PROTOCOL

A cohort for evaluation of open-label PrEP delivery and PrEP preferences among African women

The INSIGHT cohort: ***Insights to advance PrEP discovery and delivery for African women***

Version 2.0

13 October 2022

Funding:

Bill and Melinda Gates Foundation

STUDY TEAM

Coordinating Center

Connie Celum, MD, MPH, co-Principal Investigator
Renee Heffron, PhD, co-Principal Investigator
Deborah Donnell, PhD, co-investigator
Jennifer Velloza, PhD, co-investigator
Adrienne Shapiro, MD, PhD, co-investigator
Meighan Krows, BA, Cohort Project Manager
Susan Morrison, MD, MPH, Safety Physician
Rachel Johnson, MPH, ICRC Managing Director
Sue Peacock, MS, Data Manager & Analyst

Steering committee

Connie Celum, MD, MPH, co-Principal Investigator
Renee Heffron, PhD, co-Principal Investigator
Brenda Gati Mirembe, MBChB, co-Principal Investigator
Victor Omollo, MBChB, MPH, co-investigator
Nelly Mugo, MBChB, MPH, co-investigator
Linda-Gail Bekker, MBChB, PhD, co-investigator
Sinead Delany-Moretlwe, MBChB, DrPH, PhD, co-investigator
Nyaradzo Mgodi, MBChB, MMed, BSC, co-investigator
Rebeca Plank, MD, MPH, co-investigator
Jennifer Velloza, PhD, co-investigator
Meighan Krows, BA, Cohort Project Manager

Collaborators and implementing partners

<u>eSwatini</u>
Harriet Nuwagaba-Biribonwoha, MBChB, ICAP, Eswatini Prevention Center, Mbabane

<u>Kenya</u>
Elizabeth Bukusi, MBChB, M.Med, MPH, PhD, PGD, MBE, Kenya Medical Research Institute, KEMRI Center for Microbiology Research RCTP, Kisumu

<u>Malawi</u>
Rachel Chihana Kawalazira, MBBS, MSc, Queen Elizabeth Central Hospital, Kamuzu University of Health Sciences- Johns Hopkins Research Project, Blantyre

<u>South Africa</u>
Zinhle Zwane, MBChB, Setshaba Research Centre, Soshanguve
Philip Kotze, MBChB, Masters in Internal Medicine, Qhakaza Mbokodo Research Clinic, Ladysmith
Katherine Gill, MBChB, MPH, Desmond Tutu HIV Foundation, Masiphumulele Site, Cape Town
Cheryl Louw, MBChB, Madibeng Centre for Research, Brits
Noluthando Mwelase, MBChB, University of the Witwatersrand, Helen Joseph Hospital-Clinical HIV Research Unit, Johannesburg
Pippa Macdonald, MBChB, MRCP, Desmond Tutu Health Foundation, Emavundleni Research

Centre, Cape Town
Melissa Senne, MBChB, Aurum Rustenburg Clinical Research Centre, Rustenburg
Ravindre Panchia, PharmD, Chris Hani Baragwanath Academic Hospital, University of the Witwatersrand, Perinatal HIV Research Unit-HIV Prevention CRS, Soweto
Alastair van Heerden, PhD, Human Sciences Research Council, Center for Community Based Research (CCBR), Pietermaritzburg
Shannon Bosman, MBChB, University of Cape Town, Human Sciences Research Council, Center for Community Based Research (CCBR), Pietermaritzburg
Manjeetha Jaggernath, MBChB, University of the Witwatersrand, Match Research Unit (MRU), Durban
Remco Peters, MD, PhD, Foundation for Professional Development, Ndevana Community Research Site, East London
Sinead Delany-Moretlwe, MBBCh, PhD, Wits Reproductive Health & HIV Research Unit (Wits RHI) Ward 21Clinical Research Site, Johannesburg
Amy Ward, MBBCh, University of Cape Town (UCT) - Khayelitsha CRS, Cape Town
Phillip du Preez, MBChB, DipPEC, University of Cape Town (UCT) – Khayelitsha CRS, Cape Town
Pearl Selepe, MBChB, Aurum Klerksdorp Clinical Research Centre, Klerksdorp
Logashvari Naidoo, MBChB, SA Medical Research Council - Chatsworth Clinical Research Site, Chatsworth, Durban

Uganda
Brenda Gati Mirembe, MBChB, MSc, Makerere University/Johns Hopkins University (MU-JHU) Care Ltd, Kampala
Clemensia Nakabiito,MBChB,MMed, Makerere University/Johns Hopkins University (MU-JHU) Care Ltd, Kampala

Zambia
Margaret Kasaro, MBChB, MScPH, Department of Obstetrics and Gynecology, University of North Carolina School of Medicine, Chapel Hill, United States, University of North Carolina – Global Projects Zambia, Kamwala Health Centre, Lusaka
Nelly Mwamba Mandona, MBChB, Department of Obstetrics and Gynecology, University of North Carolina Global Projects, Kamwala Health Centre, Lusaka
Ben Chi, MD, MSc, Department of Obstetrics and Gynecology, University of North Carolina School of Medicine, Chapel Hill, United States

Zimbabwe
Nyaradzo Mgodi, MBChB, MMed, BSC, University of Zimbabwe Clinical Trials Research Centre, Harare

I. SUMMARY

The World Health Organization recommends daily oral PrEP containing tenofovir for the prevention of HIV infection in persons at substantial HIV risk. Open label PrEP studies have demonstrated very high uptake, adherence, and effectiveness of oral PrEP in heterosexual African HIV serodiscordant couples and men who have sex with men in the Americas and Europe, and high uptake with modest persistence among young African women.

Young African women are an important population for PrEP implementation, with one of the highest annual HIV incidence rates globally, even in recent HIV prevention trials which provided the best available standard of prevention services (condoms, STI services, and counseling). Women age <25 years represent three of the four million young people living with HIV in Africa. Given the high HIV incidence and evidence for high effectiveness of PrEP when adherence to product use is high, PrEP delivery, uptake and adherence need to be optimized for young African women. The impact of PrEP will be greatest if the subset of young women who are at highest risk of HIV infection are motivated to use PrEP and are able to establish daily pill-taking habits and sustain high adherence while they remain at risk.

This protocol describes an observational cohort study of PrEP delivery to young women in eSwatini, Kenya, Malawi, South Africa, Uganda, Zambia, and Zimbabwe. Daily oral PrEP is a component of standard of care (SOC) for HIV prevention in these countries. However, PrEP persistence has been a challenge in open-label studies and programmatic delivery, and understanding strategies to support PrEP persistence and user values and preferences related to long-acting PrEP are needed. Thus, we propose to conduct an open-label cohort study to evaluate oral PrEP uptake, persistence, and user rankings of product forgiveness and product and delivery attributes for long-acting PrEP. The prospective cohort study of open label FTC/TDF will enroll sexually active HIV negative women ages 16-30 in African sites which have been enrolling women in the phase 3 IMPOWER 22 randomized double blind efficacy trial of monthly oral islatravir compared to an active comparator, daily oral FTC/TDF.

Design: Prospective, observational, open-label cohort study to evaluate daily oral PrEP uptake, adherence, persistence and preferences for attributes of PrEP formulations among young women in eSwatini, Kenya, Malawi, South Africa, Uganda, Zambia, and Zimbabwe. Follow up will be for 6 months.

Population: 3000 HIV uninfected women ages 16-30 enrolled in prospective cohort

Study Sites:

- ICAP, Eswatini Prevention Center, Mbabane, eSwatini
- Kenya Medical Research Institute-Center for Microbiology Research, Kisumu, Kenya
- Kamuzu University of Health Sciences- Johns Hopkins Research Project, Blantyre, Malawi
- Setshaba Research Centre, Soshanguve, South Africa
- Qhakaza Mbokodo Research Clinic, Ladysmith, South Africa
- Masiphumulele, Desmond Tutu HIV Foundation, Cape Town, South Africa
- Madibeng Centre for Research, Brits, South Africa
- Helen Joseph Hospital-Clinical HIV Research Unit, Johannesburg, South Africa
- Emavundleni Research Centre, Desmond Tutu HIV Foundation, Cape Town, South Africa
- Aurum Rustenburg Clinical Research Centre, Rustenburg, South Africa
- Perinatal HIV Research Unit-HIV Prevention CRS, Soweto, South Africa
- Human Sciences Research Council, Center for Community Based Research (CCBR), Pietermaritzburg, South Africa

- Match Research Unit (MRU), Durban, South Africa
- Ndevana Community Research Site, East London, South Africa
- Wits Reproductive Health & HIV Research Unit-Wits RHI Ward 21, Johannesburg, South Africa
- University of Cape Town (UCT)- Khayelitsha CRS, Cape Town, South Africa
- Aurum Klerksdorp Clinical Research Centre, Klerksdorp, South Africa
- South Africa Medical Research Council - Chatsworth Clinical Research Site, Durban, South Africa
- Makerere University/Johns Hopkins University (MU-JHU) Care Ltd, Kampala, Uganda
- Kamwala Health Centre, Lusaka, Zambia
- University of Zimbabwe Clinical Trials Research Centre (UZ-CTRC), Harare, Zimbabwe

Approach: This project will offer a PrEP delivery package within a prospective cohort study of sexually active HIV negative women ages 16-30 in locations in eSwatini, Kenya, Malawi, South Africa, Uganda, Zambia, and Zimbabwe to understand PrEP uptake, use, persistence and preferences for attributes of PrEP products and PrEP delivery with a focus on long-acting PrEP.

PROSPECTIVE COHORT STUDY OF OPEN LABEL PrEP UPTAKE AND USE IN YOUNG WOMEN

The World Health Organization released guidelines in 2015 which recommend PrEP as part of standard of care for HIV prevention among all persons at substantial HIV risk and in 2016 released implementation guidance. Among young women, a priority population at substantial risk for HIV, we will screen for HIV infection and deliver daily, oral PrEP to those who are HIV-negative and accept, following WHO and national PrEP implementation guidance. Women will be enrolled in the cohort based on an interest in HIV prevention and regardless of their decision to initiate or not initiate PrEP at enrollment or during follow-up. HIV-uninfected women who choose to initiate PrEP will be offered daily oral FTC/TDF with counseling about their risk and the importance of adherence to receive a prevention benefit from PrEP. Brief PrEP adherence counseling will be delivered, and address barriers and facilitators to PrEP initiation, use, and continuation. Uptake, adherence, and persistence will be assessed. We will conduct discrete choice experiments to understand users' preferences about attributes of PrEP formulations, dosing frequency, packaging, and aspects of PrEP delivery.

Objective 1: Estimate HIV incidence using the recency testing on samples from women who screen out due to HIV infection, as well as assess HIV incidence prospectively in the cohort.

To provide information for ongoing and future HIV prevention trials, a recency testing algorithm (RITA) including an HIV antibody avidity test and HIV viral load will be implemented to obtain an estimate of background HIV incidence across sites. Screening processes for this open-label PrEP cohort will recruit women interested in PrEP and not pre-screen out women who are known to be living with HIV in order to use the recency assay to identify women who are recently infected (i.e., within the past 2 years). For women who screen out for PrEP eligibility due to HIV infection, a cross-sectional measure of background HIV incidence can be obtained using a recency testing algorithm (RITA) combined with clinical data (HIV viral load, history of prior HIV diagnosis, ART use). There is limited experience with this approach implemented during screening for trial enrollment in terms of identifying women with recent infection in order to provide a cross-sectional estimate of HIV incidence, which can be used as a counterfactual measure of HIV incidence in HIV prevention efficacy trials with active comparators and no placebo.

Objective 2: Assess the characteristics of women who initiate PrEP compared to those who do not initiate PrEP.

A critical aspect of implementation and cost-effectiveness of PrEP for young African women will be the motivation of young women who are at highest risk of HIV acquisition to utilize evidence-based HIV prevention strategies. We will collect data on STI prevalence, contraception use, sexual behavior, risk perception as correlates for PrEP uptake, persistence and adherence. Adherence will be measured by the timing of PrEP refills, self-reported PrEP use, and drug level testing for tenofovir (TFV) levels . PrEP adherence will be assessed during periods of risk, based on behavioral data and self-perceived risk. Participants in this cohort will be informed of other HIV prevention efficacy trials.

Objective 3: Evaluate young women's preferences for attributes of long-acting formulations of PrEP, using a discrete choice experiment.

A discrete choice experiment will be used to assess women's preferences around PrEP delivery form (pill and injection), dosing frequency, and relative dose forgiveness for different PrEP formulations. We will also assess preferences related to PrEP delivery, such as places of access, frequency of visits, lab monitoring, product packaging, storage, and willingness to pay. Attributes and attribute levels will be finalized based on expert consultations and informal conversations with young women and community advisory boards across the study sites. We will estimate preference weights for each attribute level, explore differences in our findings by geography, age, and PrEP experience, and conduct a trade-offs analysis between pairs of attributes.

Objective 4: Assess the acceptability of a patient-facing PrEP decision support tool to provide young women more informed choice about PrEP options.

Long-acting PrEP options are becoming available, including the monthly dapivirine ring and injectable cabotegravir which have been shown to be safe and effective and possibly monthly oral islatravir and/or every six monthly injectable lenacapavir which are currently in efficacy trials. Young women will need to make informed choices about daily oral PrEP or long-acting PrEP. A patient-facing decision support tool about PrEP options will be evaluated with respect to its utility in assisting young women to consider their HIV prevention needs and PrEP preferences. We will assess whether women who have high vs low adherence to oral PrEP are more likely to indicate a preference for long-acting formulations, as well as other predictors of interest in long-acting PrEP.

Objective 5: Assess HLA genotypes to determine the breadth of variants present in young women from East and southern Africa

A major goal for prevention of viral infections, such as HIV and HPV, is to develop T cell vaccines that will elicit a strong immune response in diverse populations. There is one cluster of genes called the human leukocyte antigen (HLA) complex that is a well-known hotspot for disease associations. These cell-surface proteins regulate the immune system in humans and these proteins are present on the surface of cells, and they help the immune system distinguish foreign "invaders" such as viruses and bacteria from the body's own cells. Variants in the HLA genes are associated with infectious diseases like HIV. The set of HLA protein variations in an individual help define what that individual's immune system regards as self, and also helps define what groups of foreign viral proteins (are more or less likely to elicit a strong host immune

response. HLA variants or type influences a person's immune response to T cell vaccines. Additional data are needed about the breadth of HLA types among Africans, where limited information about HLA types is available and T cell vaccines for HIV, HPV, HSV, and other viral infections are critically needed. The burden of HIV, HPV, and HSV is very large among young African women who would be a priority population for T cell vaccines against viral infections. Aggregate results will be used to inform development of vaccines against HIV and other infections.

II. BACKGROUND & RATIONALE

PrEP efficacy and safety in placebo-controlled trials

Four randomized, placebo-controlled trials with daily oral tenofovir disoproxil fumarate (TDF) or TDF co-formulated with emtricitabine (FTC) (FTC/TDF) demonstrated the efficacy of PrEP for HIV prevention. Efficacy was strongly related to adherence, which ranged from 52% to 82% based on blood tenofovoir testing in a subset of participants;[1-4] the presence of tenofovir in blood was associated with an 85-99% protection against HIV acquisition.[5] PrEP was efficacious for HIV prevention for women and men, exposed to HIV through both vaginal and anal sex, and from a wide variety of geographies.

Two trials did not demonstrate PrEP protection in preventing HIV in young African women given low adherence to study product use during the trials; a number of hypotheses have been proposed, including young women's low or inaccurate HIV risk perception; ambivalence about using antiretroviral drugs for HIV prevention; concerns about side effects; stigma; reactions of others; partner support; disclosure of study participation, and special concerns related to participating in a placebo-controlled trial (e.g., concerns about randomization to placebo or a product of uncertain efficacy, and motivation to access health care and other services rather than testing candidate products).[6-9]

PrEP was demonstrated to be well-tolerated in all clinical trials, with <10% having mild gastrointestinal symptoms (e.g., nausea, diarrhea or flatulence) in the first few weeks of PrEP initiation that resolved, and rarely led to discontinuation of drug. PrEP was also demonstrated to be highly safe: <1% had a significant decline of renal function and a slight decline seen on average (still within the normal range) was reversible upon discontinuation.[10] No significant liver or hematologic toxicity was observed in any PrEP trials. PrEP did not reduce the effectiveness of hormonal contraception.[11] For women who became pregnant and used PrEP during early pregnancy, there were no significant increases in adverse pregnancy outcomes, including low birth weight or congenital malformations.[12] Lastly, antiretroviral resistance was rarely observed (<2%) in seroconverters on PrEP and was primarily observed in a small number of persons with unrecognized acute HIV infection at PrEP initiation.

In September 2015, the World Health Organization issued guidelines recommending PrEP be offered to all persons at substantial HIV risk worldwide. As of late 2021, >80 countries have launched PrEP programs enabling more than 1.5 million PrEP initiations in the third quarter of 2021 alone.[13]

PrEP uptake, adherence and effectiveness in open label demonstration projects

Randomized clinical trials (RCTs) of PrEP differ substantially from real-world settings, as participants may be motivated to take part in HIV prevention trials for a variety of reasons, including access to quality health services and monetary reimbursement for study visits. Trial participants are also reminded on a monthly basis that they may be in a placebo arm and not receiving active product, and that the active product has not been determined to be effective—all factors that may influence adherence behavior. Thus, PrEP uptake and adherence among participants in RCTs who

are randomized to placebo or active product and are counseled about unknown product efficacy may not predict PrEP uptake and adherence among at-risk participants who are offered open-label product and counseled about known efficacy of the product and the importance of adherence to achieve protection.

Open-label studies of oral PrEP have demonstrated effectiveness against incident HIV to a degree that is greater than seen in the placebo-controlled efficacy trials, an unexpected and very encouraging development. An open-label study of daily oral PrEP that assigned MSM to immediate versus deferred PrEP access in the United Kingdom indicated 86% effectiveness among the immediate PrEP arm.[14] High effectiveness was also seen in a placebo-controlled study among MSM in France and Canada using intermittent, event-driven dosing of oral FTC/TDF when compared to the placebo arm.[15] These studies indicate high adherence to oral PrEP among MSM who have self-identified as being at high risk of acquiring HIV, in the context of known efficacy and when delivered in clinical settings provided by non-research staff with quarterly visits and brief adherence counseling.

The Partners Demonstration Project was an open-label, demonstration project among high-risk African heterosexual HIV serodiscordant couples; 20% of whom were <25 years old, that evaluated daily oral PrEP in HIV uninfected individuals as a bridge to ART initiation among their HIV-infected partners.[16] Notably, PrEP uptake was high (95% at enrollment), PrEP adherence was high (86% with detectable tenofovir), ART initiation was high (80% by 12 months with 90% viral suppression), and HIV incidence was reduced by an estimated 96% based on modeling of expected HIV incidence among HIV serodiscorant couples with similar risks of HIV acquisition.[17]

A high priority has been to evaluate PrEP uptake and adherence among young African women now that efficacy has been demonstrated in other populations. PrEP adherence was high among African women in the context of open label use in the Cape Town site in the HPTN 067/ADAPT study of varying PrEP dosing strategies, where half of the participants were ≤25 years. Adherence was highest in the daily dosing arm: 92.5% of women at week 10 and 79.3% at week 30 who had reported sex in the prior week had detectable tenofovir in plasma.[18] Similarly, in the open label study following the Botswana TDF2 study of FTC/TDF among young women, 87% of women had detectable drug in plasma.[19]

More recent PrEP demonstration projects of open label FTC/TDF among young African women have indicated that PrEP uptake is high (>90%) but that young women have challenges with PrEP adherence and persistence. In the HPTN 082 study, 22% of young women in Zimbabwe and South Africa had high adherence to oral PrEP at month 6 based on intracellular tenofovir diphosphate levels (TFV-DP) ≥700 fmol/punch.[20] In the 3P study in Cape Town, approximately half of women had TFV-DP levels ≥700 fmol/punch at month 6.[21] TFV-DP levels ≥700 fmol/punch were associated with 100% efficacy among men who have sex with men in the iPrEX open label extension.[22] In the POWER study of 2550 young women in Kisumu, Kenya and Johannesburg and Cape Town, South Africa, 94% initiated PrEP, the drop-off was steep at one month (31% had a refill at one month), and one-third persisted with PrEP use through six months.[23]

These demonstration projects indicate that persons at-risk are motivated to use PrEP when counseled about efficacy in an open-label context and a subset are able to use daily oral PrEP with high adherence, achieving higher effectiveness than was observed in placebo-controlled trials. The POWER and other demonstration projects of oral FTC/TDF have also demonstrated challenges with PrEP adherence and persistence among young African women. However, longer-acting PrEP formulations may offer greater flexibility and higher coverage than daily oral PrEP.

Long-acting PrEP with known efficacy: Dapivirine ring and injectable cabotegravir

Given the barriers younger women have experienced with daily pill-taking for HIV prevention, longer-acting PrEP formulations such as the monthly dapvirine vaginal ring (DVR) might be easier for young women to use. Dapivirine is a non-nuclesoide reverse transcriptase inhibitor with broad activity against multiple HIV subtypes, which is released in the vagina with very low rates of systemic absorption. In two placebo-controlled efficacy trials of the DVR, the efficacy was 27-31%.[24, 25] In the ASPIRE trial, post-hoc analyses indicated higher efficacy (56%; 95% CI 31-71%) among women over the age of 21 years, and no efficacy (-27%; 95% CI -133- 31) in women age 18-21 years, which was also correlated with reduced adherence among younger women.[24] In the RING efficacy trial of the dapivirine ring, there was no difference in efficacy among women less than or equal to 21 years of age compared to women greater than 21 years.[24] In the HOPE open-label extension study of the ring, uptake was high, 89% of rings had residual dapivirine levels indicating some use, and HIV-1 incidence was 50-62% lower than the counterfactual HIV incidence from the placebo arm of the ASPIRE trial, suggesting higher effectiveness than in the placebo-controlled trial.[26] Similarly high uptake, adherence, and a 62% reduction in simulated HIV incidence was observed in the DREAM open-label extension study.[24] Encouragingly, MTN 034 (the REACH study), a cross-over study of six months of oral FTC-TDF PrEP and six months of monthly dapivirine ring followed by a choice period, showed that the majority of 16-21 year old women enrolled in South Africa, Uganda, and Zimbabwe had high adherence to both oral PrEP and the dapivirine ring.[27] The WHO recommends the ring as a new choice for HIV prevention among women at substantial risk of HIV infection.[28]

HPTN 083 and HPTN 084 were phase 2b/3 randomized, double-blind clinical trials of injectable long-acting cabotegravir, an integrase inhibitor. HPTN 083 was an international multicenter efficacy trial which enrolled transgender women (TGW) and cisgender men who have sex with men (MSM) and HPTN 084 enrolled African cisgender women. In the primary results of HPTN 083 among TGW and MSM, 12 incident and four baseline infections occurred in the cabotegravir arm of the study (0.37 infections per 100 person-years) compared to 39 incident and three baseline infections in the FTC/TDF arm (1.22 infections per 100 person-years), demonstrating that CAB-LA was superior to daily oral TDF-FTC in preventing HIV infection among MSM and transgender women.[29] In the participants in whom HIV infection was diagnosed after exposure to CAB-LA, INSTI resistance and delays in the detection of HIV infection were noted. No safety concerns were identified. Among African cisgender women enrolled in HPTN 084, 38 women in the trial acquired HIV – 4 randomised to the long-acting cabotegravir arm and 34 to the daily, oral FTC/TDF arm. This translated to an HIV incidence rate of 0.21% (95% CI 0.06% – 0.54%) in the cabotegravir group and 1.79% (95% CI 1.24%-2.51%) in the FTC/TDF group. While both methods were highly effective at preventing HIV acquisition, long-acting cabotegravir was 89% (95% CI 68-96%) more effective than FTC/TDF.[30] The HPTN 083 and 084 efficacy trials results show that CAB-LA is significantly more effective in preventing HIV acquisition than oral PrEP, in part due to suboptimal adherence to daily oral PrEP. FDA approved CAB-LA in December 2021, and demonstration projects are planned to guide implementation, including how offering choice of products, HIV testing protocols for CAB-LA, and product introduction and delivery of dapivirine vaginal ring and CAB-LA in different contexts, in part through the USAID-funded MOSAIC consortium.

Candidate long-acting PrEP agents under evaluation: Islatravir

Another promising PrEP candidate for HIV prevention is monthly oral islatravir. Islatravir (ISL) is the first member of a new class of antiretroviral agents, known as NRTTIs, which block HIV reverse transcriptase and causes chain termination by blocking translocation.[31, 32] High potency against wild-type and resistant variants of HIV virus and a long half-life make ISL a suitable candidate for further development as a novel, long-acting PrEP agent. The comprehensive preclinical safety evaluations of ISL, including developmental toxicity studies, have not revealed toxicities of concern at acceptable exposure margins. In a rhesus macaque SHIV intrarectal challenge model, ISL

provided protection against infection at drug levels that are projected to be achieved with the 60 mg dose regimen used in IMPOWER 22 and 24. [33]

In an intensive safety study (known as MK-8591-16), which was conducted in Israel, South Africa, and the US starting in 2019, a decrease was seen in lymphocytes, but almost all lymphocyte counts remained in the normal range.[34] In a combination HIV treatment study called IMAGINE, people living with HIV were randomized to receive islatravir and one of three doses of an experimental nonnucleoside reverse transcriptase inhibitor drug called MK-8507. In November 2021, the monitoring group for the IMAGINE study recommended that dosing of study medication be stopped because of a decrease in total lymphocytes and CD4 lymphocytes. In December 2021, the US FDA put a clinical hold on the islatravir PrEP program and required that IMPOWER 22 and IMPOWER 24 participants stop receiving study medications, and that white blood cells, lymphocytes and CD4+ cells be conducted monthly.[35] Through a protocol amendment, IMPOWER 22 and 24 participants now have monthly monitoring of lymphocytes and CD4 counts to determine the proportion with decreased lymphocytes and the time to recovery while being provided active, open-label daily FTC-TDF PrEP.

In September 2022, Merck announced that it will not pursue islatravir for HIV prevention, but will continue to work on clinical development of other potential long-acting oral PrEP agents, including MK 8527 which is in the same class of nucleoside reverse transcriptase and translocation inhibitors. As that compound enters clinical evaluation, it will be important to assess preferences of users about trade-offs in terms of dosing frequency and forgiveness for late dosing would be useful in informing decisions about long-acting PrEP agents as different drug formulations are being tested for potential inclusion in efficacy trials.

Another promising long-acting PrEP agent is the HIV capsid inhibitor, lenacapavir, which also has very high potency *in vitro* and *in vivo,* and for which there is not preexisting resistance in persons living with HIV regardless of treatment history. [36] Lenacapavir can be dosed daily or weekly orally and every six months subcutaneously. Lenacapavir is being studied for HIV prevention among cisgender women and men who have sex with men in the PURPOSE 1 and 2 trials using every six month subcutaneous dosing of 927 mg, respectively, and in comparison to daily FTC/TDF and FTC/TAF(NCT04925752). Participants in this cohort will be referred for screening for or other HIV prevention efficacy trials, including the ongoing PURPOSE trial of subcutaneous lenacapavir or future trials of long-acting oral PrEP, such as MK8527, if interested.

Discrete choice experiments (DCE) are commonly designed to ascertain user preferences about health care options, which can be applied in this case to product attributes of long-acting PrEP agents. [37-39] A DCE among 807 young South African men and women which focused on a single injection, two injections, or implant identified a strong preference for long-acting PrEP products. [40] MSM expressed a significantly higher preference for a product with once a year dosing than two-month dosing compared to cisgender women. This DCE did not include probes about oral monthly or every six-month subcutaneous PrEP products, or the relative weighting of dose forgiveness, side effects, and product storage which is relevant to monthly oral PrEP agents and every six month subcutaneous lenacapavir PrEP.

Rationale for an open cohort of African young women with access to PrEP

Young women are an important population for PrEP implementation in Africa, with high annual HIV incidence rates of 5-6% in recent HIV prevention trials, in the context of monthly risk reduction counseling, treatment of sexually transmitted infections (STIs), and provision of condoms.[41, 42] Women <25 years of age in sub-Saharan Africa have a higher incidence than women >25 and are the focus of the INSIGHT cohort. PrEP is a core biomedical intervention for this population, given the high efficacy of daily oral PrEP when product adherence is high. This cohort study will assess PrEP

uptake, persistence and user preferences about long-acting PrEP, as these products become available or enter advanced clinical trials.

If a new protocol to evaluate a new candidate PrEP product for HIV prevention is available, such as lenacapavir or MK8527, women in this observational cohort will have had the opportunity to experience use of daily oral TDF-based PrEP. INSIGHT participants will be counseled about HIV prevention clinical trials for which they may be eligible.. Participants' experience with daily oral PrEP in the INSIGHT cohort may inform their decision about whether to continue with open-label oral TDF-based PrEP if they can manage daily pill-taking and product storage, or to enter a trial with an experimental longer-acting PrEP medication.

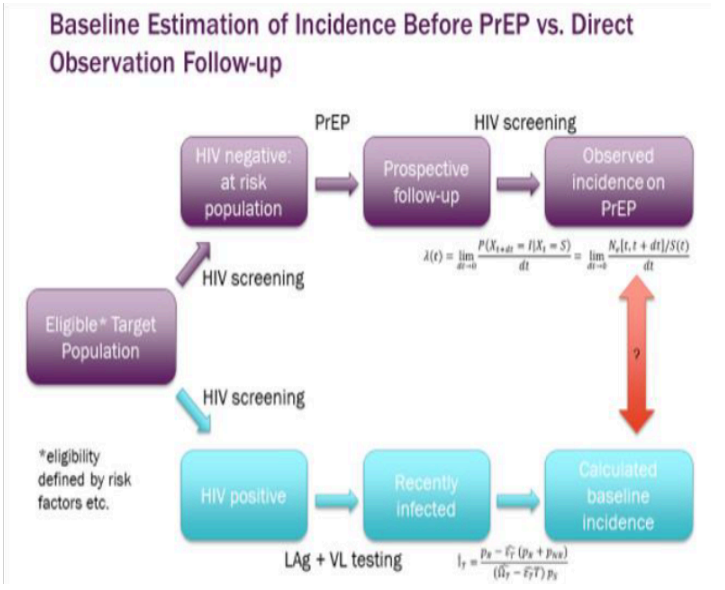
Background on recency testing to estimate background HIV incidence

Randomized placebo-controlled trials are the gold standard methodology for estimating HIV incidence and inferring causality of reduction in HIV incidence due to an intervention (e.g., PrEP or an HIV vaccine). Since placebo arms are no longer ethical for HIV prevention studies, the traditional randomized trial choices are superiority or non-inferiority trials using the standard-of-care as an active control, with the assumption that the original superiority of the standard-of-care to placebo remains constant. Superiority becomes more difficult to demonstrate with each new generation of product, given the high efficacy of the standard-of-care – in this case, TDF-based PrEP – requiring larger studies to demonstrate small incremental increases in efficacy. Non-inferiority designs depend on reliable data demonstrating superiority of the standard-of-care versus placebo for the population under study to allow establishing appropriate non-inferiority margins. Such data are not yet available that establish the level of TDF-based PrEP adherence that is associated with high efficacy among women.

With two active study intervention arms, it may not be possible to reliably assess the relative reduction in HIV infection risk between the two arms if very few infections occur because both active products successfully decrease risk. Adherence to daily oral PrEP tends to decline over time. In both the HPTN 083 and HPTN 084 trials, CAB-LA was demonstrated to have superior efficacy to daily oral FTC-TDF. However, the challenges will increase as more efficacious comparators (e.g., CAB-LA) are used in future efficacy trials. In an effort to mitigate this future risk in the evaluation of efficacy of new PrEP products without a placebo comparator arm, the Forum for Collaborative Research convened experts in 2020-21 to discuss alternative research designs to evaluate the efficacy of new PrEP products, including the use of a counterfactual estimate of background HIV incidence as an external 'placebo' control.[43]

A cross-sectional incidence assay antibody avidity test and HIV viral load combined with clinical characteristics (ART exposure and timing of HIV diagnosis) can distinguish recent from non-recent infection (Figure 1). The Limiting Antigen Avidity Enzyme Imunoassay (LAg), a widely used test originally developed at the CDC, measures the avidity of HIV binding antibodies in a person's blood sample. The results are interpreted based on whether the normalized optical density, a quantitative measure, falls below (recent) or above (non-recent) a selected threshold. Higher normalized optical density reflects more tightly binding antibodies indicating a longer duration of infection. Two key parameters of each RITA algorithm are the mean duration of recent infection (MDRI) and false recency ratio (FRR), and must be within specific ranges to estimate HIV incidence with reasonable precision. Ideally, a bigger MDRI and smaller FRR are better. Recency antibody avidity assays have been combined with other lab-based assessments (e.g. viral load, CD4) and clinical characteristics (history of HIV diagnosis, ART use) to create multi-assay recency algorithms with improved performance characteristics.

Figure 1: Cross-sectional estimate of HIV incidence from Collaborative Forum for HIV research 2021



In an evaluation of the recency testing algorithm among antenatal clients in western Kenya, female sex workers in Zimbabwe, and HIV counseling and testing services including partners of persons living with HIV, the proportion of HIV infected persons among whom the recency testing algorithm identified as recent HIV infections ranged from 2.3% to 12.4, with 23.8% among a small subset of partners of persons known to be living with HIV.[44] In all three settings, clinical information improved the positive predictive value of the recency algorithm, based on ART initiation dates with further investigation and/or testing for ARV metabolites.

The INSIGHT study will use the limiting antigen avidity assay (HIV-1 LAg; Sedia Biosciences Corp, 2016 and Maxim Biomedical Inc, 2019) and viral load, which is now widely used for HIV incidence estimation in surveillance and research studies[45, 46]. The manufacturers of the LAg Avidity assay recommend using the assay in an algorithm where individuals with VL <1000 copies/mL are classified as having non-recent infection. This algorithm is currently being used in large surveys conducted as part of the PEPFAR-supported Population-based HIV Impact Assessment. (PHIA). Kassanjee, et al, developed an estimator and statistical inference methods for using the RITA to estimate incidence; these methods have recently been further explored by Gao et al.[43] This methodology will be used to estimate the background HIV incidence rate in this study.[47]. To provide more information about whether clinical information and ARV testing provides additional information to accurately eliminate people who have been infected for more than 2 years, which could affect the estimated HIV incidence based on the recency testing and RITA, questions will be asked at screening about timing of their last HIV test, prior ART or PrEP use, and plasma samples will be archived for retrospective testing of ARV metabolites.

PrEP decision support tool

Patient-facing decision support tools (DSTs) have been used successfully to improve patient knowledge of available options, involvement in shared decision-making, and accuracy of patients' perceived risk in a range of health care contexts.[48, 49] Applying this approach to HIV prevention can support patients to assess their risk for HIV and make value-congruent choices. This is particularly true as DSTs provide information in a standardized way and facilitate patients' decision-making to integrate their values and preferences with clearly-presented evidence[49, 50] about clinical and prevention options; these attributes may be particularly beneficial in situations where providers ask sensitive questions about sexual behavior and patients make decisions about potentially stigmatized services, such as HIV prevention methods. Further, DSTs may be particularly beneficial in busy health care environments, or in the context of offering new services, where clinicians may be less knowledgeable and confident in their counseling, all of which are relevant to PrEP delivery in Africa.

Through the USAID-funded POWER open label PrEP demonstration project in Kenya and South Africa,[23] we developed and evaluated an electronic, tablet-based, patient-facing DST called My PrEP for young African women (https://witsrhi-mypreptool-client.herokuapp.com/).My PrEP is the first DST for patients focused on supporting decisions about HIV prevention, which was evaluated in a randomized control trial in a public health facility in Johannesburg, South Africa, to test whether use of the DST positively influenced PrEP initiation (primary outcome), PrEP continuation, and experiences of PrEP services, compared to standard of care counseling. PrEP initiation, was very high (>90%) overall and PrEP continuation was twice as high (20% vs 11%) among women who were randomized to use the My PrEP DST.[51] This improvement in one month PrEP continuation among women who used the My PrEP DST is encouraging, given the high early drop-off observed in demonstration projects of daily oral PrEP, including the POWER study. [23]

HLA testing for evaluation of feasibility of development of T cell based vaccines for HIV, HPV or other viral pathogens

A major goal for prevention of viral infections, such as HIV and HPV, is to develop T cell vaccines that will elicit a strong immune response in diverse populations. There is one cluster of genes called the human leukocyte antigen (HLA) complex that is a well-known hotspot for disease associations. The HLA cluster is named for the group of proteins it encodes, called the human leukocyte antigen (HLA) complex. These cell-surface proteins regulate the immune system in humans. These proteins are present on the surface of cells, and they help the immune system distinguish foreign "invaders" such as viruses and bacteria from the body's own cells. Variants in the HLA genes are associated with infectious diseases like HIV. The set of HLA protein variations (which are called alleles) in an individual help define what that individual's immune system regards as self, and also helps define what groups of foreign proteins (for example, viral proteins) are more or less likely to elicit a strong host immune response. HLA variants or type influences a person's immune response to T cell vaccines. Additional data are needed about the different HLA types of Africans, where limited information about HLA type is available and T cell vaccines for HIV, HPV, HSV, and other viral infections are critically needed. The burden of HIV, HPV, and HSV is very large among young African women who would be a priority population for T cell vaccines against viral infections. HLA testing will be conducted among INSIGHT participants who consent to HLA testing and will be performed at the African Health Research Institute in KwaZulu-Natal, South Africa. Individual results will not be provided to participants as HLA typing is not clinically relevant for participants in the INSIGHT cohort. Aggregate results will be used to inform development of vaccines against HIV and other infections.

II. STUDY DESIGN

This project will offer PrEP to young women in eSwatini, Kenya, Malawi, South Africa, Uganda, Zambia, and Zimbabwe. We will initiate a prospective cohort study of sexually active HIV negative cisgender

women ages 16-30 in order to assess PrEP uptake, adherence, and user preferences about PrEP formulations and delivery. We will incorporate PrEP delivery into sexual and reproductive health counseling and contraceptive services for young women. Based on current WHO guidelines, PrEP delivery will include the following components:

- **HIV testing** will be conducted at enrollment, month one, and quarterly with risk reduction messaging and PrEP provision at each visit in accordance with national guidelines.
- **Provision of condoms and contraception** in accordance to local guidelines.
- **Diagnosis and treatment** of sexually transmitted infections.
- **PrEP** will be offered in the form of daily generic oral TDF-based PrEP. For young women taking PrEP, baseline creatinine testing will be done, in accordance with national guidelines. Hepatitis B testing will also be done according to national guidelines. PrEP can be initiated at the same day as the hepatitis B and creatinine testing is obtained, with a call back if the participant is hepatitis B surface antigen positive or has a creatinine clearance <60 ml/min. PrEP will be discontinued if HIV seroconversion occurs and according to national guidelines.

Study-specific procedures including PrEP delivery and monitoring, are detailed in Table 3.

COHORT STUDY OF PrEP IN YOUNG WOMEN

Study design

This is a prospective cohort study of sexually active HIV negative cisgender women ages 16-30 in eSwatini, Kenya, Malawi, South Africa, Uganda, Zambia, and Zimbabwe. Women will be engaged for HIV testing and those who are living with HIV will be engaged for HIV recency estimation. HIV-negative women will be offered screening for the cohort without stipulation to their initial decision about use of open-label, daily oral PrEP, to be provided according to the PrEP delivery package detailed above. We will assess sociodemographic and behavioral characteristics of women at baseline and during follow-up; motivations to take PrEP; the proportion and characteristics of women initiating PrEP; timing of PrEP initiation; duration of use and factors associated with PrEP discontinuation; patterns of PrEP use as associated with sexual activity, pregnancy and contraception, and the proportion of women who have high adherence to PrEP, based on multiple measures (self-report, pharmacy refill, retrospective drug level testing), and correlated with behavioral factors. We will assess HIV incidence among PrEP users and non-users, drug resistance and natural history among HIV seroconverters.

Objective 1: Estimate HIV incidence using the recency testing on samples from women who screen out due to HIV infection, as well as assess HIV incidence prospectively in the cohort.

To provide information for ongoing and future HIV prevention trials, the a recency testing algorithm (RITA) including an HIV antibody avidity test and HIV viral load will be implemented to obtain an estimate of background HIV incidence across sites. Screening processes will not exclude women who are known to be living with HIV in order to use the recency assay to identify women who are recently infected (i.e., within the past 2 years) and women whose infections are recent and unknown. For women who screen out due to HIV infection, a cross-sectional measure of background HIV incidence can be obtained using a recency testing algorithm (RITA) combined with clinical data (HIV viral load, history of prior HIV diagnosis, ART use). There is limited experience with this approach implemented during screening for trial enrollment in terms of identifying women with recent infection in order to provide a cross-sectional estimate of HIV incidence, which can be used as a counterfactual measure of HIV incidence in HIV prevention efficacy trials with active comparators and no placebo.

Objective 2: Assess the characteristics of women who initiate PrEP compared to those who do not initiate PrEP.

A critical aspect of implementation and cost-effectiveness of PrEP for young African women will be the motivation of young women who are at highest risk of HIV acquisition to utilize evidence-based HIV prevention strategies. We will collect data on STI prevalence, contraception use, sexual behavior, risk perception as correlates for PrEP uptake, persistence and adherence. Adherence will be measured by the timing of PrEP refills, self-reported PrEP use, and drug level testing for tenofovir (TFV) levels. PrEP adherence will be assessed during periods of risk, based on behavioral data and self-perceived risk. Participants in this cohort will be informed about other HIV prevention efficacy trials.

Objective 3: Evaluate young women's preferences for attributes of long-acting formulations of PrEP, using a discrete choice experiment.

A discrete choice experiment will be used to assess women's preferences around PrEP delivery form (e.g., pill and injection), dosing frequency, and relative dose forgiveness for different PrEP formulations. We will also assess preferences related to PrEP delivery, such as places of access, frequency of visits, lab monitoring, product packaging, storage, and willingness to pay. Attributes and attribute levels will be finalized based on expert consultations and informal conversations with young women and community advisory boards across the study sites. We will estimate preference weights for each attribute level, explore differences in our findings by geography, age, and PrEP experience, and conduct a trade-offs analysis between pairs of attributes.

Objective 4: Assess the acceptability of a patient-facing PrEP decision support tool to provide young women more informed choice about PrEP options.

Long-acting PrEP options are becoming available, including the monthly dapivirine ring and injectable cabotegravir which have been shown to be safe and effective and possibly monthly oral islatravir and/or every six monthly injectable lenacapavir which are currently in efficacy trials. Young women will need to make informed choices about daily oral PrEP or long-acting PrEP. A patient-facing decision support tool about PrEP options will be evaluated with respect to its utility in assisting young women to consider their HIV prevention needs and PrEP preferences. We will assess whether women who have high vs low adherence to oral PrEP are more likely to indicate a preference for long-acting formulations, as well as other predictors of interest in long-acting PrEP.

Objective 5: Assess HLA genotypes to determine the breadth of variants present in young women from East and southern Africa

A major goal for prevention of viral infections, such as HIV and HPV, is to develop T cell vaccines that will elicit a strong immune response in diverse populations. There is one cluster of genes called the human leukocyte antigen (HLA) complex that is a well-known hotspot for disease associations. These cell-surface proteins regulate the immune system in humans and these proteins are present on the surface of cells, and they help the immune system distinguish foreign "invaders" such as viruses and bacteria from the body's own cells. Variants in the HLA genes are associated with infectious diseases like HIV. The set of HLA protein variations in an individual help define what that individual's immune system regards as self, and also helps define what groups of foreign viral proteins (are more or less likely to elicit a strong host immune response. HLA variants or type influences a person's immune response to T cell

vaccines. Additional data are needed about the different HLA types of Africans, where limited information about HLA type is available and T cell vaccines for HIV, HPV, HSV, and other viral infections are critically needed. The burden of HIV, HPV, and HSV is very large among young African women who would be a priority population for T cell vaccines against viral infections. Aggregate results will be used to inform development of vaccines against HIV and other infections.

Population

Sexually active cisgender women ages 16-30.

Eligibility

At screening:

- Age 16-30 years
- Able and willing to provide written informed consent; parental assent will be obtained for 16 and 17 year old women if required by national guidelines
- Recently sexually active (defined as having had vaginal intercourse at least once in the previous three months)
- Interested in use of PrEP for HIV prevention

For eligibility of enrollment into longitudinal cohort with open label PrEP use:

- HIV uninfected based on negative HIV rapid tests
- Women are eligible to participate regardless of prior PrEP use and regardless of pregnancy or contraception use at enrollment

Sample size

Enrollment of up to 3000 HIV uninfected women ages 16-30 in a prospective cohort (up to 150 women per site), across all sites

Recruitment

Each site has established local recruitment and screening methods that operationalize protocol-specified requirements for eligibility determination in a manner that is tailored to and most efficient for the local study setting and target study population. For purposes of including women with recent infection HIV infection for estimation of background HIV incidence, sites will not prescreen women based on their HIV testing history or HIV infection status.

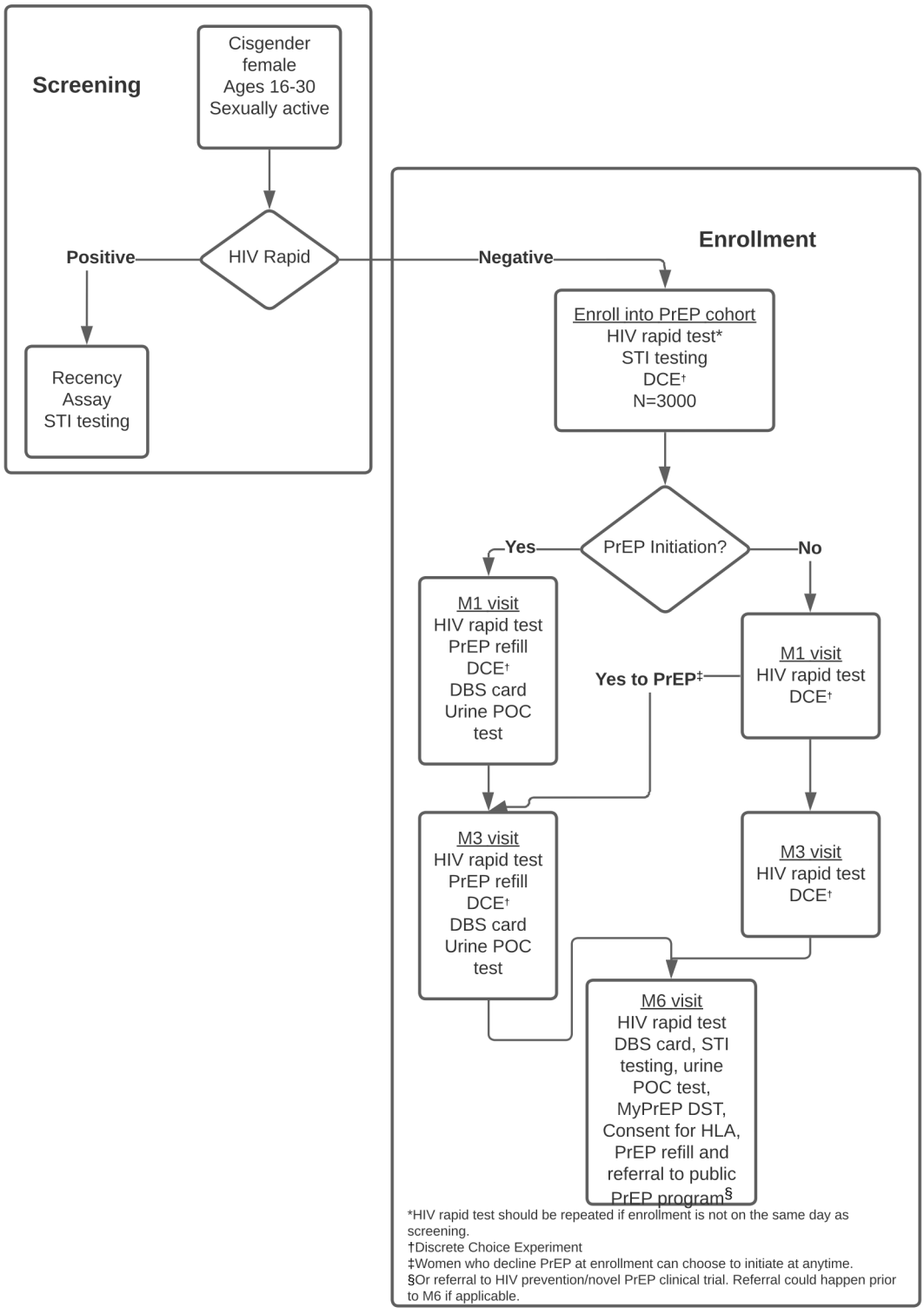
Each site will use a variety of recruitment approaches that works best for the local setting. Recruitment may be conducted through the following possible approaches: community events and mobilization, partnerships with voluntary counseling and testing centers and programs, home-based and mobile HIV testing programs, family planning clinics, youth clinics, post-abortion clinics, and pharmacies that provide emergency contraception and post-exposure prophylaxis (e.g., for sexual assault) and via social media outlets popular among young people. Recruitment materials will educate women about HIV, sexual health, and risks in their community, the effectiveness of PrEP for HIV prevention, and the benefits of HIV prevention services. Recruitment will occur over approximately 3 months.

Study procedures

Specific study procedures are shown graphically in Figure 2 and detailed in Tables 4 and 5. Visits will take place at screening, enrollment, 1 month, 3 and 6 months after enrollment. The following will occur at screening:

- Questionnaire about demographics, HIV testing history, sexual behavior in the prior 3 months, PrEP use, and current health, including acute HIV and COVID symptoms
- HIV testing according to national algorithms will be conducted to establish participant eligibility for the longitudinal PrEP cohort. Women who have reactive HIV point-of-care test will also have the following procedures:
    - Confirmatory testing using fourth generation antigen/antibody test
    - HIV antibody avidity testing and viral load testing for HIV recency assay
    - Archival for testing of antiretrovirals
    - STI testing for syphilis, chlamydia, gonorrhea, HPV and trichomonas will be conducted
    - Referral to provider for HIV care

Figure 2: INSIGHT Study flow diagram



Women who have a negative HIV point-of-care test will continue to enrollment, which may happen on the same day as screening. PrEP can be initiated at enrollment, given that based on multiple PrEP demonstration projects, >99% of women have normal creatinine clearance and are hepatitis B surface antigen negative. PrEP can be initiated at a follow-up visit based on the woman's preference.

The following will take place at enrollment:

- A brief questionnaire on HIV risk perception, motivations for HIV prevention, contraceptive use and fertility intentions will be administered by research staff during one-on-one interviews.
- STI testing for syphilis, chlamydia, gonorrhea, and trichomonas will be conducted.
- The VOICE risk score will be calculated based on behavioral characteristics and baseline STIs.
- Provide contraception if indicated
- Participants will have urine pregnancy testing if they have missed menses or at their request.
- A questionnaire capturing a Discrete Choice Experiment (DCE) will be administered by trained research staff
- Counseling about PrEP use and adherence. Counseling about PrEP during pregnancy and breastfeeding and dispensation of PrEP during pregnancy and breastfeeding will follow national guidelines. Participants will also be counseled about risk reduction and HIV prevention.
- Offer and dispense PrEP. Women who accept to take PrEP will also have the following:
    - Serum collected for creatinine and hepatitis B surface antigen testing.

Women who have symptoms potentially consistent with acute HIV infection (e.g., fever, rash, headache, pharyngitis) will also be offered enrollment into the cohort and have an offer of PrEP deferred for 2-4 weeks at which time repeat serologic testing will be performed (and, if positive, will result in study exclusion, HIV viral load and CD4 count will be obtained and the woman will be linked to HIV care and treatment services).

All women enrolled in the study will return for follow-up visits at 1 month, 3 months, and 6 months post enrollment. Women will have the option to accept or refuse PrEP at each study visit.

At the 1 month and 3 month visit the following will occur:

- HIV rapid testing
- Brief quantitative behavioral and clinical interviews about their interest in PrEP, sexual behavior, contraceptive use, and fertility intentions.
- Symptom directed physical exam
- Provide contraception if a woman chooses, after contraceptive counseling
- STI testing for syphilis, chlamydia, gonorrhea, and trichomonas may be conducted if clinically indicated.
- Participants will have urine pregnancy testing as clinically indicated (e.g., missed menses, participant request).
- A questionnaire capturing a Discrete Choice Experiment (DCE) will be administered by research staff.
- Counseling about PrEP use and adherence. Counseling about PrEP during pregnancy and breastfeeding and dispensation of PrEP during pregnancy and breastfeeding will follow national guidelines. Participants will also be counseled about risk reduction and HIV prevention.
- Offer and dispense PrEP. Women who are initiating PrEP will have a blood specimen collected for creatinine and hepatitis B surface antigen testing.
- Women who have been taking PrEP will have a dried blood spot (DBS) collected to be used for batched retrospective testing for TFV-DP levels as an objective marker of PrEP adherence in the prior 4-6 weeks on a subset of participants.[52]
- Urine for point-of-care tenofovir testing[53-56] with adherence counseling

At the 6 month visit the following will occur:

- HIV rapid testing
- Brief quantitative behavioral and clinical interviews about their interest in PrEP, sexual behavior, contraceptive use, and fertility intentions.
- Symptom-directed physical exam
- Provide contraception if indicated

- STI testing for chlamydia, gonorrhea, HPV and trichomonas (if sensitive pathogen-specific lab testing is available) will be conducted.
- Participants will have urine pregnancy testing as clinically indicated (e.g., missed menses, participant request).
- Women who have been taking PrEP will have a dried blood spot (DBS) collected to be used for batched retrospective testing for TFV-DP levels as an objective marker of PrEP adherence in the prior 4-6 weeks on a subset of participants.
- The MyPrEP decision support tool will be administered on a tablet or laptop with a questionnaire about PrEP preference and acceptability of the decision support tool. https://witsrhi-mypreptool-client.herokuapp.com/
- Urine point-of-care tenofovir assay to evaluate recent adherence and targeted counseling
- Provision of one month PrEP (if taking PrEP) and referral to public PrEP program or HIV prevention/novel PrEP clinical trials.
- Participants 18 – 30 years old will be informed of the option to consent for HLA testing. Women who consent will have blood drawn to be stored for HLA testing.

Interim visits may occur at any time during the study, including for treatment of STIs and ascertainment of whether their partner has been offered STI treatment. All interim contacts and visits will be documented in participants' study records and on applicable CRFs.

HPV testing

HPV testing will be performed by the central laboratory and results provided to participants. Counseling messages around high risk HPV types and next steps for those with a high risk HPV types regarding a Pap smear which will follow national guidelines.

HIV testing and seroconversion

HIV testing will be performed following national HIV testing algorithms. HIV testing will be accompanied by counseling, and all counseling and testing approaches will be in accordance with national HIV counseling and testing guidelines.

All potential seroconversions will be confirmed using HIV EIA. At the seroconversion visit, participants will have blood specimens collected for assessment of CD4 count, and HIV plasma viral load levels. In addition, DBS will be archived for determining TFV-DP levels in the blood and plasma for antiviral resistance testing. Some sites will also collect specimens for recency testing. Participants will have a swab collected for HPV testing. Seroconverters will be referred to local HIV care centers with their lab results from their post- seroconversion visit as well as to other support services and exited from the study.

If a study participant presents to an interim visit with symptoms suggestive of acute HIV infection syndrome, rapid HIV testing will be performed, as at a scheduled visit, and PrEP will be withheld if a positive rapid test result is documented.

Adherence support

At follow-up visits, study staff will conduct a urine point of care tenofovir assay to evaluate PrEP use in the prior 4 days and offer adherence support and work with all participants to identify problems impacting adherence, generate solutions, and decide on a plan to implement the solutions. The sessions may include: PrEP information review (i.e., why adherence is important); exploring motivations for PrEP adherence; identifying adherence facilitators and barriers, including relationship dynamics and

disclosure of PrEP use; problem-solving; and skill-building around adherence. At each visit, women will be asked if they are motivated to take PrEP (e.g., based on their sexual activity) and encouraged to continue (or discontinue) based on their circumstances and preferences. Women who choose to take PrEP will be encouraged to take PrEP as close to daily as possible.[52]

Adherence measurements

PrEP coverage will be calculated by dividing the number of pills available over time between refills. Participants will have a urine point-of-care tenofovir assay conducted at each visit to evaluate recent adherence and assist in providing targeted counseling. A DBS sample from scheduled visit will be archived for possible future testing for intracellular tenofovir diphosphate levels as an objective measure of adherence in the prior 4-6 weeks.

Retention

Retention procedures will reflect local retention approaches used by local public health clinics. Each site will develop retention methods tailored to and most efficient for the local setting. Physical tracing of participants will occur on a case-by-case basis and in particular for follow-up of safety issues and for HIV assessment at the end of the study.

Discrete choice experiments

We will conduct a discrete choice experiment with participants across all study sites at the enrollment, Month 1, and Month 3 study visits that is embedded into the set of quantitative questionnaires administered. Discrete choice experiments can be used to engage respondents in considering a set of attributes that compose a potential HIV prevention product and in making choices that indicate the attributes and tradeoffs most salient for future product uptake and adherence. Our enrollment and Month1 discrete choice experiment will focus on tradeoffs and preferences for product attributes. From our review of the literature and prior experience conducting HIV prevention trials with adolescent girls and young women in Southern and Eastern Africa, we expect that our Enrollment and Month 1 discrete choice experiment will include product attributes related to: delivery form, dosing frequency, forgiveness of dosing intervals (i.e., pharmacokinetic properties that require more stringent adherence to dosing), size of pill, reversibility, and/or side effects or potential for weight gain. Our Month 3 discrete choice experiment will focus on tradeoffs and preferences for product delivery such as delivery location, dosing method, packaging, privacy of product storage, clinical monitoring, and willingness to pay for private sector provision of PrEP.

Table 1 provides a list of potential levels for each of these PrEP product attributes to be assessed at enrollment and month 1, and **Table 2** provides a list of potential levels of PrEP delivery attributes to be assessed at month 3. We will refine our set of attributes and attribute levels, and develop visual and narrative descriptions for each attribute and level, based expert consultations with HIV prevention researchers, young women, and community advisory boards in the different country contexts. We plan to refine our attribute lists shown in Tables 1 and 2 to include 4-6 attributes and no more than 100 possible combinations of scenarios for each discrete choice experiment. Prior to launching our discrete choice experiments, we will pre-test the attributes and levels and their visual descriptions with approximately 5 participants at each of the study sites to elicit their feedback and refine questions.

Table 1. Discrete choice experiment about PrEP product attributes, for further refinement with experts and community advisory boards, to be administered at enrollment and month 1

Attributes	Level 1	Level 2	Level 3	Level 4
Delivery form	Oral pill	Injection	N/A	N/A
Dosing	One pill monthly	Injection every two months	Injection every three months	Injection every six months

Dosing forgiveness	Need to take a dose within one week of planned dose	Need to take a dose within 2 weeks of planned dose	Need to take within 1 month of planned dose	N/A
Size of pill	Big (FTC/TDF size)	Small (Islatravir 60 mg size)	Smaller (Islatravir 20 mg size)	N/A
Reversibility and impact on risk of antiviral resistance	Stays in body for 1 wk after last dose	Stays in body for 1 month after last dose	Stays in body for 6 months or longer after last dose	N/A
Weight loss or gain per year	5 kg weight loss	2 kg weight loss	2 kg weight gain	5 kg weight gain
Antiretroviral or monoclonal antibody-based prevention	Antiretroviral	Immune-based (e.g., monoclonal antibody)		

Table 2. Discrete choice experiment about PrEP delivery attributes and levels, for further refinement with experts and community advisory boards, to be administered at month 3

Attributes	Level 1	Level 2	Level 3	Level 4
Delivery place	Health clinic	Pharmacy	Mobile clinic or van	N/A
Dosing method	Take at home	Take in clinic (and don't take pills home)	N/A	N/A
Packaging	Blister pack	Pill bottle	N/A	N/A
Privacy of product storage for non clinic-based products	Can keep in purse/personal possessions	Can keep in bathroom	N/A	N/A
HIV testing	Home blood self-test	Clinic rapid HIV test	N/A	N/A
Willingness to pay for private sector PrEP	Not willing to have a cost	$2 cost	$5 cost	$10 cost

The discrete choice experiment will utilize a D-efficient algorithm to construct a fractional factorial experimental design. Attributes and levels will be grouped into scenarios. For example, a set of 4 attributes with 2 levels each would yield 16 combinations (2x2x2x2) of scenarios before the exclusion of any nonsensical combinations. These could be divided into 2 blocks of 8 questions each. We will create block sizes based on our final number of attribute and level combinations. Each respondent will be randomly assigned to one block of DCE questions, which present two hypothetical scenarios comprised of one level of each of the attributes and ask the participant to then choose their preferred HIV prevention product that meets the descriptions of Scenario A or Scenario B. Each question will require women to make tradeoffs among PrEP product attributes; tradeoffs will vary systematically across questions. Following each choice, participants will also be asked if they would prefer the chosen product, no protection, or for their male partners to use condoms in lieu of the chosen product.

HLA Testing

, South Africa, following their SOPs Individual r

participants Aggregate

results will be used to inform development of vaccines against HIV and other infections.

Data collection

Interviewer-administered questions about demographics, sexual behavior, contraception, fertility intentions, and clinical history will occur at Screening, Enrollment, Months 1, 3, and 6 utilizing a secure, encrypted electronic database. At month 6, PrEP preference will be ascertained after women view the My PrEP DST, as well as a questionnaire about the utility and acceptability of the My PrEP DST in providing information about other PrEP options (e.g., the monthly dapivirine ring and injectable cabotegravir).

At Enrollment, Month 1 and Month 3 visits, a DCE survey will be included in the set of interviewer-administered questionnaires and the DCE scenarios will be programmed as part of the data collection tools. A trained data collector will introduce the survey to participants, including the goal of preventing HIV and new and upcoming PrEP products. Participants will be told that the goal of the DCE survey is to establish her preferences for HIV prevention products based on a number of product attributes. The data collector will describe each attribute with a visual and narrative descriptions and participants need to answer a comprehension question about the graphics before continuing. Then, the data collector will present a pair of scenarios using attribute cards. The participant will be asked to select their preferred HIV prevention product in each pair and the data collector will mark their response on the tablet. The DCE will continue until all sets of scenarios are completed. Women will receive the same sequence of DCE scenarios at enrollment and month 1 to determine whether product attribute preferences have changed after taking oral PrEP for a month.

Statistical power and analysis

The primary aims of this project are to: 1) assess the background HIV incidence rate through use of the recency assay to determine recent infections among those who screen out due to HIV infection. 2) assess PrEP uptake and persistence through 6 months; 3) evaluate users preferences for attributes of long-acting PrEP products and aspects of PrEP delivery; 4) describe user preferences for different products and the alignment with this self-reported preference with the outcome of the decision support tool; 5) describe the range of HLA types in participants. All analyses will be conducted using SAS 9.4 (Cary, NC), Stata, or R.

Aim 1: *The expected precision of the estimate of HIV incidence*, based on the use of the LAg + VL RITA in the Clade C setting (MDRI = 118, FRR = 1.5%) is given in Table 3.

Table 3: Estimated precision of HIV incidence using the LAg+ VL RITA for women who screen out due to HIV infection

Approximate number of women screened to enroll 3000 HIV-uninfected women	HIV Prevalence	HIV Incidence in the screened population of women	Expected number of recent infections	Expected incidence estimate from RITA method (95% CI)
3300	5%	3%	32	3.0 (2.0, 4.5)
3400	7.5%	4%	48	4.0 (2.9, 5.6)
3500	10%	5%	66	5.0 (3.7, 6.7)

Aim 2: *Estimates of the proportion initiating oral PrEP* in the cohort of 3000 will have a 95% confidence interval with a half-width not exceeding +/-1.8%. Logistic regression, accounting for repeated measures as appropriate, will be used to assess associations between covariates (e.g., demographic and risk characteristics) and PrEP uptake and adherence; a cohort of 3000 yields high power to detect associations with 80% power for Odds Ratio (OR) = 1.23.

Aim 3: *Discrete choice experiment analysis*. We will use a random logit-parameters model to estimate preference weights for each attribute level. Larger positive weights will indicate a greater preference for

that attribute level, while smaller negative weights will indicate less preference. The relative importance of an attribute overall will be depicted by the distance between the most and least preferred levels. We will graphically depict the mean preference weight estimate for each attribute level relative to the mean attribute effect normalized around zero. Preferences for product form in the Enrollment and Month 1 discrete choice experiment depend on the frequency of dosing (e.g., daily dosing will only be presented for tablets only and not rings and injections), so models will include an interaction term for frequency and delivery form. We will also explore differences in product preferences by geography, age, and prior PrEP experience. We will descriptively compare product preferences at enrollment and Month 1 by graphically depicting product preferences by time point. Finally, for the enrollment and Month 1 discrete choice experiment, we will conduct a trade-off analysis whereby we will use preference weights to explore the minimum acceptable dosage that a product would need to offer for participants to be willing to trade one attribute level for another. Prespecified subgroup analyses will include age (16-21, 22-25, 25-30), country and region (East and southern Africa), prior PrEP use, contraceptive use, VOICE risk score <5 and ≥5). Latent class analysis will be conducted to determine characteristics of women who prefer specific long-acting PrEP formulations and PrEP delivery models. All analyses will be conducted using SAS 9.4 (Cary, NC).

Aim 4: *My PrEP decision support tool*. We will conduct descriptive analyses of the proportion of women who would prefer daily oral PrEP, dapivirine ring, and injectable cabotegravir at month 6 after using the My PrEP decision support tool. We will assess predictors of their PrEP preference, including age, country/region, 3 month TFV-DP concentrations in DBS, VOICE risk score[57], time-dependent sexual behavior, and risk perception.

Aim 5: We will conduct descriptive analyses of the frequency of HLA types present in young women in the study and we will assess geographic correlates of the most common HLA types.

IV. RISKS AND BENEFITS TO PARTICIPANTS

Participants may experience discomfort or pain when undergoing a finger prick or phlebotomy. They also may feel dizzy or faint, and/or develop bruising, swelling, or infection where the needle is inserted.

Participants may become embarrassed, worried, or anxious when completing their HIV risk assessment and/or receiving HIV counseling. They also may become worried or anxious while waiting for their HIV test results. Participants who learn that they have HIV may experience anxiety or depression related to their test results. At all study sites, individual counseling will be provided by experienced counselors and clinicians.

Although sites will make every effort to protect participant privacy and confidentiality, it is possible that participants' involvement in the study could become known to others, and that social harms may result. Social harms include any negative consequences that happen to a participant as a result of their study participation. Examples of social harm include being treated unfairly or discriminated against, loss of employment, or trouble being accepted by family, friends or partners, etc. Although we anticipate few social harms related to participation in the study, we will monitor them closely throughout the study.

All participants who experience side effects or other clinical events during the study will receive follow-up by local study staff. Serious adverse events will be reported following local guidelines and followed through resolution. If treatment is required beyond the capacity of the study staff, study clinicians will refer the participant to appropriate services or organizations that can provide appropriate care.

V. HUMAN SUBJECTS CONSIDERATIONS

The study protocol, site-specific informed consent forms, participant education and recruitment materials, and other requested documents—including any subsequent modifications—will be reviewed and approved by the IRBs/ECs responsible for oversight of research conducted at the study sites. Subsequent to initial review and approval, the responsible IRBs/ECs will review the study at least annually.

Informed consent

Written informed consent will be obtained from each study participant prior to enrollment. Parental assent for 16 and 17 year old women will be obtained if required by national guidelines and/or local regulatory bodies. Participants will be offered copies of the informed consent forms. Each study site is responsible for developing study informed consent forms for local use that describe the purpose of the study, the procedures to be followed, and the risks and benefits of participation, in accordance with all applicable regulations, based on the samples provided in the Appendix. Each site also is responsible for translating the forms into local languages and verifying the accuracy of the translation by performing an independent back-translation, which will be reviewed and approved by the University of Washington Coordinating Center.

Study records

Each study site will establish a standard operating procedure for confidentiality protection. Each site will ensure that study records including administrative documentation and regulatory documentation as well as documentation related to each participant enrolled in the study, including informed consent forms, locator forms, case report forms, notations of all contacts with the participant, and all other source documents are stored in a secure manner.

Participants' study information will not be released without their written permission, except as necessary for oversight by:

- The Protocol Chairs or designees
- Study funders
- Site IRB/ECs
- University of Washington

Table 4. Procedures for INSIGHT Cohort Study of PrEP in Young Women

	Screening	Enrollment	M1 and M3	M6
Obtain informed consent	X			
Apply inclusion/exclusion criteria	X			
Collect/update locator information	X		X	
Collect/update demographic information	X			
HIV testing and counseling according to national algorithm	X		X	X
Risk reduction counseling and condom promotion and provision	X		X	X
Acute HIV assessment	X		X	X
Behavioral data collection*	X	X	X	X
Medical history and contraception use data collection	X	X	X	X
STI Testing (syphilis, gonorrhea, chlamydia and trichomonas) Syphilis testing at enrollment only		X	[X]	X
Human papillomavirus (HPV) testing				X
Urine pregnancy testing (as clinically indicated)		X	[X]	[X]
Urine POC tenofovir testing			X	X
Hepatitis B testing (HBsAg) and Creatinine†		X		
Discrete choice experiment data collection		X	X	
Dispense oral tenofovir-based PrEP tablets		X	X	
Assess date of previous PrEP refill^			X	X
Collect self-reported adherence data^			X	X
DBS Collection for archive^			X	X
Administer MyPrEP decision support tool and evaluation				X
Provide 1 month of PrEP and refer to local PrEP providers and/or HIV prevention trial				X
Consent for HLA testing and sample collection				X

E = Enrollment
(*) Behavioral data collection may include the following topics: sexual behavioral, alcohol and substance use, depression indicators, HIV risk perception, fertility intentions, stigma and social support, interest in participating in future PrEP trials, or other sociobehavioral data to inform PrEP use.
† Hepatitis B Surface antigen testing and serum creatinine testing should be conducted at PrEP initiation.
(^) If taking PrEP
[ ] as indicated
DBS = dried blood spots

Table 5. Procedures for women with a positive HIV rapid test

	S	M1, M3, and M6
Fourth generation HIV EIA antigen/antibody test	X	X
LAg antibody avidity test*	X	X
Plasma viral load, and plasma for archive*	X	
STI testing for syphilis, chlamydia, gonorrhea, and trichomonas	X	
Human papillomavirus (HPV) testing	X	X
CD4, HIV plasma viral load, plasma for resistance testing, DBS collection for archive		X
Refer to local HIV care providers	X	X

*The Recency Testing Algorithm (or RITA) includes LAg (antibody avidity test), plasma viral load and archive for testing of antiretroviral metabolites, which will be performed for women who test HIV positive at screening and women in South Africa and Eswatini who test positive during follow up.

References

1. Grant RM, Lama JR, Anderson PL, McMahan V, Liu AY, Vargas L, Goicochea P, Casapia M, Guanira-Carranza JV, Ramirez-Cardich ME, Montoya-Herrera O, Fernandez T, Veloso VG, Buchbinder SP, Chariyalertsak S, Schechter M, Bekker LG, Mayer KH, Kallas EG, Amico KR, Mulligan K, Bushman LR, Hance RJ, Ganoza C, Defechereux P, Postle B, Wang F, McConnell JJ, Zheng JH, Lee J, Rooney JF, Jaffe HS, Martinez AI, Burns DN, Glidden DV. Preexposure chemoprophylaxis for HIV prevention in men who have sex with men. N Engl J Med. 2010;363(27):2587-99. Epub 2010/11/26. doi: 10.1056/NEJMoa1011205. PubMed PMID: 21091279; PMCID: 3079639.

2. Baeten JM, Donnell D, Ndase P, Mugo NR, Campbell JD, Wangisi J, Tappero JW, Bukusi EA, Cohen CR, Katabira E, Ronald A, Tumwesigye E, Were E, Fife KH, Kiarie J, Farquhar C, John-Stewart G, Kakia A, Odoyo J, Mucunguzi A, Nakku-Joloba E, Twesigye R, Ngure K, Apaka C, Tamooh H, Gabona F, Mujugira A, Panteleeff D, Thomas KK, Kidoguchi L, Krows M, Revall J, Morrison S, Haugen H, Emmanuel-Ogier M, Ondrejcek L, Coombs RW, Frenkel L, Hendrix C, Bumpus NN, Bangsberg D, Haberer JE, Stevens WS, Lingappa JR, Celum C, Partners Pr EPST. Antiretroviral prophylaxis for HIV prevention in heterosexual men and women. N Engl J Med. 2012;367(5):399-410. Epub 2012/07/13. doi: 10.1056/NEJMoa1108524. PubMed PMID: 22784037; PMCID: PMC3770474.

3. Choopanya K, Martin M, Suntharasamai P, Sangkum U, Mock PA, Leethochawalit M, Chiamwongpaet S, Kitisin P, Natrujirote P, Kittimunkong S, Chuachoowong R, Gvetadze RJ, McNicholl JM, Paxton LA, Curlin ME, Hendrix CW, Vanichseni S. Antiretroviral prophylaxis for HIV infection in injecting drug users in Bangkok, Thailand (the Bangkok Tenofovir Study): a randomised, double-blind, placebo-controlled phase 3 trial. Lancet. 2013;381(9883):2083-90. Epub 2013/06/19. doi: 10.1016/S0140-6736(13)61127-7. PubMed PMID: 23769234.

4. Thigpen MC, Kebaabetswe PM, Paxton LA, Smith DK, Rose CE, Segolodi TM, Henderson FL, Pathak SR, Soud FA, Chillag KL, Mutanhaurwa R, Chirwa LI, Kasonde M, Abebe D, Buliva E, Gvetadze RJ, Johnson S, Sukalac T, Thomas VT, Hart C, Johnson JA, Malotte CK, Hendrix CW, Brooks JT. Antiretroviral preexposure prophylaxis for heterosexual HIV transmission in Botswana. N Engl J Med. 2012;367(5):423-34. Epub 2012/07/13. doi: 10.1056/NEJMoa1110711. PubMed PMID: 22784038.

5. Hendrix CW. Exploring concentration response in HIV pre-exposure prophylaxis to optimize clinical care and trial design. Cell. 2013;155(3):515-8. Epub 2013/11/19. doi: 10.1016/j.cell.2013.09.030. PubMed PMID: 24243011.

6. Ware NC, Wyatt MA, Haberer JE, Baeten JM, Kintu A, Psaros C, Safren S, Tumwesigye E, Celum CL, Bangsberg DR. What's love got to do with it? Explaining adherence to oral antiretroviral pre-exposure prophylaxis for HIV-serodiscordant couples. Journal of acquired immune deficiency syndromes. 2012;59(5):463-8. Epub 2012/01/24. doi: 10.1097/QAI.0b013e31824a060b. PubMed PMID: 22267018; PMCID: 3826169.

7. Amico KR, Mansoor LE, Corneli A, Torjesen K, van der Straten A. Adherence support approaches in biomedical HIV prevention trials: experiences, insights and future directions from four multisite prevention trials. AIDS Behav. 2013;17(6):2143-55. Epub 2013/02/26. doi: 10.1007/s10461-013-0429-9. PubMed PMID: 23435697; PMCID: PMC3672509.

8. van der Straten A, Stadler J, Montgomery E, Hartmann M, Magazi B, Mathebula F, Schwartz K, Laborde N, Soto-Torres L. Women's experiences with oral and vaginal pre-exposure prophylaxis:

the VOICE-C qualitative study in Johannesburg, South Africa. PloS one. 2014;9(2):e89118. Epub 2014/03/04. doi: 10.1371/journal.pone.0089118. PubMed PMID: 24586534; PMCID: 3931679.

9. Thomson KA, Baeten JM, Mugo NR, Bekker LG, Celum CL, Heffron R. Tenofovir-based oral preexposure prophylaxis prevents HIV infection among women. Curr Opin HIV AIDS. 2016;11(1):18-26. doi: 10.1097/COH.0000000000000207. PubMed PMID: 26417954; PMCID: PMC4705855.

10. Mugwanya KK, Wyatt C, Celum C, Donnell D, Mugo NR, Tappero J, Kiarie J, Ronald A, Baeten JM, Team PPS. Changes in glomerular kidney function among HIV-1-uninfected men and women receiving emtricitabine-tenofovir disoproxil fumarate preexposure prophylaxis a randomized clinical trial. JAMA Internal Medicine. 2015;175(2):246-54. doi: 10.1001/jamainternmed.2014.6786. PubMed PMID: WOS:000349120100024.

11. Murnane PM, Celum C, Mugo N, Campbell JD, Donnell D, Bukusi E, Mujugira A, Tappero J, Kahle EM, Thomas KK, Baeten JM, Team PPS. Efficacy of preexposure prophylaxis for HIV-1 prevention among high-risk heterosexuals: subgroup analyses from a randomized trial. AIDS. 2013;27(13):2155-60. doi: 10.1097/QAD.0b013e3283629037. PubMed PMID: WOS:000326703500015.

12. Mugo NR, Hong T, Celum C, Donnell D, Bukusi EA, John-Stewart G, Wangisi J, Were E, Heffron R, Matthews LT, Morrison S, Ngure K, Baeten JM, Team PPS. Pregnancy incidence and outcomes among women receiving preexposure prophylaxis for HIV prevention a randomized clinical trial. Jama-J Am Med Assoc. 2014;312(4):362-71. doi: 10.1001/jama.2014.8735. PubMed PMID: WOS:000339257800023.

13. AVAC. PrEPWatch New York, NY USA. Available from: https://www.prepwatch.org/.

14. McCormack S, Dunn D. Pragmatic open-label randomised trial of preexposure prophylaxis: The PROUD Study. Conference on Retroviruses and Opportunistic Infections; February 23-26 Seattle, WA USA 2015.

15. Molina J-M, Capitant C, Charreau I, Meyer L, Spire B, Pialoux G, Chidiac C, Delfraissy J-F, Tremblay C. On Demand PrEP with oral TDF-FTC in MSM: results of the ANRS Ipergay trial. Conference on Retroviruses and Opportunistic Infections; February 23-26 Seattle, WA USA 2015.

16. Kahle EM, Hughes JP, Lingappa JR, John-Stewart G, Celum C, Nakku-Joloba E, Njuguna S, Mugo N, Bukusi E, Manongi R, Baeten JM, Partners in Prevention HTS, the Partners Pr EPST. An empiric risk scoring tool for identifying high-risk heterosexual HIV-1-serodiscordant couples for targeted HIV-1 prevention. Journal of acquired immune deficiency syndromes. 2013;62(3):339-47. doi: 10.1097/QAI.0b013e31827e622d. PubMed PMID: 23187945; PMCID: 3620695.

17. Baeten J, Heffron R, Kidoguchi L, Celum C, Mugo N, Bukusi E, Katabira E, Asiimwe S, Haberer J, Donnell D. Near elimination of HIV transmission in a demonstration project of PrEP and ART. Conference on Retroviruses and Opportunistic Infections; February 23-26 Seattle, WA USA 2015.

18. Bekker L-G, Hughes J, Amico R, Roux S, Hendrix C, Anderson PL, Dye BJ, Elharrar V, Stirratt MJ, Grant R. HPTN 067/ADAPT Cape Town: A comparison of daily and nondaily PrEP dosing in African women. Conference on Retroviruses and Opportunistic Infections; February 23-26 Seattle, WA USA 2015.

19. Henderson F, Chirwa, L., Williams, T., Borkowf, C., Kasonde, M., Mutanhaurwa, R., Matlhaba, O., Hageman, K., Casillaas, P. Characteristics and oral PrEP adherence in the TDF2 open-label extension in Botswana. 8th IAS Conference on HIV Pathogenesis, Treatment and Prevention; July 19-22 Vancouver, BC, Canada 2015.

20. Celum C, Hosek S, Tsholwana M, Kassim S, Mukaka S, Dye BJ, Pathak S, Mgodi N, Bekker LG, Donnell DJ, Wilson E, Yuha K, Anderson PL, Agyei Y, Noble H, Rose SM, Baeten JM, Fogel JM, Adeyeye A, Wiesner L, Rooney J, Delany-Moretlwe S. PrEP uptake, persistence, adherence, and effect of retrospective drug level feedback on PrEP adherence among young women in southern Africa: Results from HPTN 082, a randomized controlled trial. PLoS Med. 2021;18(6):e1003670. doi: 10.1371/journal.pmed.1003670. PubMed PMID: 34143779; PMCID: PMC8253429.

21. Celum CL, Gill K, Morton JF, Stein G, Myers L, Thomas KK, McConnell M, van der Straten A, Baeten JM, Duyver M, Mendel E, Naidoo K, Dallimore J, Wiesner L, Bekker LG. Incentives conditioned on tenofovir levels to support PrEP adherence among young South African women: a randomized trial. J Int AIDS Soc. 2020;23(11):e25636. doi: 10.1002/jia2.25636. PubMed PMID: 33247553; PMCID: PMC7695999.

22. Grant RM, Anderson PL, McMahan V, Liu A, Amico KR, Mehrotra M, Hosek S, Mosquera C, Casapia M, Montoya O, Buchbinder S, Veloso VG, Mayer K, Chariyalertsak S, Bekker LG, Kallas EG, Schechter M, Guanira J, Bushman L, Burns DN, Rooney JF, Glidden DV, iPrEx study t. Uptake of pre-exposure prophylaxis, sexual practices, and HIV incidence in men and transgender women who have sex with men: a cohort study. Lancet Infect Dis. 2014;14(9):820-9. doi: 10.1016/S1473-3099(14)70847-3. PubMed PMID: 25065857; PMCID: PMC6107918.

23. Celum C, Bukusi E, Bekker L-G, Delany-Moretlwe S, Kidoguchi L, Omollo V, Rousseau E, Travill D, Morton J, Mogaka F, O'Malley G, Barnabee G, van der Straten A, Donnell D, Parikh U, Kudrick L, Anderson P, Haberer J, Wu L, Heffron R, Johnson R, Morrison S, Baeten J, POWER Study Team. PrEP initiation, persistence, and HIV seroconversion rates in African adolescent girls and young women (AGYW) from Kenya and South Africa: the POWER demonstration project. HIVR4P Conference (virtual); January 27-28 and February 3-4, 2021. p. Abstract PE16.9.

24. 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, Hillier S, MTN-ASPIRE Study Team. Use of a vaginal ring containing dapivirine for HIV-1 prevention in women. N Engl J Med. 2016;375(22):2121-32. Epub 2016/02/24. doi: 10.1056/NEJMoa1506110. PubMed PMID: 26900902; PMCID: PMC4993693.

25. Nel A, van Niekerk N, Kapiga S, Bekker LG, Gama C, Gill K, Kamali A, Kotze P, Louw C, Mabude Z, Miti N, Kusemererwa S, Tempelman H, Carstens H, Devlin B, Isaacs M, Malherbe M, Mans W, Nuttall J, Russell M, Ntshele S, Smit M, Solai L, Spence P, Steytler J, Windle K, Borremans M, Resseler S, Van Roey J, Parys W, Vangeneugden T, Van Baelen B, Rosenberg Z, Ring Study T. Safety and efficacy of a dapivirine vaginal ring for HIV prevention in women. N Engl J Med. 2016;375(22):2133-43. doi: 10.1056/NEJMoa1602046. PubMed PMID: 27959766.

26. Baeten J, Palanee-Phillips T, Mgodi N, Mayo A, Szydlo D, Ramjee G, Gati Mirembe B, Mhlanga F, Hunidzarira P, Mansoor L, Siva S, Govender V, Makanani B, Naidoo L, Singh N, Nair G,

Chinula L, Parikh U, Mellors J, Balán I, Ngure K, van der Straten A, Scheckter R, Garcia M, Peda M, Patterson K, Livant E, Bunge K, Singh D, Jacobson C, Jiao Y, Hendrix C, Chirenje Z, Nakabiito C, Taha T, Jones J, Torjesen K, Nel A, Rosenberg Z, Soto-Torres L, Hillier S, Brown E, MTN-025/HOPE Study Team. Safety, uptake, and use of a dapivirine vaginal ring for HIV-1 prevention in African women (HOPE): an open-label, extension study. Lancet HIV. 2021;8(2):e87-e95; PMCID: PMC8038210.

27. Nair G, Ngure K, Szydlo D, Brown E, Akello C, Palanee-Phillips T, Macdonald P, Siziba B, Hillier S, Garcia M, Johnson S, Ievy I, McClure T, Soto-Torres L, Celum C. Adherence to the dapivirine vaginal ring and oral PrEP among adolescent girls and young women in Africa: Interim results from the REACH study. 11th IAS Conference on HIV Science (virtual); July 18-20 2021. p. Abstract OALC01LB.

28. World Health Organization. WHO recommends the dapivirine vaginal ring as a new choice for HIV prevention for women at substantial risk of HIV infection 2021 [updated January 26]. Available from: https://www.who.int/news/item/26-01-2021-who-recommends-the-dapivirine-vaginal-ring-as-a-new-choice-for-hiv-prevention-for-women-at-substantial-risk-of-hiv-infection.

29. Landovitz RJ, Donnell D, Clement ME, Hanscom B, Cottle L, Coelho L, Cabello R, Chariyalertsak S, Dunne EF, Frank I, Gallardo-Cartagena JA, Gaur AH, Gonzales P, Tran HV, Hinojosa JC, Kallas EG, Kelley CF, Losso MH, Madruga JV, Middelkoop K, Phanuphak N, Santos B, Sued O, Valencia Huamani J, Overton ET, Swaminathan S, Del Rio C, Gulick RM, Richardson P, Sullivan P, Piwowar-Manning E, Marzinke M, Hendrix C, Li M, Wang Z, Marrazzo J, Daar E, Asmelash A, Brown TT, Anderson P, Eshleman SH, Bryan M, Blanchette C, Lucas J, Psaros C, Safren S, Sugarman J, Scott H, Eron JJ, Fields SD, Sista ND, Gomez-Feliciano K, Jennings A, Kofron RM, Holtz TH, Shin K, Rooney JF, Smith KY, Spreen W, Margolis D, Rinehart A, Adeyeye A, Cohen MS, McCauley M, Grinsztejn B, Team HS. Cabotegravir for HIV prevention in cisgender men and transgender women. N Engl J Med. 2021;385(7):595-608. doi: 10.1056/NEJMoa2101016. PubMed PMID: 34379922; PMCID: PMC8448593.

30. World Health Organization. Trial results reveal that long-acting injectable cabotegravir as PrEP is highly effective in preventing HIV acquisition in women 2021. Available from: https://www.who.int/news/item/09-11-2020-trial-results-reveal-that-long-acting-injectable-cabotegravir-as-prep-is-highly-effective-in-preventing-hiv-acquisition-in-women.

31. Michailidis E, Huber AD, Ryan EM, Ong YT, Leslie MD, Matzek KB, Singh K, Marchand B, Hagedorn AN, Kirby KA, Rohan LC, Kodama EN, Mitsuya H, Parniak MA, Sarafianos SG. 4'-Ethynyl-2-fluoro-2'-deoxyadenosine (EFdA) inhibits HIV-1 reverse transcriptase with multiple mechanisms. J Biol Chem. 2014;289(35):24533-48. doi: 10.1074/jbc.M114.562694. PubMed PMID: 24970894; PMCID: PMC4148878.

32. Grobler J, Fillgrove K, Hazuda D, Huang Q, Lai M, Matthews R, et al. MK-8591 potency and PK provide high inhibitory quotients at low doses QD and QW. Conference on Retroviruses and Opportunistic Infections; March 4-7 Seattle, WA USA 2019. p. Abstract 481.

33. Markowitz M, Gettie A, St Bernard L, Andrews CD, Mohri H, Horowitz A, Grasperge BF, Blanchard JL, Niu T, Sun L, Fillgrove K, Hazuda DJ, Grobler JA. Once-weekly oral dosing of MK-8591 protects male rhesus macaques from intrarectal challenge with SHIV109CP3. J Infect Dis. 2020;221(9):1398-406. doi: 10.1093/infdis/jiz271. PubMed PMID: 31175822.

34. Hillier S, Bekker L-G, Riddler S, Hendrix C, Badal-Faesen S, Rasmussen SJ, Schartz H, Macdonald P, Lombaard J, Caraco Y, Peer A, Patel M, Evans BG, Homony B, Nedrow K, Teal V, Hwang P, Robertson M, Plank R. Safety and Pharmacokinetics of Oral Islatravir Once Monthly

for HIV Pre-exposure Prophylaxis (PrEP): Week 24 Analysis of a Phase 2a Trial 11th IAS Conference on HIV Science (virtual); July 18-22 2021. p. Abstract OALC01LB3.

35. Merck & Co I. Merck announces clinical holds on studies evaluating islatravir for the treatment and prevention of HIV-1 infection. Available from: https://www.merck.com/news/merck-announces-clinical-holds-on-studies-evaluating-islatravir-for-the-treatment-and-prevention-of-hiv-1-infection/2021.

36. Dvory-Sobol H, Shaik N, Callebaut C, Rhee MS. Lenacapavir: a first-in-class HIV-1 capsid inhibitor. Curr Opin HIV AIDS. 2022;17(1):15-21. Epub 2021/12/07. doi: 10.1097/coh.0000000000000713. PubMed PMID: 34871187.

37. Reed Johnson F, Lancsar E, Marshall D, Kilambi V, Mühlbacher A, Regier DA, Bresnahan BW, Kanninen B, Bridges JF. Constructing experimental designs for discrete-choice experiments: report of the ISPOR Conjoint Analysis Experimental Design Good Research Practices Task Force. Value Health. 2013;16(1):3-13. Epub 2013/01/23. PubMed PMID: 23337210.

38. Wang Y, Wang Z, Wang Z, Li X, Pang X, Wang S. Application of discrete choice experiment in health care: a bibliometric analysis. Front Public Health. 2021;9:673698. Epub 2021/06/22. doi: 10.3389/fpubh.2021.673698. PubMed PMID: 34150710; PMCID: PMC8212992.

39. Vickerman P, Quaife M, Kilbourne-Brook M, Mvundura M, Eakle R, Terris-Prestholt F. HIV prevention is not all about HIV - using a discrete choice experiment among women to model how the uptake and effectiveness of HIV prevention products may also rely on pregnancy and STI protection. BMC Infect Dis. 2020;20(1):704. Epub 2020/09/27. doi: 10.1186/s12879-020-05399-4. PubMed PMID: 32977745; PMCID: PMC7517801.

40. Minnis AM, Atujuna M, Browne EN, Ndwayana S, Hartmann M, Sindelo S, Ngcwayi N, Boeri M, Mansfield C, Bekker LG, Montgomery ET. Preferences for long-acting pre-exposure prophylaxis (PrEP) for HIV prevention among South African youth: results of a discrete choice experiment. J Int AIDS Soc. 2020;23(6):e25528. Epub 2020/06/17. doi: 10.1002/jia2.25528. PubMed PMID: 32544303; PMCID: PMC7297460.

41. Van Damme L, Corneli A, Ahmed K, Agot K, Lombaard J, Kapiga S, Malahleha M, Owino F, Manongi R, Onyango J, Temu L, Monedi MC, Mak'Oketch P, Makanda M, Reblin I, Makatu SE, Saylor L, Kiernan H, Kirkendale S, Wong C, Grant R, Kashuba A, Nanda K, Mandala J, Fransen K, Deese J, Crucitti T, Mastro TD, Taylor D. Preexposure prophylaxis for HIV infection among African women. N Engl J Med. 2012;367(5):411-22. Epub 2012/07/13. doi: 10.1056/NEJMoa1202614. PubMed PMID: 22784040.

42. Marrazzo J, Ramjee G, Nair G, Palanee T, Mkhize B, Nakabiito C, Taljaard M, Piper J, Gomez Feliciano K, Chirenje M, VOICE Study Team. Pre-exposure prophylaxis for HIV in women: daily oral tenofovir, oral tenofovir/embricitabine, or vaginal tenofovir gel in the VOICE study (MTN 003). Conference Retroviruses and Opportunistic Infections; March 3-6 Atlanta, GA USA 2013. p. Abstract 26LB.

43. Gao F, Bannick M. Statistical Considerations for Cross-Sectional HIV Incidence Estimation Based on Recency Test 2021. Available from: https://arxiv.org/abs/2106.01997.

44. Rice BD, de Wit M, Welty S, Risher K, Cowan FM, Murphy G, Chabata ST, Waruiru W, Magutshwa S, Motoku J, Kwaro D, Ochieng B, Reniers G, Rutherford G. Can HIV recent infection surveillance help us better understand where primary prevention efforts should be targeted? Results of three pilots integrating a recent infection testing algorithm into routine programme

activities in Kenya and Zimbabwe. J Int AIDS Soc. 2020;23 Suppl 3(Suppl 3):e25513. Epub 2020/07/01. doi: 10.1002/jia2.25513. PubMed PMID: 32602625; PMCID: PMC7325505.

45. Duong YT, Kassanjee R, Welte A, Morgan M, De A, Dobbs T, Rottinghaus E, Nkengasong J, Curlin ME, Kittinunvorakoon C, Raengsakulrach B, Martin M, Choopanya K, Vanichseni S, Jiang Y, Qiu M, Yu H, Hao Y, Shah N, Le LV, Kim AA, Nguyen TA, Ampofo W, Parekh BS. Recalibration of the limiting antigen avidity EIA to determine mean duration of recent infection in divergent HIV-1 subtypes. PloS one. 2015;10(2):e0114947. doi: 10.1371/journal.pone.0114947. PubMed PMID: 25710171; PMCID: PMC4339840.

46. Duong YT, Dobbs T, Mavengere Y, Manjengwa J, Rottinghaus E, Saito S, Bock N, Philip N, Justman J, Bicego G, Nkengasong JN, Parekh BS. Field validation of limiting-antigen avidity enzyme immunoassay to estimate HIV-1 incidence in cross-sectional survey in Swaziland. AIDS Res Hum Retroviruses. 2019;35(10):896-905. doi: 10.1089/AID.2018.0284. PubMed PMID: 31204867.

47. Kassanjee R, Pilcher CD, Busch MP, Murphy G, Facente SN, Keating SM, McKinney E, Marson K, Price MA, Martin JN, Little SJ, Hecht FM, Kallas EG, Welte A, Consortium for the E, Performance of HIVIA. Viral load criteria and threshold optimization to improve HIV incidence assay characteristics. AIDS. 2016;30(15):2361-71. doi: 10.1097/QAD.0000000000001209. PubMed PMID: 27454561; PMCID: PMC5024345.

48. Stacey D, Legare F, Col NF, Bennett CL, Barry MJ, Eden KB, Holmes-Rovner M, Llewellyn-Thomas H, Lyddiatt A, Thomson R, Trevena L, Wu JH. Decision aids for people facing health treatment or screening decisions. Cochrane Database Syst Rev. 2014(1):CD001431. Epub 2014/01/29. doi: 10.1002/14651858.CD001431.pub4. PubMed PMID: 24470076.

49. Mathijssen EGE, van den Bemt BJF, van den Hoogen FHJ, Popa CD, Vriezekolk JE. Interventions to support shared decision making for medication therapy in long term conditions: A systematic review. Patient Educ Couns. 2020;103(2):254-65. Epub 2019/09/09. doi: 10.1016/j.pec.2019.08.034. PubMed PMID: 31493959.

50. Sewell WC, Solleveld P, Seidman D, Dehlendorf C, Marcus JL, Krakower DS. Patient-led decision-making for HIV preexposure prophylaxis. Curr HIV/AIDS Rep. 2021;18(1):48-56. Epub 2021/01/09. doi: 10.1007/s11904-020-00535-w. PubMed PMID: 33417201; PMCID: PMC8086908.

51. Seidman D, Traveill D, Celum C, Dehlendorf C, Mdlovu M, Zewdie D, Donnell D, Morton J, Baeten J, Delany-Moretlwe S. MyPrEP Decision Support Tool increases PrEP persistence in adolescent girls and young women attending an urban primary health care clinic in South Africa. HIVR4P Conference (virtual); January 27-28 and February 3-4 2021. p. Abstract PE01.62LB.

52. Cottrell ML, Yang KH, Prince HM, Sykes C, White N, Malone S, Dellon ES, Madanick RD, Shaheen NJ, Hudgens MG, Wulff J, Patterson KB, Nelson JA, Kashuba AD. A translational pharmacology approach to predicting outcomes of preexposure prophylaxis against HIV in men and women using tenofovir disoproxil fumarate with or without emtricitabine. J Infect Dis. 2016;214(1):55-64. doi: 10.1093/infdis/jiw077. PubMed PMID: 26917574; PMCID: PMC4907409.

53. Drain PK, Kubiak RW, Siriprakaisil O, Klinbuayaem V, Quame-Amaglo J, Sukrakanchana PO, Tanasri S, Punyati P, Sirirungsi W, Cressey R, Bacchetti P, Okochi H, Baeten JM, Gandhi M, Cressey TR. Urine tenofovir concentrations correlate with plasma and relate to tenofovir disoproxil fumarate adherence: a randomized, directly observed pharmacokinetic trial (TARGET

Study). Clin Infect Dis. 2020;70(10):2143-51. Epub 2019/07/18. doi: 10.1093/cid/ciz645. PubMed PMID: 31314073; PMCID: PMC7201421.

54. Stalter RM, Baeten JM, Donnell D, Spinelli MA, Glidden DV, Rodrigues WC, Wang G, Vincent M, Mugo N, Mujugira A, Marzinke M, Hendrix C, Gandhi M. Urine tenofovir levels measured using a novel immunoassay predict human immunodeficiency virus protection. Clin Infect Dis. 2021;72(3):486-9. Epub 2021/02/03. doi: 10.1093/cid/ciaa785. PubMed PMID: 33527128; PMCID: PMC7850546.

55. Spinelli MA, Glidden DV, Rodrigues WC, Wang G, Vincent M, Okochi H, Kuncze K, Mehrotra M, Defechereux P, Buchbinder SP, Grant RM, Gandhi M. Low tenofovir level in urine by a novel immunoassay is associated with seroconversion in a preexposure prophylaxis demonstration project. Aids. 2019;33(5):867-72. Epub 2019/01/17. doi: 10.1097/qad.0000000000002135. PubMed PMID: 30649051; PMCID: PMC6375797.

56. Gandhi M, Bacchetti P, Spinelli MA, Okochi H, Baeten JM, Siriprakaisil O, Klinbuayaem V, Rodrigues WC, Wang G, Vincent M, Cressey TR, Drain PK. Brief Report: Validation of a Urine Tenofovir Immunoassay for Adherence Monitoring to PrEP and ART and Establishing the Cutoff for a Point-of-Care Test. Journal of acquired immune deficiency syndromes. 2019;81(1):72-7. Epub 2019/01/22. doi: 10.1097/qai.0000000000001971. PubMed PMID: 30664078; PMCID: PMC6456396.

57. Balkus JE, Brown E, Palanee T, Nair G, Gafoor Z, Zhang J, Richardson BA, Chirenje ZM, Marrazzo JM, Baeten JM. An empiric HIV risk scoring tool to predict HIV-1 acquisition in African Women. Journal of acquired immune deficiency syndromes. 2016;72(3):333-43. Epub 2016/02/27. doi: 10.1097/QAI.0000000000000974. PubMed PMID: 26918545; PMCID: PMC4911322.