CHAMPS: CHOICES FOR ADOLESCENT PREVENTION METHODS FOR SOUTH AFRICA

Pilot study B: "PlusPills"

A Demonstration Open Label Study to Assess the Acceptability and Use of Truvada Pre-exposure Prophylaxis in Healthy, HIV-Uninfected Adolescents, 15-19 Years of Age.

Sponsored by:

Desmond Tutu HIV Foundation

University of Cape Town.

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Division of AIDS (DAIDS), United States (US) National Institute of Allergy and Infectious Diseases (NIAID) and US National Institutes of Health (NIH)

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LIST OF ABBREVIATIONS

AE	Adverse Event
AIDS	Acquired Immune Deficiency Syndrome
CRF	Case Report Form
CRO	Contract Research Organization
DAIDS	Division of AIDS
DBS	Dried Blood Spot
DTHF	Desmond Tutu HIV Foundation
DSMB	Data Safety Monitoring Board (DSMB)
FDA	Food and Drug Administration
FTC	Emtricitabine
GCP	Good Clinical Practice
HCT	HIV Counseling and Testing
HIV	Human Immunodeficiency Virus
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
MCC	Medicine Control Council
N	Number (typically refers to participants)
NIAID	National Institute of Allergy and Infectious Diseases
NIH	National Institutes of Health
PEP	Post-Exposure Prophylaxis
PrEP	Pre-Exposure Prophylaxis
PI	Principal Investigator
QA	Quality Assurance
QC	Quality Control
SAE	Serious Adverse Event

SMC	Safety Monitoring Committee
SOP	Standard Operating Procedure
TDF	Tenofovir Disoproxil Fumarate

INVESTIGATOR SIGNATURE PAGE

Version 2.0

Sponsored by:

Desmond Tutu HIV Foundation

The signature below constitutes the approval of this protocol and the attachments, and provides the necessary assurances that this study will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to all applicable legal and regulatory requirements and regulations as well as ICH and SA GCP guidelines.

I, as the Principal Investigator, agree to conduct this study in full accordance with the provisions of this protocol. Publication of the results of this study will be governed by DTHF policies.

I have read and understand the information in this protocol and will ensure that all associates, colleagues, and employees assisting in the conduct of the study are informed about the obligations incurred by their contribution to the study.

Principal Investigator:

Signed: _____ Date: _____

Name:

Title:

PROTOCOL SUMMARY

Purpose:	To assess the Acceptability, safety and use of daily oral PrEP (FTC/TDF or Truvada®) in healthy, HIV-uninfected adolescents, 15-19 years of age
Primary objective	1. To evaluate the Acceptability and Use of a daily regimen of oral PrEP (FTC/TDF), as a component of a comprehensive HIV prevention package [with HIV testing, STI management, risk reduction counseling, access to condoms, PEP, counseling and referral for male circumcision (for boys)], for adolescents between 15 and 19 years of age. 2. To evaluate the safety of a daily regimen of oral PrEP (FTC/TDF), as a component of a comprehensive HIV prevention package [with HIV testing, STI management, risk reduction counseling, access to condoms, PEP, counseling and referral for male circumcision (for boys)], for adolescents between 15 and 19 years of age.

Secondary objective	1. To evaluate adherence to a daily regimen of oral PrEP (FTC/TDF), as a component of a comprehensive HIV prevention package for adolescents between 15 and 19 years of age. 2. To evaluate change in sexual activity, perceptions of sexual risk, risk compensation, and health behaviours, including condom use, in adolescents, between 15 and 19 years of age, who take a daily regimen of oral PrEP (FTC/TDF) over a 12 month period. 3. To assess study participants' and their partners' perceptions on key issues associated with oral PrEP (FTC/TDF), including adherence barriers, adherence facilitators, and general product knowledge, as part of a comprehensive HIV prevention package [with HIV testing, STI management, risk reduction counseling, access to condoms, PEP, counseling and referral for male circumcision(for boys)]. 4. To assess HIV incidence in study participants during the course of study participation
Exploratory objectives	1. To explore the utility of Dried Blood Spot (DBS) and the impact of biofeedback of results as an adherence enhancing strategy, among HIV-negative adolescents, between 15 and 19 years of age 2. To explore the relationship between daily PrEP usage and sexual practices and behavior in adolescents.

Design	The study is designed as an open-label, single arm cohort study, to evaluate the Accetability, safety and Use of daily oral PrEP (FTC/TDF) in 150 adolescents (approximately 75 participants at each site), ages 15-19 years, their adherence to study product, and any changes in their sexual and health behaviors over a 12-month (52 week) period. All participants will complete an initial (12 week) 3- month period, during which they will receive PrEP as part of a combination prevention package. At all subsequent visits, participants will be offered the opportunity to hear real-time feedback of drug level data as part of their adherence counseling or they may choose to have adherence counseling without the feedback of drug level data. The decision about feedback as well as self reported adherence will be captured via interviewer administed questionnaires at each follow up visit. At the first 3 month (week 12) visit and 3 monthly (weeks 24, 36, 48) intervals thereafter participants will be offered the following options: full package + PrEP, stop PrEP and continue with rest of package or alternatively re-start PrEP if previously stopped. This will occur during protocol-specified study visits. Participants will be followed regardless of PrEP usage for a total of 12 months (52weeks). PrEP may be stopped at any other clinic visit but recommencement can only occur at a scheduled visit when all medical criteria are met including a negative HIV test. Adherence counselling will be offered at every visit with options to have drug level feedback or not as part of this counselling.
Study site	The study will be conducted at The Desmond Tutu HIV Foundation research site in Masiphumelele, Cape Town and the Perinatal HIV Research Unit (PHRU) site in Soweto, near Johannesburg.
Study drugs	FTC/TDF or Truvada® is a 200mg/300mg fixed dose combination tablet containing emtricitabine (FTC) and tenofovir disoproxil fumarate (TDF).
Study population	Healthy, HIV-uninfected adolescents, 15 and 19 years of age
Number of participants	150 enrolled participants (approximately 75 participants at each site)

Treatment Regimen	Participants will be provided with a supply of FTC/TDF tablets, taken orally, once daily for first 3 months. Thereafter, these tablets will only be supplied to those who indicate willingness to take PrEP and who do not have a clinical contraindication to do so.
Study Duration	Participants will be scheduled to participate in the study for 12 months or 52 weeks. Accrual will require approximately 4 months (16 weeks).
Duration of participation	Each participant will be scheduled to receive study product for 52 weeks.
Primary endpoints	Acceptability o The proportion of participants who report willingness to use the study regimen, take up PrEP and remain on PrEP as part of a comprehensive prevention package. o Assessment of acceptabiltiy as per questionnaire administered at study end. Use o Number of adolescents who continue to use PrEP after the initial 3 month period. o The total time on PrEP for each adolescent and for the cohort as a whole by self report. Safety o Grades 2, 3, and 4 clinical and laboratory adverse events;

Secondary endpoints	Adherence: Adherence to daily regimens of oral PrEP as evidenced by the use of self-report, pill counts, and proportion of participants on FTC/TDF who have detectable drug levels, in those participants who have indicated willingness to take PrEP and who have had tablets administered o Proportion of doses that are taken as instructed. o Proportion of blood samples with detectable drug levels o Proportion of adolescents with detectable drug levels who report using PrEP o Proportion of scheduled HIV testing appointments missed, in relation to individual characteristics (age, sex, number of partners, use of other prevention methods) and the characteristics of the product. Sexual Behavior o Reported number of steady and casual sex partners, condom use (and change after introduction of study product), substance use prior to or during sex, as evidenced by participant responses to interviewer-administered questionnaires and focus groups. HIV Incidence HIV infection, as measured by seroconversion of study participants during the approximate 12 months (52 weeks) of follow-up.

Exploratory endpoints	Impact on adherence of drug (FTC/TDF) levels as measured in Dried Blood Spot/Plasma given as biofeedback o Number of counselling opportunities in which drug level feedback is requested vs total number of counseling events o Number and nature of participants who request drug level feedback. o Correlation between self reported adherence and drug levels at each visit for each participant o Correlation between self reported adherence and drug levels at each visit in the study overall. o Proportion and number of participants whose adherence ito study product improves when receiving the results of DBS/Plasma compared to those who do not receive feedback of results as measured by endpoints above. Relationship between daily PrEP usage and sexual practices and behavior in adolescents o Sexual behavior data obtained using a questionnaire and focus group.

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2 BACKGROUND

2.1 HIV PREVALENCE AND ADOLESCENTS

Young people remain at the centre of the HIV/AIDS epidemic in terms of rates of infection, vulnerability, impact, and potential for change. In 2008, young people accounted for 40% of all new HIV infections in 15-49 year olds. Almost 3000 young people are infected with HIV each day. One third of women who are living with HIV are between 15 and 24 years of age. More than 4.3 million young people worldwide are believed to be living with HIV, and a majority of them are unaware of their HIV status (UNAIDS, 2009).

2.2 HIV PREVALENCE AND ADOLESCENTS IN SOUTH AFRICA

South Africa has one of the highest HIV prevalences in the world, with an estimated 17% of the population aged 15-49 infected (Shisana O, et al 2009, 2014). As in other African countries, HIV incidence rates in South African women peak in the 15-24 age group, while HIV incidence rates in men tend to be higher in slightly older age groups. (Hallett T, et al 2010, Rehle T, et al 2010) Our best modelling estimates suggest that in South Africa an estimated 36% of all heterosexual transmission of HIV occurs in the 15-24 age group, and that this proportion is substantially higher (up to 45%) among women (Johnson L, et al 2009). From this it is clear that young people, and young women especially, are a key target in preventing the spread of HIV at the population level.

South African adolescents are at risk for HIV infection for a number of reasons. Behavioural research indicates that sexual activity is initiated at an early age in South African (mean age of 14.6 years), and that young people have multiple partners and use condoms less consistently compared to older age groups. For example, research conducted among high school students in Cape Town demonstrated that initiation of sexual activity for many youth begins as early as age 13 (13% among girls and 31% among boys). A substantial proportion (14% of girls and 26% of boys) at the average age of 13 years reported that they intended to have sexual intercourse in the next 6 months (Matthews C, et al 2009). More than half of South Africans aged 15–24 years, have had sex by age 18 (Shisana o et al 2005,2014h). Once sexually active, adolescents engage in sexual behaviour that continues to place them at risk. In a review of unsafe sexual behaviour among South African youth,

50 to 60% reported not using condoms (Eaton L, et al 2003). Findings from a national survey indicated a high incidence of multiple concurrent partners in adolescents (Pettifor et al; 2004) and this is often related to a history of substance use and early sexual experience (Mpofu E, et al 2006). Transgenerational and transactional sex have both been shown to be frequent behaviours among South African youth and both are associated with HIV.

Adolescents are a diverse population and given their unique psychosocial, cognitive, physiological, and neurological developmental issues, they urgently require targeted, innovative, and responsive HIV prevention technologies and products that address these needs and help them to adopt health behaviours.

2.3 CHAMPS: CHOICES FOR HIV ADOLESCENT METHODS OF PREVENTION IN SOUTH AFRICA

Since HIV made its debut almost 30 years ago, much has been learnt about prevention of the disease. Knowledge about HIV transmission, safer sex practices, pre-and post-exposure prophylaxis, male circumcision, the role of key interventions to prevent HIV transmission from mother-to-child, harm reduction initiatives for people who use drugs and rights-based approaches have dramatically altered the prevention landscape.

Presently, however, there is no single intervention that protects all susceptible individuals against HIV. Currently available and anticipated prevention methods, both biomedical and behavioural, will only provide a degree of protection. Additionally, research in sub-Saharan Africa, which has previously emphasized a “one size fits all” approach to behavioural prevention strategies, and has generally assumed that prevention interventions of demonstrated efficacy and acceptability in adults will be easily generalizable to adolescents.

In the context of this emerging evidence for efficacy and adaptability of various HIV prevention options and their appropriateness for adolescents, the CHAMPS (Choices for HIV Adolescent Methods of Prevention in South Africa) project will address this gap through a novel approach to combining different HIV prevention strategies
Into an optimized prevention ‘menu’ for adolescents, from which young women and men at risk of

HIV infection may choose a particular combination of strategies to meet their specific needs and circumstances. The negative results from the randomized placebo controlled trials of VOICE (MTN 003) and FEMPREP conducted among African women in which low levels of study product was found in participants samples have made the conduct of the CHAMPS studies more compelling than ever: it may be that small open label studies that are able to interrogate reasons why individuals may be interested in PrEP as a prevention intervention but then discontinue medication when no longer desirable as well as whether the role of choice and mode of administration may have an impact in overall effectiveness.

The CHAMPS project will be comprised of three pilot studies rolled out as a series of small, focused, interrelated protocols. Each study will examine specific questions or research gaps related to adolescents (ages 15-19 years old) and one of the following HIV prevention strategies:

1. Modes of PrEP administration “Uchoose”,
2. Pre-exposure prophylaxis- (PrEP) “Pills plus”,
3. Male circumcision “Macho”.

Each of the study protocols will submitted for ethical and regulatory approval separately.

The findings from the three pilot studies will feed into a fourth, separately proposed study that will examine adolescents’ decision making, the efficacy of a ‘menu’ approach for HIV prevention options, and the impact of messaging about each option on the adolescents’ selection. This will have a large social marketing component: “iChoose”.

Results from all four studies will be used to inform epidemiological modeling and costing exercises in order to inform how an HIV prevention ‘menu’ should be constructed and promoted among young people for maximum benefit. The first modeling analysis will focus on the effect of the specific prevention package on HIV incidence in adolescents participating in a trial setting, over the duration of the trial. The second modeling analysis will focus on the impact of the prevention package on HIV incidence in the general population over the longer term, taking into account the extent to which adolescents interact with the adult population and the extent to which adherence to the intervention is sustained as adolescents enter into adulthood. Both modeling exercises will attempt to assess which components of the intervention package have the greatest impact and

which components are relatively cost-effective, in order to inform the selection of interventions that are evaluated in efficacy trials.

2.4 ORAL PRE-EXPOSURE PROPHYLAXIS (PREP) AS AN HIV PREVENTION INTERVENTION

For adolescents and young adults, the use of PrEP may be most useful in preventing HIV infection during the high-risk years of youth. A growing body of neurobiological research and imaging studies suggest that adolescents may be especially prone to engage in risky behaviors, including sexual risk and substance abuse, due to developmental changes in the brain (Galvan et al., 2007). Thus, PrEP in youth may be viewed as a time-limited strategy that can bridge the developmental period between sexual debut and adulthood.

While the potential relevance and plausibility of an oral PrEP strategy as a safe, powerful and time-limited tool for HIV prevention among high risk people is widely acknowledged (Cohen et al, 2008), a number of questions regarding the use of PrEP still need to be addressed. These issues include, but are not limited to, the identification of the best drug(s) and optimal dosing regimens in terms of efficacy, safety, adherence and cost-efficiency, designing an effective message that does not reduce the salience of reducing sexual risk behaviors, and the acceptability of a PrEP prevention strategy within different populations. Many of these issues have been or are being studied currently among adult population [see Section 2.6.5. For an overview]. However, there are no data for adolescents and young adults. Thus, the feasibility of recruiting and retaining youth participants in a PrEP study, the evaluation of the acceptability of such a study among adolescents, and the evaluation of adherence to the PrEP regimen are all issues that need to be urgently addressed.

2.5 STUDY HYPOTHESIS AND RATIONALE

This study aims to assess the acceptability, and use, primarily, as well as adherence, and safety of daily oral PrEP (FTC/TDF) for HIV-1 prevention, among 150 male and female adolescent participants at two sites (with approximately 75 participants at each site), ranging in ages between 15 and 19 years old. Willing participants will be asked after consent and enrollment to take daily oral PrEP for 3 months. After this period they will be asked to say whether they would like to continue or discontinue oral PrEP as part of a prevention package whilst continuing follow up. This question will

be posed at the following 2 three monthly intervals (Month 6 (24 weeks) and month 9 (36 weeks) until a full 12 months of follow up are complete. Participants will be encouraged to remain on the full prevention package including PrEP but will also be informed that should they wish to stop PrEP they can be followed without PrEP usage. They will be offered PrEP as part of the full package at the next 3-month visit. All participants will complete a questionnaire that will explore choices around use/non-use of PrEP at these visits and will also complete a short acceptability questionnaire. In addition for those who self report PrEP usage, adherence will be assessed.

The rationale for this study design is based on some of the feedback received from the VOICE and FEMPREP studies. Women in these studies reported high PrEP usage, remained in study and yet drug levels indicated very poor PrEP usage (Marazzo et al CROI 2013). Some rationale for this has been that PrEP acceptability was low, but with a keen perception among participants that study participation hinged on pill adherence. Thus, despite information that drug levels would be assessed, participants chose to report pill usage falsely. By making it very clear that trial participation does NOT hinge on PrEP usage (other than the first 3 months) we hope that we will get a more accurate assessment of real PrEP usage. We also hope that if participants really want to be taking PrEP, that adherence to product will persist. Other open label studies such as iPrEx OLE suggest this may be the case. By designing the study with an “opt out” arm we hope that we will create an authentic comparator group for participants taking oral PrEP (FTC/TDF) persistently and adherently, in order to assess any significant differences in adolescents taking oral PrEP (FTC/TDF) versus those who choose NOT to do so. We recognize that these may include demographic differences but may also include perceptions of risk, sexual activity, etc. In addition, we hope that this will give us a true sense of pill usage among this population- data that is currently unknown and required in order to more accurately model the impact of this intervention in this age group.

Both groups will be treated equally, except for administration of TDF/FTC therapy to those who select to include PrEP in their prevention package.
It was felt by the protocol team that the question of use and acceptability would best be answered by employing an open label design, The three month initial phase will mean that everyone will at least be exposed to 3 months of PrEP usage.

Adherence to medication can be measured in different ways depending on the condition and the

medication in question. Besides usual patient self report of doses correctly taken, adherence may be calculated by performing pill counts on pill returns, or else symptoms may be monitored or drug levels in blood or urine measured. In HIV treatment, plasma viral load is measured to ensure appropriate response to therapy but is also used in practice as a measure of adherence. In the latter case, viral load suppression or not may be used during counseling to probe whether a patient has been adherent to antiretrovirals or not. Up until recently, the use of antiretrovirals as prophylaxis for HIV prevention has been difficult to monitor but increasingly more laboratories are setting up assays to measure drug levels in plasma, cells and even in dried blood spots. To date, this data has been used to confirm or refute self-reported adherence in prevention trials. In this protocol, we would like to explore the feasibility of drug levels of TDF/FTC derived from DBS to enhance adherence counseling. Drug levels will be performed real time during the study. Participants who have indicated PrEP usage and who return to the study site will be asked about their adherence. They will be asked to grade their adherence on a scale since the last visit. They will also be asked specific questions about missed doses as well as barriers and facilitators to adherence. They will then be asked whether they wish to have their drug levels disclosed to them. If they choose yes, they will be told the level and motivational counseling will be structured around this result. Should they choose NOT to have the level disclosed to them, they will be asked to give a reason and to guess what they think it may be. This data will be recorded on a CRF.

All participants will be offered motivational adherence counselling on their return visit as long as they are taking PrEP (this will apply should they stop and restart PrEP during the course of the study). Participants at each visit will also be asked whether they wish to receive feedback of plasma drug levels, in order to explore the impact of this intervention on adherence. Participants who choose on a follow up visit to NOT receive their blood drug levels will still receive the standard adherence counselling during their study visit. In participants who have opted NOT to take PrEP they will be followed up as usual with risk reduction counseling, but without additional PrEP adherence counseling. A safety team will also review blood drug levels and in a case where excessively high blood levels are reported, staff will be informed to investigate possible pill overusage. This information WILL be relayed to the site staff regardless of randomisation to ensure follow up with participants on possible drug over-use. In addition, drug levels will be available to site staff regardless of whether participants choose to hear the results of not. Counselors will be trained in motivational counseling and will also be trained on how to use the drug levels during

counseling if participants request this.

Dried Blood Spot sampling is an easy and inexpensive way of collecting, shipping and storing blood samples. It represents an alternative to the body fluid based method (plasma, liquid blood or serum). As a microsampling technique, it has gained increasing importance since this method offers strong advantages compared to the conventional collection and analysis of blood or plasma samples. These advantages include the need for remarkably lower blood volumes and easier shipping and storage, at ambient temperatures. This leads to a simplification of the blood collection process and a reduction of the costs involved. In addition, it offers the possibility of both cellular and non-cellular drug levels which may indicate more consistent adherence (in the case of cellular drug levels) than recent drug levels (non-cellular). This negates the need for large amounts of blood collection, cellular extraction and special storage required in order to assay peripheral blood mononuclear cells. These samples will be collected along with the plasma samples for drug levels, and stored.

DBS analysis for TDF drug levels has now been sufficiently validated such that concurrent plasma levels are not required (Castillo-Mancilla et al 2013). DBS cellular assays are still being validated and so whilst these tests will be done later, for the purposes of this proposal, the equivalent non-cellular assay will be done on the DBS in order to provide real time feedback to the randomised participants within the next monthly visit. The DBS will be from venous (as to capillary) blood which is currently validated.

We hypothesize that oral, daily PrEP (FTC/TDF) will be acceptable and used by HIV-negative adolescents, 15-19 years of age and in those who opt to use PrEP, PrEP adherence will be enhanced through client centered, motivational adherence counselling that includes feedback about blood drug levels.

The study will focus on adolescents in South Africa, where HIV prevalence among youth is high but involvement in HIV prevention clinical studies has been low. The study's outcomes will contribute to important prior and current research and will ultimately help build an innovative menu of prevention approaches for adolescents that allows for developmental variation and cultural

sensitivity.

Recent findings show both safety and efficacy of PrEP in adult populations (including men and transgender women who have sex with men; discordant heterosexual couples, and uninfected heterosexual men and women). [See section 2.6.5: Studies of Tenofovir and PrEP in Human Participants]. In addition, the iPrEx OLE study enrolled youth to receive PrEP and two adoelscents studies, ATN 110 and 113 are currently enrolling young MSM aged 15-22years in the USA.

Given the scarcity of data for PrEP and adolescents and as gaps in our knowledge persist, the integration of adolescents into HIV biomedical research is critical for the following reasons:

- Outcomes from research involving adolescents may strengthen capacity to create efficacious country-level heath policies and prevention programmes that are truly responsive to the needs of this population.

- Research suggests that any prevention strategy would be well targeted to young people at the time of sexual debut in order to reduce the steep increase in incidence rates seen in youth shortly thereafter. Sexual debut in South Africa occurs at a mean age of 14.6 years. To this end, a number of research agencies, researchers, and the US Food and Drug Administration advise that adolescents are included in safety studies as soon as safety and efficacy of a prevention strategy has been shown in adult populations. It is further recommended in these and other related documents that this be done in a stepwise fashion with gradual roll down in age (US Food and Drug Administration; 2006).

- Due to the distinct physical, social, emotional, and cognitive differences between adults and adolescents, it is necessary to test safety and acceptability of interventions in the population in question and not merely extrapolate from adults. It cannot be assumed that results of adult HIV prevention trials will fully apply to this younger age group.

- Lastly, it seems both timely and necessary to conduct related research in the South African context, where the greatest burden of adolescent HIV incidence and prevalence is felt.

2.6 STUDY PRODUCTS

2.6.1 FTC/TDF (emtricitabine, tenofovir disoproxil fumarate)

FTC/TDF or Truvada® is a fixed-dose combination of emtricitabine or FTC (5-fluoro-1-(2R,5S)-[2-(hydroxymethyl)-1,3-oxatholan-5-yl]cytosine) and tenofovir or TDF (9-[(R)-2[[bis[[(isopropoxycarbonyl)oxy]methoxy]phosphinyl]methoxy]propyl]adenine fumarate), hereafter referred to as FTC /TDF. FTC and TDF are reverse transcriptase inhibitors that have been licensed for the treatment of HIV-1 infection in adults and pediatric patients, 12 years and older (Truvada, GILEAD Sciences 2011) by the U.S. Food and Drug Administration (FDA) and, in 18 years and older, by the Medicines Control Council (MCC) in South Africa. Additionally, an application for PrEP licensure approval has recently been submitted to the Food and Drug Administration (FDA), and in January 2012, the FDA has approved Viread® (tenofovir disoproxil fumarate) in combination with other antiretroviral agents for the treatment of HIV-1 infection in pediatric patients ages 2-12 (Viread, Gilead Sciences 2013) and FTC is approved for use in children 3 months and older (Emtriva, Gilead Sciences 2012).

2.6.2 Choice or product.

TDF and FTC have demonstrated outstanding safety and efficacy in human clinical trials (CDC 2011). TDF has characteristics that make it suitable for evaluation as a chemoprophylaxis agent. These characteristics include: prolonged intracellular half-life that allows once-a-day dosing, high levels of tolerability, potent antiviral effects, and selection of drug-resistant variants that have mutations associated with diminished viral replication capacity. There are more than 3 million patient years of experience with Tenofovir based products worldwide. It is also the most tested antiviral agent for purposes of HIV prophylaxis and is currently FDA (USA) approved for this purpose in MSM and at risk heterosexual individuals.

2.6.3 Strength of Study Product

Co-formulation of FTC and TDF has been approved by the FDA and MCC for use for treatment of HIV-1 infection, in combination with other antiretroviral drugs. This once daily

film-coated tablet contains the active ingredients of 200 mg of FTC and 300 mg of TDF, which is the FDA's recommended dose of Truvada for treating HIV-infected adults and adolescents 12 years and older. Further information on Truvada® is available in the current package insert.

2.6.4 Animal Studies of Tenofovir and PrEP

Much of the interest in PrEP stems from studies using TDF in rhesus monkeys. In the first studies investigators injected macaque monkeys with large doses of simian-human immunodeficiency virus (SHIV) containing roughly 1000 times the viral load equivalent of that in human semen during acute HIV infections. The macaques were given subcutaneous injections of TDF once daily for 4 weeks starting either 48 hours before, 4 hours after, or 48 hours after intravenous challenge with SIV. All 10 control animals had established viremia within 3 weeks, while the 15 macaques that received TDF prior to viral challenge remained SIV-uninfected for 56 weeks.

A subsequent study examined use of TDF to prevent SIV transmission via weekly rectal exposure of SHIV in doses that were about five times higher than the amount of HIV ribonucleic acid (RNA) in human semen during acute HIV infection (Subbarao et al., 2006). Twelve male macaques were included in the study – four received once-daily oral TDF, four received once-weekly oral TDF, and four control animals received no TDF. Macaques receiving once-daily TDF became infected after a median of six weeks, while those receiving the drug once weekly became infected after a median of seven weeks. One monkey receiving daily TDF remained uninfected after all 14 SHIV exposures. The control animals not receiving TDF became infected after receiving a median of 1.5 virus inoculations (i.e., between weeks 1 and 2).

Another study used the same low-dose challenge model to evaluate the efficacy of TDF combined with another drug, FTC (Garcia-Lerma et al., 2006). Six macaques received once-daily injections of TDF and FTC while six animals served as controls. Four controls became infected after four challenges (5/6 controls were infected by the 10th challenge) while none

of the recipients of TDF/FTC became infected even after 14 challenges. The results were highly statistically significant. Just released results from a continuation of this study investigated the use of PrEP to prevent rectal HIV transmission in macaques. Results showed that macaques in any of the four treatment groups were less likely to become infected than those in the comparison condition. In particular, all of the macaques that received the TDF/FTC combination were protected from infection (Garcia-Lerma et al., 2008).

The most recently published PrEP study in animals investigated vaginal transmission of HIV in humanized bone marrow liver thymic (BLT) mice. This study, using TDF/FTC, found that PrEP using ARVs was highly effective for preventing vaginal HIV transmission. The authors report that none (0%) of the BLT mice that received PrEP became infected after inoculation with HIV as compared to 88% of BLT mice that did not receive PrEP. Thus, BLT mice pretreated with ARVs were resistant to intravaginal HIV infection (Denton et al., 2008). Finally, a paper presented at the 2008 International AIDS Society conference reported on the efficacy of a TDF/FTC topical gel applied vaginally in macaques. All macaques receiving the gel had complete protection against multiple exposures (Parikh et al., 2009).

Two abstracts presented at the 2009 Conference on Retroviruses and Opportunistic Infections (CROI) showed additional promising results for PrEP in animal studies. Dobard and colleagues (2012) demonstrated that both TDF and FTC/TDF offered complete protection against SHIV among macaques after repeated vaginal exposure. Garcia-Lerma and colleagues (2009) presented data that showed protection against HIV in macaques who received FTC/TDF intermittently. These animal studies suggest that FTC/TDF as PrEP does not need daily dosing and that there are several highly protective intermittent PrEP modalities (Cong M-E, et al 2011).

2.6.5 Studies of Tenofovir and PrEP in Human Participants

These and other encouraging animal studies have prompted investigators to initiate multiple clinical studies of PrEP, which have provided further data on its safety and efficacy. A summary of completed and ongoing PrEP studies is contained in Table 1 below.

Table 1. Completed and Ongoing Studies of Oral PrEP

Study	Population	N	Results
CAPRISA 004 *South Africa*	Women	889	39% [CI = 6-60] efficacy coitally-dependent vaginal TFV gel
iPrEx *Brazil, Ecuador, Peru, South Africa, Thailand, US*	Gay men, other MSM, transgender women	2499	42% [CI = 18-60] efficacy daily oral FTC/TDF
TDF2 Study *Botswana*	Men and women	1200	62% [CI = 22-83] efficacy daily oral FTC/TDF
Partners PrEP Study *Kenya, Uganda*	Serodiscordant couples	4758	67% [CI = 44-81] efficacy daily oral TDF 75% [CI = 55-87] efficacy daily oral FTC/TDF
FEM-PrEP *Kenya, S Africa, Tanzania*	Women	1950	Futility of daily oral FTC/TDF 6% [CI = -52-41]
VOICE *South Africa, Uganda, Zimbabwe*	Women	5029	Futility of daily vaginal TFV gel 14.7% [CI = -21-40] Futility of daily oral TDF -48.8% [CI = -129-3] Futility of daily oral FTC/TDF -4.2% [CI = -49-27]
Bangkok Tenofovir Study *Thailand*	IDUs	2400	49% [CI = 10-72] efficacy daily oral TDF
FACTS 001 *South Africa*	Women	2900	Coitally-dependent vaginal TFV gel enrolling *Results expected in 2015*

Results from iPrEx study, released in 2010, showed that in men and transgender women who have sex with men, taking a daily TDF or TDF/FTC reduced the risk of acquiring HIV. A total of 2499 HIV-seronegative men or transgender women who have sex with men were randomly assigned to receive FTC/TDF or placebo once daily. Ten participants were found to have been infected with HIV at enrollment, and 100 became infected during follow-up (36 in the FTC–TDF group and 64 in the placebo group), indicating a 44% reduction in the incidence of HIV (95% confidence interval, 15 to 63; P=0.005) (Grant RM, et al 2010).

An open-label extension or “rollover” of the iPrEx study will provide TDF/FTC for 72 weeks to all HIV-negative iPrEx participants who wish to wish to enroll. The goal of the study is to get information on how to improve adherence, and whether people are more likely to take the pill now that it has shown partial efficacy in preventing HIV infection. It will also provide additional safety data. Participants who became HIV-positive during the iPrEx study or between the study and the start of the rollover study will also be eligible to join the study for follow-up. This study began in early 2011 and plans to report its findings in early 2013. In

addition to collecting longer-term data on PrEP efficacy and safety, iPrEx OLE's site, Project PrEPare Chicago, will explore the acceptability and feasibility of a PrEP trial among YMSM in the area. Approximately 99 YMSM between the ages of 18 and 22 years inclusive will be recruited for participation in this study. An additional 15-20 youth age 16 and 17 years will be recruited for the focus groups.

Another success occurred when results were announced in 2011 by the Partners PrEP study, which demonstrated that HIV infection among discordant heterosexual couples can be prevented by taking oral PrEP daily. Through May 31, 2011, a total of 78 HIV infections occurred in the study: 18 among those assigned TDF, 13 among those assigned to FTC/TDF, and 47 among those assigned placebo. Thus, those who received TDF had an average of 62% fewer HIV infections (95% CI 34 to 78%, p=0.0003) and those who received FTC/TDF had 73% fewer HIV infections (95% CI 49 to 85%, p<0.0001) than those who received placebo. (Baeten J, et al 2012) Additionally, PrEP was found to be safe: the rate of serious medical events was similar for those assigned to TDF, FTC/TDF, and placebo. Pregnancy rates were similar across the three arms and there was no evidence that TDF or FTC/TDF was associated with pregnancy complications. Adherence to the daily PrEP medication was very high – more than 97% of dispensed doses of the study medications were taken. More than 95% of participants were retained in study follow-up. The Partners PrEP Study is continuing: those receiving TDF and FTC/TDF PrEP will continue on those medications and those receiving placebo will start TDF or FTC/TDF PrEP.

A recent sub analysis (Celum C, et al, 2013) of the Partners PrEP data showed that point efficacy in higher risk (higher incidence) participants (including women <30 years) was still 77% (Truvada) and 72% (Tenofovir) albeit with wide confidence intervals.

Whilst other sub group analyses have shown reasons for concern around adherence to daily PrEP regimens in younger participants, these same studies have confirmed high rates of HIV acquisition in this same age group.

Additionally, the CDC TDF2 study in Botswana found that a once-daily tablet of TDF/FTC reduced the risk of acquiring HIV infection by roughly 63% among uninfected heterosexual men and women in the study. Overall, a total of 1,219 HIV-uninfected heterosexual male

and female participants (aged 18-39) in Botswana were enrolled in the TDF2 study and randomly assigned to take a daily TDF/FTC pill or a placebo pill. Three participants were determined to be HIV-infected at the time of enrollment, and 16 of the participants randomized never began study medication. Those individuals were excluded from these analyses, which include data on the remaining 1,200 participants who were HIV-negative at the time of enrollment and began study medication (54.7 percent male, 45.3 percent female). In the primary analysis, among the 601 participants who received TDF/FTC, there were nine who became infected with HIV during the study. Among the 599 individuals who received a placebo, 24 became infected with HIV during the study, translating into a statistically significant overall reduction in risk of 62.6 percent (Baeten J, et al. 2012).

However, despite this recent groundbreaking efficacy data, other studies have demonstrated different results. FEM-PrEP, a Phase III trial designed to assess the safety and effectiveness of a daily oral dose of TDF/FTC for HIV prevention among women in sub-Saharan Africa, was stopped in April 2011, following a scheduled interim review of study data. The trial's Independent Data Monitoring Committee advised that the study would be highly unlikely to demonstrate TDF/FTC effectiveness in preventing HIV infection in the study population, even if it continued to its originally planned conclusion. However, no safety issues were reported.

The VOICE Study – Vaginal and Oral Interventions to Control the Epidemic – was designed to evaluate the safety and effectiveness of two ARV-based approaches for preventing sexual transmission of HIV in 5,029 women from Uganda, South Africa and Zimbabwe, as well as determining which of these types of administration women were more likely to follow: applying vaginal gel daily or taking an ARV tablet once a day.The pill options included Tenofovir or Truvada and both the gel and pill arms were placebo controlled. In September 2011, an interim review of VOICE determined that it was not possible to show whether oral TDF tablets were any better than a placebo for preventing HIV in the women assigned to that study group. The Data Safety Monitoring Board (DSMB) therefore recommended that the women randomized to the oral TDF tablet group discontinue their use of the study product. This recommendation at the time did not apply to the women in the groups using

either the TDF gel or oral TDF/FTC tablets, or the corresponding placebos, and as a result, the DSMB recommended that these four study groups continue in VOICE. In November 2011, an additional interim review of safety and efficacy data led the DSMB to recommend discontinuation of the vaginal gel arm. However, on both occasions the DSMB did not raise any safety issues. The oral Truvada arm and placebo pills arms continued, but in March 2013, .researchers announced that none of the interventions tested—daily oral tenofovir, daily oral TDF/FTC (Truvada), and daily 1% vaginal tenofovir gel—provided additional protection against HIV in the study, likely because few of the women in the trial used the products as directed. This low adherence explains the lack of benefit and is consistent with data from other trials that found a correlation between higher levels of adherence and protection from HIV.

Results from VOICE provide an urgent reminder that products must meet the needs of the people using them. While disappointing, the results lend new urgency to understanding the needs and desires of women who need HIV protection and also direction to the search for additional safe and effective HIV prevention options for women.There is now an even more critical need to explore why VOICE, FEM-PrEP and the other PrEP trials had seemingly different findings. PrEP has been shown to be efficacious in three clinical trials (Partners PrEP, TDF2 and Global iPrEx) and has been licensed for prevention in MSM and heterosexuals by the FDA. On the other hand, two clinical trials (FemPrEP and VOICE) have shown no efficacy of PrEP and this has been shown to be due to low uptake and usage of study product. In addition to differences in adherence to the study product, there may have been important differences in the study populations related to sexual activity, other sexually transmitted infections or levels of inflammation that can affect HIV susceptibility. It is increasingly accepted however, that product usage has been the greatest driving force in differences in efficacy in these clinical trials.

These studies also highlight the key role of CHAMPS in providing currently unavailable data on the feasibility of, acceptability of, and, most significantly, adherence to PrEP in other at-risk populations, such as adolescents. Given that PrEP is a novel prevention method shown to be efficacious that is immediately available, it is urgent to understand in carefully designed open label studies which individuals may take PrEP, under which circumstances

and what the barriers and faciltators to uptake and consistent adherence may be.

2.6.6 Studies of FTC and TDF in Children and Adolescents

A review of the current published literature on the feasibility and acceptability of biomedical prevention strategy use in adolescents revealed no single study of PrEP's utility, feasibility, or acceptability, targeting an adolescent sample less than 18 years, globally. While data is emerging on the use of PrEP in youth aged 18 to 22 years in the USA (Hosek et al; 2013), this may not be applicable to a younger African population.

Happily, ATN 110 and 113 are currently underway and are demonstration projects of Truvada as PrEP in young MSM in the USA. Age group here is 15-24 years. Encouragingly, regulators have approved proxy parental consent waiver in MSM <18 years of age (personal communication: S Hosek, B Kappiogannis).

Data supporting the adolescent indication for FTC/TDF PrEP or Truvada is based on studies of the individual components of FTC and TDF. Available data from Gilead Sciences suggest that both TDF and FTC are relatively well-tolerated in adolescents, with safety and pharmacologic profiles similar to those observed in adults.

The safety and efficacy of FTC or EMTRIVA in adolescents is supported in three open-label, non-randomized clinical studies. FTC was administered to 169 HIV-1 infected treatment-naive and experienced (defined as virologically suppressed on a lamivudine [3TC] containing regimen for which FTC was substituted for 3TC) participants between 3 months and 21 years of age (mean age 7.8 years). Participants received once-daily EMTRIVA oral solution (6 mg/kg to a maximum of 240 mg/day) or EMTRIVA capsules (a single 200 mg capsule once daily) in combination with at least two other antiretroviral agents. Through 48 weeks of therapy, the overall proportion of participants who achieved and sustained an HIV-1 RNA <400 copies/mL was 86%, and <50 copies/mL was 73%.

Assessment of adverse reactions is based on data from Study 203, an open label, uncontrolled study of 116 HIV-1-infected pediatric and adolescent participants who received FTC through 48 weeks. The adverse reaction profile observed during these clinical trials was

consistent to that of adult clinical trial participants, with the exception of the occurrence of anemia and higher frequency of hyperpigmentation in adolescents and children.

The safety of TDF or VIREAD in adolescent and paediatric participants, aged 2 to less than 18 years, is supported by data from two randomized trials (Studies 352 and 321) in 184 HIV-1 infected participants, who received treatment with VIREAD or placebo/active comparator, in combination with other antiretrovirals, for 48 weeks.

In Study 352, 92 treatment-experienced participants, 2 to less than 12 years of age, with stable, virologic suppression on stavudine (d4T)- or zidovudine (AZT)-containing regimen were randomized to either replace d4T or AZT with VIREAD (N = 44) or continue their original regimen (N = 48) for 48 weeks. Five additional participants over the age of 12 were enrolled and randomized, but were not included in the efficacy analysis. After 48 weeks, all eligible participants were allowed to continue in the study receiving open-label VIREAD. At Week 48, 89% of subjects in the VIREAD treatment group and 90% of subjects in the d4T or AZT treatment group had HIV-1 RNA concentrations <400 copies/ml. The adverse reactions observed in participants were also consistent with those observed in clinical trials in adults, including those related to lumbar spine bone mineral density and bone turnover.

In Study 321, 87 treatment-experienced participants 12 to less than 18 years of age were treated with VIREAD (N=45) or placebo (N=42) in combination with an optimized background regimen (OBR) for 48 weeks. The mean baseline CD4 cell count was 374 cells/mm^3 and the mean baseline plasma HIV-1 RNA was 4.6 log10 copies/mL. At baseline, 90% of subjects harbored NRTI resistance-associated substitutions in their HIV-1 isolates. Overall, the trial failed to show a difference in virologic response between the VIREAD and placebo treatment groups. However, these data taken together, suggest that the pharmacokinetic profile of TDF in participants 2 to less than 18 years of age (at the recommended doses) is similar to that found to be safe and effective in adult clinical trials. Clinical safety issues and adverse reactions identified in these trials are consistent with those observed in adult clinical trials, such as bone mineral density, renal toxicity, and gastrointestinal side effects.

Overall, these data suggest that there are similar potential safety concerns for FTC and TDF in both adolescent and adult populations. However, the long-term safety of PrEP for prevention in adolescents is unknown. More research is urgently needed to improve on the existing safety and efficacy profiles of these drugs, both individually and in combination. Substantial work is also required to measure the effect of knowledge of PrEP efficacy on risk behavior and adherence of adolescents.

2.6.7 Concerns and Potential Risks Regarding Use of PrEP

Several concerns regarding the use of PrEP remain and warrant further discussion.

Truvada in HIV+ populations

Among HIV infected populations, antiretroviral medication-associated alterations in metabolic systems such as dyslipidemia, fat redistribution, and insulin resistance, cardiovascular disease, lower bone mineral density, osteopenia, osteroporosis and renal disease have been shown. However, there are some favorable safety data on Truvada® that have allowed licensure for use in HIV-infected youth down to age 12 years.

Adverse Drug Events: The risk of adverse drug events resulting from chronic ART in uninfected individuals must be evaluated. Most current PrEP trials use TDF with or without FTC. These agents were chosen as a result of promising data from animal studies as well as the overall low rate of toxicity associated with these agents. TDF is associated with low-level side effects including nausea, vomiting, and loss of appetite. Side effects associated with FTC/TDF include diarrhea, nausea, fatigue, headache and rash (CDC, 2011). There have also been reports of impaired kidney function and bone density reduction among HIV-positive individuals on these medications, which were mostly reversed when the person stopped taking the drug (CDC, 2011). Liu and colleagues (Liu A, et al. 2011) studied a subsample of US iPrEx participants (n=200) and found a 1.1% net decrease in mean BMD in the TDF vs pre-treatment or placebo group at the femoral neck (95% CI 0.4 to 1.9%, p = 0.004) and a 0.8% net decline at the total hip (95%CI 0.3 to 1.3%, p = 0.003). These declines in BMD in the TDF group were most prominent during the first 12 to 15 months of treatment. The authors

conclude that TDF use resulted in a small but statistically significant decline in BMD at the total hip and femoral neck in HIV- negative men participating in a PrEP trial (Liu et al., 2011).

The iPrEx trial found that daily use of PrEP with FTC/TDF was safe and generally well tolerated, with no difference in adverse events between study drug and placebo arms (Grant et al., 2010). There were no differences between groups in laboratory abnormalities related to liver function, pancreatitis, electrolytes, glucose, phosphate and CBC. Nausea was the most common side effect. Data on markers of bone turnover, renal tubular toxicity, and parathyroid hormone concentrations have not yet been reported on iPrEx participants.

Both TDF and FTC are highly active against hepatitis B virus (HBV) and are recommended as part of the ART regimens in HIV/HBV co-infected individuals. However, HBV exacerbations (or increases in HBV load and abnormalities of liver function indicating liver damage) have been reported after stopping TDF, adefovir (a nucleotide similar to TDF) or 3TC (closely related to FTC) in approximately 20% of persons with chronic active hepatitis B (Lim SG, et al. 2002). The frequency of exacerbations of hepatitis B in persons starting antiviral drugs with normal or near normal liver function tests is not known, and may be lower than has been observed in clinical trials of persons with active HBV disease. In HBeAg-positive and HBeAg-negative studies in participants with compensated liver disease at baseline, the exacerbations associated with discontinuing antiviral drugs were not generally accompanied by hepatic decompensation.

Viral Resistance: A third area of concern is the risk of viral resistance in individuals who become HIV-infected despite the use of PrEP. Results on viral resistance among non-human primates exposed to TFV have been mixed (Atchison, 2008; Johnson, 2006). In treatment settings with HIV-infected individuals, appearance of the K65R mutation associated with TFV resistance is infrequent. Atchison and colleagues (2008) report that there was no evidence of mutations in an adherent research participant who seroconverted after one month of daily TDF exposure. The authors suggest that preventative use of antivirals, as opposed to treatment use, may not engender drug resistance because the viral populations being inhibited are too small to readily generate resistant mutants. In addition, recent studies

have suggested that ARV-resistant HIV strains may be less readily transmissible (Turner et al., 2004; Yerly et al., 2004), which could diminish concerns regarding resistance among people using ARVs for prevention (Gay et al., 2008). In response to community concerns about the risk of resistance from PrEP studies in Cameroon, Smith and colleagues (Smith, et al 2006) performed mathematical modeling of 600 participants receiving prophylaxis in the Botswana TFV study, which revealed that less than 1 percent of the predicted seroconverters would acquire or develop a TFV-resistant strain.

Finally, a case study published recently reports on a patient treated with PrEP for repeated high-risk exposures who subsequently seroconverted. This patient demonstrated TDF/FTC susceptible HIV, low post-seroconversion HIV RNA levels, and slow kinetics of seroconversion. Thus, drug resistance to TFV did not occur and the clinical course of HIV may have been attenuated (Prada et al., 2010).

Because PrEP is not triple combination therapy, the concern about PrEP participants who may sero-convert then develop drug resistance has been raised. Results from the iPrEx trial demonstrate very little drug resistance, with no-one developing resistance to tenofovir. Three cases of FTC-resistant infections occurred in iPrEx participants who were already newly HIV-infected at enrollment. No drug resistance was observed among those who became infected during the study (Grant et al., 2010). In the TDF2 trial, two cases of drug resistance emerged. One participant in the active drug arm with unrecognized acute wild-type HIV infection at enrollment demonstrated high levels of K65R, M184V and A62V. One participant in the placebo group showed K65R only in very low levels (<1%) (Thigpen et al., 2011).

Non-Adherence: It is important to closely assess whether individuals at risk for HIV infection will be willing and able to maintain consistent use of a daily medication regimen that is used for prevention and thus, not treating an illness they have. Additionally, close monitoring of adherence is necessary to be certain that a PrEP study is evaluating PrEP rather than PEP. Results of medication adherence from the Peterson and colleagues (Peterson, et al. 2007) PrEP study demonstrated adherence rates of approximately 74%

across sites. The most commonly noted reasons for missing medications included missed or late clinic visits and pregnancy, for which participants were taken off the study drug. Preliminary results from the Bangkok PrEP study show participant adherence rates of 92% in the week prior to study visit (Choopanya et al., 2013). According to investigators in the Partners PrEP study, participants achieved adherence levels of 99% during an average four-month period during the two-year study (Haberer et al., 2011). However, both iPrEx, CAPRISA 004 and VOICE data demonstrate the bias of self-report in over-reporting adherence. In the iPrEx trial, non-adherence to study medication was strongly associated with infection risk with only 9% of those newly infected having detectable drug in their blood (Grant et al., 2010), despite high levels of self-reported adherence. Thus, optimizing adherence and its measurement is critical for interpretation of efficacy data and implementation planning (Buchbinder & Liu, 2011). Recent thinking has described 3 phases to adherence: initial uptake, persistence or continued usage and finally quality of the adherence to sustained use in terms of numbers of prescribed doses taken (Bangsberg DR, et al 2001). This proposal aims to investigate all 3 aspects of adherence: uptake, persistent use and quality of adherence. Use of drug levels real time is explored as a way to enhance the ongoing quality of medication adherence over time.

Behavioral Disinhibition: Some have raised the concern that individuals may increase risk-taking behaviors if they believe that PrEP will prevent HIV transmission – this is called "behavioral disinhibition." These concerns have been addressed to some degree in a previous (Peterson et al., 2007) PrEP study. Regarding sexual risk behaviors, the mean number of sexual partners during the previous month dropped from 21 partners at screening to 14 partners at follow-up. Condom use actually increased from 52% at screening to 92% at 3, 6, & 9-month visits and 95% at the 12-month visit (Guest et al., 2008; Peterson et al., 2007). In the Bangkok study of IDUs, injection risk behavior also decreased, with 14% of participants reporting needle sharing before enrollment and 4% of participants reporting needle sharing at 12-month follow-up (Choopanya et al., 2013). Two completed studies of PEP have also examined the data for evidence of behavioral disinhibition (Martin et al., 2004; Schechter et al., 2004). Both studies reported no associated increase in risk behaviors among PEP users. Furthermore, the majority of participants in both studies

reported a significant decrease in sexual risk behaviors as compared to baseline. It is understood however, that this phenomenon should be monitored in adolescent populations.

Concerns regarding the use of PrEP, while valid, must be weighed against the risks associated with continued high infection rates in higher-risk communities such as adolescents. We have carefully designed this study to evaluate the specific protocol components that would be necessary in a future effectiveness study of PrEP among youth and to evaluate the aforementioned concerns regarding behavioral disinhibition and medication adherence. While the proposed study is not designed to determine the efficacy of PrEP, this developmental work will provide important data regarding promising strategies for introducing new HIV-prevention interventions into adolescent populations.

3 OBJECTIVES

3.1 PRIMARY OBJECTIVES

- To evaluate the acceptability, safety and use of a daily regimen of oral PrEP (FTC/TDF), as a component of a comprehensive HIV prevention package [with HIV testing, STI management, risk reduction counseling, access to condoms, PEP, counseling and referral for male circumcision (for boys)], for adolescents between 15 and 19 years of age.

3.2 SECONDARY OBJECTIVES

- To evaluate adherence to a daily regimen of oral PrEP (FTC/TDF), as a component of a comprehensive HIV prevention package for adolescents between 15 and 19 years of age.

- To evaluate change in sexual activity, perceptions of sexual risk, risk compensation, and health behaviours, including condom use, in adolescents, between 15 and 19 years of age, who take a daily regimen of oral PrEP (FTC/TDF) over a 12 month period.

- To assess study participants' and their partners' perceptions on key issues associated with oral PrEP (FTC/TDF), including adherence barriers, adherence facilitiators, and general product knoweldge, as part of a comprehensive HIV prevention package [with HIV testing, STI management, risk reduction counseling, access to condoms, PEP, counseling and referral for male circumcision(for boys)].
- Incidence of HIV infection, as measured by seroconversion of study participants during the approximate 12 months (52 weeks) of follow-up.

3.3 EXPLORATORY OBJECTIVES

- To explore the utility of Dried Blood Spot (DBS)/Plasma drug levels and the impact of biofeedback of results as an adherence enhancing strategy among HIV-negative adolescents between 15 and 19 years of age

- To explore the relationship between daily PrEP usage and sexual practices and behavior in adolescents.

4 STUDY DESIGN

4.1 IDENTIFICATION OF STUDY DESIGN

We propose an open-label phase II cohort study, to evaluate the acceptability, safety and use of, daily oral PrEP (FTC/TDF) in 150 HIV-negative adolescents at two sites (approximately 75 participants at each site), ages 15-19 years, as well as adherence to medication in participants who choose to have biofeedback of drug levels versus those who choose not to and any changes in their sexual and health behaviors over a 12-month (52 week) period. Enrolled participants will be stratified by gender (33% Male: 66% Female). Out of the 75 participants at each site, approximately 25 adolescent males and 50 adolescent females will be enrolled. This oversampling of women is to account for the fact that although oral PrEP is relevant to both genders, young women are more vulnerable to HIV acquistion in South Africa.

After a period of community engagement and general education about prevention packages including PrEP, participants will be invited to screen for this study. Those who are considered eligible will be asked to return for an enrollment visit. At enrollment, all participants who still wish to take part will be asked to take PrEP as part of a comprehensive prevention package for at least 3 months (12 weeks). During the first 3 months (12 weeks), participants will attend monthly (4 weekly) clinic visits for adherence counselling, trouble shooting, HIV testing and dried blood spot/ plasma drug level sampling.

Researchers will use dried blood / plasma drug level sampling, combined with the reporting of results to individuals by the next visit, as an adherence enhancing strategy for those participants who elect to receive this information during adherence counselling at follow up visits. Those participants who agree to it, will receive blood drug level results during personal counseling in month 2 and 3 (weeks 8 and 12). Those who choose not to get this information will receive standard motivational adherence counseling during their study visits. Study staff will explore through standard questionnaires the reasons for not receiving drug level data.

Participants will be asked at the 3-month visit whether they would like to continue PrEP for a further 3 months. Those who opt out will continue to be followed in all aspects of the study except for distribution of Truvada pills. All participants will receive a brief questionnaire to explore reasons

for continuing or stopping PrEP. A short acceptability questionnaire will also be administered. This opportunity to "opt out" or "opt back in" will occur at 3 monthly visits until Week 36. Followup will continue until week 48. Those who opt out at a 3 monthly visit will be asked whether they wish to restart at the next 3 monthly visit. Participants will also be advised that they may "opt out" of PrEP in their prevention package at any scheduled visit or at any time in consultation with clinic staff. They will be expected to return all study product and will not be issued TDF/FTC. They may "opt back in" on a subsequent study visit if all eligibility criteria are met and after a negative HIV test is obtained. At each study follow up visit, participants will be asked to grade their adherence on a visual scale, they will also be asked whether they wish to receive drug levels and their response and reasons for this will be captured. They will then receive motivational adherence counseling with or without drug levels depending on their choice at the time. Monthly scheduled visits will occur until month 3, thereafter scheduled visits will be 3 monthly.

Whilst every effort will be made to encourage adherence to PrEP in the first 3 months, poor adherence during those months will NOT preclude participation after 3 months. Every effort will be made to ascertain level of use and reasons for less than optimal use.

Additionally, two focus groups will be conducted at each site during the study period. The first focus group will be conducted prior to study initiation (within 3-4 weeks) with as yet non-enrolled participants from the community setting (n= 6-8). This size is recommended when conducting focus groups on non-commercial topics (Krueger, R.A and Casey, M.A (2008). *Focus groups: a practical guide for applied research*. London: Sage Publications Ltd). This first group will address a number of questions including adolescents' attitudes towards and knowledge of PrEP, in particular, adolescent perceptions of taking drugs previously reserved for HIV treatment as a form of prevention; what some of the barriers and facilitators of PrEP use may be, where they would like to access these drugs outside of the research setting ; whether taking PrEP might identified individuals as high-risk and therefore stigmatise them; whether enhanced protection against HIV infection provided by PrEP might lead to sexual disinhibition or risk compensation; whether adolescents will still use condoms in order to protect against other STI's; and what factors might impact on adherence. This will be seen as perceptions (and identify misperceptions) in agroup of as yet uninitiated and perhaps uninformed youth.This data will be gathered and used for the "social marketing objective of CHAMPS-SA, to inform some of the issues that must be considered when creating demand for

youth PrEP. The data will NOT be used to inform the protocol nor will any changes to protocol be made based on this. Parental/ guardian consent and adolescent assent will be obtained for all focus group participants. These FG participants (aged 15-19 years) will be actively recruited from the potential pool of participants for the cohort study.

The second focus group will be conducted in two groups with enrolled participants (n= 6-8 in each separate group) at each site, to be scheduled in the last four weeks of study follow up. It will address a number of questions including participants' attitudes towards PrEP, in particular, their experience taking and general acceptability of the drug; where they would like to access these drugs in the future; whether taking PrEP resulted in identification of individuals as high-risk and stigmatization; whether enhanced protection against HIV infection provided by PrEP led to sexual disinhibition or risk compensation; whether participants still used condoms in order to protect against other STI's; and what factors (such as appearance changes as a result of drug side-effects) impacted on adherence. In addition, they will be asked what the impact of real time (whilst this does not mean on the day of testing, it is used to denote during the study at the next visit) drug levels were in terms of adherence counseling and how they felt about receiving these results at study visits. This data will inform the nature of design of PrEP roll oput for youth in the future. Parental/ guardian consent and adolescent assent will be obtained for all focus group participants. In order to ensure a good spread of FG participants, the follow up cohort will be divided into 2 groups: those who chose PrEP and were adherent at least 80% of the follow up time and those who did not choose PrEP or were adherent <50% of the time. 6-8 participants will be randomly selected from each group and then invited to participate in the 2 FGs. The data from these focus groups may be reviewed by Research Ethics Committee members, Data Safety Monitoring Committee members and the sponsors (NIAID), FDA and/or MCC.

4.2 SUMMARY OF MAJOR ENDPOINTS

Primary endpoints:

Acceptability

- The proportion of participants who report willingness to use the study regimen, take up PrEP and remain on PrEP as part of a comprehensive prevention package.

- Assessment of acceptabiltiy as per questionnaire administered at study end.

Use

- Number of adolescents who continue to use PrEP (as indicated by DBS/ plasma levels) after the initial 3 month period
- The total time on PrEP for each adolescent (as indicated by DBS/plasma levels) and for the cohort as a whole in those individuals who indicated PrEP use by self report at the beginning of each 3 month period.

Safety

- Grades 2, 3, and 4 clinical and laboratory adverse events;

Secondary endpoints:

Adherence:

- Adherence to daily regimens of oral PrEP as evidenced by the use self-report, pill counts, and proportion of participants on FTC/TDF who have detectable drug levels. Proportion of blood samples with detectable drug levels
- Proportion of adolescents with detectable drug levels who report using PrEP
- Proportion of doses that are taken as instructed.

Sexual and other Behaviors

- Reported number of steady and casual sex partners, condom use (and change after introduction of study product), substance use prior to or during sex, as evidenced by participant responses to interviewer-administered questionnaires and focus groups.
- Proportion of scheduled HIV testing appointments missed, in relation to individual characteristics (age, sex, number of partners, use of other prevention methods) and the characteristics of the product.

HIV infection,

- as measured by seroconversion of study participants during the approximate 12 months of follow-up.

Exploratory endpoints:

Impact on adherence of providing information on drug (FTC/TDF) levels (as measured in Dried Blood Spot/Plasma) given as feedback during counseling sessions.

- Number of counselling opportunities in which drug level feedback is requested vs total number of counseling events
- Number and nature of participants who request drug level feedback.
- Correlation between self reported adherence and drug levels at each visit for each participant
- Correlation between self reported adherence and drug levels at each visit in the study overall.
- Proportion and number of participants whose adherence ito study product improves when receiving the results of DBS/Plasma compared to those who do not receive feedback of results as measured by endpoints above.
- Relationship between daily PrEP usage and sexual practives and behavior in adolescents
- Sexual Behaviour Data obtained using a questionnaire and focus groups.
-

4.3 DESCRIPTION OF STUDY POPULATION

The study population will consist of 150 healthy, HIV-negative adolescents, between the ages of 15 and 19 years, who will be enrolled with consent of a parent or guardian and meet the criteria in Section 5. To achieve balance in baseline characteristics, stratified randomization will be used. A total of 75 participants will be enrolled at each study site, consisting of 30 adolescent males and 45 adolescent females.

All participants will be offered study product and followed for the first 3 months. At the 3-month visit, all participants will be asked whether they wish to continue with study product. At every subsequent three monthly scheduled visit until month 9, participants will be asked by a study staff member again about their choice regarding the study product. Participants will be offered the option to continue, stop or re-start the study product at these visits as long as no contra-

inducations to PrEP usage and their HIV test is negative.
Participants can opt out of the prescribed study product regimen at any time, but these participants will be asked to report to the study site, return all medication and still attend scheduled visits.
Follow up period is 12 months in all.

4.4 TIME TO COMPLETE ENROLLMENT

The maximum allowable time between screening and enrolment per participant is 40 days.
Following enrollment into the study, each participant will be followed for a total of 12 months.
Time to complete total enrollment of participants is expected to be completed within 8 months.

4.5 EXPECTED DURATION OF PARTICIPATION

All participants will complete 12 months (52 weeks) of study duration in total.

4.6 STUDY SITES

There are two proposed study sites. The first is a site managed by Desmond Tutu HIV Foundation (DTHF) at the Institute of Infectious Disease and Molecular Medicine, University of Cape Town. The DTHF site in Masiphumelele is approximately 20km south of Cape Town where DTHF has been working since 1999. Several cross-sectional and cohort studies focusing on adolescents have been successfully conducted in this under resourced community of 22 000 people. In 2005, DTHF demonstrated that the mean HIV prevalence in the 11-19 yr old was 11%; and the HIV prevalence was 5% in the local high school (the adult HIV prevalence is 26%). Sexual risk assessment suggests that young people in this community practice a range of high risk HIV behaviors. The site has a long-established relationship with community stakeholders, highly experienced study staff, a youth center offering peer-focused activities as well as sexual and reproductive health services, and an active adolescent CAB.

The Perinatal HIV Research Unit (PHRU) site is based in in Soweto, near Johannesburg. Soweto is a sprawling collection of formal and less formal townships around 40 kilometres from Johannesburg in Gauteng. It has a population of approx 1 000 000, and an unemployment rate of over 60%. The HIV prevalence of Soweto is approximately 11%, with adolescent prevalence of 2%.

Both sites have worked together with the South Africa AIDS Vaccine Initiative (SAAVI) and the HIV AIDS Vaccine Ethics Group (HAVEG) to develop resources that ensure that the current ethico-legal framework for adolescent involvement in vaccine studies is implemented, and both sites also have well-established adolescent community advisory boards.

5 STUDY POPULATION

5.1 SELECTION OF STUDY POPULATION

The inclusion and exclusion criteria in Sections 5.2 and 5.3 will be used by study staff to ensure the appropriate selection of study participants.

5.2 INCLUSION CRITERIA

Participants must meet all of the following criteria to be eligible for inclusion in the study:

1. Age 15 to 19 years (inclusive) at screening, verified per study site SOPs
2. Able and willing to provide written informed consent/ assent (age dependant) to be screened for and to take part in the study
3. Have a guardian who is able and willing to provide written informed consent for their child to be screened for and to take part in the study
4. Able and willing to provide adequate locator information, as defined in site SOPs
5. HIV-uninfected based on testing performed by study staff at screening and enrollment
6. Sexually active, as defined as a minimum of one act of (penile vaginal)sexual intercourse in the last 12 months, per self-report
7. (For female participants) Negative pregnancy test at screening and enrollment and per participant report, does not intend to become pregnant in the next 12 months
8. (For female participants) Using an effective method of contraception at enrolment, and intending to use an effective method for the study duration; effective methods include low dose oral, implant or injectable hormonal methods.
9. Does not report intention to relocate out of the study area during the course of the study
10. Does not have job or other obligations that would require long absences from the area (> 4 weeks at a time)
11. Willing to undergo all study-required procedures
12. At screening and enrollment, agrees not to participate in other research studies involving drugs or medical devices for the next 12 months

5.3 EXCLUSION CRITERIA

Participants who meet any of the following criteria, at baseline, are excluded from the study:

- As determined by the Site Investigator, any significant uncontrolled, active or chronic disease process such as but not limited to diabetes, hypertension, and other diseases involving the cardiovascular, pulmonary, gastrointestinal, genitourinary, musculoskeletal, and central nervous systems
- Confirmed ≥ Grade 2 hypophosphatemia
- Presence of serious psychiatric symptoms (e.g., active hallucinations)
- Visibly distraught at the time of consent (e.g., suicidal, homicidal, exhibiting violent behavior)
- Intoxicated or under the influence of alcohol or other drugs at the time of consent
- Acute or chronic hepatitis B infection (i.e. if hepatitis B surface antigen positive)
- Hep B seronegative and refuses vaccination.
- Renal dysfunction (Creatinine Clearance < 75 ml/min);
  (Use Cockroft-Gault equation:

  Male $\frac{(140-age)* \ Weight(Kg)}{Serum\ Creatinine\ (mg\ per\ dl)*72}$ = ml/min

  Female $\frac{(140-age)* \ Weight(Kg)}{Serum\ Creatinine\ (mg\ per\ dl)*72}$ = ml/min * 0.85

  Serum Creatinine conversion Factors
  Creatinine (mg/dl) = Creatinine (µmol)/ 88.4
  Creatinine (mg/dl) = Creatinine (mmol)/ 88.4 *1000

- Urine dipstick for protein and glucose, excluding 1+ or greater
- Any history of bone fractures not explained by trauma
- Any Grade ≥ 2 toxicity on screening tests and assessments
- Concurrent participation in an HIV vaccine study or other investigational drug study
- Known allergy/sensitivity to the study drug or its components
- Use of disallowed medications (see section 6.5)

Note: Otherwise eligible participants with an exclusionary test result may be re- tested during the screening process. If a participant is re-tested and a non- exclusionary result is documented within 40 days of providing informed consent for screening, the participant may be enrolled.

5.4 STRATEGIES FOR RECRUITMENT

Adolescents will be recruited through community outreach, by targeting schools, youth groups, sport clubs, taxi ranks, and other points of convergence in the community. In addition, local HCT centres and primary health care clinics will be targeted. Well-established relationships with community stakeholders exist at both proposed study locations and these will be capitalised on.

DTHF's adolescent CAB has also assisted researchers in developing strategies to enhance adolescent participation in studies. The Future Fighters have assisted with the development of many stakeholder engagement initiatives, aimed at strengthening recruitment and retention mechanisms, including drama, poetry, rap, song, and dance performances in their local settings. Media is also widely incorporated into their recruitment strategies, including MXIT, Facebook and other social networks.

5.5 STRATEGIES FOR RETENTION

Given the study sites' previous experience with the South African Studies on HIV in Adolescents (SASHA) Project, funded by the EDCTP, the study staff have an in-depth understanding of youth friendly health services, age-appropriate counseling techniques, and adolescent-specific recruitment and retention strategies. Attempts will also be made to engage adolescent participants in a number of activities, including pairing participants with one another to offer support and encouragement to complete the study, where adolescents are willing to do so.

Other mechanisms that will be used during the study, to ensure maximum retention, such as:

- Collection of detailed locator information at the study screening visits, and active review and updating of this information at each subsequent visit
- Use of visit reminder strategies (these have been tried and tested by this adolescent community and are acceptable)

- Follow-up on missed visits
- Mobilization of trained outreach workers to assist with follow up
- Regular communication with the study community at large to increase awareness of HIV and explain the purpose of HIV prevention research in adolescent populations and the importance of completing research study visits

5.6 CO-ENROLLMENT GUIDELINES

Co-enrollment in other research studies, which do not involve investigational agents or active study products or medical devices, is permitted.

6 STUDY PRODUCT

6.1 REGIMEN

The regimen for enrolled study participants who choose to receive the study product during the 12 months of follow up is a FTC/TDF (Truvada®) tablet taken orally, once daily. For any missed doses, participants will be instructed to take the next scheduled dose.

6. 2 FTC/TDF FORMULATION

FTC/TDF or Truvada® is a 200mg/300mg fixed dose combination tablet containing emtricitabine (FTC) and tenofovir disoproxil fumarate (TDF). FTC is a synthetic nucleoside analogue of cytidine. (See Section 2.4: Study Products). One FTC/TDF tablet contains 200 mg FTC plus 300 mg of TDF. FTC/TDF should be stored at 25°C. Excursions are permitted between 15°C and 30°C.

6.3 STUDY PRODUCT SUPPLY AND ACCOUNTABILITY

FTC/TDF tablets will be supplied by Gilead Sciences (Foster City, CA, USA). FTC/TDF tablets (30 tablets per bottle) are packaged in bottles with a child-resistant screw cap. In addition to the tablets, each bottle contains a silica gel desiccant to protect the product from humidity and polyester packing material that cushions it during handling and shipping. Gilead will prepare bottles of study agent that are each labeled with the active agents and the expiry date.

6.3.1 Pharmacy Facilities and Drug Dispensing

A pharmacist will be responsible for dispensing the drug to each study participant. Only participants with negative HIV test results, will be dispensed the study drug. At enrollment, participants who take study medication will receive a prescription that will include the participant ID. Detailed instructions for receipt, handling, storage, dispensing, accountability, retrieval of unused study products from participants will be provided in site-specific SOPs and South Africa's Good Pharmacy Practice Guidelines.

6.3.2 Retrieval of Unused Study Drug

The study pharmacist will document all product returns and store any unused study product

in a designated area of the pharmacy. At the end of the study, any unused product will be destroyed, per GCP guidelines and instructions received by Gilead Sciences.

6.4 STUDY PRODUCT ADHERENCE ASSESSMENT

Adherence to study product will be measured by the use of self-report, pill counts, and proportion of participants on FTC/TDF who have detectable drug levels.

Comprehensive and age-appropriate study product adherence counseling will be provided to all study participants who receive study product, at every visit (until week 48,) to help ensure high rates of study product use. Counseling will address such topics as personal barriers and facilitators to using PrEP, remembering to use the study product daily, reminders to contact study staff with questions about study product use, and not to distribute or share their study products to other people. The current client centered counseling methodology applied by both sites for the FACTS 001 study (both sites are involved in this adult microbicide study) is being adapted for adolescent appropriateness and will be applied in this study. This will also be adapted to include or not include (depending on participant choice) the incorporation of drug level data back to the participant. It is envisaged that the adaptation will include modifications around daily use vs BAT24 (regimen in FACTS001), Oral PrEP vs topical and a youth centered approach vs an adult approach. It will have all the elements of being client centered, with emphasis on finding barriers and facilitators of adherence in a non-judgemental approach.
For the participants who select biofeedback during counseling, results from blood plasma or dried blood spots, which indicate their drug levels, will be fed back to participants at scheduled follow up visits. Participants may choose differently at each feedback session. In cases where drug levels indicate overuse study staff will be informed to intervene.

6.5 CONCOMITANT MEDICATIONS AND PROCEDURES

With the exception of medications listed as prohibited (see below, this section), enrolled study participants may use concomitant medications during study participation. All concomitant medications, including prescribed and over-the-counter Preparations, vitamins and nutritional supplements, recreational drugs, and herbal Preparations reported within the 70 days prior to study enrollment and throughout the course of the study will be recorded on the Case Report

Forms (CRF) designated for that purpose. Medications used for the treatment of AEs that occur during study participation also will be recorded on applicable study case report forms.

Should participants report use of any of the following medications, they will be required to discontinue use of study drug: interleukin therapy, medications with significant nephrotoxic potential (including but not limited to amphotericin B, aminoglycosides, cidofovir, foscarnet and systemic chemotherapy), and medications that may inhibit or compete for elimination via active renal tubular secretion (including but not limited to probenecid). In addition, if a participant requests post-exposure prophylaxis (PEP) for HIV exposure, they will be referred to a health care provider for evaluation. If a participant starts ARV therapy for PEP, they should hold study medications until completion of the course of PEP.

7 STUDY PROCEDURES

An overview of the study visits and evaluations schedule is presented in **Table 1: Schedule of Study Visits and Procedures.**

Scheduled visits for participants include the following;

- Screening
- Enrollment
- Follow up Visits (initial product use period: Weeks 4-12; visits at wk 4,8,12)
- Follow-up Visits (optional product use period: Weeks 13- 48; visits at wk 24,36,48)
- Final Study Visit (week 52)

7.1 SCREENING VISIT

Screening procedures may take place up to 40 days prior to a participant's enrollment. It is expected that, in most cases, all required screening procedures would be completed at one visit. However multiple visits may be conducted within this time period to complete all required screening procedures, if necessary. Written informed consent for screening is obtained before any screening procedures are initiated. For participants who do not meet the eligibility criteria, screening is discontinued once ineligibility is determined. If HIV-infection is identified as the reason for ineligibility, counseling and referral to appropriate treatment site will be performed.

Screening procedures are as follows:

- Administrative/Behavioural Procedures
    - Obtain written informed consent for enrollment, from participant and his/her parent or guardian
    - Assessment of understanding for informed consent form
    - Identification number assignment
    - Locator information
    - HIV pre-and post-test counseling, inlcuding risk reduction counselling
    - Provision of condoms
    - Schedule next visit (if applicable)

- Reimbursement.

- Clinical Procedures
  - Medical eligibility information
  - Medical history
  - Physical exam, including Tanner staging
  - Syndromic treatment for STI, if clinically indicated
  - Offer of STI testing and treatment for participant and partner(s) if indicated
  - Ascertainment of current contraceptive method and contraceptive counseling
  - Contraceptive counselling and provision of contraception as appropriate
  - Blood collection
  - Hep B vaccination if non-immune by serologic testing. (This will be given at 0,1 and 6 months; Wks 0,4, 24)

- Laboratory Procedures
  - HIV serology
  - Hepatitis B surface antibody and antigen testing (test results will be given to participants approximately one week after the test and vaccination will be provided during screening window)
  - Herpes (HSV-2), and a swab
  - Gonorrhea and Chlamydia *
  - Urine dip stick
  - Aspartate aminotransferase/alanine aminotransferase (AST/ALT) testing
  - Serum chemistries, including creatinine, glucose, electrolytes, and lipase
  - Full Blood Count
  - Urine pregnancy testing (for females)

* The swab will be self collected vaginal swab for girls and a urine test for boys.

7.2 ENROLLMENT VISIT

Day 0 for the participant will be the day of the Enrollment Visit:

- Administrative/Behavioural Procedures

- Locator information (update)
- Review of study procedures (ongoing consent)
- HIV pre-and post-test counseling, inlcuding risk reduction counselling
- Provision of condoms
- Eligibility assessment (including review of all screening documentation)
- Baseline sexual risk behavior questionnaire (for all enrolled participants)
- Reimbursement
- Schedule next visit (if applicable)

- Clinical Procedures
  - Review of all prior screening documentation
  - Update medical history and/or current medications, if applicable
  - Re-confirmation (by participant self-report) of medical eligibility information
  - Syndromic treatment for STI, if clinically indicated
  - Offer of STI testing and treatment for participant and partner(s) if indicated
  - Confirmation of current contraceptive method and contraceptive counseling
  - Contraceptive counselling and provision of contraception as appropriate
  - Disclosure of available test results, which must be made available to participant prior to administration of study product
  - Hepatitis B vaccination, if indicated
  - Update Medical History
  - Provision of study drug and instructions

- Laboratory Procedures
  - Urine pregnancy testing (for females)
  - HIV rapid testing
    - At all visits
    - As clinically indicated

7.3 FOLLOW UP VISITS (FOR WEEKS 4, 8, 12)

All enrolled study participants will complete 4 weekly follow-up visits for the first 12 weeks, targeted to occur every 28 days after the participant's study enrollment date (Day 0). Target dates are set based on the enrollment date, and do not change if subsequent actual visits take place before or after the target date. As it will not always be possible to complete monthly follow-up visits on the targeted dates, follow-up visits may be completed within an approximate 2-week window around the target date (-/+7 days from the target date). Thereafter visits will be 12 weekly with similar windows applying.

The following procedures will be completed at each initial Follow-Up Visits; Wks 4, 8, 12:

- Administrative/Behavioural Procedures
    - Locator information (update)
        - At all visits
    - HIV pre-and post-test counseling, including risk reducation counselling
        - At all visits
    - Social harms and/or benefits
        - At all visits
    - Sexual risk behavior questionnaire
        - At all visits
    - Acceptability questionnaire
        - At all visits
    - Provision of condoms
        - At all visits
    - Reimbursement
        - At all visits
    - Schedule next visit
        - At all scheduled visits, except Final Study Visit

- Clinical Procedures
    - Contraceptive counselling and provision as appropriate
        - At all visits
    - Targeted Physical exam

        - As clinically indicated
    - Update medical and menstrual history and/or current medications if applicable
        - At all visits
    - Record/update adverse events (AEs) applicable
        - At all visits
    - Hepatitis B vaccination, if indicated
        - At Enrollment (wk 0), month1 (Wk 4) and Month 6 (Wk 24)
    - Provision of study drug and instructions
        - At weeks 4, 8 .

- Laboratory Procedures
    - HIV rapid testing
        - At all visits
        - As clinically indicated
    - STI testing
        - Herpes (HSV-2),
        - Chlamydia and Gonorrhea testing (wk 12 only)
    - Urine dip stick testing
        - Every 3 months; At wk 12 only
    - Aspartate aminotransferase/alanine aminotransferase (AST/ALT) testing
        - Every 3 months; at wk 12 only
    - Serum chemistries, including creatinine, glucose, electrolytes, and lipase
        - Every 3 months, at wk 12 only
    - Full blood count testing
        - Every 3 months; at wk 12 only
    - Haematocrit testing
        - Weeks 4 and 8
    - Urine pregnancy testing (for females)
        - At all visits
    - Contraceptive counseling
        - At all visits

- TDF/FTC drug levels via venous blood sampling and preparation of dried blood spots for storage.
    - At all visits, Wks 4, 8 and 12.

7.4 FOLLOW UP VISITS (AFTER WEEK 13 AND UP TO WEEK 48; VISITS AT 24, 36, 48)

For the initial product usage lead-in period (Weeks 4-12), study participants will be asked to adhere to the study product. After the 12 week lead in period, participants will be asked at subsequent 12 weekly visits whether they wish to continue PrEP, stop PrEP or restart PrEP as part of their prevention package (Week 12, 24 and 36). All participants regardless of product usage will be followed for the duration of the study. Participants will be advised to make these decisions at scheduled study visits. Reasons for decision will be enquired upon and recorded in CRFs. Participants will also however be told they can contact study site at any time and also when they should with-hold PrEP for medical reasons.

Participants will complete scheduled 4 weekly follow-up visits until week 12. Thereafter, all visits will be 12 weekly regardless of PrEP addition to the prevention package or not. Target dates are set based on the enrollment date, and do not change if subsequent actual visits take place before or after the target date.

As it will not always be possible to complete follow-up visits on the targeted dates, follow-up visits may be completed within an approximate 2-week window around the target date (-/+7days from the target date).

The following procedures will be completed at each Follow-Up Visit (wks 24, 36, 48):

- Administrative/Behavioural Procedures
    - Locator information (update)
        - At all visits
    - HIV pre-and post-test counseling, including risk reducation counselling
        - At all visits
    - Social harms and/or benefits
        - At all visits
    - Sexual risk behavior questionnaire

        - At all visits
    - Provision of condoms
        - At all visits
    - Provision of study drug (for participants who choose to receive study product)
        - at visits Wk 12, 24, 36 .
    - Acceptability assessment
        - at visits Wk 12, 24, 36, 48.
    - Adherence Counselling (if participant is on study product)
        - at visits Wk 12, 24, 36, 48 (week 48 visit will be feedback on last 3 months only since no more product will be offered).
    - Feedback of plasma drug level/DBS results (to participants on study product who agree to receive this information at the time of adherence counseling.)
        - At visits Wk 12, 24, 36, 48.
    - Adherence assessment (including pill counts) and counselling (for participants who choose to receive study product)
        - At visits Wk 12, 24, 36, 48
    - Study drug supplies and instructions/counseling (for participants who choose to receive study product)
        - At all visits where study product is administered week 12, 24, 36
    - Reimbursement
        - At all visits
    - Schedule next visit
        - At all scheduled visits, except Final Study Visit

- Clinical Procedures
    - Contraceptive counselling and provision as appropriate
        - At all visits
    - Physical exam
        - At week 48
        - As clinically indicated
    - Update medical and menstrual history and/or current medications if applicable

        - At all visits
    - Record/update adverse events (AEs) applicable
        - At all visits

- Laboratory Procedures
    - HIV rapid testing
        - At all visits
        - As clinically indicated at unscheduled visits (reported exposures)
    - STI testing
        - Herpes (HSV-2),
        - Chlamydia, and Gonorrhea testing (0, 12, and 48 weeks)
    - Urine dip stick testing
        - Every 12, 24, 36, 48 weeks
    - Aspartate aminotransferase/alanine aminotransferase (AST/ALT) testing
        - Every 12, 24, 36, 48 weeks
    - Serum chemistries, including creatinine, glucose, electrolytes, and lipase
        - Every 12, 24, 36, 48 weeks
    - Full Blood Count testing
        - Every 12, 24, 36, 48 weeks
    - Urine pregnancy testing (for females)
        - At all visits
    - Contraceptive counseling
        - At all visits
    - Measurement of study drug levels by Plasma/DBS
        - At 12, 24, 36, 48 weeks.

7.5 INTERIM VISITS

Participants may make interim contacts and unscheduled visits at their request, or as deemed necessary by the Site Investigator or designee, at any time during the study. All interim contacts and unscheduled visits will be documented in the participant's study file. When an interim contact or unscheduled visit occurs in response to AEs, a study clinician will clinically assess the reported

event and provide, or refer the participant for, appropriate medical care. Study participants will be instructed to contact their study clinic in the event of any AE. Participants will also be instructed to seek immediate emergency care (even from other providers) if they consider they require it. The AE will be reported on the appropriate CRF.

Some examples of reasons for an interim visit are:

- To report an AE;
- To get more condoms or study product;
- To address any contraceptive needs;
- To ask questions of study staff;
- To discuss problems with study adherence;
- To perform an interim examination (e.g., follow-up on an AE or participant request); and
- To provide lab results not available at the last follow-up visit.

If a participant is contacted when s/he missed a visit, staff will try to obtain her reasons for missing a visit. This information may be used to try to improve overall retention in the study.

7.6 FINAL STUDY VISIT (WEEK 52) OR TERMINATION VISIT (AND AT THE TIME OF ANY PERMANENT STUDY PRODUCT TERMINATION OR STUDY PRODUCT DISCONTINUATION)

Participants who reach week 52 will follow procedures included in the table of study procedures on page 72. This includes provision of any outstanding test results and final interviews. In addition a DBS/ plasma will be performed for drug levels at the final study visit.

Participants who have chosen to discontinue the product prior to the routine protocol-required withdrawal at Week 52 should continue routine follow-up visits. All protocol-required interviews and procedures, besides study product administration and drug levels, should be continued until Final Study Visit.

If a participant discontinues study product following instruction from the Investigator or wishes to withdraw permanently from the study, visit procedures as per week 48 will be conducted. The participant will then return for a final study visit (week 52) if possible.

The following procedures will be completed the final visit (wk 52 the final visit):

- Administrative/Behavioural Procedures
    - Locator information (update)
        - At all visits
    - HIV pre-and post-test counseling, including risk reducation counselling
        - At all visits
    - Social harms and/or benefits
        - At all visits
    - Sexual risk behavior questionnaire
        - At all visits
    - Provision of condoms
        - At all visits.
    - Acceptability assessment
        - Wk 52.
    - Feedback of plasma drug level/DBS results (to participants on study product who agree to receive this information at the time of adherence counseling.)
        - At visits Wk 12, 24, 36, 48.
    - Reimbursement
        - At all visits

- Clinical Procedures
    - Contraceptive counselling and provision as appropriate
        - At all visits
    - Physical exam
        - As clinically indicated
    - Update medical and menstrual history and/or current medications if applicable
        - At all visits
    - Record/update adverse events (AEs) applicable
        - At all visits

- Laboratory Procedures
    - HIV rapid testing

        - At all visits
    - Aspartate aminotransferase/alanine aminotransferase (AST/ALT) testing
        - Wk 52
    - Serum chemistries, including creatinine, glucose, electrolytes, and lipase
        - Wk 52
    - Urine pregnancy testing (for females)
        - At all visits
    - Contraceptive counseling
        - At all visits
    - Measurement of study drug levels by DBS for those participants on study prouct up to and including wk36
        - Wk 52

7.7 CLINICAL EVALUATIONS AND PROCEDURES

Full physical exams will be performed at screening and week 48 and targeted exams will be performed at other study visits as required. Clinical symptoms will be systematically assessed in a structured medical history at screening and enrollment (wk 0), Wks 4, 8, 12 and then every 12 weeks for the length of the trial.

Full physical exams include the following assessments:
Vital signs:

- Oral temperature
- Blood pressure
- Pulse
- Respirations

Measurements of:

- Weight
- Height

Clinical assessments of:

- Head and eyes
- Ears, nose, and throat
- Neck
- Lymph nodes
- Heart
- Lungs
- Abdomen
- Extremities
- Neurological
- Skin
- Breasts
- Tanner stage

Additional assessments may be performed at the discretion of the examining clinician in response to symptoms or illnesses present at the time of the exam.

7.8 LABORATORY EVALUATIONS AND PROCEDURES

Laboratory evaluations will include the following:

- Hepatitis B surface antigen and antibody testing
    - At Screening

- Urine pregnancy test
    - At every visit

- HIV serology
    - At every visit

- HSV-2 serology
    - At screening, Week 12, 48
- Chlamydia, and Gonorrhea.

- At screening, Week 12, 48

- Serum chemistries, creatinine only
  - Week 52

- AST, ALT
  - Screening, Week 12, 24, 36, 48 and 52

- Full Blood Count
  - Screening, Week 12, 24, 36, 48

- Haematocrit
  - Week 4, 8, 52

- DBS / Plasma drug level sampling
  - Week 4, 8, 12, 24,
  - Week 36, 48, for those who remain on study product
  - Week 52, Plasma only for those who remain on study product
- Urine dip stick
  - Screening, Week 12, 24, 36, 48

The location of laboratory evaluations will depend on laboratory capacity.

7.9 BEHAVIOURAL EVALUATIONS AND PROCEDURES

Using interviewer administered questionnaires the following behaviors of participants will be recorded and assessed over the 52 weeks of study participation at scheduled study visits:

- Study product adherence, with measures of barriers and facilitators of adherence (for focus group with enrolled participants who receive study product), including a visual scale.
- Product acceptability
- Sexual activity

- Condom use, including frequency of condom use when having sex and condom use at last sex
- Willingness to have real time drug level data and reasons for or against.
- Estimation of drug levels if not willing to have data shared.

All focus groups will be conducted by a study staff member, who will be trained by an expert socio-behavioural researcher. Focus groups will address a number of questions including adolescents' attitudes towards PrEP; adolescent perceptions of taking drugs previously reserved for HIV treatment as a form of prevention; where they would like to access these drugs; whether taking PrEP might identify individuals as high-risk and therefore stigmatise them; whether enhanced protection against HIV infection provided by PrEP might lead to sexual disinhibition or risk compensation; whether adolescents will/do still use condoms in order to protect against other STI's; what factors (e.g. appearance changes as a result of drug side-effects) might/do impact on adherence; where adolescents would like to access the drugs. They will also examine willingness to have drug levels shared and impact of hearing actual drug levels during counseling.

Parental/ guardian consent and adolescent assent will be obtained for all focus group participants (see Appendices 16.3 and 16.4).

7.10 PROCEDURES FOR PARTICIPANTS WHO TEMPORARILY HOLD OR DISCONTINUE STUDY PRODUCT

7.10.1 Participants Who Become Infected with HIV

If a participant becomes HIV-infected at any time after enrolment into the study, the study product will be immediately terminated (if applicable) and the protocol-specified visit schedule will be followed, for participants who choose to be maintained in the study. In addition, extra interim visits will be added to their schedule for psychosocial support, if needed. These visits will occur in addition to study visits, although they can be combined with regularly-scheduled study visits.

If a participant tests positive on two rapid HIV antibody rapid tests, they will be considered HIV-infected and will receive post-test counseling on these results. Participants with an indeterminate

HIV test result will be asked to provide a blood sample for ELISA testing, to confirm whether they are HIV-infected.

Participants will be allowed as much time and given as much support as they need to cope with the positive result. The counselor disclosing the result will encourage the participant to identify a trusted adult (not necessarily the parent/ guardian) that they would like to disclose to. If necessary, this adult will be called into the clinic to help support the participant [see Section 16.5 for more detail, including the HIV testing algorithm].

The participant will also be given a referral letter for counseling and support in the community. The participant will also be reassured that they can return to the clinic at any time during clinic hours for support. Clinic staff will make telephone contact with the service to which they are referring the participant.

If both rapids are positive blood will be sent for confirmatory viral load testing. When these results are available the participant will be recalled and following another pretest information session, a blood sample for CD4 count as well as resistance and genotype testing will be obtained. The participant will be followed up at the study site for the duration of the study, and will receive a CD4 count at 3-monthly intervals and psychosocial support for disclosure, to ensure that initial care and counselling is well-managed. After the Final Study Visit, the research team will link the participant into long-term HIV care and treatment at one of the existing local health facilities.

7.10.2 Participants Who Become Pregnant

If a female participant becomes pregnant after enrolment into the study, the study product will be immediately terminated, the protocol-specified visit schedule will be followed (for participants who choose to be maintained in follow-up), and the participant will be followed until delivery. The participant will be counseled about available options and appropriate referrals will be made depending on the participants' choice. Participants will also be encouraged to disclose their pregnancy results to a trusted adult (not necessarily the parent/ guardian) [See Section 9.3 for more details].

7.10.3 Management of Hepatitis B

Hepatitis B surface antigen and antibody testing will be conducted at screening for all potential participants. All adolescents who are not immune will be vaccinated for hepatitis B prior to enrollment. Participants will receive their first dose when they receive their results during the screening window, followed by another dose after 30 days (ideally at enrolment). The final dose will occur at approximately 6 months after the first dose, once they are enrolled and participating in the study. Potential participants with positive HepBsAg results will be referred for care and treatment of active infection and cannot be enrolled.

If symptoms or signs of clinical hepatitis are present in a participant during the course of the study, the Site Investigator or designee will temporarily hold oral study product and test the participant for hepatitis (including HBsAg plus any other testing indicated by the local standard of care). If hepatitis B infection is confirmed, the participant will be referred for appropriate care.

7.10.4 Participants Who Temporarily Hold or Discontinue Product Use (Initiated by Participant)

For participants who independently choose to discontinue use of the study product (either temporarily or permanently), the protocol-specified visit schedule will be followed (for participants who choose to be maintained in follow-up), with the exception of administration of study product.

7.11 SPECIMEN PREPARATION, HANDLING AND COLLECTION

Each study site will subscribe to the standards of good clinical laboratory practices (GCLP) and site-specific SOPs for proper collection, processing, labeling, transport, and storage of specimens at the local laboratory. All left over samples after testing, will be destroyed.

7.12 BIOHAZARDOUS WASTE

The Principal Investigator will ensure that biohazardous waste will be contained according to institutional, transportation/carrier, and all applicable regulations.

Table1: Schedule of Study Visits and Procedures

Nb. Screening visit (up to -4 weeks); Enrollment (0 weeks); Final visit (52 weeks).

Visit week	**Prior**	**Screen~~ing~~**	**Enrolment**	**4**	**8**	**12**	**24**	**36**	**48**	**Final 52**
Obtain written informed consent for screening and enrolment, from participant and his/her guardian		X								
Assessment of understanding for ICF		X								
Identification number assignment		X								
Locator information		X	X	X	X	X	X	X	X	X
HIV pre-and post-test counselling		X	X	X	X	X	X	X	X	X
Eligibility assessment (including review of all screening documentation)			X							
Sexual risk behavior questionnaire			X	X	X	X	X	X	X	X
Acceptability questionnaire				X	X	X	X	X	X	X
Adherence assessment and counselling				X	X	X	X	X	X	
Feedback of DBS or plasma results to those who agree to this.				X	X	X	X*	X*	X*	
Provision of condoms, condom counselling and rest of prevention package (bar PrEP)		X	X	X	X	X	X	X	X	X
Study product supplies and instructions *Only to those who indicate willingness to use.			X	X	X	X*	X*	X*		

Visit week	**Prior**	**Screening**	**Enrolment**	**4**	**8**	**12**	**24**	**36**	**48**	**Final 52**
Reimbursement	X	X	X	X	X	X	X	X	X	X
Schedule next visit (if applicable)		X	X	X	X	X	X	X	X	*
Focus group (including assent/consent)	X									X
Obtain/update medical history		X	X	X	X	X	X	X	X	X
Conduct physical exam Incl TS at enrollment and week 48		X	*	*	*	*	*	*	X	*
Disclose available test results		X	X	X	X	X	X	X	X	X
Provide or refer for contraception		X	X	X	X	X	X	X	X	*
Contraceptive counseling		X	X	X	X	X	X	X	X	X
Record/update AEs including social harms/benefits			X	X	X	X	X	X	X	X
Treat or prescribe treatment Syndromic treatment for STIs		*	*	*	*	*	*	*	*	*
Hepatitis B sAb/sAg testing		X								
Hepatitis B vaccination		*	*				*			
HIV serology		X	X	X	X	X	X	X	X	X
Herpes (HSV-2)		X				X			X	
Chlamydia, and Gonorrhea testing. **Females low vaginal self-swab** **Males Urine**		X				X			X	
Serum chemistries		X				X	X	X	X	
Creatinine Clearance										X
ALT/AST serology		X				X	X	X	X	X
Haematocrit				X	X					X
Full Blood count		**X**				X	X	X	X	
Measurement of study drug levels (DBS and plasma for drug levels				X	X	X	X #	X #	X #	X #
Measurement of study drug levels by DBS only										X #

Visit week	**Prior**	**Screening**	**Enrolment**	**4**	**8**	**12**	**24**	**36**	**48**	**Final 52**
Urine pregnancy testing		X	X	X	X	X	X	X	X	X
Urine dip stick testing		X				X	X	X	X	
Adherence counseling				X	X	X	X	~~X~~		
* IF clinically indicated, per local standard X = Mandatory **# =** on PrEP										

8 ASSESSMENT OF SAFETY

The Principal Investigator, site investigators and designated clinical staff are responsible for continuous and close safety monitoring of all study participants and for alerting the Safety Monitoring Committee (see Section 10.5), if unexpected safety concerns arise. Study sites will have written procedures for ensuring prompt reporting to the local Independent Ethics Committees, of any unanticipated problems involving risks to study participants or others. Safety of the adolescent participants in this study are of paramount concern.

- Primary safety monitoring and safeguarding of individual study participants is the responsibility of study staff, under the direction of the IoR. The IoR and designated study staff also are responsible for submitting case report forms to the SMC and EAE reports to the DAIDS RSC, such that relevant safety data are available in a timely manner for other study-specific safety monitoring procedures, as follows:

- The DAIDS RSC, DAIDS RAB Safety Specialist, and DAIDS PSB Medical Officers will review all EAE Forms received for PlusPills and follow up on these reports with site staff, the Protocol Team, and drug regulatory authorities when indicated.

- The PSRT will routinely review safety data reports and will meet approximately once per month or as needed via conference call to discuss cumulative study safety data and any potential safety concerns.

- The Study Monitoring Committee (SMC) also will periodically review study data with a focus on performance indicators such as participant accrual and retention, protocol adherence, and data quality. While site staff is not typically involved in these reviews, site staff should be aware that the SMC might make recommendations to DAIDS and/or the protocol team that could affect the study and sites in significant ways. These decisions are based on a detailed review of the available study data and careful consideration of ongoing participant safety and study viability.

This section presents information related to adverse event (AE) reporting and participant safety monitoring in Plus Pills. Please also refer the following resources relevant to AE assessment and reporting:

  - DAIDS Table for Grading Adult and Pediatric Adverse Events (Toxicity Table), version 2.0 dated Nov 2014

  - Manual for Expedited Reporting of Adverse Events to DAIDS, Version 2 (DAIDS EAE Manual), dated January 2010

  - DAERS Reference Guide for Site Reporters and Study

Physicians

- Package Insert for Emtricitabine/Tenofovir Disoproxil Fumarate (Truvada)
- Package Insert for Emtricitabine
- Package Insert for Tenofovir Disoproxil Fumarate

8.1 ADVERSE EVENT PROCEDURES AND REPORTING REQUIREMENTS

An Adverse Event (AE) is defined as any untoward medical occurrence in a study participant, from the time of enrollment through when s/he terminates from the study; it does not necessarily have a causal relationship with the study product. As such, an AE can be an unfavorable or unintended sign (including an abnormal laboratory finding, for example), symptom or disease temporally associated with the use of a study product, whether or not considered related to the product. This definition is applied to all participants beginning from the time of enrollment.

Study site staff will document in source documents and the appropriate AE Log CRF all AEs reported by or observed in enrolled study participants regardless of severity and presumed relationship to study product. The severity of clinical symptoms will be scored using the DAIDS Table for Grading the Severity of Adult and Pediatric AEs, Version 2.0 Dated Nov 2014. The Investigator or designee must determine the severity of the AE and document it on the appropriate CRF (AE Form). Each adverse event that the participant reports will be graded for severity according to the DAIDS grading scale.
If not on the grading scale then the following scale will be applied:

- **Mild:** participant was able to perform all normal activities.
- **Moderate:** the participant had to discontinue some activities due to the adverse event.
- **Severe:** the participant was incapacitated by the adverse event and unable to perform normal activities.
- **Life-threatening** participant experienced extreme limitation in activity, significant assistance required; significant medical intervention / therapy required, hospitalisation or hospice - care probable.

An AE **does not** include:

- Pre-existing diseases or conditions present or detected prior to start of study intervention that do not worsen.

- Medical or surgical procedures (e.g. surgery, endoscopy, tooth extraction, transfusion); the condition that leads to the procedure is an adverse event.
- Situations where an untoward medical occurrence has not occurred (e.g. hospitalization for elective surgery, social and/or convenience admissions).

All AEs will be captured regardless of the association or otherwise to the study intervention and reported on the AE CRF in accordance with study specific procedures. All AE reports will contain at least the date the AE occurred, a brief description of the event, the relationship to study intervention, the action taken, the outcome, date resolved, and the severity of the event.
Suspected, Unexpected Serious Adverse Reactions (SUSARS) will also be reported after the protcol-defined AE reporting period, if the study staff become aware of these at any time.

Requirements, definitions and methods for expedited reporting of Adverse Events (AEs) are outlined in Version 2.0 of the DAIDS EAE Manual, which is available on the RSC website at *http://rsc.tech-res.com/safetyandpharmacovigilance*.

The DAIDS Adverse Experience Reporting System (DAERS), an internet-based reporting system, must be used for expedited AE reporting to DAIDS. In the event of system outages or technical difficulties, expedited AEs may be submitted via the DAIDS EAE Form. For questions about DAERS, please contact DAIDS-ES at *DAIDS-ESSupport@niaid.nih.gov*. Site queries may also be sent from within the DAERS application itself.

Where DAERS has not been implemented, sites will submit expedited AEs by documenting the information on the current DAIDS EAE Form. This form is available on the RSC website: *http://rsc.tech-res.com/safetyandpharmacovigilance/*. For questions about expedited reporting, please contact DAIDS RSC *DAIDSRSCSafetyOffice@tech-res.com*.
Designated study staff will submit AE information and any other relevant safety information to the local Ethics Committee(s) in accordance with EC requirements.

Reporting Requirements for this Study

- The SAE Reporting Category, as defined in Version 2.0 of the DAIDS EAE Manual, will be used for this study.
- The study agents for which expedited reporting are required are: Tenofovir and Emtracitabine as a single combined formulation known as TRUVADA.

- AEs and SAEs will be reported throughout the period of trial follow up.

8.1.1 Social Harms Reporting

The study site teams will monitor for and track unanticipated problems related to study procedures and/or to participation in the study, until participants' time of termination from the study. Study site staff will provide clinically appropriate treatment and/or referrals should any such problems occur.

8.2 EXPEDITED ADVERSE EVENTS (EAE)

The expedited AE reporting period for this study is as per the EAE manual, from study enrollment until study completion or discontinuation of the subject from study participation for any reason. After the protocol-defined AE reporting period, unless otherwise noted, only SUSARs as defined in version 2.0 of the EAE manual will be reported to DAIDS if the study staff become aware of the events on a passive basis (from publicly available information).

All unexpected SAEs related to the study product observed in the clinical trial will be reported to the FDA in accordance with 21 CFR 312.32 (IND Safety Reports).

FOR FURTHER DETAILS SEE APPENDIX 16.9

8.3 LOCAL REGULATORY REQUIREMENTS

In addition to submitting EAE information to the DAIDS Safety Office through the Regulatory Support Center (RSC), the investigators will submit AE information in accordance with local regulatory agencies' or other local authorities' requirements.

8.3 (i) Serious Adverse Events (SAEs) are defined by the ICH E2A definition, as described in Version 2 (January 2010) of the *DAIDS EAE Manual*, section 2.1, Seriousness. An SAE is any untoward medical occurrence following any exposure to the study agent that:

- Results in death,

- Is life-threatening, (*The term "life-threatening" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.*)

- Requires inpatient hospitalization or prolongation of existing hospitalization, (*Per ICH SAE definition, hospitalization itself is not an AE, but is an outcome of the event.*)

*The following types of hospitalization do **not** require expedited reporting to DAIDS:*

- *Any admission unrelated to an AE (e.g., for labor/delivery, cosmetic surgery, administrative or social admission for temporary placement for lack of a place to sleep),*

- *Protocol-specified admission (e.g., for a procedure required by protocol), or*

- *Admission for diagnosis or therapy of a condition that existed before receipt of study agent(s) **and** has not increased in severity or frequency as judged by the clinical investigator. (**NOTE**: A new AIDS-defining event in a subject already known to be HIV-infected would be considered an increase in severity of a pre-existing condition [HIV infection] and would therefore be reportable.)* Results in persistent or significant disability/incapacity, Is a congenital anomaly/birth defect,

- *Clinically insignificant physical findings at birth, including those regarded as normal variants, do not meet reporting criteria. If a clinically significant anomaly is reported, all other findings (including those of no individual significance) should be included in the same report. For example, an isolated finding of polydactyly (extra fingers or toes) or Mongolian spot in an infant with no other findings would not be reported as an SAE, but polydactyly or Mongolian spot occurring with a major cardiac defect would be reported and included in the SAE report.*

- *Information about congenital anomalies can be found on the Centers for Disease Control and Prevention (CDC) website: http://www.cdc.gov/ncbddd/bd/monitoring.htm – Guidelines for Conducting Birth Defects Surveillance, National Birth Defects Prevention Network (NBDPN), Appendix 3.1. Direct link to document: www.nbdpn.org/current/resources/sgm/appendix3-1.pdf. This website listing should not restrict the reporting of anomalies that the site investigator deems important for the sponsor to know.* Is an important medical event that may not be immediately life- threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above. Examples include the following: intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; development of drug dependency or drug abuse; etc.

9 CLINICAL MANAGEMENT

9.1 TOXICITY MANAGEMENT

Full physical exams will be performed at screening and week 48. Targeted physical exams will be performed at other visits as needed. Clinical symptoms will be systematically assessed in a structured medical history at screening and enrollment, monthly for three months, and then every 12 weeks for the remaining length of the trial (Months 5-12).
In general, all participants who develop a Grade 1 or 2 AE, regardless of relatedness to the study product, may continue use of the study drug per protocol.

Grade 3: Study drug use should be temporarily discontinued in consultation with the PSRT in Participants, who develop a Grade 3 AE or toxicity that is not specifically addressed below regardless of study product relatedness. In general, and unless otherwise decided in consultation with the PSRT, the investigator should re-evaluate the participant at least weekly for up to 2 weeks (or for 2 weeks following the receipt of the results for lab toxicities) to document resolution of toxicity to less than Grade 2. The study drug should be permanently discontinued if improvement to severity ≤ Grade 2 cannot be documented within 4 weeks of receipt of the initial result. If study drug use is resumed and the same Grade 3 AE recurs at any time, the IoR/designee must hold product use and consult the PSRT for further guidance on frequency of reevaluation or progression to permanent discontinuation of the study drug.

For all Grade 4 laboratory-identified or clinical toxicities, the study product will be withheld. Laboratory toxicity will be promptly confirmed by repeating the test on an additional specimen, preferably within seven days. If Grade 4 toxicity is also present on repeat testing of additional specimen and is considered to be related to study medication, the study product will be permanently discontinued. Study product may be resumed after resolution to Grade 1 of any Grade 4 laboratory toxicity or clinical event considered to be not related to study product based on the judgment of the Site Investigator after consultation with the PSRT. If the toxicity recurs to Grade 3 or higher after study product is restarted, the study product will be permanently discontinued.
Participants will be asked to report AEs at every study visit. Clinical AEs will be evaluated by the investigator or designee who has clinical qualifications. Any Grade 3 and 4 clinical AEs will be referred

to a Site Investigator at the time of the visit. A back-up coverage schedule will be developed and posted to assure that a study physician or nurse is available at all times.

In addition to the informal safety monitoring done by the Site Investigator and study clinician, the Protocol Safety and Review Team (PSRT) will conduct interim reviews of safety data and study conduct. These reviews will take place approximately every **month,** or as needed. Any discontinuation and potential resumption of study product will be managed in consultation with the PSRT (see section 10.5 for additional detail).

9.1.1 Nausea, Vomiting, and Diarrhea

Participants with Grade 1 or 2 nausea, vomiting, or diarrhea may be treated symptomatically with hydration, oral antiemetic therapies or antiemetic suppositories at the discretion of the site investigator or designated clinical staff. The site investigator should order any clinically relevant laboratory analyses (per judgment of the site investigator/or designee). Participants should be reminded to take study drug with food. Participants with Grade ≥ 3 nausea, vomiting, or diarrhea, for which an alternative etiology is not established, must discontinue the study drug temporarily until grade 2 or lower and be treated symptomatically. Should condition(s) not improve to Grade <2 within 7 days, the site investigator/designee should consult the PSRT for guidance on continuing the temporary discontinuation or progressing to permanent discontinuation of study drug. Repeat episodes of these events will be handled independently, and the instruction above will be followed for each event.

9.1.2 Management of ALT/AST Elevations

All study participants will either be immune to HBV at study entry, or will receive HBV vaccination. Therefore, HBV infection is not likely to be a cause of AST/ALT elevations. Careful assessments should be done to rule out the use of alcohol, lactic acidosis syndrome, non-study medication-related drug toxicity, herbal medications/supplements, or viral hepatitis as the cause of elevation in AST or ALT of any grade. The participant must be carefully assessed for any symptoms or signs of hepatotoxicity, including fatigue, malaise,

anorexia and nausea, jaundice, acholic stools, right upper quadrant pain, or hepatomegaly. If the AST/ALT elevation is considered most likely to be due to concomitant illness or medication, standard management, including discontinuation of the likely causative agent, if possible, should be undertaken. If symptoms or signs of clinical hepatitis are present, study drug must be held or discontinued.

Grade 1 transaminase elevation:
For study participants with less than Grade 1 AST and ALT at study entry, an increase to Grade 1 AST or ALT even in an asymptomatic participant may be of concern. AST and ALT must be repeated as soon as possible (at most within 1 week of the receipt of the results). Study drug may be continued while repeating AST and ALT at the discretion of the investigator provided the participant is asymptomatic. Should the repeat AST and ALT testing indicate a continuation of Grade 1, the PSRT should be immediately consulted. In the case of symptomatic participants, study drug will be held temporarily, and management (including resumption of study drug) should be arranged in consultation with the PSRT.

Grade 2 transaminase elevation:
Participants should have AST/ALT re-checked as soon as possible (at most within 1 week of the receipt of the results) and then be followed weekly until levels are Grade < 1. The frequency of follow up may be altered at the discretion of the site investigator following consultation with the PSRT. Study drug may continue at the discretion of the investigator provided the participant is asymptomatic. In the case of symptomatic participants, study drug will be held temporarily, and management (including resumption of study drug) should be arranged in consultation with the PSRT.

Grade 3 transaminase elevation:
Study drug should be temporarily held for any Grade 3 AST or ALT. Participants should have AST/ALT re-checked as soon as possible (at most within 1 week of the receipt of the results). Participants should then be followed weekly until levels are Grade < 1. Resumption of study drug should be arranged in consultation with the PSRT.

Grade 4 transaminase elevation:
Study product should be permanently discontinued for any Grade 4 AST and/or ALT. Appropriate care and management of the participant will be ensured.

If the investigator has determined in consultation with the PSRT that the case has stabilized, it may be possible to decrease the frequency of follow-up laboratory testing in addition to resumption of study drug.

9.1.3 Management of Creatinine Clearance

After enrollment, if the calculated creatinine clearance is less than <75ml/min, the study product should be temporarily held and confirmed within one week of the receipt of the results, and the PSRT should be consulted. If the creatinine is confirmed to be <75ml/min, the study product must be permanently discontinued.

9.1.4 Management of Hypophosphatemia

Grades 1 and 2 hypophosphatemia:
The phosphate should be repeated within 2 weeks of the receipt of any initially abnormal results. Supplemental phosphate should be given with phosphate-rich food or fluid with or without neutral phosphate solution. Other causes of phosphate loss should be evaluated. Unless other temporary study drug hold requirements apply, study drug need not be held.

Grade 3 hypophosphatemia:
The phosphate should be repeated within 1 week of receipt of any initially abnormal results, and should be accompanied by serum creatinine testing and urine dipstick for protein/glucose. Supplemental phosphate should be given with phosphate-rich food or fluid with or without neutral phosphate solution, and other causes of low phosphate should be investigated. Participants with any of the following results (of tests accompanying the repeat phosphate test) will have study drug held:

- Proteinuria >2+
- Glycosuria >2+

• Creatinine > ULN
• Creatinine clearance <LLN

Participants may continue study drug provided that:
• Study drug hold is not otherwise indicated (*e.g.*, due to the results of creatinine, creatinine clearance, urine protein, and/or urine glucose)
• Phosphate levels will be retested approximately weekly until return to <Grade 2, unless other retesting schedule has been advised by the PSRT

Grade 4 hypophosphatemia:
The phosphate should be repeated within 1 week of the receipt of any initially abnormal results, and should be accompanied by serum creatinine testing and urine dipstick for protein/glucose. Supplemental phosphate should be given with phosphate-rich food or fluid with or without neutral phosphate solution. Other causes of low phosphate should be investigated.
Participants will have study drug held, and the PSRT must be immediately contacted. Phosphate levels will be retested approximately weekly until return to <Grade 2, unless another retesting scheduled has been advised by the PSRT.

Participants may resume study drug, provided that:
• Study drug hold is not otherwise indicated (*e.g.*, due to the results of serum creatinine, creatinine clearance, urine protein, and/or urine glucose)
• The phosphate level has returned to <Grade 2
• A request to resume study drug is approved by the PSRT

PSRT notification should occur for any result >Grade 2 for protein or glucose measured by urine dipstick performed at the time of confirmatory draw for a phosphate level.

9.1.5 Proteinuria

Proteinuria will be assessed by urine dipstick. A finding of 1+ proteinuria should be confirmed

with a second urine dipstick performed no earlier than one week. Proteinuria of 2+ or greater does not need to be confirmed at a separate visit. The site investigator/designee should temporarily hold study drug in the following circumstances:

• Detection of 3+ or greater proteinuria at any visit. Study drug should be held regardless of serum creatinine or phosphorus results obtained at the time of proteinuria detection. Urine dipstick testing and serum creatinine and phosphate should then be performed monthly for at least three months.

• Detection of 2+ proteinuria. Study drug should be held until results of serum creatinine results obtained at the time of proteinuria detection are available. Study drug hold should continue if hold criteria outlined for serum creatinine are met. If neither value meets criteria for study product hold, study drug should be resumed.

• Detection of 1+ proteinuria confirmed on two separate visits. Study drug should be held only if serum creatinine or phosphorus results obtained at the time of detection of proteinuria meet hold criteria.

9.1.6 Glycosuria

Glycosuria will be assessed by urine dipstick. A finding of 1+ glycosuria should be confirmed with a second urine dipstick performed no earlier than one week but no later than 2 weeks after detection of the first 1+ glycosuria. Glycosuria of 2+ or greater does not need to be confirmed at a separate visit.

The severity of glycosuria is graded using the same grading scale as for proteinuria. The site investigator/designee should temporarily hold study drug in the following circumstances:

• Detection of 3+ or greater glycosuria at any visit. Study drug should be held regardless of serum creatinine or phosphorus results obtained at the time of proteinuria detection. Urine dipstick testing and serum creatinine and phosphorus should then be performed monthly for at least three months.

• Detection of 2+ glycosuria. Study drug should be held until results of serum creatinine and phosphorus results obtained at the time of glycosuria detection are available. Study drug hold should continue if hold criteria outlined for serum creatinine and/or phosphorus are met. If neither of these values meets criteria for study drug hold, study drug should be resumed.

• Detection of 1+ glycosuria confirmed on two separate visits. Study drug should be held only if serum creatinine or phosphorus results obtained at the time of detection of glycosuria meet hold criteria.

9.2 HEPATITIS B INFECTION

Adolescents who test positive for Hepatitis B surface antigen (HBsAg) during screening, or demonstrate signs or symptoms of Hepatitis B during the study, will be will be referred for appropriate care. If Ag positive at screening, participants are ineligible for study participation. All HBsAB sero-negative adolescents who have no history of previous vaccination, will be vaccinated, during the screening period, 30 days after the initial injection (ideally at enrollment), and then again after 24 weeks. It is important to note that participants who are Hep B infected may incur a "Hep B viral flare" on cessation of TDF/FTC therapy. This should be monitored for and appropriately managed should it occur.

9.3 PREGNANCY

All participants will be provided with male and/or female condoms. As participants will be required to be sexually active in order to enroll in the study, females will be required to use condoms as well as take low dose, combination oral or injectable hormonal contraception, in addition to receiving contraceptive counseling throughout the duration of study participation. Pregnancy testing is performed at all study visits and participants are encouraged to report all signs or symptoms of pregnancy to study staff. The Site Investigator or designee will discontinue drug permanently, counsel any participant who becomes pregnant regarding possible risks to the fetus according to site SOPs. The Site Investigator/designee also will refer the participant to all applicable services; however, sites will not be responsible for paying for pregnancy-related care. Youth-friendly sexual reproductive health services are available free of charge at care facilities in site surrounds. A

participant who is pregnant will continue to be followed until the pregnancy outcome is ascertained but will not receive any study product.

9.4 CRITERIA FOR EARLY TERMINATION

Participants may voluntarily withdraw from the study for any reason at any time. The Principal Investigators may withdraw participants to protect their safety, and/or if participants are unable or unwilling to comply with study procedures.

9.5 TREATMENT FOR SEXUALLY TRANSMITTED INFECTIONS

Participants will be tested for HSV-2, chlamydia, and gonorrhea during screening, week 12 and at week 48.. All participants will receive screening and treatment for STIs throughout the study and their identified partners will be managed using syndromic management of STIs according to South African STI guidelines.

9.6 MANAGEMENT OF HIV INFECTION

Refer to Section 7.10.1 for specific study procedures regarding participants who become infected with HIV at any time during the study.

9.7 CRITERIA FOR DISCONTINUATION

The criteria for permanent discontinuation of further study product for an individual participant are:

- Product-related toxicity (see Section 9.1)
- Requirement for prohibited concomitant medications
- HIV infection
- Pregnancy/lactation
- Completion of study as defined in the protocol
- Request by participant to terminate study product
- Any conditions or clinical reasons that will threaten safety and well-being of participant

The criteria for premature discontinuation of further study participation for an individual participant are:

- Lost to follow up as per site SOP
- Participant repeatedly non-compliant with study product as prescribed
- Pregnancy/lactation
- Request by participant to withdraw from study
- Request of the primary guardian or caregiver if s/he thinks the study is no longer in the best interest of the participant
- Participant judged by the Site Investigator to be at significant risk of failing to comply with the provisions of the protocol as to cause harm to self or seriously interfere with the validity of study results
- At the discretion of the Independent Ethics Committee, Medicine Control Council, Site Investigator, or pharmaceutical supporter.
- DAIDS, NIAID, the Office of Human Research Protection (OHRP), and the FDA as regulatory entities may also discontinue the study at their discretion.

10 STATISTICAL CONSIDERATIONS

10.1 OVERVIEW AND SUMMARY OF DESIGN

The study is designed as an open-label phase 2 demonstration project, to evaluate the acceptability, safety, feasibility, as well as the adherence to daily oral PrEP (FTC/TDF) for HIV-1 prevention, among 150 male and female adolescent participants at two sites (with approximately 75 participants at each site), ranging in ages between 15 and 19 years old, over a 12 month period. The study will also investigate the uptake and utility of feedback to the participants real time about drug levels obtained from dried blood spots/plasma during adherence counselling.

10.2 STUDY ENDPOINTS

Primary Acceptability/Use Endpoints:

Consistent with the primary study objective to evaluate the acceptability and use of daily oral PrEP (FTC/TDF) in HIV-negative adolescents, ages 15-19 years, the following primary safety endpoints will be assessed:

- The proportion of participants who report willingness to use the study regimen, take up PrEP and remain on PrEP as part of a comprehensive prevention package.
- An acceptability questionnaire will be administered at the final study visit to assess the delivery of PrEP and the content of the study visits, including the user-friendliness of the medication regimen (including an assessment of side effects), the delivery format, the dosing strategy, and the clinic visit schedule.
- Number of adolescents recruited, enrolled, and retained in the study.

Primary Safety Endpoint:

- Grades 2, 3, and 4 clinical and laboratory adverse events;

Secondary Endpoints:

Consistent with the secondary study objectives to evaluate the adherence and sexual behaviour of daily oral PrEP (FTC/TDF) in HIV-negative adolescents, ages 15-19 years, the following endpoint will be assessed:

Adherence Endpoint:

- Adherence to daily regimens of oral PrEP as evidenced by self-report, pill counts, and proportion of participants assigned to FTC/TDF who have detectable drug levels.
    - Proportion of doses that are taken as instructed.

Sexual behaviour

- Reported number of steady and casual sex partners, condom use (and change after introduction of study product), substance use prior to or during sex, as evidenced by participant responses to interviewer-administered questionnaires and focus group.
- Proportion of scheduled HIV testing appointments that are missed, in relation to individual characteristics (age, sex, number of partners, use of other prevention methods) and the characteristics of the product.

Consistent with the exploratory objective to assess the HIV incidence in study participants during the course of study participation, the following endpoint will be assessed:

- HIV infection, as measured by seroconversion of study participants during the approximate 12 months of follow-up

Exploratory Endpoints:

- Consistent with the exploratory study objective to explore the feasibility of biofeedback of Blood Spot results as an adherence enhancing strategy in 150 HIV-negative adolescents, ages 15-19 years, the following exploratory endpoints will be assessed:
    - Proportion and number of participants who are tested using DBS and received results of DBS compared to participants who are tested using DBS but do not receive biofeedback of results.
    - Number of counselling opportunities in which drug level feedback is requested vs total number of counseling events
    - Number and nature of participants who request drug level feedback .
    - Correlation between self reported adherence and drug levels at each visit for each participant
    - Correlation between self reported adherence and drug levels at each

visit in the study overall.

- Proportion and number of participants whose adherence ito study product improves when receiving the results of DBS compared to those who do not receive feedback of results as measured by endpoints above.

Consistent with the exploratory study objective to investigate the relationship between daily PrEP usage and sexual practices and behavior in adolescents, the following exploratory endpoints will be assessed

Sexual behaviour data obtained using questionnaires and a focus group.

10.3 STUDY HYPOTHESIS

The DTHF protocol and research teams hypothesize that oral once daily PrEP (TDF/FTC) will be acceptable and utilized safely by healthy adolescents, between the ages of 15-19 years.

10.4 SAMPLE SIZE CONSIDERATIONS

The sample size calculation is based on the ability to detect the measure the primary objectives (acceptability and use) in the participant population. The table below shows the precision (as 95% confidence limits) provided by various sample sizes in detecting the occurrence of acceptability endpoints (with a frequency non- uptake and use varying from 5%-20%).

Acceptability will be measured by proportion of youth who take up PrEP and remain on PrEP as part of a comprehensive prevention package. Also they will complete an acceptability questionnaire.

	*Precision **		
Frequency	*n=100*	*n=135*	*n=170*
5%	1.6; 11.2	2.1; 10.4	2.4; 9.8
10%	4.9; 17.6	5.7; 16.8	6.4; 16.2
15%	8.6; 23.5	9.9; 22.8	10.7; 22.2
20%	12.7; 29.1	14.2; 28.6	15.3; 28.1

* Asymptotic (exact) binomial 95% confidence limits

Based on these calculations, we anticipate that 135 participants, rounded up to 150 participants to account for premature censoring (due to loss to follow-up and/or withdrawal of consent, estimated at maximum 10%) will be required to detect non-acceptabiltiy endpoints that occur in 10% of subjects with approximately 5% precision.

10.5 DATA AND SAFETY MONITORING AND REVIEW

In addition to the informal safety monitoring done by the Site Investigator and study clinician, DTHF will convene an independent Protocol Safety Review Team (PSRT). The roles of the PSRT are:

- To conduct interim reviews of primary safety data as well as study conduct and progress, including rates of participant accrual, retention, rates of adherence to study product and protocol, as well as HIV rates. These reviews will take place approximately **every month,** or as needed. The PSRT may recommend early termination of the study or modification when there is clear evidence of harm towards participants. The PSRT will make a recommendation to the SMC for immediate review of data.

- To respond to queries from site staff on eligibility determination and conditions for exclusion from initial drug dosing.

- To consider and rapidly respond to queries from study staff regarding study drug dosing discontinuation or resumption following occurrence of toxicities as outlined in Section 9 of the study protocol. Additionally, when a site reports any condition that results in study drug being held with resumption pending PSRT consultation, the PSRT will be convened via conference call to make a final determination (unless this is done via email in the interim).

- To respond to queries from the study team when information is needed to guide clinical data management and safety reporting. The Principal Investigator is designated as the point person for queries, and will consult with other PSRT members as needed.

In addition, the Safety Monitoring Committee (SMC) will conduct interim reviews of safety data as well as study conduct and progress, including rates of participant accrual. Retention, rates of

adherence to study product and protocol, as well as HIV rates. These reviews will take place approximately every 3 months, or as needed. The SMC may recommend early termination of the study or modification when there is clear evidence of harm towards participants. Should the SMC or the PSRT detect evidence of harm such that the recommendation for halting or modifying the study is made, then this will be communicated to the PI, The protocol team and the DAIDS prevention division. The IRB and MCC will also be informed of the discontinuation of the study and/or the modification and reasons for modification of the study. All further enrollment, and study activities other than safety follow up will be put on hold. Participants, guardians and CABS will be notified as soon as possible after next steps are identified.

10.6 DATA ANALYSIS PLAN

A customized data entry and management system will be implemented for the project in Microsoft Access. Data will be analysed using the statistical programme STATA (Stata Corporation, College Station, Texas, USA). Simple descriptive statistics including frequency distributions will be used to assist in data cleaning and summarization.

The analysis plan for each of the study objectives (per 10.2 above) is detailed below. (Note that throughout the analysis, all statistical tests will be 2-sided using an alpha of 0.05.)

Endpoints:

A. PRIMARY

1. Primary: Use

Number of adolescents who continue to use PrEP after the initial 3 month period and the total time on PrEP for each adolescent and for the cohort as a whole.

Analysis:

Proportions of participants (a) willing to use and (b) taking up PrEP will be described with point estimates and exact 95% confidence intervals. “Remaining on PrEP” will be defined as any self-reported use of PrEP at each study interval (regardless of adherence) over the 9-month follow-up period, as a binary outcome. The first 3-month “use” will be 100% for all 150 participants. We will use product-limit methods to examine ‘survival’ proportions for participants remaining on PrEP, accounting for censoring due to loss to follow-up. We will (i) examine the reasons for discontinuation

and (ii) examine the baseline and/or pre-LTF characteristics of those LTF, and compare to those retained, in order to understand the possible associations between LTF and adherence and/or sexual risk taking. While our preliminary analyses will presume this censoring is uninformative, we will include analyses that assume LTF are non-adherent. Our intention is to (i) examine the reasons for discontinuation and (ii) examine the baseline and/or pre-LTF characteristics of those LTF, and compare to those retained, in order to understand the possible associations between LTF and adherence and/or sexual risk taking. While our preliminary analyses will presume this censoring is uninformative, we will include analyses that assume LTF are non-adherent. In subsidiary analyses for this primary endpoint, we will also examine the factors associated with PrEP willingness, uptake and "remaining on PrEP" using standard methods (including chi-square and exact tests for the comparisons of proportions, and log-rank tests for the comparison of 'survival' curves in product-limit analysis).

2. Primary: Acceptability

An acceptability questionnaire will be administered 3 monthly to assess reasons for continuing, stopping or restarting PrEP. A further questionnaire will be administered at the final study visit to assess the delivery of PrEP and the content of the study visits, including the user-friendliness of the medication regimen (including an assessment of side effects), the delivery format, the dosing strategy, and the clinic visit schedule.

Analysis Plan:

This acceptability questionnaire will contain both binary items as well as continuous (interval) measures from Likert-type items. Analysis of data from this questionnaire will begin with standard descriptive statistics for each item, overall and by key participant subgroups (a priori, these will be based on participant age, gender, sexual activity during the study and PrEP adherence during the study). We will compare responses to acceptability items using standard methods, including chi-square and exact tests; Student's t- and rank-sum tests, replaced by analysis of variance or u-tests for global comparisons across polytomous groupings.

3. Primary: Safety

Grades 2, 3, and 4 clinical and laboratory adverse events

Analysis:

This analysis will be based on descriptive statistics.

B. Secondary Endpoints:

1. Secondary: Adherence

Adherence to daily regimens of oral PrEP as evidenced by the use self-report, pill counts, and proportion of participants on FTC/TDF who have detectable drug levels.

Proportion of doses that are taken as instructed.

Proportion of blood samples with detectable drug levels

Proportion of adolescents with detectable drug levels who report using PrEP

Analysis Plan:

There are 3 different measures of PrEP adherence that will be used for the primary adherence endpoint: Participant self-report, pill count results, and detectable drug levels. While the distributions of each of these measures may vary, a priori we anticipate that analysis of each of these 3 measures will use two different binary metrics from data at each study visit: (i) perfect adherence (defined as adherence data that do not suggest any missed doses, e.g., pill count data consistent with daily dosing, or no missed doses detected on self-report); and, (ii) effective adherence (defined as adherence levels that are consistent with protection against HIV exposure based on available data from PrEP efficacy trials, e.g., >85% doses taken, from pill count, or self-report; or therapeutic drug levels on biological assays). Note that drug levels will be used in analyses of effective adherence only. Analyses of adherence data will be based on the binary constructs of perfect and effective adherence as well as continuous measures of the proportion of PrEP doses taken; both the binary and continuous constructs will be analysed at each study visit (repeated measures) and in the overall study period (through aggregation of measures from each study visit).

The analysis for this primary endpoint is largely descriptive, with the estimates of adherence and their 95% confidence intervals reported for different adherence measures for the cohort overall as well as a priori subgroupings by age, gender and sexual activity during the study. Subsidiary analyses will develop models to examine the predictors of adherence within the cohort; given the sample size, such analyses will have limited statistical power and should be considered exploratory. For repeated measures of adherence from each study visit, we will use a generalized linear modelling approach that includes fixed effects (e.g., participant characteristics) and random effects (e.g., characteristics of study visits). Following the GLLAMM routine in Stata, this will include mixed-effects linear models (for continuous measures of adherence) with maximum-likelihood extensions to binary adherence endpoints. (Skrondal A, Rabe-Hesketh S. Generalized latent variable modeling: multilevel,

longitudinal and structural equation models. Boca Raton: Chapman and Hall, 2004.)
This approach converges with that of generalized estimating equations based on the Huber-White sandwich variance estimator.

2a. Secondary: Sexual Activity

Reported number of steady and casual sex partners, condom use (and change after introduction of study product), substance use prior to or during sex, as evidenced by participant responses to interviewer-administered questionnaires

Analysis plan:

The key analysis question for this secondary endpoint is whether different measures of sexual risk change with the availability and/or uptake of PrEP (in the initial 3-month mandatory study follow-up period) compared to periods "off-Prep". The measures of sexual risk include continuous measures (number of sexual partners) as well as binary measures (casual sex partners yes/no, substance use prior to sex, consistent condom use during sex). All measures are visit-specific, with a maximum of 12 measures during the study, per participant. In analysis, we will first use graphical approaches to display the proportions of participants reporting binary sexual risk behaviours (or means of continuous measures) at each study visit over the 12-month period. Following this, we will use repeated measures methods (as described above) for both binary and continuous dependent variables, with PrEP access treated as a binary variable distinguishing visits in on vs. off PrEP phases; in the first instance, these models will not include other covariates.

2b. Proportion of scheduled HIV testing appointments that are missed, in relation to individual characteristics (age, sex, number of partners, use of other prevention methods) and the characteristics of the product.

Analysis:

"Missed appointments" will be defined as participants being >7 days late for a visit scheduled on a 28-day cycle. This measure will be analysed as a binary variable following the repeated measures approaches described above.

3. Secondary: HIV Incidence

HIV infection, as measured by seroconversion of study participants during the approximate 12 months of follow-up

Analysis:

The incidence of HIV will be described using person-time (rates per 100 person years of observation)

and product-limit (survival proportion) approaches. For both methods, the date of seroconversion will be the midpoint of the interval between the last negative and first positive HIV test. For participants lost to follow-up, the date of censoring will be one day after the last visit attended.

C. Exploratory Endpoints:

1. Exploratory: Dried Blood Spot/plasma biofeedback

Correlation of self reported adherence and presence of drug levels in participants who are tested using plasma drug levels or DBS and received results compared to participants who are tested using plasma/DBS but do not receive biofeedback of results.

Analysis:

These data will be described as proportions at each study visit; while we will calculate differences in proportions attending between participant who do and do not receive biofeedback results, no formal statistical tests will be used for this exploratory endpoint.

2.Exploratory: Sexual behaviour by coital diaries

Sexual behaviour data obtained using a questionnaires and focus group.

Analysis:

Data from questionnaires will be compared to self-reported sexual behaviour on a per participant and per visit basis. While this endpoint is exploratory, we anticipate using the distributions of the observed data to defined post-hoc boundaries of acceptable agreement, and then use this to estimate the proportion of participants with acceptable versus unacceptable agreement at each visit, and overall during the study.

Analysis of Focus Group data:

All focus groups and interviews will be transcribed and then analysed using Framework Analysis (Ritchie and Lewis; 2003). This approach was developed in the 1980's by researchers at the UK National Centre for Social Research and has been used extensively for applied or policy relevant qualitative research (Pope et al; 2000). It uses an analytical framework to organize data according to key themes, concepts and emergent categories in grids or matrices. This method facilitates both between case and within case analysis to look for patterns and connections. It provides a systematic, consistent and transparent approach to handling data that also enables analysis to go beyond description to interpretation where appropriate. In addition, it facilitates the linking of findings with

those of quantitative research, which will be relevant in comparing, contrasting and enhancing findings collected quantitatively in this study, in particular on PrEP acceptability and adherence. In addition, this triangulation of methods (qualitative and quantitative) has been advocated as an approach to increase the validity of findings (Mays and Pope; 2000, Shenton; 2004).

Up to three researchers experienced in qualitative data analysis will form the data analysis team and all will be trained on the process of Framework analysis to ensure a consistent approach to analysis. The initial coding framework will be developed and agreed on by the team after coding of half the transcripts at each time point. However, as this is an iterative process, the framework may be amended as coding of the second transcript ensues. Any amendments will be discussed and agreed upon by the team. Each transcript will be coded by two researchers and assessed for consistency in coding. Inconsistencies between two coders will be brought to the data analysis team and discussed until agreement is reached.

11 DATA HANDLING AND RECORD KEEPING

11.1 DATA MANAGEMENT RESPONSIBILTIES

Data collection is the responsibility of the research site staff under the supervision of the Site Investigator.
Case Report Forms (CRFs) will be developed by a multidisciplinary team of study staff members.

11.2 SOURCE DOCUMENTS AND ACCESS TO SOURCE DATA

Each participant will be allocated a study reference or participant identification number. All data will only be identified by this unique reference number. Data will be stored in a way in which participant identity is protected in a locked cupboard in a locked room on clinic premises and will be entered into computer by reference number only on password-protected computers. Consent forms with participant names and reference numbers will be kept separately from other data in a locked cupboard on clinic premises. Data will be stored for three years after the completion of the research, per DAIDS policy. Throughout this time, data held on computer will only be accessible by members of the research team who will have access to the computer system by way of security passwords. If the results of this research are published or presented, only group information will be given, not names of people in the study.

The Site Investigator or designee will maintain, and store securely, complete, accurate and current study records throughout the study, in accordance with local regulations. All study-related records must be maintained on site for the entire period of study implementation. No study records may be moved to an off-site location or destroyed prior to receiving approval from DTHF and/or DAIDS.

11.3 QUALITY CONTROL AND QUALITY ASSURANCE

Each site will be required to develop a robust SOP for quality control and quality assurance procedures.

12 CLINICAL SITE MONITORING

Regular study monitoring will be conducted internally by DTHF or outsourced to an external contract research organization (CRO).

Study monitors will visit the sites to do the following:

- Review procedures and documentation
- Assess compliance with the study protocol, GCP guidelines, and applicable regulatory requirements
- Perform source document verification to ensure the accuracy and completeness of study data
- Assess implementation and documentation of internal site quality management procedures

Site Investigators will allow study monitors to inspect site facilities and documentation (e.g., informed consent forms, clinic and laboratory records, other source documents, case report forms), as well as observe the performance of study procedures. Investigators also will allow inspection of all study-related documentation by authorized representatives of DAIDS and local regulatory authorities, if necessary.

Details of the specific monitoring plan will be contained in the site-specific SOPs and will include information, such as who will conduct the monitoring, at what frequency monitoring will be done, and at what level of detail monitoring will be conducted.

13 HUMAN SUBJECT PROTECTIONS

See Section 14: Ethical Considerations for more information regarding this topic.

13.1 INDEPENDENT ETHICS COMMITTEE AND REGULATORY APPROVAL

Prior to implementation of this protocol, and any subsequent full version amendments, each site will have the protocol and the protocol consent form(s) approved, as appropriate, by the local ethics committee and the South African Medicine Control Council.

13.2 DAIDS PROTOCOL REVIEW

DTHF will submit the protocol and all required documents to the DAIDS Program Officer for review and approval. The RSC Human Subjects Protection (HSP) team is responsible for reviewing all Informed Consents (ICs) during review at the P/CSRC, Regulatory Review, and Protocol Registration. These include ICs for DAIDS-sponsored network and investigator-initiated protocols supported through DAIDS' grants. Prior to implementation of this protocol, and any subsequent full version amendments, each site must have the protocol and the protocol informed consent form(s) approved, as appropriate, by their local institutional review board (IRB)/ethics committee (EC) and any other applicable regulatory entity (RE). Upon receiving final approval, sites will submit all required protocol registration documents to the DAIDS Protocol Registration Office (DAIDS PRO) at the Regulatory Support Center (RSC). The DAIDS PRO will review the submitted protocol registration packet to ensure that all of the required documents have been received. Site-specific informed consent forms (ICFs) WILL be reviewed and approved by the DAIDS PRO and sites will receive an Initial Registration Notification from the DAIDS PRO that indicates successful completion of the protocol registration process. A copy of the Initial Registration Notification should be retained in the site's regulatory files.

Upon receiving final IRB/EC and any other applicable RE approval(s) for an amendment, sites should implement the amendment immediately. Sites are required to submit an amendment registration packet to the DAIDS PRO at the RSC. The DAIDS PRO will review the submitted protocol registration packet to ensure that all the required documents have been received. Site-specific ICF(s) WILL NOT be reviewed and approved by the DAIDS PRO and sites will receive an Amendment Registration

Notification when the DAIDS PRO receives a complete registration packet. A copy of the Amendment Registration Notification should be retained in the site's regulatory files.

For additional information on the protocol registration process and specific documents required for initial and amendment registrations, refer to the current version of the DAIDS Protocol Registration Manual.

This protocol has also been submitted to the US Food and Drug Administration (FDA) as this study will be conducted under a US Investigational New Drug Application (IND). Implementation of this protocol must comply with US FDA and Office for Human Research Protection (OHRP).

13.3 RISK/BENEFIT STATEMENT

The administration of the study product carries more than minimal risk to participants but holds out the prospect of direct benefit, based on the adult data available. These risks will be reduced as far as possible by extensive monitoring of participant health and well-being as well as provision of a comprehensive package of HIV prevention options, counseling, and psychosocial support. In South African ethical guidelines for child research, the following is permissible, that the research involved more than minimal risk but provides possible benefit for the child participants, and the degree of risk must be justified by the potential benefit (DOH, 2004, px) and the research interventions present more than minimal risk but hold out the prospect of direct benefit for the participant, and the risks must be justified by the anticipated benefit (DOH, 2006, px).

Risks

No new or unexpected side effects are observed with the FTC 200 mg/TDF 300 mg combination tablet versus when each drug is given separately.

The most common risks and side effects from the study drug include headache, dizziness, fatigue, difficulty sleeping, depression, abnormal dreams, diarrhea, nausea (upset stomach), vomiting, headache, rash, gas, and skin darkening of the palms and/or soles.

Less common but more serious risks may include:

- Liver problems

- Inflammation of the pancreas
- Anemia
- Lactic acidosis (a buildup of a chemical called lactate in the body that can cause symptoms of unexplained weight loss, stomach discomfort, nausea, vomiting, fatigue, cramps, muscle pain, weakness and shortness of breath)
- Lipodystrophy--changes in fat distribution in your body such as an increase in fat around the waist, back of the neck and breast areas, and thinning of the face, legs and arms—but unlikely with short term use
- Decreased kidney function
- Metabolic disorders
- Changes in bone mineral density
- Allergic reactions (symptoms may include fever, rash, upset stomach, vomiting, loose or watery stools, abdominal pain, achiness, shortness of breath, a general feeling of illness or a potentially serious swelling of the face, lips, and/or tongue)

No controlled human studies of FTC among pregnant women have been conducted. No data on excretion of FTC/TDF in human breast milk have been reported.

Protection against risks

Side effects: Monitoring for kidney function loss will be done frequently during the course of the study such that problems will be detected early and study drug withheld. Serum chemistries and full blood countwill be monitored for other possible side effects. Persons with abdominal or other symptoms thought to be due to study drug may have drug held. Monitoring for depression will occur at every visit.

As all participants will be required to be sexually active in order to enroll in the study, All partipants will be required to use condoms and will receive risk reduction counselling, which will include education about safer sex and condom provision. However, female participants will be required to use condoms as well as a low dose, combination contraception, in addition to receiving contraceptive counseling throughout the duration of study participation. As a result, the risks to pregnancy will be limited in this study. Study participants will be counseled that study drug should not be shared with

any individual.

Sexual disinhibition: Risk reduction counselling and condom provision will be performed at every visit.

Social harms: Adolescents will have access to psychosocial **suppor**t and counseling services provided. Should additional support be required for some participants due to study-related harms, referrals will be made to community-based services as needed.

Benefits

This research protocol contains interventions and procedures that at least hold out the prospect of benefit for adolescent participants. While there are some procedures which are unlikely to hold out the prospect of benefit and for which the intention is to generate knowledge (e.g. questionnaire administration), this protocol does contain several elements that hold out the prospect of a health-related benefit for those taking part.

An increased awareness of HIV and decreased or altered risk behaviour due to risk reduction counseling and regular testing may benefit participants**.**

All participants will receive a comprehensive **HIV prevention package**, which includes:

- Risk reduction counselling
- Free condoms and condom counselling
- Screening and treatment for STIs (syndromic management of STIs).
- Counselling & referral for other HIV prevention interventions (e.g., male circumcision and Post Exposure Prophylaxis), as per national policies

Participants will also have access to a package of **sexual and reproductive health care**, including STI syndromic treatment (see above), regular pregnancy testing and if necessary, counseling and contraceptive counseling and access.

Adolescents will have regular monitoring for **general health** and receive appropriate management for identified conditions through appropriate referrals, and this may be of benefit to them.

Adolescents will have access to **psychosocial suppor**t through the counseling services provided at all sites. Should additional support be required for whatever reason (e.g. social harm), appropriate referrals will be made to community-based services.

Participants and others may benefit in the future from information learned from this study. Participants may appreciate the opportunity to contribute to the field of HIV prevention research. Information learned in this study may lead to the development of safe and effective interventions to prevent HIV transmission.

Taken together, in a country with a significant adolescent HIV epidemic and within a context of frequently inadequate and inaccessible primary health care for youth, the presence of study interventions and procedures that hold out the prospect of benefit can be argued to be in the `best interests' of the individual adolescent trial participants. While none of the enrolled participants will be in ill health, many of these participants may be *susceptible* to acquiring certain health conditions. It is at the very least not against the best interests of the individual child participants to take part in a study that comprises several procedures and interventions that hold out the prospect of benefit. Moreover, given the high rate of HIV incidence in South African youth, it is in the best interests of adolescents as a class to have access to a formulation of PrEP which has been appropriately tested for safety, dosage, and acceptability amongst adolescents thus providing adolescents with a potential biomedical HIV prevention option.

In terms of South African guidelines for child research (see 13.3 above) the risks of procedures/ interventions that hold out the prospect of direct benefit can exceed minimal risk however the risks must be justified by the anticipated benefits (the risk-benefit ratio). In terms of South African guidelines, the risks of procedures/ interventions that do not hold out the prospect of direct benefit must represent a minor increase over minimal risk and be justified by anticipated knowledge to be generated (the risk-knowledge ratio). This study protocol has attempted to identify which study components do, and do not, hold out the prospect of benefit, and has attempted to reduce risks of all components to an acceptable minimum, and to ensure that risk-benefit/ knowledge ratios are satisfied.

13.4 INFORMED CONSENT AND ASSENT PROCESS

Parental/ guardian consent and adolescent assent for both screening and study enrollment will be obtained prior to screening. For participants that are eligible for the study, a private informed assent/consent session will be held with each individual potential participant and their guardian, during which the study will be explained in an age-appropriate way. The assent/consent process will include a thorough review of any other current knowledge of the safety and protective effects of FTC/TDF pre-exposure prophylaxis.

The informed consent and assent forms will include information about the study and individual request for consent of participants' guardians and assent of the participants to participate in the study.

Each study site is responsible for developing study informed consent and assent forms for local use,and translating these forms into local languages (if needed).

It will be emphasized that participation is voluntary and that participants are free to withdraw from the study at any stage without any disadvantage to them.

The informed consent and assent process will cover all elements of informed consent required by research regulations. In addition, the process specifically will address the following topics:

- The need to practice safer sex behaviors.
- The importance of adherence to the study drugs, visits, and procedures schedule.
- The potential risks of study participation (and what to do if such risks are experienced).
- The potential social harms associated with study participation (and what to do if such harms are experienced).
- The potential benefits of study participation.
- The right to withdraw from the trial at any time
- Confidentiality and the limits of confidentiality.

The potential participant and guardian should be given sufficient time and necessary information to consider the benefits and risks of involving the participant in the clinical trial.

An assessment of understanding will be conducted at screening to ensure that guardian consent and participant assent are informed.

The name of investigators(s) who are responsible for conducting the study and direct contact details (telephone, address, e-mail) will be given to all participants and their guardians.

Adolescents can consent independently to some procedures in the study--that is they should consent independently to:

- Terminations of pregnancy at any age. However, study staff members will advise adolescents to "consult with their parents, guardian, family members or friends" before the termination.
- HIV testing
- Medical treatment, including STI and HIV treatment
- Contraceptives access and contraceptive advice and information, including emergency contraceptives

For further details on the development of this latter recommendation, please see **Appendix 16.10: Selected Ethical-Legal Norms in Child and Adolescent HIV Prevention Research in South Africa: Consent, Confidentiality and Mandatory Reporting.**

13.5 PARTICIPANT CONFIDENTIALITY

Participant confidentiality is strictly held in trust by the participating investigators, their staff, and the pharmaceutical sponsor(s). Every effort will be made to maintain participants' confidentiality. All data will be identified only by a unique participant number and kept in confidential files. All study documentation including questionnaires and informed consents will be kept in locked cupboards. Consent documents will be kept separately from questionnaires. No individual identifying information will be collected or disclosed in reports, publications, or presentations. See Section 14: Ethical Considerations for more information regarding the topic of privacy.

For further details on the development of the following recommendations please see **Appendix**

16.10: Selected Ethical-Legal Norms in Child and Adolescent HIV Prevention Research in South Africa: Consent, Confidentiality and Mandatory Reporting[1]

It is recommended that:

- STI results, HIV, and pregnancy test results are given to the adolescents and not their parents
- Adolescents who acquire conditions with long-term physical and emotional complications will require on-going support, and therefore, it is in their best interests to disclose changes in their health status to a trusted adult within a reasonable timeframe. Accordingly, adolescents who become HIV positive or pregnant ought to be required to identify and disclose this information to a trusted adult (not necessarily the parent or guardian).
- Young adolescents (between the age of 15 and 16 or below the age of consent to sex), who are infected with an STI, will also be asked to disclose this information to a trusted adult.
- With older adolescents (16-19 years), the results of the sexual risk assessment not be given to their parents.
- With younger adolescents (15-16 years), parents may legally receive this information but they will be asked to agree not to be informed, given that safeguards like counseling and access to services are built in to the trial.

It is further recommended that:

- If participants are being sexually abused, deliberately neglected, or abused in a manner causing physical injury, then, because of their age, certain persons (e.g. medical practitioners, nurses, workers at youth care centers) will be required by law to report this abuse or neglect to designated child protection organizations, the provincial department of social development or police officials (s110 of the Children's Act, 2010). Some study staff members may fall into these designated categories and be obliged to report.
- Where sexual offenses are being committed against children (including rape and commercial sex work) then site staff should comply with laws requiring them to report to the South African Police Service (the Criminal Law, Sexual Offences and Related Matters Amendment Act, No. 32 of 2007).

- The circumstances in which adolescent information will be kept private should be stipulated in the consent and assent forms, to enable parents and participants to have a good understanding of the privacy norms and what results parents will or will not have access to. Based on this understanding, children or their parents may or may not agree to enrolment.
- More specifically, a parent or legal guardian who is providing consent will need to understand that he or she will not receive feedback from site staff regarding the participant's risk behavior, contraceptive usage, STI or HIV results, or pregnancy results; however, the participant will be asked to disclose to a trusted adult in the event of a positive HIV result, or pregnancy result, and will receive appropriate support services. Parents and legal guardians will also need to understand that they themselves may not be informed directly by site staff, in the event that a report must be made by law to an authority. It is possible that some parents or guardians may exercise their right to refuse enrolment on these grounds. Participants will need to understand that their parents and guardians will not be informed about their risk behavior, HIV, STI, or pregnancy results, but that there are instances where site staff will be required by law to make reports (for example, in instances of abuse). It is possible that participants may exercise their right to refuse enrolment on these grounds.
- Note: DAIDS, IRB/ECs, OHRP, FDA, NIAID, MCC, other government or regulatory agencies will have access to the subject's record.

13.6 COMPENSATION

Participants may receive monetary remuneration at the end of each scheduled visits in the amount that will be reviewed and approved by the Independent Ethics Committees at each site and approved by the local CABs.
In addition, a light snack and refreshment may be provided at each study visit.

13.7 STUDY DISCONTINUATION

The study may be discontinued at any time by DTHF, DAIDS, NIAID, the pharmaceutical supporter(s) or designee, the MCC, the Independent Ethics Committees, the Office of Human Research Protection (OHRP), and the FDA or other government and regulatory agencies as part of their duties to ensure that study participants are protected.

14 ETHICAL CONSIDERATIONS

This study will be approved by DAIDS, Independent Ethics Committees, and South Africa's Medicines Control Council prior to implementation. This study will be conducted according to the protocol as well as ICH and South African Good Clinical Practices.

Community participation: Prior to study enrolment, key youth organizations will be educated about the study and their concerns and inputs solicited. Community structures like the adolescent CAB will be included to ensure that community views and perspectives are appropriately canvassed. In addition, CABS will be engaged to advise on informed consent procedures and forms, recruitment procedures, and retention of participants in the study. Organizations that serve and medically treat adolescents will be engaged to ensure that adolescent needs are met.

Selection of participants aged 15-19 years. Although the age of lawful consent to sex in South Africa is 16 years, there is abundant evidence that South African adolescents are sexually-active at a significantly earlier age, as discussed in Section 1. It is therefore imperative that prevention interventions (ranging from behaviour change to biomedical intervention) acknowledge this and engage with those under 16 years. Risk reduction counselling (see below for further details) will be provided at every opportunity, as part of the HIV pre- and post- test counselling process.

Study procedures and risk minimization: When adolescents are enrolled in this study, they will undergo an assessment of understanding; medical history and targeted physical exam; pregnancy testing and pregnancy counseling and prevention; HIV testing; risk behavior assessment and risk reduction; and PrEP administration and acceptability assessment. It is possible that adolescents, if they choose to take product, may increase their sexual risk behavior because of expectations of protection against HIV. Sexual risk will be carefully monitored and risk reduction counseling provided. In order to minimize the possible impact of risk compensation, counseling will emphasize high levels of personal risk (Cassell et al; 2006). STI (including HIV) and pregnancy testing may be stressful, but quality counseling and access to services as required will offset this risk.

Section 71C of South Africa's new National Health Act requires ministerial consent for so-called "non

therapeutic research" (NTR). Although there is no current definition in law for NTR, ethical guidelines do distinguish between research that does (and does not) hold out the prospect of benefit for the child-participant.

According to the South African ethical framework, clinical trial interventions that will not hold out the prospect of direct benefit must be limited to minimal risk or a "minor increase over" minimal risk. However, interventions that hold out the prospect of direct benefit are not expressly capped, but the risks must be minimized and reasonable in relation to potential benefits (DOH GCP 2006; DOH, 2004). Study-related risks will be reduced as far as possible by extensive monitoring of participant health and well-being as well as provision of a comprehensive package of HIV prevention options, counseling, and psychosocial support. (See Section 13.3 for Risk/Benefit Statement).

Consent for study enrolment: In accordance with South African guidelines for clinical trials and general research, consent for enrolment will be sought from a parent or legal guardian (DOH, GCP, 2006; DOH, 2004).

Disclosure of sexual activity to parents: It is recognized that disclosure of information regarding sexual activity may be problematic for adolescents and/or parents and where required, mediation and facilitation of adolescent disclosure of sexual activity will take place. Effective ways of doing this will be negotiated and developed with adolescents, and will be documented for future clinical practice.

Mandatory Reporting: It is recommended that all abuse and neglect be reported to the relevant authorities and will be managed per site-specific SOPs. It is also recommended that sexual offenses involving children be reported to the relevant authorities, including rape and commercial sex work.

However, certain types of sexual offenses will not be reported, more specifically underage sex or sexual activity that appears 'consensual' in nature and non-exploitative in nature. If participants, aged 15 years, report being sexually involved with older adolescent partners (with more than a 2 year-age gap), study staff will not report the partner unless the sex/activity is clearly exploitative and after further investigation and assessment by the trial site team. Site staff will consider the age

differential as well as other aspects of the relationship.

In all instances of under-age sex, adolescents will be ensured of access to appropriate services (eg. contraceptive services, risk reduction counseling).

Ethical review: In addition to review by South Africa's Medicine Control Council (MCC) and relevant local research Ethics Committees, an adolescent community advisory board will be asked to make inputs into appropriate aspects of the study implementation.

Schooling: Study participation will not interfere with school attendance; clinic hours will fall outside of core school hours.

Standard of prevention: HIV Counselling and Testing (HCT) has been promoted as an effective tool for the reduction of risk of HIV infection. A study in Kenya reported positive risk behaviour changes up to 6 months after voluntary counselling and testing (VCT), including fewer sexual partners, increased condom use as well as fewer reported symptoms of sexually transmitted infections (Arthur et al; 2007). A further study in Zambia found sustained (although imperfect) condom use in discordant couples after VCT (Allen et al; 2003). Pre and post HIV test counseling, including risk reduction counseling (tailored to adolescents), will therefore be performed at every visit. Trained and qualified study personnel will provide age –appropriate pre-HIV test, risk reduction and post HIV test counseling at each visit, according to the site standard operating procedures (SOPs) **[see Appendix 16.5 for HIV Pre/Post Test Counseling Procedures and Appendix 16.6. for Risk Reduction Counseling Procedures].** Study sites will document their counseling policies and procedures prior to study implementation for purposes of staff training, quality assessment, and study monitoring. The counseling process will include information on HIV, safer sex practices, and risk reduction. The objective of counseling is to ensure that study participants have sufficient knowledge about HIV infection to understand what the test is for, the implications of a positive or negative result and the care available for HIV infection locally. In addition, risk reduction counseling, safe sex practices and methods of avoidance of transmission will be discussed with all participants regardless of their HIV test results. The content of risk reduction counseling will include facilitating participants to work on reducing their risk through modification of specific risk behaviours identified by the adolescents and counselors. This approach is based on psychological constructs identified as significant in facilitating

behaviour change, and will include enabling participants to assess the costs and benefits of their risk behaviour/s, setting behavioural goals, identifying barriers to goal fulfillment and developing confidence to fulfill goals. Adolescent participants will be invited to bring their sexual partner/s to the clinic for risk reduction counseling and/or HCT if they wish.

Adolescents will also have access to post-exposure prophylaxis. Male adolescents will be provided with information on the benefits of circumcision.

HSV-2, chlamydia, and gonorrhea will be tested for and treated (as needed) during study screening, Month 3, and at the last study visit. Other STIs will be treated syndromically.

All adolescents taking part in the study will have access to male and female condoms and combination, low-dose oral contraception will be provided.

Standard of care: As above, the adolescent will be given HIV pre and post test counseling support (see Appendix 16.5 for HIV Pre/Post Test Counseling Procedures), including risk-reduction counseling (see Apppendix 16.6. for Risk Reduction Counseling Procedures) and support for disclosure to a responsible adult.

Any seroconversions that occur will be referred to the local health facility, and the necessary assistance provided to remove barriers to treatment access. See Section 7.8.1 for complete overview of study procedures for HIV-infected participants.

Health benefits: [see Benefits Section, under 13.3]

Social harms monitoring: At every visit, social impact questions will be included in the assessments to determine whether study participation is having a negative psycho-social impact. In addition to documenting social harm events, participants' experience of the event will be elicited as well as their perception of its severity and any resolution strategies they may have adopted (Milford et al; 2007). Where necessary, counseling services will provide support and in addition, other ways of moderating social harm will be developed and documented. This information will inform a protocol for future use in delivering adolescent services and in conducting adolescent prevention research in South Africa.

Results dissemination plan: Study results will be communicated back to participants and community

representatives through DTHF's established infrastructure (adolescent and adult CABs), as well as through participant information sheets that summarize the key findings from the study (to those participants expressing desire to be informed). Results may be published or presented at conferences to make information available to a wider community.

15 PUBLICATION POLICY

DAIDS and DTHF policies will govern publication of the results of this study. Any presentation, abstract, or manuscript will be submitted to DTHF and DAIDS for review prior to submission.

16 APPENDICES

16.5 HIV PRE/POST-TEST COUNSELING PROCEDURES (INCLUDING HIV TESTING ALGORITHM)

HIV Counseling Procedures

For HIV testing within the study, where the consent for study participation includes HIV testing, written consent for each individual HIV test within the study need not be obtained, however verbal consent should be confirmed. Pre and post test counseling is always performed.

Pretest counseling:

a) The counseling staff deliver pre-test counseling, which includes:

- An explanation of the test, and the window of infection with a negative test;
- Basic information on HIV transmission and prevention
- The significance of the potential test result
- A reminder that although their test result is confidential, should the result be positive, staff will encourage the adolescent to share their result with a trusted adult
- Discussion regarding who the participant might share their result with if positive
- An explanation that a participant may be infectious even if their test result is negative.

b) The staff member evaluates the psychological stability of the participant and the possible impact of testing positive at the pre-test visit.

Post-test counseling:

a) If the result is negative, the counseling staff:

- Discusses protection during the window period of a negative test; and
- Discusses HIV test intervals, as appropriate.
- Provides risk reduction counseling (see below)

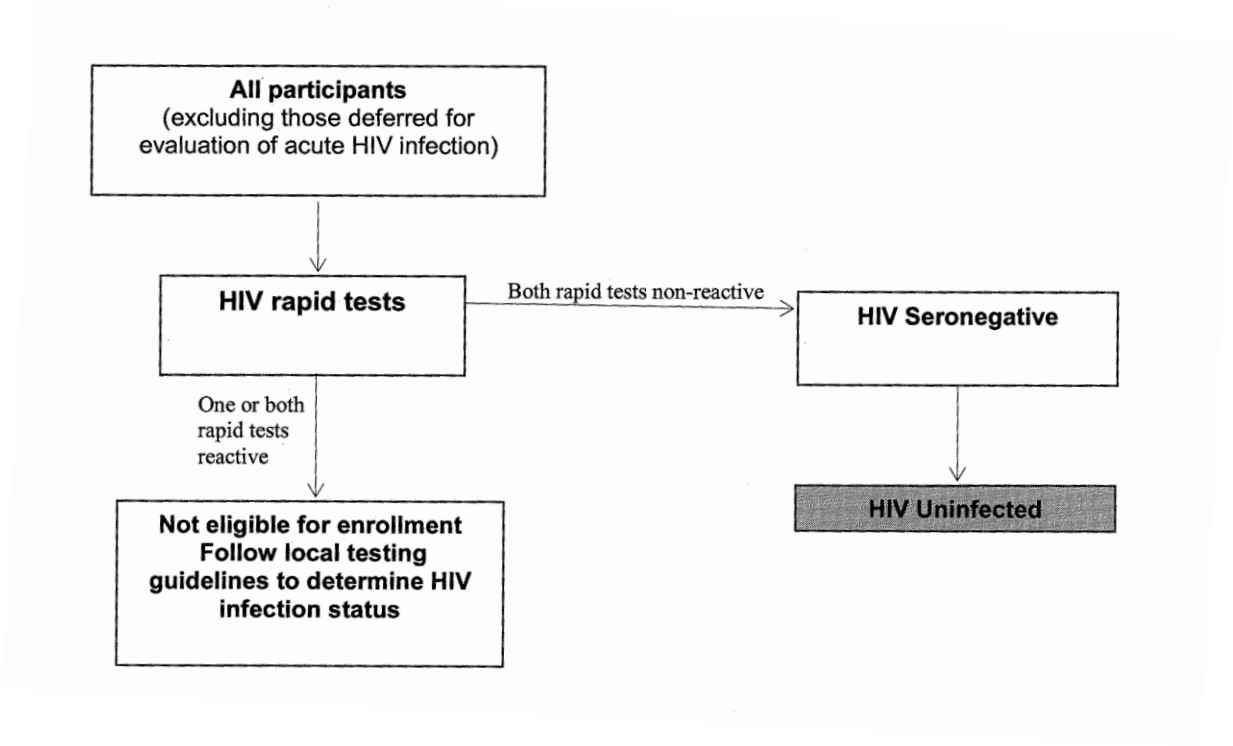
b) If the result is indeterminate, the counseling staff discusses its significance with the participant. A repeat test is performed.

c) If the participant's result is positive, a second rapid test is performed. If this is positive, blood is drawn for a confirmatory laboratory test and a CD4 count. If the second rapid test result is negative, a confirmatory laboratory test should also be performed.

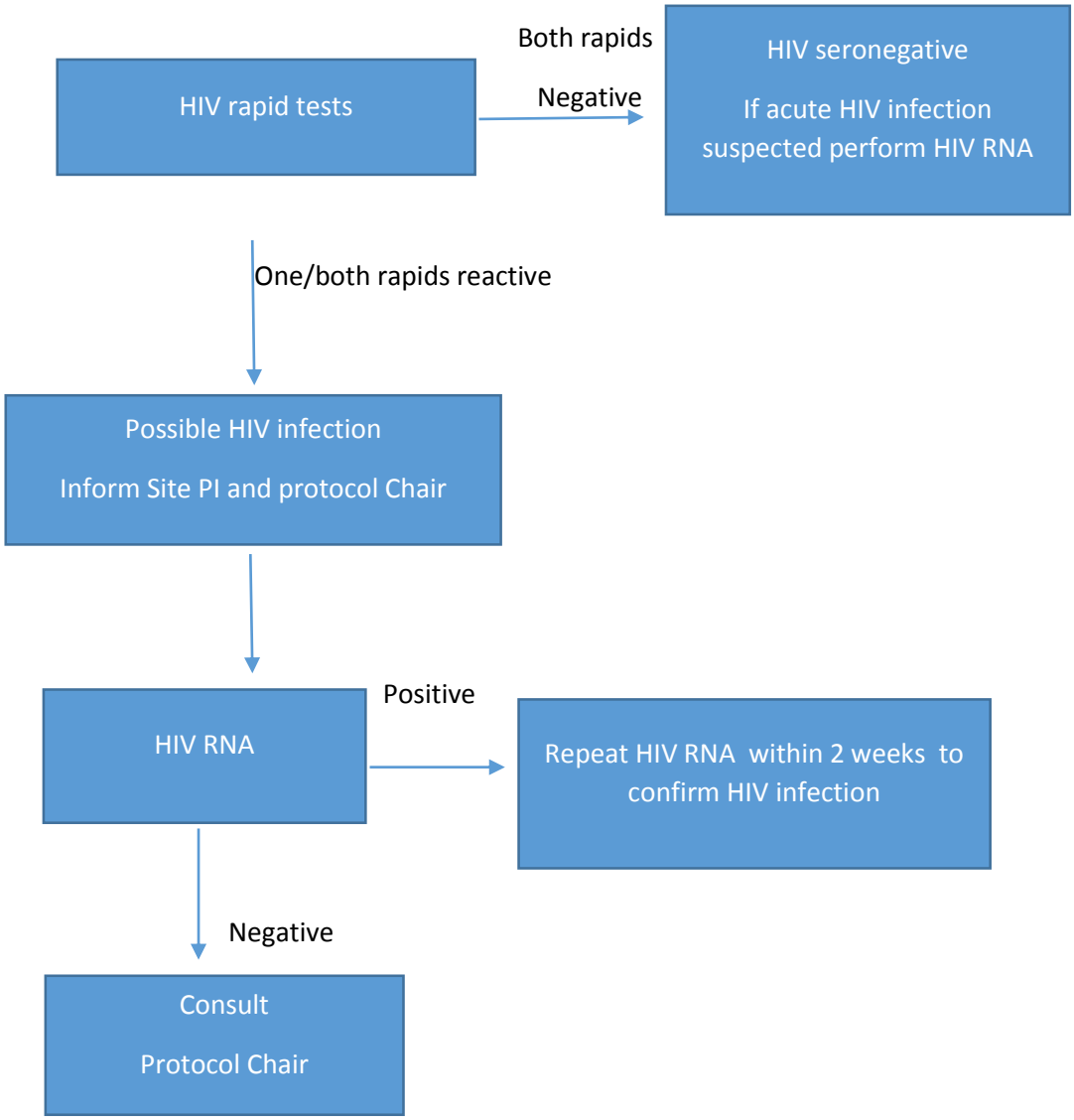
d) If a positive result is confirmed:

- The counseling staff/study physician shares the participant's result with them in a sensitive and neutral manner, allowing them time for the information to be understood and absorbed
- The counseling staff/study physician discusses the difference between HIV and AIDS, treatment options, transmission issues, and the risks and benefits of partner notification, as well as the risks and benefits of notifying a trusted adult and how this might be done.
- If this occurs at screening, the counseling staff/study physician explains to the participant that inclusion in study is not possible and refers the participant to a service provider/ clinic for further evaluation, management and support.
- If a participant tests positive at any other visit, they can remain in the study and complete all study activities as planned including continuing to receive the vaccine (if they have consented to receive it). Further visits for psychosocial support and clinical management should be planned with the participant, per site-specific procedures.
- Personalized referral to services for long term clinical management, and follow-up to ensure adolescent attendance should take place
- Details of any community support groups and other relevant organizations should be passed on to the participant

16.6 HIV Algorithm for Screening and Enrolment



16.7 HIV Algorithm for Follow-up visits



2nd Confirmatory Test

Positive – Confirmed HIV- Infected inform Protocol Chair

Indeterminate/ Negative - Consult with Protocol Chair for next steps

16.8 RISK REDUCTION COUNSELING PROCEDURES

Risk Assessment

a) The counseling staff member assesses the individual's risk factors for acquiring infection, including:

- Sexual activity
- Type of sex (vaginal, anal, oral)
- Reasons for being in a sexual relationship
- Number of sex partners (casual and steady) and sexual activities
- Sex with someone known to be HIV positive
- Sex with someone more than 2 years older or younger
- Sharing needles or having sex with someone who shares needles
- History of STI's and having sex with someone who has a history of STI's, especially genital lesions;
- Sex in exchange for drugs, money or other inducements
- Use of substances (e.g. alcohol) in connection with sexual activities
- Condom use

b) Included in the risk assessment, should be an assessment of the participant's knowledge of modes of HIV transmission and the impact of risk taking behaviors. Basic information on HIV transmission and prevention; this should focus on, but not be limited to, areas identified during risk assessment where knowledge was incomplete

c) The counseling is focused on the participant's individual risk factors and situation.

d) The counseling staff member and participant set manageable goals for risk reduction.

e) At each visit, the counseling staff member and the participant reassess the participant's behavior and risk factors, and if necessary, adjust the goals.

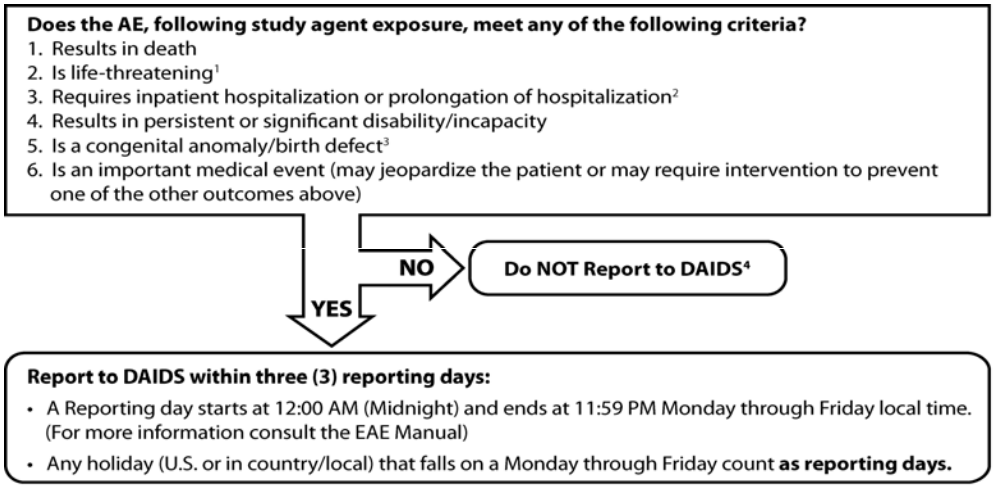
Risk reduction counseling for those who are HIV positive

Where participants have just learnt of their HIV-positive status, their immediate concerns may not be regarding risk reduction. It may be more appropriate to provide in depth risk reduction counseling (as above) at further visits.

Nonetheless, it is important to convey to adolescents that they are most infectious in the first few months after becoming HIV infected and should therefore take steps to protect others. In addition, they may be more susceptible to other STIs and it is therefore important that they protect themselves. This information at least should be communicated at the same visit where they learn of their HIV-positive status.

16. 9

Expedited Adverse Event Reporting Requirements for Pluspills:



1."Life-threatening" refers to an event in which the patient was at risk of death at the time of the event. It does NOT refer to an event that hypothetically might have caused death if it were more severe.

[2] Per the ICH SAE definition, hospitalization is NOT an adverse event (AE), but is an outcome of the event. **DO NOT REPORT**: Any admission unrelated to an AE (e.g., for standard labor/delivery, cosmetic surgery, administrative or social admission for temporary placement for lack of a place to sleep); protocol-specified admission (e.g., for a procedure required by protocol); admission for diagnosis or therapy of a condition that existed before receipt of study agent(s) **and** has not increased in severity or frequency as judged by the clinical investigator. (**NOTE**: A new AIDS-defining event in a subject already known to be HIV-infected would be considered an increase in severity of a pre-existing condition [HIV infection] and **would be** reportable.)

[3] Clinically insignificant physical findings at birth, including those regarded as normal variants, do NOT meet reporting criteria. If a clinically significant anomaly is reported, all findings (including those of no individual significance) should be included in the same report. For example, do NOT report an isolated finding of polydactyly (extra fingers or toes) or Mongolian spot in an infant. But if either finding occurred with a major cardiac defect, report all findings in the SAE Report.

[4] Please ensure that any other protocol-specific reporting requirements are met.

Contact Information for the DAIDS Safety Office: Website: http://rsc.tech-res.com - **Email:** DAIDSRSCSafetyOffice@tech-res.com

Office Phone: 1-800-537-9979 (U.S. only) or +-301-897-1709 **– Fax:** 1-800-275-7619 (U.S. only) or +1-301-897- 1710 (*Office Phone and Fax are accessible 24 hours per day)*

Mailing Address: DAIDS Safety Office 6500 Rock Spring Drive, Suite 650, Bethesda, MD 20817

Reporting Adverse Events in an Expedited Manner

The timeframe for expedited reporting of individual AEs begins when the clinical research site recognizes that an event meets SAE criteria for expedited reporting to DAIDS. The day that the site becomes aware of the event is considered Day 1. Clinical research sites must submit AEs to the DAIDS Safety Office immediately, and no later than 3 reporting days after the site becomes aware of an event that meets criteria for expedited reporting.

"Reporting days" are those that count toward the 3-day timeline provided for reporting of EAEs to DAIDS. The criteria used to determine reporting days are as follows:

- A reporting day starts at 12:00 AM (midnight) and ends at 11:59 PM local time.

- A day is counted as a reporting day regardless of the time of day that awareness occurred. The day a site indicates that site personnel became aware of an EAE that meets reporting criteria shall count as day 1 (even if it is 23:00) if that day occurs on a reporting day (i.e., Monday through Friday). If that day occurs on a non-reporting day (i.e., Saturday or Sunday), then the next reporting day shall count as day 1.

- Monday through Friday count as reporting days.

- Saturday and Sunday are not considered reporting days.

- Any holiday (U.S. or in-country/local) that occurs on a Monday through Friday counts as a reporting day. The figure above details EAE reporting requirements. For each PlusPills participant, the EAE reporting period begins with study enrollment (Day 0), and ends with the participant's termination visit. All EAEs should be reported to the DAIDS Regulatory Support Center (RSC) using the internet- based DAIDS Adverse Experience Reporting System (DAERS).

The process of EAE reporting via DAERS involves a designated "Study Reporter" creating an electronic EAE report and a designated "Study Physician" reviewing the EAE report, signing the EAE report with an electronic signature, and submitting the EAE report to the DAIDS RSC. If an EAE report is not completed and submitted within three reporting days of site awareness of the EAE, an explanation must be entered in DAERS before the report can be submitted.

DAERS also may be used to modify or update an EAE report or to withdraw an EAE report that was submitted in error.

DAERS incorporates a report printing function that should be used to print all EAE reports — including modifications and updates — for filing in participant study notebooks. Automated email messages confirming submission of EAE reports also should be printed and filed with the print- out of the associated EAE report.

In the event that DAERS cannot be accessed (e.g., due to poor internet connectivity), paper-based EAE reporting should be used, per instructions provided in the *Manual for Expedited Reporting of Adverse Events to DAIDS*. Completed paper EAE Forms may be faxed or digitally scanned and emailed to the DAIDS RSC via email. The EAE Form and form completion instructions are available on the DAIDS RSC web site (http://rsc.tech-res.com). Contact details for submission of EAE Forms to the RSC are provided in the *Manual for Expedited Reporting of Adverse Events to DAIDS*.

IMPORTANT: Sites must submit an AE CRF to DAIDS along with any SAE/EAE. The following data points must be exactly the same on both the AE Log submitted to EAE Report submitted to DAERS:

- Participant ID

- Onset Date
- Severity of event
- Relationship to study product
- Adverse Event Term (Diagnosis)

It is important to remember that if the site updates any of these data points on one document that same change must be made on the other.

16.10 : SELECTED ETHICAL-LEGAL NORMS IN CHILD AND ADOLESCENT HIV PREVENTION RESEARCH IN SOUTH AFRICA: CONSENT, CONFIDENTIALITY AND MANDATORY REPORTING [revised]

Suggested citation: Strode, A. & Slack, C. (2013). Selected ethical-legal norms in child and adolescent HIV prevention research: Consent, confidentiality and mandatory reporting [revised]. NIH, Desmond Tutu HIV Foundation (DTHF) and European and Developing Countries Clinical Trials Partnership (EDCTP): 2013.

Comments to Catherine Slack (*slackca@ukzn.ac.za*) or Ann Strode (*strodea@ukzn.ac.za*) at the HIV AIDS Vaccines Ethics Group (HAVEG), University of KwaZulu-Natal (UKZN) South Africa
http://www.saavi.org.za/haveg.htm

Updated 4 June 2013

INTRODUCTION

The HIV AIDS Vaccines Ethics Group (HAVEG) at the University of KwaZulu-Natal (UKZN) was funded through the European and Developing Countries Clinical Trials Partnership (EDCTP) to develop resources on the ethical-legal framework for researchers and research ethics committees (RECs) working with adolescent HIV prevention trials. This memo was originally designed to assist and guide researchers working on the South African Studies on HIV in Adolescents (SASHA) project. The aim of the SASHA study was to build stakeholder capacity for adolescent prevention trials. The memo has been revised, updated and adapted to assist other protocol developers and protocol reviewers by identifying key ethical-legal issues in adolescent HIV prevention trials and describing the legal obligations relating thereto. Current funding to update this resource is received from the National Institutes of Health via the Desmond Tutu HIV Foundation (DTHF).

Key legal complexities in HIV prevention research with adolescents include:

- Who consents for trial enrolment? Who consents to the health-related interventions in the trial?
- What components of the trial should adolescents enjoy confidentiality for?
- What disclosures are likely to trigger reporting obligations?
- What should researchers do to intervene to assist adolescents when key problems are picked up?

Based on the current ethical-legal framework, this memo has identified nine key norms which should apply to adolescent HIV prevention trials. These are:

1. A parent or legal guardian (LG) should provide consent for adolescents to take part in prevention trials;
2. Adolescents should consent independently to key trial components, even though their parents/ LGs will provide consent to enrolment in the trial;
3. Adolescents should enjoy confidentiality for key trial components;
4. Adolescents' right to confidentiality can be limited and adolescents could be asked to disclose to otherwise confidential information to a trusted adult in certain instances;
5. Parent s/ LGs *and* adolescent should understand what information will or will not be made available to parents/ LGs;
6. If adolescents are being abused, neglected or maltreated, this should be reported to authorities and adolescents should be assisted;
7. If adolescents are engaged in underage sexual relationships that are consensual but exploitative, this should be reported to the authorities and the adolescents should be assisted;
8. There is no legal obligation to report other offenses but adolescents should be assisted; and
9. Parents/ LGs *and* adolescents should consent to confidentiality limits posed by reporting to authorities.

These are each discussed in more detail below:

1: A parent or legal guardian (LG) must provide consent for adolescents to take part in prevention trials

1. The first norm is that a parent or LG must provide consent for trial enrolment.

2. How was this established? Currently, there is no clear legal standard specifying when children can independently consent to research, however, there are ethical norms. The Department of Health's GCP (2006) guidelines[1] provide that children cannot consent on their own to clinical trials and that consent must be obtained from a parent or a LG. The National Health Research Ethics Council guidelines (2004)[2] allow that adolescents can only consent unassisted to minimal risk research (where research risks are approximate to those of the child's everyday life). Clinical trials are generally held to present a higher standard of risk than this, therefore, consent from a parent or LG must be secured.

3. Parents or LGs must consent to adolescent enrolment only when they understand the implications for their children and themselves. Some of the norms relating to the manner in which the trial will be run (described in more detail below) may be unacceptable to a parent, for example, the protocol may provide that parents will not necessarily be told that their child is pregnant or that their child elected to have the pregnancy terminated with the assistance of researchers. Therefore, in such situations parents or LGs may refuse to enrol their child in the

trial. Adolescents themselves must provide assent to participation. Some norms may be also unacceptable to an adolescent, for example, the obligation to disclose HIV status to a trusted adult if they test positive. Therefore, adolescents may also refuse to enrol in the study.

4. In the future, if Section 71 of the National Health Act[3] is implemented, parental/legal guardian consent will be a legal requirement for *all* health research (trial and non-trial). This change in the law will have very few repercussions in the clinical trial environment, where stakeholders are generally used to this requirement. However, repercussions will be felt by social scientists. In addition, should s71 be implemented then children will be required to "consent" rather than assent alongside their parent if they have "sufficient understanding".

2: Adolescents should consent independently to key trial components, even though their parents or LGs will provide consent to trial enrolment

1. The second norm is that even where a parent or LG provides consent for enrolment, adolescents should consent independently to certain trial components.

2. How was this norm established? According to various statutes, adolescents can consent <u>independently</u> to a number of health-related interventions, such as:
   a. **Terminations of Pregnancy** at any age (s 5, Choice of Termination of Pregnancy Act, No. 92 of 1996)[4]. However the Act requires providers to advise adolescents to "consult with their parents, guardian, family members or friends" before the termination (s 5, Choice of Termination of Pregnancy Act)[4]
   b. **HIV testing** from the age of 12 (s 130, Children's Act, No. 38 of 2010)[5] and even children below 12 can consent independently to such testing if they have "sufficient capacity"
   c. **Medical treatment** from the age of 12, including STI and HIV treatment provided the child has "sufficient maturity". In other words the child should be 12 and have the mental capacity to understand the benefits, risks, social and other implications of the treatment; and (s 129, Children's Act No. 38 of 2010)[6]
   d. **Contraceptives** and contraceptive advice, including emergency contraceptives from the age of 12 (s 134, Children's Act, No. 38 of 2010)[7]
   e. **Circumcision** at the age of 16[8]. If boys are below the age of 16, then consent must be obtained from their parent or legal guardian. The Act also requires that boys below 16 can only be circumcised for 'religious' or 'medical reasons on the recommendation of a medical practitioner' whereas those above 16 may undergo circumcision for any reason. Boys over 16 must receive counselling prior to the circumcision, and they have the right to refuse circumcision. (s12 (8) and s12(9-10) of the Children's Act No. 38 of 2005

f. **Surgical operations** at the age of 12 provided he/she (*i*) has 'sufficient maturity and has the mental capacity to understand the benefits, risks, social and other implications of the surgical operation', and (*ii*) is assisted by a parent or guardian. (See section 129(3) of the Children's Act No. 38 of 2005).

3. Another factor that is relevant to consent by adolescents within HIV prevention trials is the age at which they **can lawfully engage in sex**. This is set at 16 in the Sexual Offences Act (s 15, Criminal Law (Sexual Offences and Related Matters) Amendment Act, No, 32 of 2007). See section 7 for more detail.

4. Currently in prevention trials this means that:
   a. Adolescents, who need to be tested for pregnancy regularly as part of a prevention trial, can give their own consent for pregnancy tests from the age of 12 and could receive a TOP at any age with their own consent, provided they have the capacity to consent;
   b. Adolescents, who need to be tested for HIV regularly as part of the study, can give their own consent for these HIV tests from 12;
   c. Adolescents, who need to be tested regularly for STIs, can give consent on their own from 12 for STI testing and treatment, if required, provided they meet the capacity requirements (which could vary according the medical condition or procedure); and
   d. Adolescents wanting access to male or female condoms or other forms of contraceptives or contraceptive advice could receive these on their own from the age of 12.

3: Adolescents should enjoy confidentiality for key trial components

1. The third norm is that adolescents should enjoy confidentiality for key trial components. How was this norm established?

2. Firstly, adolescents have the right to confidentiality for the range of health-related interventions that they have consented to independently. That is:
   a. Adolescent TPs of 12 years and older (and not their parents) should receive HIV test results;
   b. Adolescents of 12 (who have capacity) and older (and not their parents) should get the results of STI tests;
   c. Adolescent TPs of 12 years and older should enjoy confidentiality for access to contraceptives;
   d. Adolescent TPs (and not their parents) should get results of pregnancy tests and/ or enjoy confidentiality for TOPs.

3. Secondly, adolescents have a right to privacy if there is an expectation of privacy that society regards as reasonable. Where the law is silent on whether a right to privacy exists, one can use the "legitimate expectation test" to establish if something should be kept private.

a. It can be argued that adolescents who are 16 years and older have the right to confidentiality regarding their sexual risk data. That is, older adolescents (and not their parents) should get the results of sexual risk assessments. This is on the grounds that older adolescents would have an expectation of privacy (which most would hold as reasonable) because adolescents can lawfully consent to sex at 16. For adolescents who are under 16, the above rationale may not hold, however, parents can agree not to be informed on the grounds that safeguards (such as counseling and access to services) will be built in to the trial.

4: Adolescents' right to confidentiality can be limited and adolescents could be asked to disclose otherwise confidential information to a trusted adult in certain instances

1. The fourth norm is that even though adolescents have rights to confidentiality, these rights can be limited.

2. How was this norm established? In law, a child's right to confidentiality regarding their health status can be limited where this is in their "best interests" (s 13(1)(d), Children's Act). In ethics, respect for emerging autonomy can be balanced by the need to minimize harms and promote welfare. In law, South African courts have generally held that the best interests of children require a wide range of factors to be considered in decision-making, including those which promote a child's physical, moral, emotional and spiritual welfare.[9] This means decision-makers must evaluate, weigh and balance these competing factors. They must also take into account the child's wishes.

3. In prevention trials, adolescents, who acquire conditions or a health status with long-term complications that need on-going support, should be asked to disclose to a trusted adult within a reasonable time-frame, because this is in their best interests. For example, maintaining confidentiality regarding a child's HIV status or their pregnancy may not be in their best interests as these are chronic, long-term conditions that require specialist treatment and emotional support.

5: Parents/ LGs and adolescents should understand what information will or will not be made available to parents/ LGs

1. The fifth norm is that both parties must understand what information will be kept confidential and what will be disclosed to another party.

2. How was this norm established? In law, consent is valid only if it is based on a full appreciation of information that most people would consider very important to know. In ethics, consent is only meaningful if it is based on a full understanding of the personal implications of research participation. In prevention trials, it is possible that the parent/ guardian may refuse enrolment when they understand these matters, or the child may refuse to take part.

6: If adolescents are being abused or neglected, this should be reported to authorities and adolescents should be assisted

1. The sixth norm is that adolescents' right to confidentiality is expressly limited where they are being abused or neglected, or are identified as being in need of care and protection.

2. How was this norm established? In terms of s 110 of the Children's Act (2010)[10] there is a broad range of persons who **must** report any child that has been sexually abused, deliberately neglected or abused in a manner causing physical injury.

3. The category of persons who must report such abuses includes medical practitioners, nurses, psychologists, social service professionals, social workers and members of staff or volunteer workers at a drop-in centres or child and youth care centres.

4. Reports must be made to designated child protection organisations, the provincial department of social development or police officials. While all research staff are not expressly included in this list, some members of the team will fall into these designated categories and are obliged to report.

5. Even if staff do not fall within a designated category obliging them to report, the Act also states that any person who, on reasonable grounds, believes that a child is in need of care and protection **may** report that belief to the provincial department of social development, a designated child protection organisation or a police official.

6. In addition, researchers should assist children by referring them for various kinds of support. Assistance could involve encouraging adolescents to reach out for all forms of adult support, including their reaching out to their parents, where this seems helpful.

7. Trial sites could partner with professional organisations to assist them to make determinations of abuse or neglect.

7: If adolescents are engaged in underage sexual relationships that are consensual but exploitative, this should be reported to the authorities and the adolescents should be assisted

1. The seventh norm is that adolescents' right to confidentiality may be expressly limited in certain circumstances, such as when certain sexual offences are being committed.

2. How was this norm established? In ethics, respect for emerging autonomy can be balanced by the need to minimize harms and promote welfare. In law, the Criminal Law [Sexual Offences and Related Matters] Amendment Act, No. 32 of 2007[11] requires any person who is aware of a sexual offence having been committed against a child to report this to the South African Police Service (SAPS).

3. This memo recommends that all instances the sexual offences of rape and commercial sex work should be reported to SAPS. In terms of rape, it is important to note that all sex (even if it is 'consensual') with persons under the age of 12 is rape in terms of the Sexual Offences Act. Therefore, even if a child participant discloses 'consensual' sex under 12, this will have to be reported as statutory rape.

4. According to the Sexual Offences Act (s 15, Criminal Law [Sexual Offences and Related Matters] Amendment Act, No, 32 of 2007) it is a sexual offence for an adult (older than 18 years) to have consensual sex/sexual activity with a child between the ages of 12 – 15 years. *This is still the case*.

5. Recently, the High Court declared certain sections of the Sexual Offences Act - which criminalized consensual sex between children (12 - 15 years) - to be unconstitutional. Resultantly *it is no longer a sexual offence if both parties to the consensual sex/sexual activity are between 12-15 years*. In addition, the court held that *it is no longer a sexual offence if children between 16 -17 years have sex with children between 12-15 years if there is two year age gap or less between the older and younger child*. This means that certain instances of consensual sex/sexual activity are no longer illegal. The Sexual Offences Act has thus (to some degree) become more aligned with the principles articulated in the Children's Act (2005) which expressly allows sexually active children under the age of 16 years to access services such as contraceptive advice and methods, HIV testing, and medical treatment.

6. This also means that *where there is a large age gap* between those in the sexual relationship or *where one party is an adult (*over 18), the older person is committing a sexual offence and the law requires that reporting to the police take place.

7. However, we have proposed a more nuanced approach:

   i. When adolescent participants (12-15) report that they are sexually involved with persons 18 years and older, site staff should be aware that this is a reportable offence. However, the partner, if known, should not be reported unless that sex/activity is clearly exploitative. This is because adolescent participants themselves (between the ages of 12 and 15) are not committing a crime by having under-age, consensual sex and because reporting – where relationships are not exploitative - is not in their best interests as it will drag young persons into the criminal justice system requiring them to give evidence in court and face possible negative consequences from their partner who faces a criminal record and being entered onto the Sexual Offences Register.

   ii. When younger adolescent participants (12 -15) report being sexually involved with older adolescent partners (with more than a 2 year-age gap) site staff should be aware that this is a reportable offence. However, the partner, if known should not be reported unless the sex/activity is clearly exploitative; after an assessment by the trial site team.

   iii. When older adolescent participants (16/17) report that they are sexually involved with younger children (with more than a 2 year age gap) site staff should be aware that this is a reportable offence. However, the adolescent participant should not be reported unless the sex/activity is clearly exploitative, in order words, after an assessment by the trial site team.

   iv. The determination of whether the sex/ sexual activity is exploitative should be made by a multi-disciplinary team who consider whether the ability of the adolescent to consent to the sexual activity has been compromised by factors such as coercion, violence or a lack of power.

8. This approach can also be defended on ethical grounds that harmful activities (such as non-consensual or exploitative sex) are reported, but that non-harmful activities (consensual and non-exploitative sex) are not reported because this is unlikely to protect children, may erode trust in adult or authority figures and may decrease the veracity of disclosures children make to research staff – impeding the ability to steer them to appropriate services.

9. This approach requires trial sites to undertake an assessment of exploitation. Site staff should consider the age differential as well as other aspects of the relationship such as where one party assumes an unfair level of benefit relative to another party. There is no easy formula for this assessment.

10. This approach should be discussed with Research Ethics Committees involved in oversight of the prevention trial.

11. Sites may wish to partner with professional organisations to assist them to make such determinations.

12. If adolescents are aware that certain categories of sexual activity, including 'exploitative' sex, may be reported to authorities, they may elect not to disclose this to site staff.

8: There is no legal obligation to report other offenses but adolescents should be assisted

1. The eighth norm is that where adolescents are acting in a way that contravenes other laws, there may be no legal obligation to report this, but there is an ethical responsibility to assist. Again, such assistance could involve encouraging adolescents to reach out for forms of adult support, including their reaching out to their parents where this seems helpful.

2. How was this norm established? The South African Schools Act (1996)[12] requires all children between the ages of 7 – 15 to attend school. The Basic Conditions of Employment Act (1997)[13] asserts that it is illegal for children under the age of 15 to work, or those between the ages of 15 and 18 to perform unsuitable work (work that places their well-being, education, physical or mental health, or spiritual, moral or social development at risk).

3. Currently, in HIV prevention trials:
   a. A researcher is not under a legal obligation to report **truancy** from school to any authority. However given that parents are required to ensure that children under 15 attend school and they may be unaware that their child is not attending, researchers may wish to inform parents of under 15 year-olds of truancy, so that parents can act to fulfil their duty. Children should also get assistance, advice and appropriate referrals. Trial attendance should not interfere with the school attendance.
   b. A researcher is not under a legal obligation to report **child labour or inappropriate work**. There may however be an ethical obligation to act in the best interests of the child by providing assistance, advice and appropriate referrals.
   c. A researcher is not under a legal obligation to report information regarding a child participant who has **committed, or is committing, crimes** (e,g., abusing substances, committing theft). However, where a child, involved in a criminal offense, is being exploited, this should be reported to the police or other relevant authorities because this amounts to ill-treatment (e.g. where a child is being forced to sell drugs by an adult). However, in the instance of criminal activity, researchers should intervene through advice and appropriate referrals.
   d. A researcher is not under a legal obligation to take further steps when a research participant informs the researcher of a **third party**, who has been the "victim" of a crime or has "committed" a crime. However, they may be under an ethical duty if a child is in clear and imminent danger, for example from a violent and abusive parent. In such a case they should

assist the child research participant to report this information to the local police or social workers for further investigation.

9: Parents/ LGs and adolescents should consent to confidentiality limits posed by reporting to authorities

1. The last norm is that both parties (parent and adolescent) must understand what information will be kept confidential and what will be disclosed to authorities.

2. How was this norm established? In law, consent is valid only if it based on a full appreciation of information most people would consider very important to know. In ethics discourse, consent is only meaningful if it is based on a full understanding of the personal implications of research participation.

3. In prevention trials, it should be explained to parents that the researchers are not necessarily required by law to tell parents if a report is made to authorities. However, each case will be approached on a individual basis with the best interests of the child being the basis for deciding whether parents should be informed by researchers.

4. In all instances, the adolescent will receive assistance, support and appropriate referrals.

5. It is possible that the parent/guardian may refuse enrolment when they understand these matters, or the child may refuse to take part.

CONCLUSION

1. Ethical-legal norms for adolescent HIV prevention trials should be understood by, and acceptable to, key stakeholders such as participating communities. Where high levels of objection to trials are anticipated, it may not be feasible to run such trials. It may be helpful to research the acceptability of such norms among participating communities.

2. It may also be helpful for researchers implementing such norms in prevention trials to monitor "events" such as mandatory reports to authorities and direct disclosures to parents to estimate frequency and impact.

3. In the long run, success of adolescent prevention trials will, in part, involve identifying and partnering with range of adolescent service organisations around sites, to assist researchers to implement their responsibilities.

Comments to Catherine Slack (*slackca@ukzn.ac.za*) or Ann Strode (*strodea@ukzn.ac.za*)

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3 Section 71 of the National Health Act No. 61 of 2003

4 Section 5 of the Choice on Termination of Pregnancy Act No. 92 of 1996

5 Section 130 of the Children's Act No. 38 of 2005

6 Section 129 of the Children's Act No. 38 of 2005

7 Section 134 of the Children's Act No. 38 of 2005

8 Section 12(8) and section 12(9-10) of the Children's Act No. 38 of 2005

9 Section 110 of the Children's Act 38 of 2010

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