish weekly groups and one-on-one meetings with peers and mentors. Case notes will document experiences of the peers and the mentees, barriers and facilitators to supporting maintaining the care of youth who are HIV positive, and satisfaction with the mentoring process. All case notes and data collected will be stripped of any identifying information about mentors or mentees, and the LCSW will provide only anonymized summary reports.

We also plan to conduct focus groups and in depth interviews with peers mentors and mentees as part of the qualitative data collection activities (see below, section VI.6)

VI.4 Social Networking HIV Testing

Social Networking used as a testing strategy is a proven method to increase access to HIV testing in hard to reach populations. To connect young MSM to testing opportunities through a familiar and trusted person within their own social networks, the CRUSH study will adapt and tailor a strategy build largely on respondent driven sampling, and on CDC pilot study conducted at multiple sites across the United States.

Enrollment of social network recruiters: CRUSH staff members will initially ask MSM of color, ages 18 to 29, who are currently receiving primary care at DYC, as well as their partners, to become recruiters. All participants will be asked to provide consent at their initial enrollment into the CRUSH study to possible participation in social network recruiting. Potential recruiters will be included on the basis of staff judgments about their likely interest and willingness to recruit members of their own social networks. Potential recruiters will be excluded if they are observed to be under the influence of alcohol or other drugs, or appear unable to fulfill the requirements of the program for any reason. Staff will invite recruiters to contact persons they personally know from their social, sexual, or drug-using networks and encourage them to be tested for HIV. As in the past, recruiters will include both HIV-positive patients and their HIV-negative partners, to ensure that participation does not identify anyone as HIV-positive. Recruiters will also be encouraged to identify themselves as CRUSH volunteers as an additional means to prevent unwanted disclosure.

Selected recruiters will be asked to participate in a brief training session, during which the Outreach Coordinator will explain social network testing, and will be reminded of the importance of maintaining confidentiality.

Recruiters will receive $10 cash (or equivalent value gift certificate) for each contact they refer who comes in for HIV testing, up to ten eligible contacts for a maximum incentive of $100. Each contact who completes an HIV rapid test session will also receive $10 (or equivalent). Contacts will bring in a card with a coded unique identifier, provided to them by their recruiter, so that both recruiter and contact may receive their incentives. The recruiter may accompany the contact for testing if both prefer, but recruiters need not accompany contacts to the HIV testing appointment. Contacts will have the option to drop in for testing during clinic hours or to schedule an appointment ahead of time.

Each recruiter will receive up to 10 cards with a coded unique identifier to give to contacts that they refer for testing. The HIV testing coordinator will coach each recruiter on how to approach potential contacts and refer them for HIV counseling, testing, and referral services. The Outreach Coordinator will

record the name and unique identifier of each recruiter enrolled in the social network testing database. The HIV testing coordinator will follow up with recruiters periodically, in person or by telephone, to review their progress in recruiting contacts and to discuss any issues that concern them. Following the first round of testing, new recruiters will be chosen based upon characteristics associated with referrals of larger numbers of higher risk contacts. In other programs for social network testing, such characteristics have included HIV-positive or HIV-negative persons who (1) had unprotected sexual intercourse or shared drug injection equipment with a person who was HIV positive or of unknown HIV status, (2) had exchanged sexual intercourse for drugs or money, or (3) were diagnosed with another sexually transmitted disease within the last 12 months.

VI.5 Clinical Supervision and Evaluation for Staff and Partners

Through our community partnership with HEPPAC, CRUSH has contracted a licensed clinical social worker (LCSW) to provide support to the members of the CRUSH staff and partner organizations, including the youth corps, the peer navigators, the retention specialist, and the peer mentors. The LCSW will provide psychosocial support and training to staff that interact directly with high risk youth, supporting staff's ability to avoid "burn out," and assessing their training needs. Weekly group meetings will be conducted of ancillary staff, including the youth corps, the peer navigators, the retention specialist and the peer mentors, covering such topics as transference and counter-transference in provider-client relationships. In addition to these weekly meetings, the clinical supervisor will host "office hours" for one on one drop-in visits from any of the CRUSH staff members, including the clinicians. The clinical supervisor will document in case notes the key issues which arise in the groups and one-on-one meetings, which will be used to support CRUSH aims. No names or identifying information will be kept in the notes, and the LCSW will remove all identifying staff information and provide only summaries of notes as part of reports. Staff will be informed during the consent process that no information provided as a part of this process will impact their employment.

To assess this strategy, we will adapt and utilize the Maslach Burnout Inventory (MBI). The MBI is a 22-item survey that assesses professional burnout in human service, education, business, and government professions mainly in the following three areas: (1) *emotional exhaustion* measures feelings of being emotionally overextended and exhausted by one's work; (2) *depersonalization* measures an unfeeling and impersonal response toward recipients of one's service, care treatment, or instruction; and (3) *personal accomplishment* measures feelings of competence and successful achievement in one's work. (Appendix 6)

The LCSW will administer this scale on semi-annually. Staff will be asked to voluntarily consent to complete the survey, which will be administered in private settings during a scheduled one-one one meeting with the LCSW. Staff will be provided a randomized code which cannot be linked to name or employment history, which will be used for each survey. Data will be summarized in bi-variate and frequency analysis.

VI.6 Qualitative Interview Methods: key informant and focus groups

Throughout the duration of the project, qualitative interviewing will take place with both HIV-positive and HIV-negative CRUSH participants, social network testing recruiters, and staff and partners participating in clinical supervision with the LCSW. **Please note:** we will submit modifications to the IRB for any interview guides, consent and recruitment procedures, and any recruitment materials that will be used for the purpose of qualitative interviewing.

Our qualitative evaluation of the CRUSH sexual health services focuses will focus on the following objectives: 1) to assess the whether and how the CRUSH program is meeting the needs of YMSMC; 2) to identify the benefits and challenges associated with the sexual health services; 3) to understand the experiences of the CRUSH clients using PrEP. We will conduct focus group discussions and in-depth interviews with a sample of CRUSH participants. We will document the experiences of

CRUSH participants on PrEP, and of those who choose to forego PrEP. We will assess the experiences of HIV positive CRUSH participants in accessing routine care and sexual health services.

For those participating in peer mentoring, we will conduct in-depth interviews with patients serving as mentors, and patients receiving mentoring services, as well as with a subset of patients receiving outreach from the retention specialist. For those CRUSH Staff and outside partners who are working with the LCSW, we will conduct in-depth interviews with CRUSH staff at two time points, before exposure to the clinical supervisor and after. CRUSH staff will be asked to describe their experiences with the work-related stress and stress management strategies. For youth who participate in social network testing, we will conduct focus groups to discuss experiences as social network recruiters; we will elicit stories about different episodes of recruiting.

A member of the study evaluation team will approach CRUSH participants to invite them to participate in an either an in-depth interview in person or by phone, or a focus groups. CRUSH staff will refer all interested youth to call a study phone line to be screened. The study evaluation team member conducting the qualitative interviewing will screen potential participants and ensure that both comfortable and motivated to collaborate as either focus group participants or in other phases of the research, as key informants. During the screening process, we will clearly explain the goals of the study, and we will describe their role as key informants rather than as passive study participants.

In-depth interviews will be conducted with all participants in person. Each interview will be approximately 45 - 90 minutes in length and audio-recorded. Focus group discussions will be approximately 90 minutes. Audio-recordings of interviews and focus group discussions will be transcribed. Verbatim transcriptions will be managed using Atlas.ti, a software program designed to assist with textual, audio and/or video-based datasets. No identifying information will be included in transcripts- the transcriber will be notified to remove names from all transcribed audio-recordings.

As the qualitative research activities will be in part guided by the experiences taking place as part of ongoing implementation of CRUSH, interview guides and procedures will be developed

specifically to areas of interest for the study. As such, the evaluation team will apply for a modification for additional research activities, and separate consents will be submitted for approval.

VII. Clinical Standard of Care Procedures for CRUSH Participants

Study staff will determine eligibility for enrollment in the overall CRUSH project according to broader inclusion and exclusion criteria described elsewhere. Those who are determined to be ineligible or uninterested in the study may continue to receive sexual health services at EBAC/DYC. We will ask participants who are eligible but choose not to enroll in CRUSH to answer questions about their choice. They may choose to decline answering these questions and continue to receive sexual health services. Individuals electing not to participate in CRUSH, who later ask to enroll, may be re-screened and enroll at a later date.

All CRUSH participants, regardless of HIV status, will be offered the opportunity to receive sexual health services. CRUSH defines the clinical testing and screening sexual health services as the following:

- HIV testing and treatment;
- Syphilis testing and treatment;
- Gonorrhea testing and treatment;
- Chlamydia testing and treatment;
- Hepatitis B screening and immunization;
- PrEP using Truvada® (for eligible HIV negative participants only)

VI1.1. Screening Visit (all participants)

On arrival to the clinic with an expressed interest to learn more about the CRUSH study, an individual will meet with a study coordinator in a private room and be screened for eligibility (as described above). When eligibility is confirmed, the screening visit will begin. Upon reviewing and acceptance of an informed consent for participation with a study coordinator, a participant will sign two

copies, as well as sign a medical records release authorization. Once written informed consent is obtained, the study staff will conduct the HIV rapid test as part of screening visit procedures. Women who screen as eligible (a woman whose has at least one known HIV positive sexual partner or is currently in a serodiscordant partnership), and of reproductive potential will have a rapid urine pregnancy test at the screening visit.

Initial HIV rapid point of care test is conducted via oral fluid specimen evaluated for HIV-1/2 antibodies. If the result is positive, a confirmatory test will be ordered and they the participant will be rescheduled to return to the clinic in 1 week for those results. Counseling will be performed, but all other screening procedures will be deferred to the subsequent visit, when HIV serostatus will be confirmed. If the confirmatory test is positive, participants will be offered enrollment in the TLC+ arm of the CRUSH project. If the confirmatory test is negative, further clinical evaluation including HIV RNA testing will be initiated.

In addition to the HIV rapid test, at screening, the following activities can also occur:

- Medical history and focused review of systems;
- STI Risk Assessment
- Targeted Physical Exam (as needed by a provider)
- Risk reduction counseling, condom distribution
- STI screening and treatment, as needed

All participants who have consented will be asked to complete an ACASI questionnaire and initial screening visit. ACASI is repeated at 0, 4, 24, and 48 weeks. Follow up appointments for study related activities are scheduled with participants and monitored through the Retention Coordinator.

VII.2 HIV Positive Participants: Treatment and Linkage to Care (TLC+)

Participants whose HIV test is positive will be offered enrollment in the enhanced treatment and linkage to care (TLC+) arm of the CRUSH study Those individuals who meet the eligibility criteria, and

who are either known positives clients of the DYC, have been referred by a community partner as HIV positive, have documentation of a positive HIV test result from a licensed laboratory in California, will also be offered enrollment to the TLC+ arm.

Routine initial clinical care of the HIV-positive participant will be according to the community standard of care, and guided by the clinical expertise of DYC and EBAC clinicians. Participants will be assessed for any urgent medical or psychosocial needs; will have an intake clinical interview and baseline physical examination; and will have laboratory specimens sent for T cell subsets, HIV viral load, and HIV genotype (resistance testing), routine blood chemistry and hematology, and screening for viral hepatitis, syphilis, and other STIs.

VII.3 HIV Negative Participants: Screening for acute or early HIV infection

In addition to rapid point-of-care HIV antibody testing, all HIV-negative CRUSH participants will have blood samples sent at every visit (whether a scheduled study visit, or an as-needed sexual health visit) for nucleic acid testing (NAT) to detect acute or early infection with HIV, and hepatitis C and B viruses (HCV and HBV). This testing is offered in collaboration with Susan Little, MD, of the University of California, San Diego Antiviral Research Center (AVRC), who is studying the utility of NAT testing for HIV in similar settings in Southern California. Specimens will be sent to the American Red Cross reference laboratory in St. Louis, MO for NAT testing, and results then processed through the AVRC's secure process. Procedures for obtaining specimens, NAT testing, and handling and releasing results are detailed in Appendix R. Our aims here are: (1) to study whether this NAT testing process can detect early HIV infection, during the "window period" in which HIV antibody testing remains negative, but during which the participant may be highly infectious to others; and (2) to evaluate the impact of being able to deliver both negative and positive test results to participants in a timely and private fashionVII.4

HIV Negative potential participants who opt out of CRUSH Eligible HIV-negatives who decline participation in CRUSH will be referred for clinical care as appropriate to other community sites. They may continue to receive routine sexual health services at the CRUSH site, without completing interviews

or participating in other research procedures. Routine sexual health services shall take place at visits on an as-needed basis, and shall include rapid point-of-care HIV antibody testing, as well as testing for STIs as guided by risk and/or signs and symptoms, and treatment for STIs as clinically appropriate according to accepted guidelines. This will include empiric treatment in some cases, particularly for suspected syphilis, herpes simplex, gonorrhea, and/or chlamydial infections, and in other cases, treatment guided by test results. All sexual health encounters will include risk reduction counseling. Antiretroviral therapy either as PrEP or PEP will not be routinely available in this setting; at-risk HIV-negatives interested in PrEP or PEP but not wishing to participate in CRUSH will be referred to other community providers.

VII.5 HIV Negative CRUSH Participants who opt out of PrEP

Eligible HIV-negatives who accept participation in CRUSH, but who choose not to receive PrEP or are deemed ineligible to do so, will receive the same routine sexual health services described above. In addition to accessing as-needed services, they will be asked to schedule regular visits for study evaluations and interviews at 1, 6, and 12 months following enrollment. At each clinical visit, whether as-needed or scheduled, CRUSH participants will undergo NAT testing for detection of early HIV infection. They will also be offered participation in peer support groups, and may be asked to serve as "seeds" for social network recruitment. CRUSH clinicians will provide routine sexual health care as well as other basic and urgent medical care. Participants with other complex medical problems will be assisted by CRUSH staff in securing appropriate referrals for ongoing clinical care.

HIV-negative participants with <u>any</u> of the following **will not be offered PrEP**:

- History of pathological bone fractures not related to trauma;
- Renal disease or known abnormal serum creatinine;
- Urine dipstick with persistent proteinuria ≥2+;

- Concomitant participation in a clinical trial using investigational agents, including placebo-controlled clinical trials using such agents; or
- Any other condition that would preclude provision of informed consent; make participation in the project unsafe; complicate interpretation of outcome data; or otherwise interfere with achieving the project objectives, based on the opinion of the investigators and/or treating clinician.
- Women who are currently breastfeeding.

VII.6 HIV Negative CRUSH Participants who opt in to PrEP

Participants who have a negative HIV1/2 antibody point of care result will receive sexual health promotion counseling at the time they are provided their results. Participants will be asked if they would like to receive PrEP as part of their participation in the study. CRUSH participants who choose not to receive PrEP at screening for CRUSH may choose to initiate PrEP at a later visit, if still eligible.

Samples will be collected for sexually transmitted infections (STI), serum HIV antibody, HBsAg and HBsAb testing. All participants who are subsequently found to be both HBsAg and HBsAb negative will be offered the hepatitis B vaccination series. Participants found to be HBsAg positive may still receive Truvada® PrEP, but will in addition be monitored according to a specific protocol. [See Appendix Q] Those found to be hepatitis B antigen positive, but who choose not to enroll in PrEP, will be referred to either their primary care provider or another community-based clinic for treatment of hepatitis B infection.

All HIV-negative participants, regardless of hepatitis B status, who are interested in receiving PrEP will receive further counseling on PrEP and, in addition to the blood work mentioned above, will have an HIV NAT sent. They will also meet with a clinician for medical history, a targeted physical exam and an assessment of PrEP eligibility according to criteria in Section IV. Assessment of eligibility will also

include an evaluation for symptoms of acute retroviral syndrome, including sore throat, fevers, sweats, headaches, myalgias or arthralgias, which are not consistent with seasonal or chronic patterns. If symptoms of acute retroviral syndrome are present in the setting of a recent high risk exposure, PrEP will be deferred until the results of the HIV NAT are back. If there has been a high risk exposure in the past 72 hours to potentially infectious body fluids from a partner who is HIV infected and who has a detectable or unknown viral load (i.e., who do not have a most recent undetectable HIV RNA below the limit of quantitation within the previous 90 days), or who is at high risk for being HIV-infected, post-exposure prophylaxis (PEP) will be offered using a recommended 3 drug regimen for 28 days. Preferred PEP regimens will be selected according to recently published guidelines of the USPHS for occupational PEP, and of the New York State Task Force.

PEP should be started as soon as possible, and before the results of RNA testing are known, and in all cases within 72 hours of the last possible exposure to HIV. If the HIV RNA test result is negative, viral symptoms resolve, and repeat rapid antibody testing is non-reactive, PEP should be discontinued and the participant may at that point be offered PrEP. If the HIV RNA test result is positive, the participant will be immediately referred to the TLC+ arm of CRUSH. Some participants with no high risk exposures in the 72 hour PEP window, but at ongoing high risk and with symptoms and/or signs highly suggestive of acute HIV infection, may elect to start presumptive highly antiretroviral therapy (HAART); these participants will be referred immediately to an expert HIV clinician.

Creatinine testing will also be performed on the screening blood sample for participants intending to receive PrEP, and a urine dipstick will be performed to assess for proteinuria. Dipstick proteinuria of 2+ or greater will exclude the participant from receiving PrEP; these participants will be referred for clinical evaluation. If the urine dipstick is 1+, PrEP will be deferred and the participant will be asked to return in one week for a repeat dipstick. If a participant's enrollment creatinine is normal and repeat dipstick remains <2+, s/he may begin PrEP.

If a PrEP candidate has an identifiable HIV-positive partner, we will attempt to obtain genotypic information about the partner's virus, in order to avoid offering Truvada® PrEP in a situation of likely exposure to a virus already resistant to both component drugs of Truvada®. We will ask the PrEP candidate to try to obtain a de-identified genotype of the seropositive partner. We will assist in providing a release of confidential medical information form for this purpose. In the event that the seropositive partner is a patient at DYC, we will ask the seropositive partner to sign a 'Release of Information' allowing the PrEP participant and the CRUSH team access to his genotype. If a CRUSH medical provider has confirmed documentation that the seropositive partner's virus is resistant to both drugs in Truvada®, or has reason to believe that this is likely the case, then the PrEP patient will be excluded from receiving Truvada® PrEP as part of CRUSH, and will be referred for expert medical consultation regarding other options. If we are unable to obtain a genotype or resistant records for the seropositive partner, and have no reason to believe that two-drug resistance is likely, we will offer Truvada® PrEP as usual.

VII.7 PrEP Initiation

The PrEP initiation visit will take place 1-2 weeks after screening, when all screening results are available. If the participant is eligible to receive PrEP, the clinician will review all lab results done at the screening visit, repeat a rapid oral HIV antibody test, and obtain a medical history along with a focused review of systems. All participants who are determined to be HBsAg negative and who do not have antibodies to hepatitis B will be offered the hepatitis B vaccination series. If high risk exposure, as described in section VI 1.1, or signs and/or symptoms suggestive of acute retroviral syndrome have occurred since the screening visit, PrEP will be withheld and the participant will be managed in accordance with the guidelines specified in the screening visit. Further STI testing will also be done if indicated. Women of reproductive potential will have a rapid urine pregnancy test. If no contraindications to receiving PrEP have been established, the risks and benefits of FTC/TDF (Truvada®) for PrEP will be reviewed, and all questions and concerns will be addressed. The participant will be instructed to take FTC/TDF daily, at the same time every day. The study coordinator or other DYC staff

member will provide risk reduction counseling, provide the participant with condoms, and schedule a follow up visit for 4 weeks. When all study activities for the day are complete and documented on a dispensing checklist, the pharmacy will dispense one bottle (30 pills) of Truvada® to the participant.

Participants found to be hepatitis B antigen positive, who choose not to take PrEP, will be referred to either their primary care provider or another community based clinic for treatment of hepatitis B infection. Participants who are HBsAg-positive and who initiate PrEP will be informed that stopping PrEP could cause a hepatitis flare and/or hepatitis B drug resistance. The clinical stage of their liver disease will be assessed at PrEP initiation (see Appendix Q), including testing for AST/ALT, total bilirubin, alkaline phosphatase, prothrombin time, and albumin, and a clinical evaluation for stigmata of cirrhosis. Participants who are HBsAg positive and who receive PrEP will have their hepatitis B DNA viral load and their AST/ALT monitored for the duration of their PrEP use and for 6 months following discontinuation of PrEP.

VII.8 One Month Visit

At the 1-month visit, participants will have a rapid HIV antibody test, sexual health promotion counseling, and PrEP-specific counseling. Participants will meet with the study clinician for a medical history and targeted physical exam. For participants who are still interested in receiving PrEP, a blood sample will be drawn for creatinine and for dried blood spot (DBS) testing of drug levels. Additionally for those participants who are HBsAg positive, blood will be drawn for ALT/AST and hepatitis B DNA. Participants who remain eligible to receive PrEP will be provided two bottles (60 pills) at this visit. Women of reproductive potential will have a rapid urine pregnancy test.

VII.9 Subsequent visits

Subsequent visits will occur according to the schedule shown in the table of Study Procedures. Following the 1 month follow up visit, participants will be asked to return to the clinic in 2 more months (at 3 months of participation), and then every 3 months thereafter for study visits (i.e., at months 3, 6, 9

and 12). These visits will be scheduled within +/-2 weeks of the target date based on PrEP initiation. Participants who elect to continue PrEP beyond 48 weeks will continue to be assessed every 3 months for the duration of the project period, or until they cease PrEP.

At quarterly visits, participants will receive rapid HIV testing and counseling, and will meet with a clinician for a medical history. If they report a possible STI exposure or have symptoms of an STI, they will be tested and treated as appropriate. Participants will also receive PrEP-specific counseling, be asked to provide a blood sample for creatinine and for dried blood spot (DBS) drug level testing, and be dispensed 3 bottles (90 pills) of PrEP. Women of reproductive potential will have a rapid urine pregnancy test at all scheduled visits. At semiannual visits, in addition to the quarterly procedures, participants will have STI and serum HIV antibody testing done, a targeted physical exam will be performed, and they will be asked to complete an ACASI questionnaire. Participants who are HBsAg positive will have ALT/AST and HBV DNA viral load testing done.

VIII. Assessments and Interventions

Assessments and interventions taking place at each visit are described below.

VIII.1 Risk assessment and clinician counseling

Risk assessments will be conducted using "Five P's," a simple approach to risk assessments for clinicians recommended by the California STD Prevention Branch (CA STD Branch, 2011).[8] The five P's stand for Partners, sexual Practices, Past STIs, Pregnancy history and plans (if relevant), and Protection from STIs. Sexual risk information will be entered into the clinical notes. The clinician will document performance of a risk assessment on the Dispensing Checklist, and perform brief counseling regarding risk reduction.

VIII.2 Pregnancy and breastfeeding assessment and counseling

Female participants of reproductive potential (anatomically female, premenopausal, with an intact uterus) will be screened at each visit for pregnancy, plans to become pregnant, and current breastfeeding.

All women who are pregnant at enrollment or become pregnant during their participation will be immediately linked to prenatal care. The clinician will:

a. Determine if women are planning to become pregnant, are currently pregnant, or are breastfeeding;

b. Disclose to women that safety for infants exposed to Truvada® during pregnancy has not been fully assessed but that no harm has been reported;

c. Do not offer (or, if already begun, cease) PrEP to women who are breastfeeding;

d. Conduct a pregnancy test and document results; if pregnant, discuss continued use of PrEP with patient and prenatal care provider;

e. Before dispensing PrEP, ensure that a urine pregnancy test is negative or, if pregnant, that the patient has been informed about Truvada® use during pregnancy; and

f. Upon discontinuation of PrEP in a pregnant participant, inform prenatal care provider of TDF/FTC use in early pregnancy and coordinate care to maintain HIV prevention during pregnancy and breastfeeding.

VIII.3 Adherence assessment and counseling

Adherence counseling (motivational counseling) will be performed at every visit while participants are receiving PrEP, as part of an Integrated Next-Step Counseling approach[9]. This client-centered approach will not be assessment-based. The counseling conversation will focus on facilitators and barriers to pill-taking, and strategies for make pill-taking more manageable for the participant. In the second portion of the visit with the study coordinator or other DYC staff member, a pill count will be conducted. Pill counts will be compared to the expected number of pills remaining, and the study coordinator will inform the participant of the degree of discrepancy. If drug levels are available from the prior visit's dried blood spot (DBS) testing, results will be shared with the participant and discussed. Adherence counseling following the model above will be repeated.

Adherence will be further assessed on the semiannual ACASI questionnaire. Additionally, at the time of each DBS collection, participants receiving PrEP will be asked about the timing of their most recent three Truvada® doses, in order to aid in interpretation of DBS results. An assessment tool used in conjunction with integrated next step counseling is included in appendix 10.

VIII.4 Medical history and focused review of systems

Symptoms of STIs including acute HIV infection will be assessed and recorded in the clinical notes according to usual clinic practice. The medical history will also ask about potential side effects of Truvada®. The clinician will verify that there are no symptoms of acute HIV on the Dispensing Checklist.

VIII.5 Targeted physical exam

The clinician will perform a targeted exam as required based upon the medical history and focused review of systems and record the results in the clinical notes.

VIII.6 Risk Reduction/Sexual health promotion counseling

Sexual health promotion counseling will be performed at every scheduled visit for all participants. The counseling approach will follow the Integrated Next-Step Counseling model. The counseling conversation will review which sexual health promotion strategies the participant uses, their facilitators and barriers to their use, and an agreement on which strategies the participant would like to continue or try to use.

VIII.7 Laboratory evaluation

The clinician will order appropriate laboratory studies at the conclusion of the visit, and check off which labs were ordered on the Dispensing Checklist. Prior to dispensing, the study coordinator or DYC staff member will verify that all required lab specimens were submitted to the on-site clinical lab.

VIII.8 Drug level assay: Dried Blood Spot Testing

Blood will be drawn, processed, stored, and shipped for dried blood spot (DBS) testing of intracellular levels of tenofovir and emtricitabine, at timepoints as shown in the schedule of visits. Drug

level data may become available before the participant's next scheduled study visit. If these data demonstrate likely inadequate adherence, the participant will be contacted and brought in for an additional visit, which will focus on adherence support using the Integrated Next-Step Counseling model.

VIII.9 STI evaluation and treatment

Sexually transmitted infections will be evaluated and treated in accordance with usual clinic procedures, which are consistent with CDC guidelines and include screening for asymptomatic infections among high risk groups (inclusive of all study participants), evidence-based treatment, expedited partner therapy, and prompt public health reporting.

VIII.10 Pharmaceutical dispensing

At PrEP initiation a staff member will provide the pharmacy the prescription for PrEP initiation and hand the bottle to the participant at the visit. At subsequent, scheduled visits the clinician may fill a prescription prior to the visit and dispense it to the participant directly after eligibility has been confirmed.

VIII.11 Participant retention

One week before each scheduled visit, the study coordinator will contact each participant to remind him/her of the date and time of the next appointment and reschedule if necessary. If a participant cannot be contacted and misses an appointment, the study coordinator will use additional contact information recorded in the medical record or at study intake to attempt to get in touch with him/her. To maximize retention, the study coordinator will also contact each participant at least once mid-way between quarterly visits to assess for any general problems that may interfere with participation, including adherence challenges, health insurance challenges, transportation barriers, social issues, etc.

After unsuccessful attempts to contact a participant for either a visit reminder or a mid-way check-in, the study coordinator will attempt to follow-up a minimum of three times. Attempts to contact the participant will cease upon participant request at any time.

VIII.12 Participant Withdrawal and Study Completion

Participants may voluntarily withdraw from the study for any reason at any time. One of the investigators also may withdraw participants from the study in order to protect their safety, staff safety, and/or if participants are unwilling or unable to comply with required study procedures. Participants also may be withdrawn if the study sponsor terminates the study prior to its planned end date. The study coordinator will administer the Study Exit Questionnaire in person if possible, and by phone if necessary, to all patients who withdraw from the study. If administration of the Study Exit Questionnaire is refused or not possible, the study coordinator will record a brief description of the circumstances of each withdrawal.

IX. Adverse Events and Toxicity Management

Symptoms and laboratory parameters associated with potential toxicities of FTC/TDF will be monitored as described above. As is true for all patients of EBAC/DYC, study participants will have received instructions for contacting the clinic to report any adverse signs or symptoms that they experience. Grade 3 or 4 adverse events, as defined by the DAIDS Table for Grading the Severity of Adult and Pediatric AEs, Version 1.0, December, 2004 (Clarification August 2009) will be recorded on the Adverse Event form. All Adverse Events will be evaluated by an EBAC/DYC clinician. Symptomatic Grade 3 events and Grade 4 adverse events will be reported to CHRP and Gilead Sciences by the investigators regardless of relation to the study drug.

IX. 1.1 Creatinine elevation

For an estimated glomerular filtration rate (eGFR) less than 60 ml/min/1.73m^2, serum creatinine will be repeated as soon as possible within 7 days. If the eGFR remains less than 60, FTC/TDF will be held until the eGFR is again greater than 60, at which point the participant may be re-challenged with FTC/TDF after consultation with the Principal Investigator (Dr. Burack). If the eGFR again falls below 60 after the drug is restarted, FTC/TDF will be permanently discontinued, and the participant will be monitored until the eGFR returns to baseline or stabilizes.

IX. 2 Urine protein detection

Any participant with protein of 1+ or greater on urine dipstick analysis will have the urine dipstick repeated within a week. If the creatinine is normal and the repeat dipstick is < 2+ the participant may remain on PrEP. Participants who have dipstick of ≥ 2+ will have PrEP discontinued and will be referred to a nephrologist. If the nephrologist does not recommend against restarting PrEP, the participant can restart. Participants with evidence of renal toxicity attributable to FTC/TDF will have the study drug stopped

IX. 3 HIV acquisition /suspected acute HIV infection

Any initially HIV-negative participant with a positive HIV test of any type during the course of the study will be instructed to come in immediately for an HIV+ (Seroconversion) visit. Patients seroconverting while on PrEP will be offered the choice to either (1) intensify to an approved 3 or 4 drug antiretroviral regimen for presumptive HIV treatment, as prescribed by an expert HIV clinician, or (2) stop taking PrEP. At the HIV+ (seroconversion) visit, the participant will have blood drawn for confirmatory HIV Western blot and quantitative HIV RNA PCR with reflex to HIV-1 genotype, as well as DBS testing for drug levels. Additional blood specimens will be sent to the UCSF laboratory of Teri Liegler, MD, for an allele-specific PCR-based assay for detection of minor variant drug resistance at FTC/TDF-selection codons. (See Appendix S.) Women of reproductive potential will have a rapid urine pregnancy test. A medical history, physical exam, risk assessment, risk reduction counseling, adherence assessment, and STI evaluation will be performed. The participant will be asked to return within one week to receive the results of the confirmatory HIV testing. For those confirmed to be HIV infected, EBAC/DYC will provide counseling and immediate linkage to HIV primary care according to usual clinic practice. HIV infected participants who had elected intensification to highly active antiretroviral therapy (HAART) will be encouraged to continue their treatment regimen until HIV primary care is established. Those confirmed to be HIV uninfected will not resume the study protocol, and, if they have elected intensification to HAART, will discontinue treatment. Some patients who prove to be HIV uninfected

may choose to restart PrEP outside this protocol, with monitoring as appropriate for the clinical circumstances under the guidance of an expert HIV clinician.

Any participant with signs and symptoms at any study visit suggestive of acute retroviral syndrome, in the setting of recent high risk behavior, but without serologic evidence of HIV infection to date, will have qualitative HIV RNA testing sent and will be offered immediate intensification to an approved 3 or 4 drug highly active antiretroviral therapy (HAART) regimen as prescribed by an expert HIV clinician. This regimen will be continued, with clinically appropriate monitoring, until results of RNA testing are obtained. If HIV RNA testing is negative, the patient will discontinue the intensification agent(s), and will be offered continued Truvada® prophylaxis, as scheduled on the PrEP protocol. If HIV RNA testing is positive, the patient will be instructed to continue HAART, and will be brought in for an HIV+ (Seroconversion) visit as above. EBAC/DYC will provide counseling and immediate linkage to HIV primary care according to usual clinic practice.

IX.4 Pregnancy

Women who become pregnant during the study may continue PrEP, particularly since risk of HIV acquisition may be higher during this period. The clinician will disclose to pregnant women and those planning pregnancy that safety for infants exposed to Truvada® during pregnancy is not fully assessed, but that no harm has been reported. Pregnant participants will be offered the options of continuing or stopping PrEP, and in all cases will be referred immediately for prenatal care. Upon discontinuation of PrEP during pregnancy, the clinician will inform prenatal care providers of TDF/FTC use in early pregnancy and will coordinate care to maintain HIV prevention during pregnancy. Participant information will be submitted to the FDA's Antiretroviral Pregnancy Registry. Women who give birth will be counseled not to breastfeed, in accordance with US guidelines. PrEP will be discontinued for any woman who intends to breastfeed.

IX..5 Social harms

Participation in the study could lead to social harms that may include loss of privacy, stigmatization, interference with employment, and coercion. Participants who report social harms will be referred to a clinician. PrEP may or may not be continued depending upon the preference of the patient and the judgment of the clinician. Social harms leading to discontinuation of study drug will be recorded on an Adverse Event form and reported to CHRP and Gilead Sciences.

X. Data collection and storage

The study coordinator will maintain a password-protected electronic list of study participants on a server accessible only to clinic staff at EBAC/DYC. Data recorded on that list will include first and last name, medical record number (for participants known to EBAC/DYC), and enrollment status (potentially interested, ineligible, not interested, currently enrolled, withdrawn, or completed). Demographic data, visit dates, clinic notes, and all laboratory data will be maintained according to usual clinic practices in EPIC, the electronic medical record at EBAC/DYC. Missed visit data will also be maintained in EPIC according to usual clinic practices.

All forms will be filed in a separate section in the paper chart reserved for CRUSH case record forms. At the time of withdrawal or study completion, data from study forms will be entered into a password-protected database. Demographic data, visit dates, and laboratory data and missed visit data from EPIC will be linked to the database by medical record number to form the data set for analysis.

Any data transferred outside of the EBAC system will be sent by secure FTP protocol or uploaded directly onto an encrypted drive.

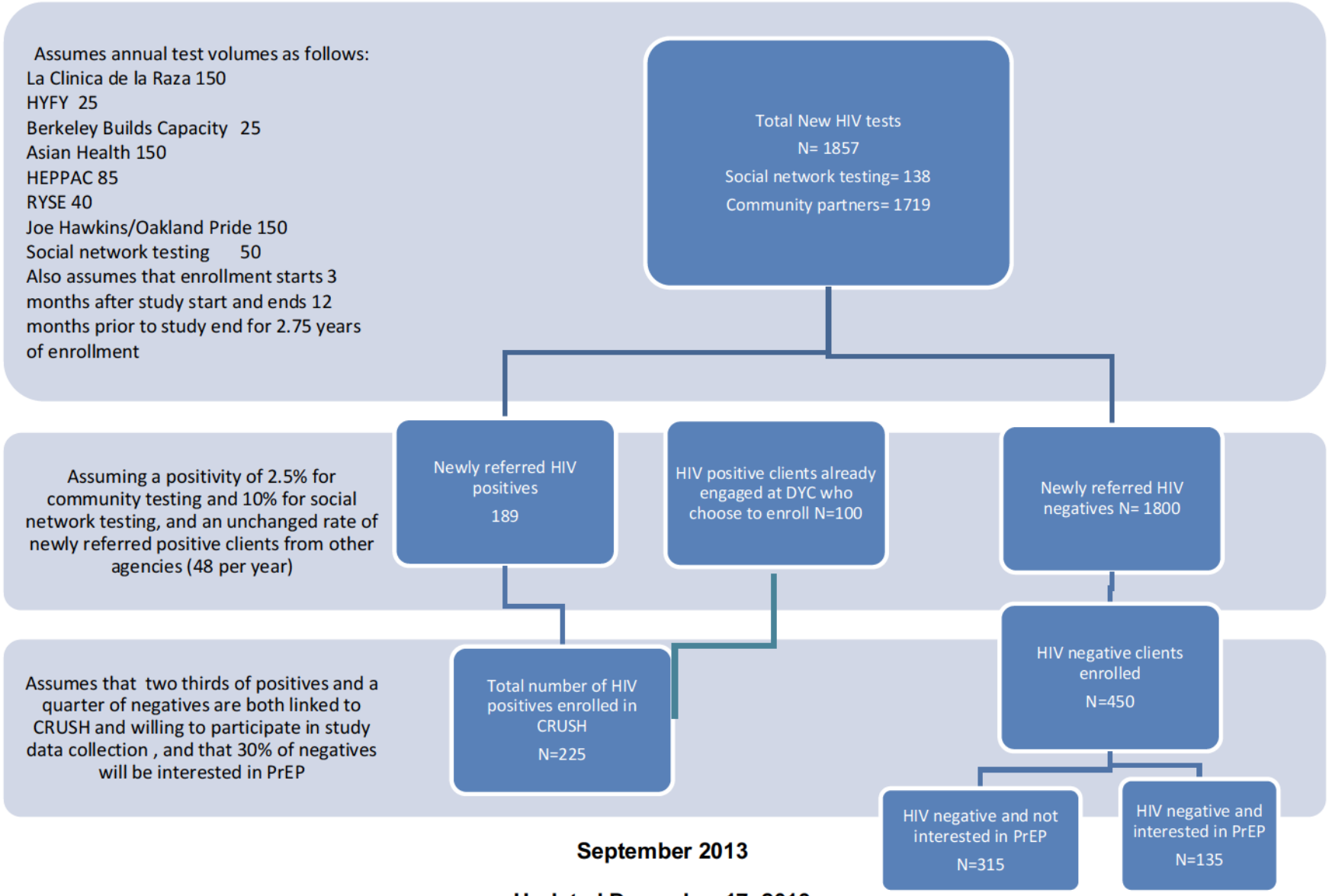
XI. References

1. Grant, R. M. *et al.* Preexposure chemoprophylaxis for HIV prevention in men who have sex with men. *N. Engl. J. Med.* **363**, 2587–2599 (2010).

2. Baeten, J. M. *et al.* Antiretroviral Prophylaxis for HIV Prevention in Heterosexual Men and Women. *New England Journal of Medicine* **367**, 399–410 (2012).
3. Thigpen, M. Daily oral anti-retroviral use for the prevention of HIV infection in heterosexually active young adults in Botswana: results from the TDF2 study. (2011).
4. Press Announcements > FDA approves first drug for reducing the risk of sexually acquired HIV infection. at <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm312210.htm>
5. Interim Guidance for Clinicians Considering the Use of Preexposure Prophylaxis for the Prevention of HIV Infection in Heterosexually Active Adults. at <http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6131a2.htm?s_cid=mm6131a2_w>
6. Interim Guidance: Preexposure Prophylaxis for the Prevention of HIV Infection in Men Who Have Sex with Men. at <http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6003a1.htm>
7. Arnold, E. *et al. Understanding the feasibility and acceptability of implementing Pre-Exposure Prophylaxis (PrEP) to prevent HIV among African American men who have sex with men and transgender people in Northern California: Final Progress Report.* (UCSF Center for AIDS Prevention Studies: San Francisco, CA, 2011).
8. California Department of Public Health Sexually Transmitted Diseases (STD) Control Branch in collaboration with the California STD/HIV Prevention Training Center A Clinician's Guide to Sexual History Taking. (2011).
9. Amico, KR, McMahan V, Goicochea P, Vargas L, Marcus JL, Grant RM, et al. Supporting study product use and accuracy in self-report in the iPrEx study: next step counseling and neutral assessment. AIDS and behavior. 2012 Jul;16(5):1243-59.
10. Giordano, T. P. *et al.* Measuring adherence to antiretroviral therapy in a diverse population using a visual analogue scale. *HIV clinical trials* **5**, (2004).
11. APHA: Adherence to HIV Treatment Regimens. at <http://www.apha.org/programs/resources/HIV+-+AIDS/reshivregimens.htm>

Appendix 1
CRUSH Study Enrollment Projection

Study Enrollment for the CRUSH Project



September 2013

Updated December 17, 2013

Appendix 2:

a. California Patient Bill of Rights

b. HIPPA Patient Information Release Form

September 2013

Updated December 17, 2013

Appendix 3:

Consent Forms

a. HIV Negatives
b. HIV Positives
c. Staff and Community Partner

Appendix 4:
Study Visit Schedule

Study Visit Schedule (

Week	Screening*	0	4	12, 24, 36, 48		Stop drug	HIV Ab+
Clinical Assessments/Interventions							
Screen inclusion/exclusion criteria	x						
Obtain informed consent	x						
Medical history and focused review of systems	x	x	x	x		x	x
STI Risk Assessment	x	x	x	x		x	x
Adherence Assessment			x	x		x	x
Targeted Physical Exam	x	x	x	x		x	x
Adherence counseling		X	x	x		x	x
Risk reduction counseling, condom distribution	x	X	x	x		x	x
Drug dispensing		X	x	x			
ACASI (weeks 0, 4, 24, 48 only)		X	X	x			
Laboratory Assessments							
Creatinine	x		x	x			
Urine dipstick protein	x	X	x	x			
Rapid urine pregnancy test (if relevant)	x	X	x	x		x	x
HBsAg (and HBsAb if not documented)	x						
ALT/AST (if HBsAg+)		X	x	x		x	X
HBV DNA + LFTs(if HBsAg+)		X	x	x		x	x
Serum HIV Ab EIA	x					x	
Rapid Oral HIV Ab	x	X	x	x		x	
HIV Ab Western Blot							x
HIV RNA Qualitative PCR	x						
HIV RNA Qualitative PCR (risk-guided)			x	x		x	
HIV RNA Quantitative PCR							x
HIV-1 genotype							x
STI laboratory evaluation	x			x		x	x
DBS Drug Level Testing			x	x		x	x
*-4 to -1 weeks							

Appendix 5:

DRAFT ACASI Behavioral Questionnaire

Appendix 6:

Maslach Burnout Inventory (MBI)

Appendix 7: Non-serious Adverse Events & Side Effects Inventory

Non-serious Adverse Events & Side Effects Inventory

Non-serious Adverse Events & Side Effects Inventory										**Subject ID :**_____
Side Effect Diagnosis (if known) or Signs/ Symptoms	**Date** of Onset	**Outcome** Date of Resolution or ↓ Check if continuing		Severity[1]	Relationship to Study Drug	Relationship to Study Procedure	Action taken with Study Drug[2]	Other action taken[3]	Was Event Serious?	PI Initials /Date
	dd/mmm/yyyy	✓	dd/mmm/ yyyy		Y/N	Y/N			Y/N	
		☐								
		☐								
		☐								
		☐								
		☐								
		☐								
		☐								

[1]Severity

1=Mild
2=Moderate
3=Severe
4=Life-Threatening

[2]Action taken with Study Drug

1=Not changed
2=Interrupted
3=Withdrawn

[3]Other Action Taken

1 = None
2 = Medication Required*
3 = Hospitalization/Prolonged Hospitalization
4 = Other Treatment Required

*Any medication taken for an AE should be recorded on the Concomitant Medication Log

Appendix 8:

Serious Adverse Event Report Form

SERIOUS ADVERSE EVENT REPORT FORM

For the purposes of this form, a serious adverse event is any untoward medical occurrence that results in death, is life-threatening, requires or prolongs hospitalization, causes persistent or significant disability/incapacity, results in congenital anomalies/birth defects, or in the opinion of the investigators represents other significant hazards or potentially serious harm to research subjects or others. A serious adverse event is considered unexpected if it is not described in the Package Insert or in the Investigator's Brochure (for FDA investigational agents), in the protocol, or in the informed consent document.

INSTRUCTIONS:
Please complete the information requested below and forward a copy to the IRB and the sponsor as soon as possible, but not later than seven (7) days in the case of death or life-threatening serious adverse events or within fifteen (15) days after the occurrence of all other forms of serious adverse events. In addition, continue to follow FDA and the NIH Office of Biotechnology Activities (OBA) reporting requirements if your research involves an IND/IDE or gene transfer.

PROTOCOL #: ____ - ____- _____	*PROTOCOL TITLE: Connecting Resources for Urban Sexual Health:*
PRINCIPAL INVESTIGATOR: *Jeffrey H. Burack, M.D.*	East Bay AIDS Center Office Phone: Fax: E-mail:
DATE OF SERIOUS ADVERSE EVENT:	____/____/_____
SUBJECT ID:	
WAS THIS AN UNEXPECTED ADVERSE EVENT?	Yes [ ] No [ ]
BRIEF DESCRIPTION OF SUBJECT(S) *(Do NOT include identifiers.)*	*SEX:* M/F *AGE*: _____ *Event*:
BRIEF DESCRIPTION OF THE NATURE OF THE SERIOUS ADVERSE EVENT:	

CATEGORY (outcome) OF THE SERIOUS ADVERSE EVENT:	***RELATIONSHIP OF SERIOUS ADVERSE EVENT TO RESEARCH:***
[ ] death [ ] disability/incapacity [ ] life-threatening [ ] congenital anomaly/birth defect [ ] hospitalization-initial or prolonged [ ] required intervention to prevent permanent impairment [ ] other	[ ] 1 = unrelated (clearly not related to the research) [ ] 2 = unlikely (doubtfully related to the research) [ ] 3 = possible (may be related to the research) [ ] 4 = probable (likely related to the research) [ ] 5 = definite (clearly related to the research)
What steps do you plan to take as a result of the adverse event reported above?	[ ] no action required [ ] continue study drug [ ] discontinue study drug [ ] other, describe:

REPORTER'S SIGNATURE:	***DATE:***
INVESTIGATOR'S SIGNATURE:	***DATE:***

Appendix 9:
PrEP Informational Fact Sheets for Participant

Appendix 10: Integrated Next Step Counseling Assessment Tool

Appendix 11: Monitoring of hepatitis B surface antigen (HBsAg) positive participants on Truvada® PrEP:

- Check both HBsAg and HBsAb on screening visit.
- If HBsAg negative and HBsAb negative, immunize with HBV series (3 injections over 6 months). Recheck HBsAb at week 48 if immunized.
- If HBsAg positive, check at baseline: AST/ALT, total bilirubin, alkaline phosphatase, prothrombin time, albumin, hepatitis B DNA quantitative PCR, and hepatitis BeAg. Perform a clinical evaluation for stigmata of cirrhosis.
- For all HBsAg positive participants, Hepatitis A total antibody and if immunize (2 vaccines 6 months apart) if seronegative.
- For all HBsAg positive participants regardless of HBeAg status, counsel participant regarding risk of HBV flare on PrEP; monitor HBV DNA quantitative PCR and ALT/AST at 3, 6 and 12 months or PrEP, and then 6 months after stopping PrEP.
- If HBeAg positive at baseline, recheck HBeAg at 3, 6 and 12 months of PrEP, or until HBeAg turns negative.
- Flares in ALT/AST, or evidence of virologic breakthrough by HBV DNA, will be managed per standard clinical protocols according to AASLD guidelines.

Appendix 12: Procedures for nucleic acid (NAT) testing for infection with HIV, HCV, and HBV

- CRUSH staff will collect blood at all visits from HIV-negative participants not receiving PrEP for HIV/HCV/HBV NAT testing.
- Each blood sample will be labeled using a unique, de-identified, five-digit number barcoded sticker provided by the Red Cross. Participants will also be given this 5-digit number so that they may retrieve their HIV test results (if negative) via the web or interactive voice response system two weeks after their test date.
- Samples will be sent in batches directly to the American Red Cross reference laboratory in St. Louis, MO for NAT testing three times a week, and CRUSH staff will notify the University of California, San Diego Antirviral Research Center (AVRC) staff via a secure web form that a NAT test was performed (only 5-digit code and test date entered).
- After the Red Cross completes NAT testing (usually within 5 days), the Red Cross will send the encrypted results electronically to the UCSD Center for AIDS Research (CFAR) Bioinformatics and Information Technologies (BIT) Core via secure FTP.
- Upon receiving the results from the Red Cross, the UCSD BIT Core will automatically decrypt the results and import them into a secure database located on servers hosted at the UCSD San Diego Supercomputing Center (SDSC) and Antiviral Research Center (AVRC).
- The decrypted results will be matched up to the 5-digit code provided by CRUSH staff to the AVRC via the above-mentioned web form. This matching allows the BIT Core to monitor the flow of data closely should any reporting fail between Oakland, the Red Cross and the AVRC.
- In cases of negative HIV NAT results, participants can obtain their results two weeks after testing via web or interactive voice response using their 5-digit code, at theearlytest.ucsd.edu
- For HIV positive results, AVRC staff and CRUSH staff will be automatically notified via email (including only 5-digit code, test date, and positive result) by BIT Core scripts. This allows

sufficient time for clinical staff to directly contact positive individuals before the two-week negative results access window opens.

- HCV and HBV negative results are not made available to participants through the web or interactive voice response, but positive results will be reported via email to AVRC and CRUSH staff so that they may directly contact participants.

UCSD Center for AIDS Research (CFAR) Bioinformatics and Information Technologies (BIT) Core security and privacy features:

The BIT Core has at its disposal 700+ processor Linux Beowulf MPI cluster, seven rack-mounted web servers, and two fault-tolerant encrypted 16TB RAID6 data storage arrays. All primary production machines are located behind a hardware firewall at the SDSC on the UCSD main campus in a server facility with biometric-based restricted access, temperature and humidity monitoring, seismic protection, 24/7 generator power backup, and continuous CCTV camera surveillance. For data and service redundancy in case of hardware or power failure at SDSC, secondary backup machines are located behind a hardware firewall at the UCSD Antiviral Research Center AVRC on the UCSD medical campus in a server room with key card-based restricted access, temperature and humidity monitoring, and 24/7 CCTV camera surveillance.

Appendix 13: Allele-specific PCR-based minor variant drug resistance assay

The development of drug-resistant virus in individuals who become infected while taking PrEP is a concern that warrants close monitoring. While the detection of FTC-TDF selected drug resistance in clinical trial participants who fail PrEP is rarely seen using conventional genotyping and ultrasensitive assays, continued study and monitoring is needed as FTC-TDF PrEP use is expanded to non-research settings. Ongoing and planned demonstration projects present an ideal opportunity to monitor the incidence and nature of drug resistance selected by PrEP.

HIV-1 drug resistance testing for the CRUSH PrEP demonstration project will be performed at UCSF's AIDS Research Institute Laboratory of Clinical Virology (ARI-UCSF LCV) using specimens collected from HIV infected participants at first evidence of infection. HIV-1 genotypic resistance testing will be performed by bulk sequencing of the protease and reverse transcriptase region using the FDA-cleared TRUGENE genotyping kit under clinical protocols. Individual drug resistance mutations and drug susceptibility interpretations are reported. For increased sensitivity, a validated allele-specific PCR-based minor variant drug resistance assay will be performed for detection of minor variant drug resistance at FTC/TDF-selection codons K65R, K70E, and M184V/I that may be present at a low level, and not detected by the sequence-based assay. The % drug resistance codon above the biologic cutoff (BCO) at each drug resistance site is reported.

A single specimen is used for both assays. Specimens of at least 1.0 mL blood plasma will be obtained from participants, spun, and frozen, then sent to Dr. Liegler's lab, with no identifying information except for a unique identifier code number. A minimum HIV-1 viral load of 500 copies/mL by standard commercial assays is required. Results will be reported back to CRUSH staff by code number.