UNIVERSITY OF CAPE TOWN

Acceptability, Safety, and Patterns of Use of oral Pre-exposure Prophylaxis to prevent HIV in Healthy, South African Adolescents

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A mini-dissertation submitted to the Health Sciences Faculty, University of Cape Town, in partial fulfilment of the requirements for the degree of Master in Public Health

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University of Cape Town

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This dissertation is my work. I had oversight of participant care and management of the project at the Cape Town site and coordination and oversight of the project at the Johannesburg site. I was also responsible for the collection, capturing, and analysis of the data and the writing of the manuscript. This protocol forms part of a larger project called CHAMPS that was designed by Professor Bekker.

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ABSTRACT

Background: HIV incidence amongst adolescents in Southern Africa remains extremely high. The importance of adolescent HIV prevention strategies in tackling the epidemic worldwide is increasingly recognised with a global target from UNICEF to reduce new adolescent HIV infections by 75% by 2020. Adolescent vulnerability to HIV infection is a result of a complex interplay between structural, economic, socio-cultural, and biological factors during a phase when behaviours associated with HIV acquisition and sexual and reproductive health-seeking are initiated. The vulnerability of young people to HIV is particularly manifest in South Africa, where young women aged 15-24 accounted for almost 40% of new HIV infections in 2017. Pre-Exposure Prophylaxis (PrEP) has been demonstrated to be effective for preventing HIV infection in adults but there is little data on its implementation among young people. Given the HIV incidence rates amongst adolescents in Southern Africa, oral PrEP for this group is likely to have an impact on population-level HIV incidence. We designed an open-label demonstration study known as Pluspills, for adolescents aged 15-19 years in South Africa to understand the safety, feasibility, and patterns of use of oral pre-exposure prophylaxis (PrEP) as part of a broad package of interventions, to prevent HIV.

Methods: Pluspills was conducted in two distinct peri-urban settings in Johannesburg and Cape Town. The aim was to study the safety and acceptability of oral PrEP (tenofovir disoproxil fumarate/Emtricitabine) in two adolescent populations in South Africa. HIV-negative participants between 15-19 years old participated in an open-label oral PrEP study over 52 weeks. Participants took daily PrEP for the first 12 weeks and were then given the choice to opt-in or opt-out of PrEP use at three-monthly intervals. Serial plasma and DBS tenofovir concentrations were measured at every PrEP refill visit, and results were discussed with participants during adherence counselling sessions. Testing for sexually transmitted infections (STI's) was conducted at baseline, twelve and forty-eight weeks.

Findings: Overall 148 participants were enrolled (median age 18 years; 67% female) and initiated PrEP. STI prevalence at the study start was high at 41% (60/148) and remained high throughout the study. The decision to stop using PrEP was made by 26 (18%) participants at

the 12-week visit. Cumulative PrEP opt-out at weeks 24 and 36 comprised 41% (60/148) and 43% (63/148) of the total cohort respectively. PrEP was relatively well tolerated with few reported adverse events. Tenofovir diphosphate (TFV-DP) levels as measured in dried blood spot samples were detectable (>16fmol/punch) in 92% (108/118)) of participants who reported PrEP use at week 12, 74% at week 24 (74/100), and 58% (22/37) by the end of the study. One HIV seroconversion occurred during the study (0.76/100 person-years) in a 19-year-old female participant who had chosen to stop taking PrEP, 24 weeks before diagnosis.

Interpretation: In this small cohort of South African adolescents at risk of HIV acquisition, PrEP was safe and well-tolerated in those who continued to use it. PrEP use decreased throughout the study as visit frequency declined. The incidence of sexually transmitted infections remained high, despite low HIV incidence. The study confirms that this population needs access to PrEP with particular attention to tailored adherence support. Young people would also possibly benefit from the option for more frequent and flexible visit schedules.

ACRONYMS:

AIDS Autoimmune deficiency syndrome

AGYW Adolescent girls and young women

CAB Community advisory board

CI Confidence intervals

DBS Dried blood spot

DTHF Desmond Tutu HIV Foundation

GCP Good Clinical Practice

HCT HIV counselling and testing

HIV Human immunodeficiency virus

HSV-2 Herpes simplex virus 2

LTFU Loss to follow up

NIH National Institutes of Health

PHRU Perinatal HIV Research Unit

PrEP Pre-exposure prophylaxis

SOP Standard operating procedures

STI Sexually transmitted infection

TFV Tenofovir

TFV-DP Tenofovir Diphosphate

VCT Voluntary counselling and testing

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Study summary

Protocol for the study of the safety and acceptability of daily oral PrEP in adolescents in South Africa.

Study Design:	Open-label, prospective cohort study in 150 adolescents in Johannesburg and Cape Town
Study Sites:	Desmond Tutu HIV Foundation Research Site in Masiphumelele and the Perinatal HIV Research Unit (PHRU) site in Soweto, near Johannesburg.
Study Population:	150 healthy HIV uninfected adolescents aged 15-19 years (approximately 75 participants at each site.)
Primary Objective:	To study the Safety and Acceptability of a daily regimen of oral PrEP (FTC/TDF), in the context of a comprehensive HIV prevention package.
Secondary Objectives:	Evaluate and describe adherence patterns, to a daily regimen of oral PrEP. Quantify numbers of STI infections at baseline, week 12, and study exit. To assess sexual behaviour at baseline and quantify any changes.
Exploratory objective:	Assess HIV incidence during the study
Treatment Regimen:	FTC/TDF tablets, taken orally, once daily for the first 3 months. Thereafter, these tablets will only be supplied to those who indicate a willingness to take PrEP. Participants are given the option to “opt-in” or “opt-out” of the study drug at each visit after 12 weeks.
Study Duration:	52 weeks

Introduction

Background

HIV and adolescents

Globally young people continue to remain key role players in HIV/AIDS epidemic in terms of vulnerability, rates of infection, and potential for change [1]. In 2015, 670 000 people between the ages of 15 and 24 years old were newly infected with HIV, and of these 250 000 were between the ages of 15 and 19 [2], making this a priority population for intervention. In 2016, three-quarters of new HIV diagnoses among adolescents occurred in Africa [3]. Many African countries have youthful populations and without intervention, estimates suggest that as many as three-quarters of a million additional adolescents could become infected between 2016 and 2030 [3]. The importance of adolescent HIV prevention strategies in tackling the epidemic worldwide is increasingly recognised with a global target from UNICEF to reduce new adolescent HIV infections by 75% by 2020 [5-8].

HIV and adolescents in South Africa

South Africa is the country with the highest burden of HIV in the world with prevalence in young women nearly four times higher than that of young men [9]. The disparity is very noticeable among 10 to 19-year-olds, with 33,000 adolescent girls becoming infected with HIV in 2018, compared to 4,200 adolescent boys [10]. From this, it is clear that young people, especially girls and younger women, are a key target group in preventing the spread of HIV at the population level [11].

South African adolescents are vulnerable to HIV infection due to a complex interplay between structural, economic, socio-cultural, and biological factors during a developmental phase when behaviors associated with HIV acquisition and sexual and reproductive health-seeking are initiated [6,12]. Despite the importance of HIV prevention efforts to support access to testing and treatment for young people, few interventions have demonstrated HIV infection risk reduction among this group in South Africa and other resource-limited settings [13-16].

The CHAMPS (CHOICES For HIV Adolescent Methods of Prevention in South Africa) studies

Since HIV made its appearance 40 years ago, much progress has been made in preventing the disease. Knowledge about HIV transmission and the role of viral load, safer sex practices, medical interventions like circumcision and PrEP, reducing mother-to-child transmission, needle exchange programmes, and rights-based approaches have drastically altered the prevention field. [17-19].

In the absence of a widely available efficacious HIV vaccine, there is currently no single intervention that protects all susceptible individuals against HIV [20]. Currently, available and anticipated prevention methods, both biomedical and behavioural, will only provide certain degrees of protection [21-23]. Additionally, research in sub-Saharan Africa had generally assumed that prevention interventions of demonstrated efficacy and acceptability in adults would be easily generalizable to adolescents [24-26].

In the context of emerging evidence for efficacy and adaptability of various HIV prevention options for adults [27-30], the CHAMPS Project (Choices for HIV Adolescent Methods of Prevention in South Africa) was conceived. The project consisted of three different independent protocols designed to explore different HIV prevention options in adolescents in South Africa. Besides medical male circumcision, and a protocol exploring different modes of PrEP delivery, Pluspills was the protocol designed to explore the feasibility, safety, and uptake of oral PrEP.

Oral PrEP as an HIV prevention Intervention

At the time when the CHAMPS Pluspills Study was conceptualized, daily pre-exposure prophylaxis with antiretroviral drugs was being evaluated in trials in key populations and diverse settings [27-32]. It was hypothesized that the use of PrEP could help prevent HIV infection during the vulnerable formative years of adulthood. [33, 34].

A growing body of neurological research and radiological studies suggested that adolescents may be more prone to engaging in behaviours that would put them at risk of HIV as a result of immature brain pathways [35]. It was hypothesized that PrEP could be viewed as a useful strategy that could bridge the vulnerable period between sexual debut and adulthood [34, 36]. It had become apparent that it was necessary to conduct studies in adolescent populations

looking at the safety, feasibility, and acceptability of various HIV prevention options so that PrEP delivery to this population would not be delayed by regulatory barriers [36].

Statement of the problem

While the potential efficacy and plausibility of oral PrEP as a safe, powerful, and time-limited tool for HIV prevention amongst key populations at risk for HIV, was widely acknowledged [37,38], several questions regarding the use of PrEP in younger people still needed to be addressed. These issues included the identification of the best drug(s) and optimal dosing regimens in terms of safety, adherence, and cost-effectiveness, and the acceptability of PrEP in this population [36]. While many of these issues had been investigated in adult populations and in young men who have sex with men in the US [40], there was a paucity of data for younger adults and adolescents in an African context [41, 42]. The feasibility of recruiting and following young 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 were all issues that needed urgent addressing.

Research question

Will adolescents who are recruited into the Pluspills study, use and adhere to oral PrEP, and will PrEP be safe and acceptable to these young people?

Research justification

Pluspills is the first study to investigate the safety and acceptability of oral PrEP within an African adolescent population. The study provides safety, acceptability, and adherence data which builds on the growing evidence from adult populations. The study was also designed to replicate real-world PrEP use and to understand patterns of use in a population that are especially at risk for HIV.

Study Objectives

Primary Objective

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 counselling, access to condoms, PEP, counselling, and referral for medical male circumcision, for adolescents between 15 and 19 years of age.

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 quantify STIs at baseline and the week 12 and exit visits. To describe sexual behaviour at baseline and assess any changes.

Exploratory objectives

To evaluate the incidence of HIV infection, as measured by seroconversion of study participants during the approximate 12 months (52 weeks) of follow-up.

Methodology

Study Design

The PlusPills study is an open-label phase 2 clinical trial designed to assess the acceptability, use, adherence to, and safety of daily oral PrEP (TDF/FTC) for HIV prevention among 150 male and female participants between 15-19 years old in Cape Town and Johannesburg (HREC ref 260/2014). 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 up in all aspects of the study except for the distribution of PrEP. At each study visit (and between study visits) after month 3 participants will be allowed to opt back in or continue without PrEP. The study was designed to try and replicate real-world PrEP use.

Figure 1. Study Design for CHAMPS: Pilot study B: "PlusPills"

PLUS PILLS	150: 15-19 years Masiphumelele and Soweto		
Basic package • HCT • MMC • PEP • Male Condoms • Female condoms	Month 0	**Screen** Package + PrEP ⬇	
	Month 1	**Enrol** Package + PrEP ⬇	DBS + real-time feedback
	Month 2	**Visit 1** Package + PrEP ⬇	DBS + real-time feedback
	Month 3	**CHOICE:** Package +/- PrEP Acceptability / Reasons for choice ⬇	DBS + real-time feedback
Choice of daily or weekly SMS **reminders**	Month 6	**CHOICE:** Package +/- PrEP Acceptability / Reasons for choice	DBS + real-time feedback

	Month 9	**CHOICE:** Package +/- PrEP Acceptability / Reasons for choice	DBS + real-time feedback
Adherence Clubs	Month 12	*Final Visit*	DBS + real-time feedback

Study population and sampling

Characteristics of the study population

150 HIV-negative adolescents at two sites (approximately 75 participants at each site), ages 15-19 years. 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 acquisition in South Africa.

Study Setting

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. HIV prevalence in this community is 22.7% (CI: 20.3%–

25.3%) [43].Several cross-sectional and cohort studies focusing on adolescents have been successfully conducted in this under-resourced community of 22 000 people [43-46]. The site has a long-established relationship with community stakeholders, highly experienced study staff, a youth centre offering peer-focused activities as well as sexual and reproductive health services.

The Perinatal HIV Research Unit (PHRU) site is based 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 an adolescent prevalence of 2% [47, 48]. 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 [49,50], and both sites also have well-established adolescent community advisory boards.

Study procedures

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 enrolment visit. At enrolment, 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 drug level sampling.

Inclusion and exclusion criteria

Inclusion criteria require that participants be sexually active; have a parental or guardian proxy give informed consent for participants <18years and assent in minors; individual consent for those >18yrs and willing to participate in study-required procedures, including taking TDF/FTC as PrEP for the first 12 weeks of the study. Potential participants were deemed ineligible if they were pregnant, breastfeeding, HIV positive, or had any significant co-morbidities: >Grade 2 hypophosphatemia; acute or chronic hepatitis B infection; renal dysfunction with creatinine

clearance <75 ml/min or a history of unexplained bone fractures. Female participants agreed to use contraceptive methods during the study with implantable, injectable, and oral hormonal contraception being provided by the study sites. All participants were evaluated for symptoms of acute HIV infection before enrolment. Participants will also be asked about their intention to relocate and the investigator will ensure that the participant is not co-enrolled in any other study.

Measurements

Study outcomes

The primary outcomes include safety, acceptability, and use of PrEP. Safety is measured by grade two, three, and four laboratory and clinical adverse events using the DAIDS table for grading the severity of adult and paediatric adverse events, version 1.0 December 2004 (clarification August 2009). Acceptability is measured by the proportion of participants who report willingness to use the study regimen, take up PrEP and remain on PrEP at each 3 month study time point. Use is defined as the number of participants who continued to use PrEP after the initial 3 month period, until the end of the study (week 48). PrEP discontinuation is defined as participants who attend a visit and refuse PrEP.

The secondary outcomes related to adherence to PrEP, sexual behaviours, and HIV and STI infections. Adherence was measured by the proportion of participants on PrEP with detectable plasma drug levels and tenofovir-diphosphate concentrations. Sexual activity was defined as a minimum of one act of self-reported vaginal sex in the last 12 months. Sexual risk behaviours included the number of regular and casual sex partners and condom use, captured by participant responses to interviewer-administered questionnaires. HIV and Herpes simplex virus type 2 (HSV-2) incidence was measured as the number of infections per person-time at risk. STI prevalence was measured as the proportion of participants with STI's at the 12 and 48-week visits.

Intracellular tenofovir-diphosphate (TFV-DP) DBS and plasma samples for tenofovir (TFV) were collected at weeks 4, 8, 12, 24, 36, and 48. TFV-DP concentrations will be measured in dried blood spots at the University of Cape Town using a validated liquid chromatography tandem mass spectrometry (LC/MS/MS) assay, originally developed and validated at the University of

Colorado [51]. Plasma tenofovir is measured with a validated LC/MS/MS assay at the University of Cape Town. Intracellular TFV-DP in DBS is used as an objective measure of product adherence with a detectable level of >16 fmol/punch and a threshold level for high adherence of 500 fmol/punch at four weeks and 700 fmol/punch thereafter, based on time for intracellular TFV-DP levels to reach steady state[52-54]. Plasma tenofovir drug concentrations were an alternative measure of product adherence with a cut-off of 10 ng/ml to indicate any use (a detectable level) and 40 ng/ml as adherent use [55].

Pregnancy testing, HIV and Hepatitis B testing and safety bloods (full blood count, creatinine, phosphate, alanine aminotransferase, aspartate aminotransferase, and urine dipstick) will be performed at screening. HIV and pregnancy tests will be taken at enrolment and weeks 4, 8, 12, 24, 36, and 48. HIV rapid testing will be done in parallel using Determine™ HIV-1/2 Ag/Ab Combo and Uni-Gold™ Recombigen® HIV-1/2. If the rapid HIV test is reactive, an HIV-1 RNA qualitative assay (Abbot) will be performed. A positive test will be confirmed with a second blood sample collected a week later. Self-collected vaginal swabs (females) and urine (males) will be collected and tested for Chlamydia trachomatis (CT) and Neisseria gonorrhea (NG) using GeneXpert® (Cepheid, Sunnyvale, CA) and HSV-2 testing (KALON) will be conducted at screening, and at weeks 12 and 48 with the appropriate treatment provided.

Safety and tolerability will be assessed at each study visit. Proteinuria, creatinine clearance, glycosuria, and liver enzymes will be monitored regularly, and all adverse events will be graded, recorded, and assessed. Neurological side effects such as headaches and dizziness, gastrointestinal side effects, and social harms will be recorded. Those who test positive for HIV at screening or throughout the study will be referred for ongoing HIV care and management. Expedited Adverse Event (EAE) reporting followed standard reporting requirements as defined in the DAIDS Manual for Expedited Reporting of Adverse Events version 2·0, March 2011, and adverse events will be discussed contemporaneously with the Protocol Safety Team. An external Data and Safety Monitoring Board will review study safety data on three occasions at six-month intervals during trial implementation and recommend whether the study continues to completion.

Data management

The collection of data is the responsibility of the data team under the supervision of the Site Investigator. Case Report Forms (CRFs) will be developed collaboratively by the research team. Each participant will be allocated a unique participant identification number. This number is linked to the participant identifying details in a link log kept by the study coordinator in a locked cupboard. Data will be stored in a locked cupboard in an access-controlled room at the research site and will be entered into a password-protected database. Consent forms with participant and guardian names and linked identification numbers will be kept separately from other data in a locked cupboard in an access-controlled room at the site. Data will be stored for fifteen years after the completion of the research, per DAIDS policy. The source documents and case report forms will be archived separately.

The Site Investigator will ensure that study records are accurately maintained throughout the study, in accordance with both international and South African regulations. All study-related records will be maintained on-site until the study is complete and the database is locked.

Quality control and quality assurance

Each site will be required to develop study-specific standard operating procedures (SOP's) and quality management plans. Regular study monitoring will be outsourced to an external contract research organization (CRO) at both sites. Study monitors will visit the sites and review procedures and documentation. They will also assess the implementation of the study protocol, and compliance with GCP (good clinical practice) guidelines, and other applicable regulatory requirements. In addition, they will perform source document verification and check that the case report forms have been accurately captured in the database. They will also assess compliance with site quality management plans.

Sample Size considerations

The sample size calculation is based on the primary endpoint of acceptability which is measured by the proportion of youth who take up PrEP and remain on PrEP as part of a comprehensive prevention package. The table below shows the precision (at 95% confidence interval) provided by various sample sizes in detecting the occurrence of acceptability endpoints (with the frequency of non- uptake and use varying from 5%-20%).

Table 1. Sample size calculation

Frequency	Sample size		
	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

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-acceptability endpoints that occur in 10% of subjects with approximately 5% precision.

Study Variables

Table 2. Study Variables

Variable	*Type*	*Categories*
Age	*Continuous*	*15 – 19*
Age (regression model)	*Categorical*	*15-17* *18 and 19*
Sex	*Categorical*	*Male* *Female*

Highest grade completed	*Continuous*	*Grade 9 - 12*
Attending tertiary education	*Categorical*	*Yes* *No*
Time in weeks	*Categorical*	*4 weeks* *8 weeks* *12 weeks* *24 weeks* *36 weeks* *48 weeks*
Site	*Categorical*	*Soweto* *Cape Town*
Consistent condom use	*Categorical*	*Yes* *No*
Transactional sex	*Categorical*	*Yes* *No*
Anal sex	*Categorical*	*Yes* *No*
Any STI at baseline	*Categorical*	*Yes* *No*
More than 1 sex partner at baseline	*Categorical*	*Yes* *No*
Had a partner in the last year who was more than 5 years older	*Categorical*	*Yes* *No*
Chlamydia	*Categorical*	*Yes* *No*
Gonorrhoea	*Categorical*	*Yes* *No*
HSV-2	*Categorical*	*Yes* *No*
Any STI *(Chlamydia or Gonorrhoea or HSV-2)*	*Categorical*	*Yes* *No*

TFV- DP levels	*Categorical*	*<16fmol/ punch* *16 -499 fmol/punch at week 4, 16-699 at all other visits* *≥ 500 fmol/punch at week 4, ≥ 700 fmol/punch at all other visits*
High adherence	*Categorical*	*TFV-DP levels < 700 fmol/ punch* *TFV-DP levels ≥ 700fmol/punch*

Statistical Analysis Plan

Descriptive analysis

Demographic and other baseline characteristics will be summarized using appropriate descriptive statistics for continuous variables, descriptive statistics include medians and interquartile ranges. Frequency tables with proportions will be used to describe categorical variables.

Logistic regression with mixed-effects modelling

Univariate and multivariable logistic regression with mixed-effects modelling will be used to compare factors affecting adherence, between youth who were adherent to PrEP (TFV-DP ≥ 700 fmol/punch) and youth who were non-adherent to PrEP.Adjustment will be made for *a priori* factors which may influence the outcome. These include age and sex, as well as the study site, time (in weeks) on the study, and sexual risk behaviours.

All data will be analysed using STATA 13.1 (StataCorp, College Station, TX, USA).

Ethical Considerations

Ethical approval

The Investigators will seek approval from the Institutional Review Boards of participating study sites, the South African Medicine Control Council, and the Division of AIDS (DAIDS) at the National Institute of Allergy and Infectious Diseases (NIAID) of the US National Institutes of Health (NIH). The trial will be conducted in compliance with the ICH-GCP and SA-GCP guidelines and will be registered in the public registry database of ClinicalTrials.gov before participant enrollment.

General Considerations

Community participation**:** Before study enrolment, key youth organizations will be engaged 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.

Selection of participants aged 15-19 years. Although the age of lawful consent to sexual intercourse in South Africa is 16 years, there is ample evidence that South African adolescents are sexually active at a much earlier age [47,55-57]. It is therefore imperative that prevention interventions 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.

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' 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 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.

Standard of prevention: HIV Counselling and Testing (HCT) has been promoted as an effective tool for the reduction of the 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 [58]. Pre and post-HIV test counselling, including risk reduction counselling (tailored to adolescents), will therefore be performed at every visit. Trained and qualified study personnel will provide age-appropriate pre-HIV tests, risk reduction, and post HIV test counselling at each visit, according to the site standard operating procedures (SOPs).

Potential Benefit

This research protocol contains interventions and procedures that at least hold out the prospect of benefit for adolescent participants. Increased awareness of HIV and decreased or altered risk behaviour due to risk reduction counselling and regular testing could benefit participants. In addition, all participants receive a comprehensive HIV prevention package including condoms, risk reduction counselling, and screening and treatment for STIs. Participants will also be referred for other HIV prevention interventions including male circumcision and post-exposure prophylaxis. Adolescents will also receive regular monitoring for general health and appropriate management for identified conditions through appropriate referrals.

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.

In terms of South African guidelines for child research the risks of 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 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 reduce the risks of all components to an acceptable minimum and to ensure that risk-benefit/ knowledge ratios are satisfied [59-61].

Potential Harm

Potential harms include side effects of the medication, social harms from study participation, and potential sexual disinhibition.

The most common risks and side effects from the study drug include headache, dizziness, fatigue, diarrhoea, nausea, vomiting, headache, and rash. Less common but more serious risks include decreased kidney function, metabolic disorders, changes in bone mineral density, and allergic reactions. At the time no controlled human studies of FTC among pregnant women had been conducted and no data on the excretion of FTC/TDF in human breast milk had been reported.

Harm reduction

Monitoring for kidney function and serum chemistry will be performed frequently during the study. Female participants are required to use hormonal contraception to prevent pregnancy and all participants receive risk-reduction counselling. The Safety team will meet regularly to discuss individual participants and study product will be held if the Site Investigators are concerned about participant safety.

Informed Consent

Parents or guardians and potential participants will be approached for consent/assent for both screening and enrolment before any study procedures are performed. Potential participants will be invited to information sessions and consent discussion groups, during which the study will be explained in an age-appropriate manner using adolescent-friendly materials. The informed consent and assent forms include information about voluntary participation, the study procedures, benefits, risks, and the option to withdraw at any point. Each study site will be responsible for developing study informed consent and assent forms for local use and translating these forms into local languages. According to South African legislation, adolescents

can consent independently to some of the procedures in the study including testing for HIV, medical treatment for STI's and family planning. Adolescents may also consent independently to the termination of pregnancy.

Confidentiality

Participant confidentiality is a cornerstone of GCP and all staff will be trained accordingly. All data will be identified only by a unique participant number. All study documentation including questionnaires and informed consents will be kept in locked rooms with lockable cupboards. All STI, HIV, and pregnancy test results will be given to the participant and not the guardian. Younger participants will be encouraged to disclose positive results to a trusted adult. This will be discussed during the informed consent process with both the participant and their guardian.

Compensation

Participants will receive monetary remuneration at the end of each scheduled visit for an amount that will be reviewed and approved by the Ethics Committees at each site and the local CABs.

Dissemination of findings

Study results will be communicated to participants and community representatives through both site's established infrastructure (adolescent and adult CABs). Results will also be disseminated nationally through the PrEP Technical Working Group and internationally through publication in peer-reviewed journals and conferences.

Logistics

Budget

The study is funded by the National Institute of Allergy and Infectious Diseases (NIAID) and the US National Institutes of Health (NIH) under an R01 grant: Bekker: R01AI094586.

Timeframe

Participants will be recruited between March 2015 and February 2016. The last participants will exit the study at the end of February 2017 and the database will be locked in April 2017. Desmond Tutu HIV Foundation also plans on applying for a supplementary grant to fund the testing of the DBS samples and is currently applying for funding.

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PART B: JOURNAL READY MANUSCRIPT

An Open-Label, phase II, Demonstration Study to Assess the Acceptability, Safety, and Patterns of Use of oral Pre-exposure Prophylaxis of tenofovir disoproxil fumarate/emtricitabine to prevent HIV in Healthy, South African Adolescents.

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Short title: Pluspills: A phase II open-label oral PrEP study in South African Adolescents.

Abbreviations: Pre-Exposure Prophylaxis (PrEP)

Key Words: PrEP; HIV Prevention; Adolescents; South Africa;

Word count: 4402

Tables: 3 (+1 in web appendix) Figures: 3

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Data Sharing: De-identified data that underlie the results in this manuscript will be made available on request.

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*As per the MPH dissertation guidelines, co-authors are not listed on the journal-ready manuscript. The contribution of collaborators and supervisors is listed in the acknowledgement section of the manuscript.

Abstract

Background: HIV incidence amongst adolescents in Southern Africa remains unacceptably high. Pre-Exposure Prophylaxis (PrEP) is an effective HIV prevention intervention but there are little data on its implementation among adolescents.

Methods: Pluspills was conducted in Cape Town and Johannesburg and aimed to investigate the safety, feasibility, and acceptability of oral PrEP (tenofovir disoproxil fumarate/Emtricitabine) as part of a comprehensive HIV prevention package in an adolescent population in South Africa. HIV-negative participants between 15-19 years old participated in an open-label oral PrEP study over 52 weeks. Participants took daily PrEP for the first 12 weeks and were then given the choice to opt-in or opt-out of PrEP use at three-monthly intervals. Serial plasma tenofovir concentrations were measured at every PrEP refill visit, and results were discussed with participants during adherence counselling sessions. Testing for sexually transmitted infections (STI's) was conducted at baseline, twelve and forty-eight weeks.

Findings: Overall 148 participants were enrolled (median age 18 years; 67% female) and initiated PrEP. STI prevalence at baseline was high 41% (60/148) and remained so throughout the study. PrEP was stopped by 26 (18%) participants at 12 weeks. Cumulative PrEP opt-out at weeks 24 and 36 comprised 41% (60/148) and 43% (63/148) of the total cohort respectively. PrEP was well tolerated with only minor adverse effects. Tenofovir diphosphate (TFV-DP) concentrations as measured in dried blood spot samples were detectable (>16fmol/punch) in 92% (108/118)) of participants who reported PrEP use at week 12, 74% at week 24 (74/100), and 58% (22/37) by study end. One HIV seroconversion occurred during the study (0·76/100 person-years) in a 19-year-old participant who had stopped PrEP 24 weeks before diagnosis.

Interpretation: In this cohort of self-selected South African adolescents at risk of HIV acquisition, PrEP appears safe and tolerable in those who continued use. PrEP use decreased throughout the study as visit frequency declined. STI incidence remained high, despite low HIV incidence. This population in Southern Africa needs access to PrEP with tailored adherence support and possibly the option for more frequent and flexible visit schedules.

Funding: National Institute of Allergy and Infectious Diseases (NIAID) of the US National Institutes of Health (NIH)

Introduction

Sub-Saharan Africa carries the largest burden of HIV globally, with an estimated 1·1 million new infections annually[1, 2]. HIV incidence amongst young people in the region remains disproportionately high, with girls accounting for three out of four new infections amongst 15-19-year-olds.[3,4] The importance of adolescent HIV prevention strategies in tackling the epidemic worldwide is increasingly recognised with a global target from UNICEF to reduce new adolescent HIV infections by 75% by 2020[3-6]. Adolescent vulnerability to HIV infection is due to a complex interplay between structural, economic, socio-cultural, and biological factors during a developmental phase when behaviours associated with HIV acquisition and sexual and reproductive health-seeking are initiated[4, 7]. The multidimensional vulnerability of adolescents and youth to HIV is particularly manifested in South Africa, where young women aged 15-24 accounted for almost 40% of new HIV infections in 2017[8-10]. Despite the importance of HIV prevention efforts to support access to testing and treatment for young people, few interventions have demonstrated HIV infection risk reduction among this group in South Africa and other resource-limited settings[11-14]. The CHAMPS (Choices for HIV Adolescent Methods of Prevention in South Africa) was a program made up of three different independent protocols designed to explore different HIV prevention options in adolescents in South Africa. Besides medical male circumcision, and a protocol exploring different modes of PrEP delivery, Pluspills was the protocol designed to explore the feasibility, safety, and uptake of oral PrEP.

PrEP has been proven to be efficacious in a variety of contexts and populations[15-17]. PrEP studies have largely focused on adults with subsequent inadequate youth representation and minimal data specifically applicable to adolescents and young people in Southern Africa[18]. While data is emerging on the use of PrEP in at-risk youth in the USA[19], this may not be broadly applicable to a younger African heterosexual population. The challenge of daily PrEP adherence in younger people in all settings is recognised, with a strong correlation between inadequate adherence to PrEP and reduced efficacy[20- 22]. Given the HIV incidence rates amongst adolescents in Southern Africa, oral PrEP for this group is likely to have an impact on population-level HIV incidence[14, 15, and 23]. To help inform PrEP implementation strategies, we designed an

open-label demonstration study known as Pluspills for adolescents aged 15-19 years in South Africa to examine the safety, use, feasibility, and acceptability of oral pre-exposure prophylaxis (PrEP) as part of a comprehensive HIV prevention package.

Methods

Study Design

The PlusPills study was an open-label phase 2 clinical trial designed to assess the acceptability, use, adherence to, and safety of daily oral PrEP (TDF/FTC) for HIV prevention among 150 male and female participants between 15-19 years old in Cape Town and Johannesburg. The study protocol was approved by the Institutional Review Boards of participating study sites, the South African Medicine Control Council, and the Division of AIDS (DAIDS) at the National Institute of Allergy and Infectious Diseases (NIAID) of the US National Institutes of Health (NIH). The trial was conducted in compliance with the ICH-GCP and SA-GCP guidelines and was registered in the public registry database of ClinicalTrials.gov (NCT02213328) before participant recruitment. The role of Gilead Sciences in the development of the protocol was limited to sections regarding the handling of study drugs.

Setting

The two study sites in Cape Town and Johannesburg serve peri-urban low-income communities with a substantial burden of HIV. Both sites have long-established relationships with community stakeholders, experienced study staff, adolescent responsive activities as well as sexual and reproductive health (SRH) services, and an active adolescent Community Advisory Board (CAB). Multiple recruitment methods were used to recruit participants including community outreach at schools, youth groups, sports clubs, local clinics transport hubs, and recruitment drives in the community. Participants were given recruitment materials (pamphlets, brochures, and flyers), and those expressing an interest in participating were invited to attend pre- screening information sessions at the research site.

Study Participants

Inclusion criteria required the following: for participants to be sexually active; have a parental or guardian proxy give informed consent for participants <18years and assent in minors; individual consent for those >18yrs and willing to participate in study-required procedures, including taking TDF/FTC as PrEP for the first 12 weeks of the study. Potential participants were deemed ineligible if they were pregnant, breastfeeding, HIV positive, or had any significant co-morbidities: >Grade 2 hypophosphatemia; acute or chronic hepatitis B infection; renal dysfunction with creatinine clearance <75 ml/min or a history of unexplained bone fractures. Female participants agreed to use contraceptive methods during the study with implantable, injectable, and oral hormonal contraception being provided by the study sites. All participants were evaluated for symptoms of acute HIV infection before enrollment.

Study Procedures:

Participants were invited to screen for this study following an HIV prevention education session. Those determined to be eligible were requested to return for an enrollment visit at which they were asked to take PrEP as part of a comprehensive prevention package for at least 12 weeks. During this time, participants made monthly visits for adherence counselling and HIV testing. Results of drug concentration sampling were used as an adherence-enhancing strategy for those participants who elected to receive this information during follow-up visits. Those who chose not to receive these results received standard motivational adherence counselling during study visits. Participants were given the option to opt-out of PrEP but to remain in the study at the 12-week visit, and then every three months thereafter until follow-up ended at week 52 (Fig 1).

Outcomes

The primary outcomes included the acceptability, use, and safety of PrEP. Acceptability was measured by the proportion of participants who reported willingness to use the study regimen, take up PrEP, and remain on PrEP at each 3 month study time point. Use was defined as the number of participants who

continued to use PrEP after the initial 12 week period until the end of the study (week 48). PrEP discontinuation was defined as participants who attended a visit and refused PrEP. Safety was measured by grade two, three, and four laboratory and clinical adverse events using the DAIDS table for grading the severity of adult and paediatric adverse events, version 1.0 December 2004 (clarification August 2009). Adverse events were characterized and compared to those seen in adult populations. PrEP was considered safe and well tolerated if the adverse events reported were similar in type and severity to those reported in adult populations.

The secondary outcomes related to adherence to PrEP, sexual risk behaviours, and HIV and STI infections. Adherence was measured by the proportion of participants on PrEP with detectable plasma drug levels and tenofovir-diphosphate concentrations. Sexual activity was defined as a minimum of one act of self-reported vaginal sex in the last 12 months. Sexual risk behaviours included the number of regular and casual sex partners and condom use, captured by participant responses to interviewer-administered questionnaires. HIV and Herpes simplex virus type 2 (HSV-2) incidence was measured as the number of infections per person-time at risk. STI prevalence was measured as the proportion of participants with STI's at the 12 and 48-week visits.

Drug concentrations: Intracellular tenofovir-diphosphate (TFV-DP) DBS and plasma samples for tenofovir (TFV) were collected at weeks 4, 8, 12, 24, 36, and 48. TFV-DP concentrations were measured in dried blood spots at the University of Cape Town using a validated liquid chromatography tandem mass spectrometry (LC/MS/MS) assay, originally developed and validated at the University of Colorado [24]. Plasma tenofovir was measured with a validated LC/MS/MS assay at the University of Cape Town. Intracellular TFV-DP in DBS was used as an objective measure of product adherence with a detectable level of >16 fmol/punch and a threshold level for high adherence of 500 fmol/punch at four weeks and 700 fmol/punch thereafter, based on time for intracellular TFV-DP levels to reach steady-state [25, 26, 27]. Plasma tenofovir drug concentrations were an alternative measure of product adherence with a cut-off of 10 ng/ml to indicate any use (a detectable level) and 40 ng/ml as adherent use[28].

Laboratory Testing: Pregnancy testing, HIV and Hepatitis B testing, and safety bloods (full blood count, creatinine, phosphate, alanine aminotransferase, aspartate aminotransferase, urine dipstick) were performed at screening. HIV and pregnancy tests were taken at enrolment and weeks 4, 8, 12, 24, 36, and 48. HIV rapid testing was done in parallel using Determine™ HIV-1/2 Ag/Ab Combo and Uni-Gold™ Recombigen® HIV-1/2. If the rapid HIV test was reactive, an HIV-1 RNA qualitative assay (Abbot) was performed. A positive test was confirmed with a second blood sample collected a week later. Self-collected vaginal swabs (females) and urine (males) was collected and tested for Chlamydia trachomatis (CT) and Neisseria gonorrhea (NG) using GeneXpert® (Cepheid, Sunnyvale, CA) and HSV-2 testing (KALON) was conducted at screening, and at weeks 12 and 48 with the appropriate treatment provided.

Safety and tolerability were assessed during the study. Proteinuria, creatinine clearance, glycosuria, and liver enzymes were monitored regularly, and all adverse events were graded, recorded, and assessed. Neurological side effects such as headaches and dizziness, gastrointestinal side effects, and social harms were recorded. Those who tested positive for HIV at screening or throughout the study were referred for ongoing HIV care and management. Expedited Adverse Event (EAE) reporting followed standard reporting requirements as defined in the DAIDS Manual for Expedited Reporting of Adverse Events version 2·0, March 2011, and adverse events were discussed and were discussed contemporaneously with the Protocol Safety Team. An external Data and Safety Monitoring Board reviewed study safety data on three occasions at six-month intervals during trial implementation and recommended that the study continues to completion.

Statistical analysis

Statistical analyses of the baseline data were performed using STATA version 14 (StataCorp). College Station, TX) Demographic and other baseline characteristics were summarized using appropriate descriptive statistics for continuous variables, descriptive statistics include medians and interquartile ranges. Factors affecting

adherence were compared between youth who were adherent to PrEP (TFV-DP ≥ 700 fmol/punch) and youth who were non-adherent to PrEP using logistic regression with mixed-effects modelling.

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The tenofovir disoproxil fumarate/emtricitabine co-formulated study medication was donated and the funding for Tenofovir drug level measurements in dried blood spots was received as a grant for this study from Gilead Sciences.

The corresponding author had full access to all of the data and the final responsibility to submit for publication.

Results

Participants and baseline characteristics

Between April 2015 and February 2016, 244 participants were screened and 148 participants enrolled across both sites (Fig 2). The most common reason for ineligibility was being unavailable for all trial visits and procedures (n=27), followed by not being sexually active (n=23), pregnancy (n=9), HIV seropositivity (n=3), and

hepatitis B surface antigen positivity (n=2). Table 1 shows cohort characteristics at enrolment. The median age of participants was 18 (IQR17-19). 99 were female (67%) and 49 were male (33%) with older female participants aged 18 and 19 comprising 42% of the cohort. Participants, less than 18 years made up 33% (48/148) of the cohort. Three-quarters of participants attended high school (n=111) and 10% (n=15) were in tertiary education. 80% (n=119) of participants lived with at least one or both parents, the remainder lived with another family member or caregiver. 28 participants were prematurely discontinued from the study with reasons for non-completion shown in figure 2. Overall study retention was 81%.

Safety and tolerability

In total, 11% (16/148) of the participants experienced either a grade 2 or 3 transient adverse health events. The most common grade 2 events were headaches and dizziness, (n=4) and nausea and vomiting (n=4). Participants also reported abdominal pain (n=2) diarrhoea (n=2) and skin rash (n= 2). Two participants experienced grade 3 weight loss, which was deemed related to the study drug and resolved fully when PrEP was discontinued. There were no bone fractures and no PrEP interruptions occurred due to renal impairment. Four participants experienced a grade 3 or 4 serious adverse event that was deemed unrelated to the study drug. Adverse events are reported in Table 4 (web appendix). One participant overdosed on study medication in a para-suicide attempt unrelated to study participation following an argument with her mother. She received support from the site, was referred for psychological support, and made a full recovery. Side effects were cited as a reason for stopping PrEP in 13% of the cohort (n=19/148). One incident of social harm was attributed to study participation, where a participant was assaulted by her partner after he found the tablets and assumed she had been concealing her HIV status. The participant was assisted to report the incident to the police, was referred for counselling, and withdrew from the study. One 14-year-old participant was inadvertently enrolled and exited from the study following a discussion with the safety team and Ethics Committee.

Sexual Risk Behaviour

The median age at sexual debut was 15 (IQR 14-16). A third of the participants (n=49/148) reported multiple partners in the last year and 20% (n=30/148) reported age-disparate relationships (sexual partners aged ≥5 years than participant) (Table 1). A third of participants=48/148 gave a history of inconsistent condom use at baseline with no significant differences between the sexes (p=0.5). Less than 10% of participants reported previous anal intercourse (n=10). More than half of the participants (n=83/148) reported alcohol use in the preceding 12 months. A quarter (n=25/148) had used recreational drugs in the previous 12 months, with marijuana as the most commonly reported drug used. (n=23/148; 15.5%).

Sexually Transmitted Infections

Table 2 shows STI prevalence during the study stratified by sex. The prevalence of sexually transmitted infections was high at baseline with 60 participants (41%) testing positive for at least one STI. Half of the females (50/99) had at least one STI at baseline versus 20% (10/49) of male participants (p= 0.001). STI prevalence remained high throughout the study despite treatment, counselling, and partner treatment. *Chlamydia trachomatis* was the most frequently occurring infection with a prevalence of 30% (45/148) at baseline, 17% (21/124) at week 12, and 26% (24/91) at study end. HSV-2 was the second most common infection with 16% (n=24/148) seropositive at baseline and the overall incidence of HSV-2 was 8·3 per 100 person-years (95% CI: 4·31 – 16). There were no incident pregnancies reported during study follow-up. There was one reported HIV seroconversion in a 19-year-old female participant who had stopped PrEP 24 weeks before diagnosis. The overall HIV incidence was 0·76 per 100 person-years (95% CI: 0·1- 4·3) and 1·16 per 100 girl-years (95% CI: 0·2- 6·29).

Acceptability

PrEP acceptability was recorded at every follow-up visit. The acceptability instrument (a twelve-item graded Likert scale) assessed the usability of PrEP and the motivation for continued PrEP use. At week 12, 83% (104/126) of participants indicated that they "liked" or would "like to continue" taking PrEP and 79% (100/126) of participants collected their PrEP prescription at the study site. At 12 weeks 98% (123/126) of

participants taking PrEP indicated that they "liked" PrEP as they felt protected from HIV. This preference remained constant throughout the study.

Medication adherence and study opt-out

DBS tenofovir levels indicated that 95% (141/148) of participants had a detectable drug level during the study with 5% (7/148) not having used PrEP at all. Plasma tenofovir levels similarly showed that 82% (121/148) of participants had a detectable drug level at any time during the study. In total 43% (63/148) of the cohort chose to stop taking PrEP at any point during the study. Side effects were the most commonly cited reason for choosing to stop (19/63, 30%). Other reasons included forgetting (15/63, 24%), tablet size (14/63, 22%), and decreased perception of risk (10/63, 16%). 8% (5/63) chose to start taking PrEP again after stopping citing increased risk as the reason.

First 12 weeks: Drug levels were relatively constant in the first three-month phase with 94% (105/112) of participants having detectable TFV-DP levels at week 4, 94% (107/113) at week 8, and 92% (108/118) at week 12. In contrast, 71% (79/112) of participants had detectable plasma tenofovir levels at week 4, 67% (76/113) at week 8, and 54% (64/118) at week 12. Thereafter, 26 participants (18%) chose to stop taking PrEP at the 12-week visit (figure 2).

Weeks 24-48: Twenty-four percent of the cohort (35/148) chose to opt out of PrEP at the 24-week visit with a further 1% (2/148) opting out of PrEP at the week 36 visit. There was also a decline in TFV-DP levels from the week 24 visit, with detectable levels seen in 74% (74/100) of participants who chose to continue PrEP. Plasma tenofovir levels declined to detectable plasma levels seen in 41% (41/100) of participants who chose to continue PrEP. This remained constant over the following 24 weeks with 58% (22/37) and 46% (17/37) of participants on PrEP having a detectable level according to DBS and plasma samples at the week 48 visit. Table 3 shows a mixed-effects logistic regression model for factors predicting adherence. Time (adjOR 0.89; 95% CI 0.86, 0.92) and age (adjOR 0.57; CI 0.40, 0.82) were the only statistically significant predictors of adherence ($p < 0.001$ and $p < 0.003$ respectively). The most common reasons given for poor adherence were that participants forgot, lost, or ran out of tablets (41%). Other reasons given included being worried about

potential side effects (6%), being too busy (5%), or being away from home (5%). Figure 3 demonstrates TFV- DP DBS levels by week.

Plasma TFV vs TFV-DP

Plasma TFV and TFV- DP drug level results were correlated and reached agreement in 77% (425/552) of samples. 13% of the samples (73/552) had high plasma TFV with low TFV- DP suggesting possible white coat dosing with a dose taken before the study visit but otherwise poor adherence in the preceding month. 10% of the samples (54/552) had low plasma TFV with high TFV-DP suggesting good adherence in the preceding month but no dosing before the study visit.

Discussion

PlusPills is the first oral PrEP study in a heterosexual adolescent population in Africa and provides important safety and adherence data for young people in South Africa and the region. Oral PrEP was safe and relatively well tolerated by participants, with reported side effects temporary and similar to those described in adult PrEP studies. Acceptability of PrEP and study participation remained high throughout.

This study demonstrated the feasibility of enrolment and retention of young men and women who appear to be at substantial risk of HIV acquisition. The significant levels of STI's both at baseline and during the study, together with self-reported sexual risk behaviour, suggest a population suitable for PrEP use, obviating the need for complex risk assessment tools for selection.

HIV incidence was low in this open-label single-arm study, with a single HIV seroconversion occurring in one participant who had opted out of PrEP earlier in the study. The incidence rate of 0.76 per 100 person-years is 73% lower than the HIV incidence rate that is estimated nationally for sexually active adolescents aged 15-19 (2.81 per hundred person-years if assuming one-third male and two-thirds female, as in our study population[21].) While this study was not powered to measure HIV incidence or designed as an efficacy study, the low incidence rate, relative to the national average, suggests a possible benefit from PrEP. The STI prevalence and incidence throughout the study indicate that young people in this setting remain engaged in sexual risk behaviour even within a context of supportive and adolescent-

responsive health services. Incorporating PrEP as an added measure into adolescent sexual and reproductive services is critical to allow holistic and targeted care for young people during this vulnerable period.

The rationale for offering PrEP opt-in and opt-out at intervals during the PlusPills study was to replicate real-world PrEP use according to "seasons" of HIV risk [29- 32]. A possible explanation for the low HIV incidence in this study despite high levels of STIs suggesting condom-less sex is that participants identified their own seasons of risk and successfully used event or season-based PrEP. This possibility warrants further study. Implementation programmes should aim to support and empower the adolescent to use PrEP for specified periods of anticipated HIV exposure instead of relying on traditional adherence messaging and measures such as pill-counts still in use in some ARV clinics in resource-limited settings. Using PrEP according to a specified season of risk should be recognised as different to event-based PrEP. The ADAPT (HPTN 067) study[33], also conducted in Cape Town albeit in a slightly older group of women, found that daily oral PrEP was more successful than intermittent use in terms of the number of sex acts that were "covered" by drug exposure. More research into dosing and dosing schedules is urgently required among young heterosexual people. An individualised and non-judgmental approach to PrEP is likely likely to improve uptake and adherence. Another consideration is that pluspills required parental proxy consent for participation of adolescents younger than 18 years. This likely led to the lower numbers of younger people in the cohort and may also have contributed to the recruitment of individuals with lower HIV incidence.

Daily PrEP adherence is a considerable challenge for younger populations, including in this study, and has been reported in North American adolescent and young adult PrEP studies. In particular, in ATN 110 [15, 34] and ATN 113 [15, 35] TFV-DP concentrations in blood samples declined as the frequency of study visits were reduced per protocol. Adherence also decreased with increasing age and this may reflect increased familial support in the younger participants who needed parental consent to participate. In pluspills, one-third of the population was younger than 18 years. Fewer than 60% of participants had detectable TFV-DP levels by week 48, and 40% of the study population had chosen to discontinue PrEP by week 36, although participants were retained in the study and continued to receive the range of adolescent-friendly SRH

services offered. This further underlines the importance of integrating PrEP into SRH services so that PrEP can be offered regularly to young people attending health services. Young people on PrEP may benefit from more frequent PrEP visits to augment and support adherence as appropriate. Work is needed to identify successful adolescent-specific strategies to address adherence including mobile technology to enhance clinic contact frequency, adherence support groups, peer mentors, and cash incentives. Longer acting strategies, like the dapivirine vaginal ring or injectable PrEP may also prove to be useful in circumventing the stigma associated with pill taking and improve adherence.

Drug levels measured in plasma and dried blood spots correlated reasonably well indicating that in this population either could be used to provide objective measures of PrEP use. In Pluspills, the recommendation to participants was that they take the oral PrEP daily and these measures provide some additional information in understanding patterns of PrEP use. In those individuals who choose to use PrEP intermittently according to sexual exposure risk, the interpretation of these measures of adherence will remain challenging.

Limitations

The need for parental consent for the minor participants posed a recruitment challenge and may have affected the generalisability of the study results. The relatively high discontinuation rate (19%) may have introduced bias and resulted in differential loss to follow up

Conclusion

This study supports the hypothesis that oral PrEP is safe and acceptable for young people while also reinforcing the view that adherence is challenging for young people. PrEP rollout in South Africa is being prioritized to groups most at risk, including sex workers, men who have sex with men, and most recently, adolescent girls. Prioritizing

PrEP for at-risk young women can be cost-effective considering that there may be costly obstacles to initiating treatment for HIV-positive youth using the same drug.[36-39]. Oral PrEP in combination with other proven HIV prevention interventions should be offered to South African adolescents and young people in a tailored fashion including developmentally appropriate support for effective PrEP use.

Research in Context

Evidence before this study:

We searched electronic databases Medline, Embase, PubMed, African Index Medicus, and the Cochrane database of systematic reviews to identify studies of PrEP in adolescents in which the primary outcomes were safety and acceptability. We included studies published up to September 2019, in any language. Our search included keywords "PrEP" OR "Pre-exposure prophylaxis OR "tenofovir/emtricitabine" AND "safety" OR "acceptability" AND "adolescent" OR "young" AND "Africa". We screened abstracts to retrieve full-text articles for assessment of eligibility and checked reference lists of relevant studies and reviews for additional references.

While there was plenty of evidence for the safety and acceptability of PrEP in adult populations and a limited number of studies in adolescent MSM in North America we were unable to find any studies meeting our search terms in African populations. Thus, the feasibility of recruiting and retaining adolescent 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 were all issues that needed to be urgently addressed.

Added-value of this study: Pluspills is the first study to investigate the safety and acceptability of oral PrEP within an African adolescent population. The study provides safety, acceptability, and adherence data which builds on the growing evidence from adult populations. The study was also designed to replicate real-world PrEP use and to understand patterns of uptake and use in a population that is especially at risk for HIV.

Implications of all the available evidence: This study supports the hypothesis that oral PrEP is safe and acceptable for adolescents. It also underscores the view that adherence is challenging for young people. PrEP rollout in South Africa is being prioritized to groups most at risk for HIV, including sex workers, men who have sex with men, and most recently, adolescent girls. An evidence base for this type of information will inform policymakers and practitioners on how to best implement and promote an oral PrEP regimen for African adolescents.

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Author contributions: KG was responsible for data collection, analysis, and interpretation of data. KG drafted and revised the manuscript. LJ and LM contributed to the conception and design of the study and analysis and interpretation of data. LJ and LM critically revised the manuscript. JD, EM TP, LF, KJ were responsible for data collection and critically revised the manuscript. RM, MW, CS, AS, HS, SH, JR, LM, GG critically revised the manuscript. LG was responsible for study design, analysis, and interpretation of data, drafting, and revision of the manuscript. All authors read and approved the final version of the manuscript.

[1]Authors to be included in the final submission to The Lancet Child and Adolescent Health: Gill K, Johnson L, Dietrich J, Myer L, Marcus R, Wallace M, Pidwell T 1, Mendel E, Fynn L, Jones K, Wiesner L, Slack C, Strode A, Spiegel H, Hosek S, Rooney J, Gray G, Bekker LG.

The CHAMPS project (Choices for HIV Adolescent Methods of Prevention in South Africa) was an NIH funded project comprising three pilot studies rolled out as a series of small, focused, interrelated protocols. Each study examined specific questions 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”

The manuscripts for “Macho” and “Uchoose” can be accessed below:

http://www.samj.org.za/index.php/samj/article/view/13090/9506

https://onlinelibrary.wiley.com/doi/10.1002/jia2.25626

Journal manuscript tables and figures

Figure 2. Study Design for CHAMPS: Pilot study B: “PlusPills

PLUS PILLS	150: 15-19 years Masiphumelele and Soweto		
Basic package • HCT • MMC • PEP • Male Condoms • Female condoms	Month 0	**Screen** Package + PrEP	
	Month 1	**Enrol** Package + PrEP	DBS + real-time feedback
	Month 2	**Visit 1** Package + PrEP	DBS + real-time feedback
	Month 3	**CHOICE:** Package +/- PrEP Acceptability / Reasons for choice	DBS + real-time feedback
Choice of daily or weekly SMS **reminders**	Month 6	**CHOICE:** Package +/- PrEP Acceptability / Reasons for choice	DBS + real-time feedback
	Month 9	**CHOICE:** Package +/- PrEP Acceptability / Reasons for choice	DBS + real-time feedback
Adherence Clubs	Month 12	*Final Visit*	DBS + real-time feedback

Table 3. Baseline demographic data

Characteristic	Female (n=99)	Male (n=49)	All (n=148)
Age, years (median, IQR)	18 (16-19)	18 (17-18)	18 (17-18.5)
Ethnicity – Black African	99 (100%)	49 (100%)	148 (100%)
Location			
Cape Town	52 (53 %)	23 (47 %)	75 (51%)
Soweto	47 (47 %)	26 (53 %)	73 (49%)
School attendance	72 (73%)	39 (80%)	111 (75%)
Highest completed grade (median, IQR)	10 (10-12)	10 (9-11)	10 (9-12)
Attending tertiary education	9 (9 %)	6 (12 %)	15 (10%)
Household			
Living with mother and/or father	82 (83%)	37 (76%)	119 (80%)
Consistent condom use in the last year	70 (71%)	30 (61%)	100 (67%)
Condom use (last sexual act)	70 (71%)	38 (76%)	108 (74%)
Any positive STI test	50 (51%)	10 (20%)	60 (41%)
Multiple partners in last year	22 (22%)	27 (55%)	49 (33%)
Had a partner > 5 years older in last year	24 (24%)	6 (12%)	30 (20%)
Transactional sex in last year	4 (4%)	1 (2%)	5 (3%)

Figure 3. Consort Diagram for CHAMPS: Pilot study B: "PlusPills"

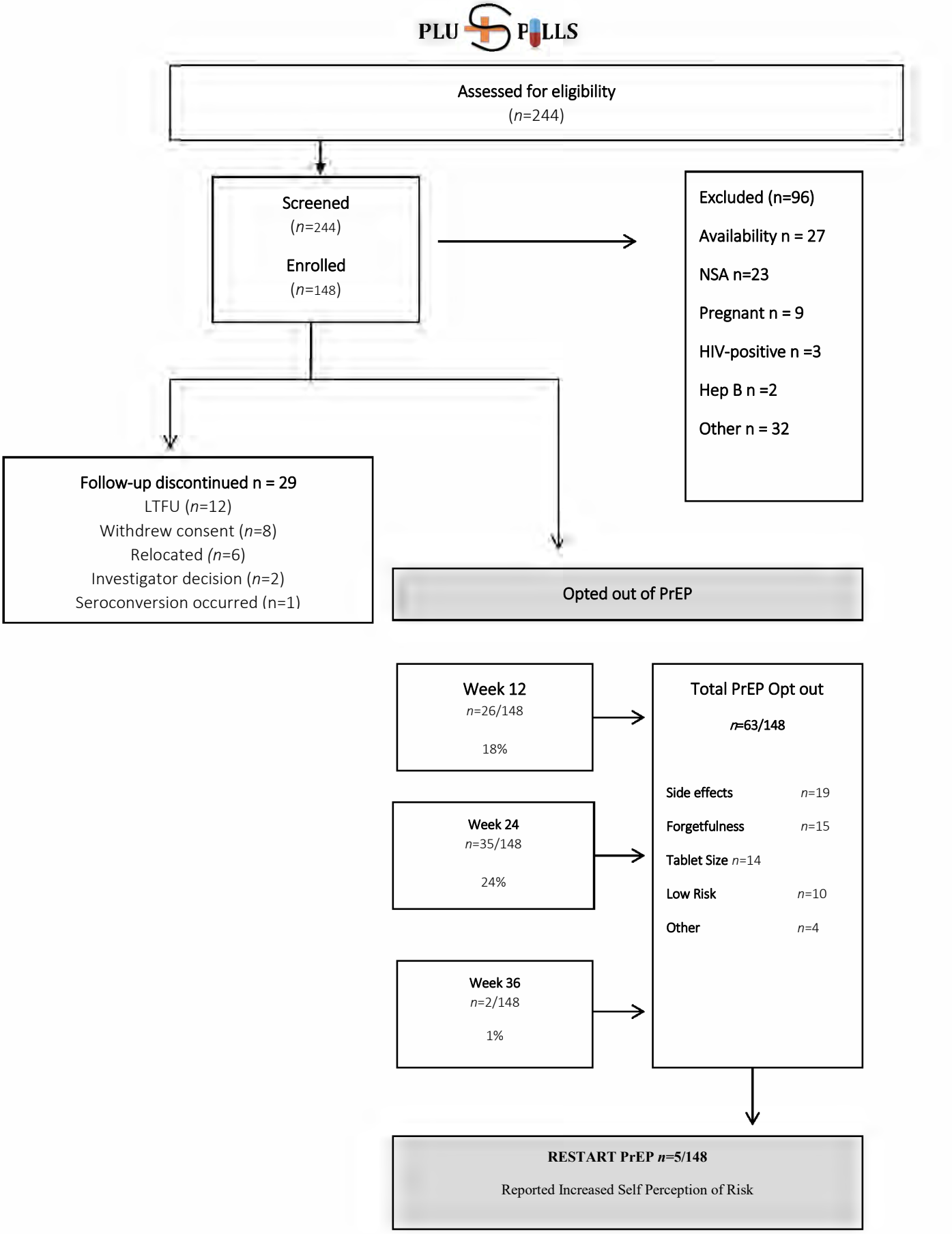

Figure 4. TFV-DP levels by week for CHAMPS: Pilot study B: "PlusPills"

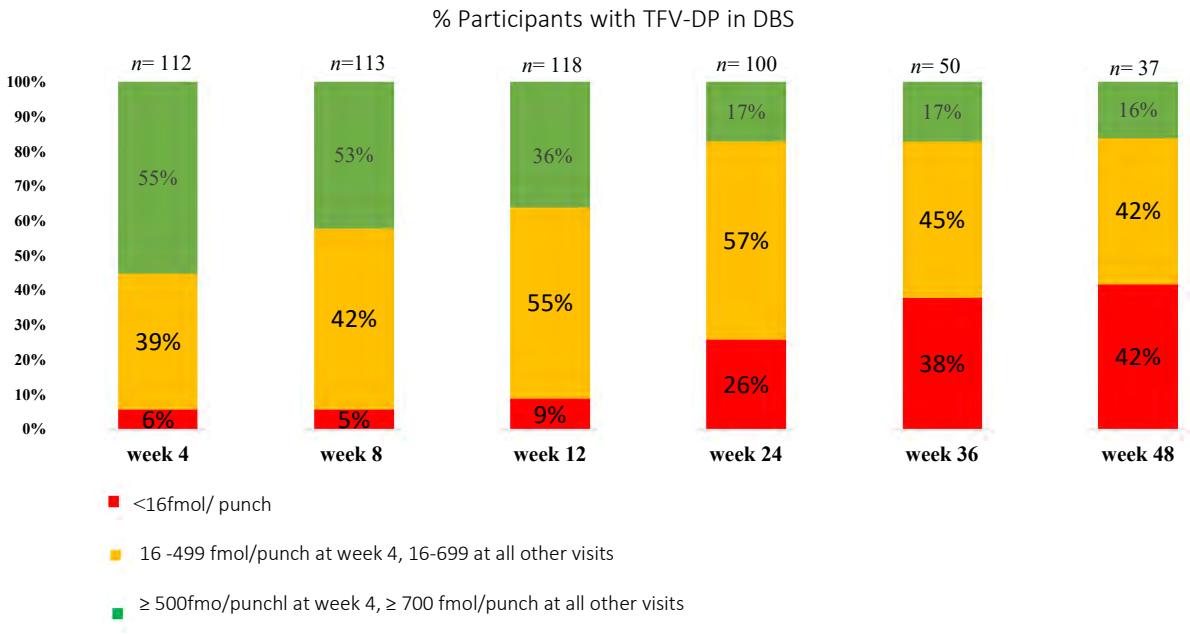

Table 4. STI prevalence by sex

	Female			Male			All		
Characteristic	Baseline (*n*=99)	W-12 (*n*=82)	W-48 (*n*=58)	Baseline (*n*=49)	W-12 (*n*=42)	W-48 (*n*=33)	Baseline (*n*=148)	W-12 (*n*=124)	W-48 (*n*=91)
Chlamydia	38 (38%)	18 (22%)	23 (40%)	7 (14%)	3 (7%)	1 (3%)	45 (30%)	21 (17%)	24 (26%)
Gonorrhoea	6 (6%)	8 (10%)	6 (10%)	1 (2%)	0	0	8 (5%)	8 (6%)	6 (7%)
Herpes	20 (20%)	20 (24 %)	18 (31%)	4 (8%)	5 (12%)	6 (18%)	24 (16%)	25 (20%)	23 (25%)
Any	50 (51%)	29 (35%)	29 (50%)	10 (20%)	6 (14%)	6 (18%)	60 (41%)	35 (28%)	37 (41%)

Table 5. Univariate factor model and Multivariable mixed-effects logistic regression model for high adherence (TFV- DP levels ≥ 700 fmol/punch)

	Univariate model			Multivariable Model		
Factor	OR	Confidence interval	P value	Adjusted OR	Confidence interval	P value
Consistent condom use	1.32	0.66 – 2.67	0.42			
Transactional sex	1.34	0.5-3.59	0.56			
Anal Sex	0.32	0.074-1.4	0.13			
STI at baseline	0.64	0.33-1.27	0.2			
Sexual debut in years	0.99	0.92 – 1.06	0.8			
>1 sex partner	1.3	0.76- 1.5	0.21			
Time in weeks	0.89	0.86 – 0.92	0.001	0.89	0.86 - 0.92	0.001
Age in years	0.65	0.5-0.85	0.002	0.57	0.40 – 0.82	0.003
Gender (male)	0.73	0.36- 1.51	0.39	0.55	0.20 – 1.47	0.3
Site (Soweto)	1.36	0.69- 2.68	0.38	1.5	0.62 – 3.91	0.34

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PART C: APPENDICES

Ethics approval for the Dissertation

UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee

Room E52-24 Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 406 6338 • **Facsimile** [021] 406 6411
Email: shuretta.thomas@uct.ac.za
Website: www.health.uct.ac.za/research/humanethics/forms

21 September 2020

HREC REF: 260/2014

Prof LG Bekker
Desmond Tutu HIV Foundation
IIDMM

Dear Prof Bekker

PROJECT TITLE: 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-MASTERS CANDIDATE-DR K GILL – GLLKAT003

Thank you for your very considered response to the Faculty of Health Sciences Human Research Ethics Committee dated 24th Jul 2014.

It is a pleasure to inform you that the HREC has **formally approved** the above-mentioned study.

Approval is granted for one year until the 30th August 2015.

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.
(Forms can be found on our website: www.health.uct.ac.za/fhs/research/humanethics/forms)

The Following documentation is noted and approved:

- Study Protocol version 1.0 dated July 2020 and appendices
- Budget summary
- Section 13 of MCC application
- Truvada IB and PI, sixth edition, 05 August 2013
- Synopsis
- PI and Key investigator's CVs, GCP certificates and Declaration
- Informed consent forms
    - Adolescent assent/consent form version 1.0
    - Legal guardian consent from version 2.0
    - Focus group adolescent assent/consent form version 1.0
    - Focus group legal guardian consent form version 1.0

We acknowledge that the student: Dr Katherine Gill – GLLKAT003 will also be involved in this study.

Please quote the HREC REF in all your correspondence.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please quote the HREC REF in all your correspondence.

Yours sincerely

PROFESSOR MARC BLOCKMAN
CHAIRPERSON, FHS HUMAN RESEARCH ETHICS COMMITTEE

HREC REF 260/2014sa

Case report forms

Case report form Demographics

Visit	Participant	Visit date
☐ **Screening**	PID INITIALS	D D M M M Y Y
	Site ☐ **PHRU** ☐ **DTHF**	

DEMOGRAPHICS

Date of birth			**Age (years)**		
Gender	☐ Male	☐ Female			
Race*	☐ Asian	☐ Black	☐ White	☐ Mixed race	☐ Other
If other, specify →					
Who do you live with?	☐ Mother	☐ Grandmother	☐ Female Guardian		
	☐ Father	☐ Grandfather	☐ Male Guardian		
If other, specify →					
Are you currently attending *school*	☐ Yes	☐ No	**Highest grade *completed***		
			Or	☐ Never attended school	
Are you currently attending a *tertiary* education institution	☐ Yes	☐ No	**If yes, please give details**		
If you are <u>not</u> currently attending school or a tertiary institution are you…	☐ At home		☐ Working	☐ Other	
			Staff Initials		
			Date		

Case report form for sexual behaviour at baseline

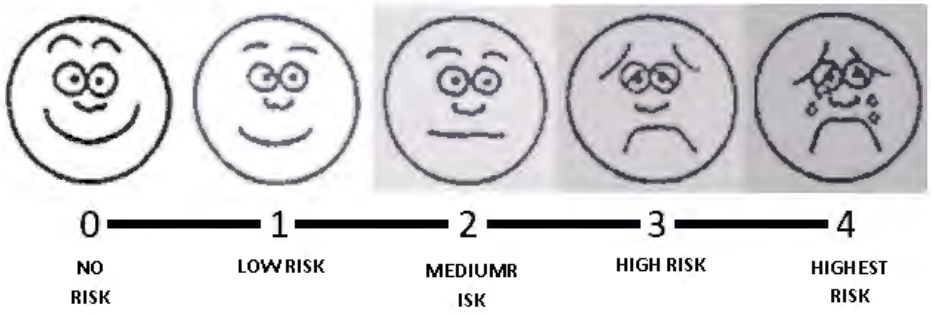
Visit	Participant	Visit date
☐ **Enrolment**	PID | INITIALS	D D M M M Y Y
	Site ☐ **PHRU** ☐ **DTHF**	

Sexual Risk Behaviour Questionnaire – Baseline

1. Have you ever had sex? (Anal sex– where the penis is put inside the anus– or vaginal sex – where the penis is put inside the vagina)	☐ Yes	☐ No → ***NOT eligible***
2. How old were you when you first had sex?		
3. Do you have any sex partners?	☐ Yes	☐ No → *skip to Q6*
4. If yes to Q3, how many sex partners do you have?	☐ One partner	☐ More than one partner
5. Is/are your partner/s aware that you are taking part in this study?	☐ Yes	☐ No

6. How at RISK are you of being infected with HIV compared to other adolescents in your community (e.g. other adolescents who live in Masiphumelele/Soweto)?				
☐ Much Less RISK	☐ Less RISK	☐ The Same RISK	☐ More RISK	☐ Much More RISK
7. How at RISK are you of being infected with HIV compared to others adolescents who live in other LOCAL communities (e.g. other adolescents who live in Khayelitsha/Mamelodi)?				
☐ Much Less RISK	☐ Less RISK	☐ The Same RISK	☐ More RISK	☐ Much More RISK
8. How at RISK are you of being infected with HIV compared to others adolescents who live in other GLOBAL communities (e.g. other adolescents who live in London, UK)?				
☐ Much Less RISK	☐ Less RISK	☐ The Same RISK	☐ More RISK	☐ Much More RISK
9. If it concerns your health, do you see yourself as someone who avoids risk?				
☐ No, Strongly Disagree	☐ No, Disagree	☐ Not Sure	☐ Yes, Agree	☐ Yes, Strongly Agree

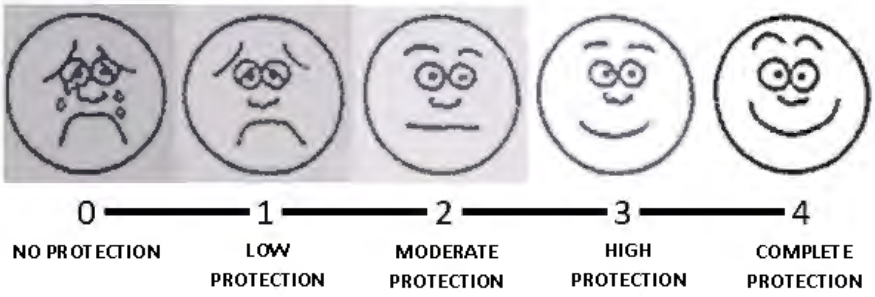
10. Please put a cross on the line below to show your best guess of how at RISK you are of being infected with HIV. 0 means you are at NO RISK; 1 means you are at LOW RISK; 2 means you are at MEDIUM RISK; 3 means you are at HIGH RISK; 4 means you are at the HIGHEST RISK.



11. Different protective strategies have different levels of protection against HIV and STIs. Please indicate the protection methods you use

☐ Condoms	☐ Withdrawal (*Removal of penis from the vagina*)	☐ Abstinence (*Not having sex*)	☐ Other - specify

12. Please put a cross on the line below to show your best guess of how PROTECTED you are against an HIV infection. 0 means you have NO PROTECTION; 1 means you have LOW PROTECTION; 2 means you have MODERATE PROTECTION; 3 means you have HIGH PROTECTION; 4 means you are have COMPLETE PROTECTION.



Skip to Q19 if no current partners

13. Have all of your current partners tested for HIV? *(Unknown partner status)*

☐ No → skip to Q15	☐ Don't think so	☐ Not sure	☐ I think so	☐ Yes

14. Are any of your sexual partners HIV positive? *(Discordance)*

☐ No	☐ Don't think so	☐ Not sure	☐ I think so	☐ Yes

15. Have you used condoms (male or female condoms) every time you had sex? *(Unprotected sex)*				
☐ No	☐ Don't think so	☐ Not sure	☐ I think so	☐ Yes
16. Have you had more than one sexual partner? *(Multiple partners)*				
☐ No	☐ Don't think so	☐ Not sure	☐ I think so	☐ Yes
17. Has/have your partner/s had more than one sexual partner? *(Multiple partners)*				
☐ No	☐ Don't think so	☐ Not sure	☐ I think so	☐ Yes
18. Have you ever had a partner 5 years or more, older than you? *(Intergenerational sex)*				
☐ No	☐ Don't think so	☐ Not sure	☐ I think so	☐ Yes
19. Have you had anal sex (where the penis is put inside the anus)? *(Anal sex)*				
☐ No	☐ Don't think so	☐ Not sure	☐ I think so	☐ Yes
20. Have you had sex with someone for food, airtime, money, clothes, a place to stay etc.? *(Transactional sex)*				
☐ No	☐ Don't think so	☐ Not sure	☐ I think so	☐ Yes
21. Have you or your partner had an STI in the last 6 months? *(STIs)*				
☐ No	☐ Don't think so	☐ Not sure	☐ I think so	☐ Yes
22. Have you injected drugs, had a tattoo, needed blood product? *(Bloods)*				
☐ No	☐ Don't think so	☐ Not sure	☐ I think so	☐ Yes
23. Asking my partner to use a condom would have a bad effect on the relationship *(No count)*				
☐ No	☐ Don't think so	☐ Not sure	☐ I think so	☐ Yes
24. Have you used alcohol in the past 12 months?				
☐ No → skip to Q25	☐ Don't think so	☐ Not sure	☐ I think so	☐ Yes

24.1 If yes, on average how many days a week do you drink alcohol?							
☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7
24.2 On an average day, how many alcoholic drinks do you have? *Please select below*							
☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7 or more

25. Have you used recreational drugs (drugs that are not for treatment of a medical condition) in the past 12 months				
☐ No	☐ Don't think so	☐ Not sure	☐ I think so	☐ Yes → specify
25.1 If yes, please specify the type of recreational drugs used				

26. In the past 12 months, how many people have you had sexual intercourse with?							
☐ 0 → skip to Q29	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7 or more
27. How many NEW sex partners did you have during the past 12 months?							
☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7 or more
28. On average how many times do you have sex per week?							
☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7 or more

29. Was a condom (male or female condom) used the last time you had sex?				
☐ No	☐ Don't think so	☐ Not sure	☐ I think so	☐ Yes
30. Do you think a properly used condom is effective for PROTECTION against an HIV infection?				
☐ No, it isn't effective at all	☐ No, it is not very effective	☐ Not sure	☐ Yes, it is slightly effective	☐ Yes, it is completely effective
31. How often do you use a condom?				
☐ Never → skip to Q31.2	☐ Almost never	☐ Not sure	☐ Almost always	☐ Always → do Q31.1, then skip Q31.2

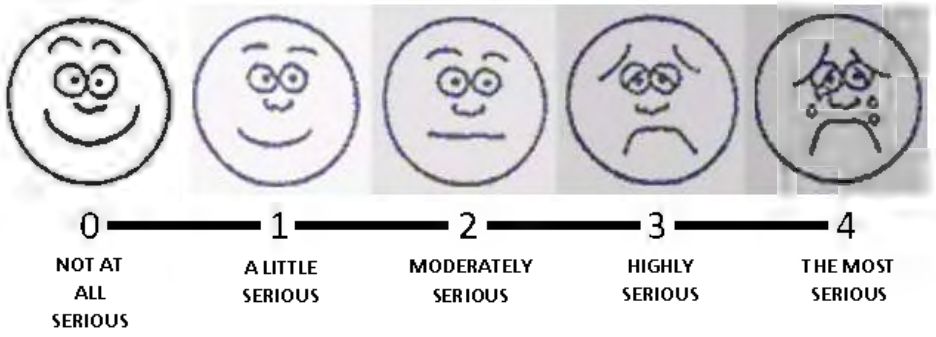
31.1 When you have used a condom, why did you use a condom?	Yes	No
To prevent pregnancy	☐	☐
To prevent HIV infection and STI's	☐	☐
It makes sex more pleasurable	☐	☐
For some other reason	☐	☐
Explain other reason		

31.2 When you have not used a condom, why do you not use a condom?	Yes	No
It makes sex less pleasurable	☐	☐
Condoms aren't available	☐	☐
Condoms ruin the experience	☐	☐
My partner does not want to use condoms	☐	☐
For some other reason	☐	☐
Explain other reason		

32. How confident are you that you can prevent an HIV infection?

☐ No Confident at All	☐ Slightly Confident	☐ Moderately Confident	☐ Highly Confident	☐ Completely Confident

33. Please put a cross on the line below to show how SERIOUS being infected with HIV would be to you. 0 means an HIV infection would be NOT AT ALL SERIOUS; 1 means it would be A LITTLE SERIOUS; 2 means it would be MODERATELY SERIOUS; 3 means it would be HIGHLY SERIOUS; 4 means it would be THE MOST SERIOUS thing that could possibly happen to you.



34. How SERIOUS would being infected with HIV be compared to getting TB (*Tuberculosis*)?

☐ Much Less SERIOUS	☐ Less SERIOUS	☐ Equally SERIOUS	☐ More SERIOUS	☐ Much More SERIOUS

35. How SERIOUS would being infected with HIV be compared to getting Hypertension (*High Blood*)?

☐ Much Less SERIOUS	☐ Less SERIOUS	☐ Equally SERIOUS	☐ More SERIOUS	☐ Much More SERIOUS

36. How SERIOUS would being infected with HIV be compared to getting cancer?				
☐ Much Less SERIOUS	☐ Less SERIOUS	☐ Equally SERIOUS	☐ More SERIOUS	☐ Much More SERIOUS
37. How SERIOUS would being infected with HIV be compared to getting another STI (e.g. *chlamydia*)?				
☐ Much Less SERIOUS	☐ Less SERIOUS	☐ Equally SERIOUS	☐ More SERIOUS	☐ Much More SERIOUS
Skip to Q39 if the participant is a male **38. How SERIOUS would being infected with HIV be compared to becoming pregnant?**				
☐ Much Less SERIOUS	☐ Less SERIOUS	☐ Equally SERIOUS	☐ More SERIOUS	☐ Much More SERIOUS
39. Have you personally known someone who has been infected with HIV?			☐ Yes	☐ No
40. Have you changed your sexual behaviour in the last 12 months?			☐ Yes	☐ No →skip to end
40.1 If yes, what sexual behaviour have you changed?			Yes	No
I use condoms more often			☐	☐
I use condoms less often			☐	☐
I have sex more often			☐	☐
I have sex less often			☐	☐
I have anal sex more often			☐	☐
I have anal sex less often			☐	☐
I use contraception more often			☐	☐
I use contraception less often			☐	☐
Other			☐	☐
If other, please specify				
This is the end of the Sexual Risk Behaviour survey for participants. Thank you for your time and participation in the survey. Please feel free to ask any questions that you might have.				
			Staff Initials	
			Date	

Case Report forms: Acceptability

PRODUCT ACCEPTABILITY (1)

1. Do you like the Truvada Pill?	☐ Yes	☐ No
2. How do you find taking a pill every day?	☐ Easy	☐ Difficult
3. How do you find remembering to take the pill each day	☐ Easy	☐ Difficult
4. What do you like about the Truvada pill? *(Choose <u>all</u> that apply)*	Yes	
It may protect me against HIV infection	☐	
It can be taken without my sexual partner's knowledge	☐	
It is easy to use	☐	
The method is under my control	☐	
It does not interrupt sex	☐	
The pill can be taken any time of day	☐	
I don't have to change my actions before or after sex	☐	
Other reason	☐	
If other reason(s), specify		
None, I did not like the pill at all	☐	
Never used the pill	☐	
5. What do you not like about the Truvada pill? *(Choose <u>all</u> that apply)*	Yes	
I have to take a pill every day	☐	
It tastes bad	☐	
It is big and hard to swallow	☐	
I can't hide it easily from my sexual partner/family	☐	
I feel badly hiding my pills from my sexual partner/family	☐	
It makes sex less pleasurable	☐	
I have to go to the clinic pharmacy to collect more medication	☐	
It makes my stomach upset	☐	
It makes me feel like I am going to vomit	☐	
It gives me a headache	☐	

It makes me dizzy	☐
I am worried people will think I am HIV-positive if they see my pills	☐
Taking the pills has other side effects, specify	☐
If other, specify other side effects	
Other	☐
If other, specify	
None, I do not dislike anything about the pills	☐
6. How many sexual partners have you had in the past month?	

Regular sexual partner

7. Was your regular sexual partner aware that you were taking the pills for HIV prevention?

☐ Yes	☐ No	☐ **I do not have a regular sexual partner** → Skip to Q9

8. If yes, what did your regular sexual partner think about the pills? *(only choose <u>one</u> answer)*	Yes
He/she liked it	☐
He/she did not like it	☐
He/she knew I was taking the pills but had no reaction	☐
I don't know	☐
Other	☐
If other, specify	

The following questions will be based on the two casual sexual partners whom you see most often

Casual sexual partner 1

9. Was your casual sexual partner aware that you were taking the pills for HIV prevention?

☐ Yes	☐ No → skip to end	☐ **I don't have a casual sexual partner** → skip to end

10. If yes, what did your casual sexual partner think about the pills? *(only choose <u>one</u> answer)*	Yes
He/she liked it	☐
He/she did not like it	☐
He/she knew I was taking the pills but had no reaction	☐
I don't know	☐
Other	☐

If other, specify	

Casual sexual partner 2

11. Was your casual sexual partner aware that you were taking the pills for HIV prevention?

☐ Yes	☐ No → skip to end	☐ **I don't have a 2nd casual sexual partner** → skip to end

12. If yes, what did your casual sexual partner think about the pills? *(only choose <u>one</u> answer)*	Yes
He/she liked it	☐
He/she did not like it	☐
He/she knew I was taking the pills but had no reaction	☐
I don't know	☐
Other	☐
If other, specify	

Thank you. This is the end of the CRF.

Staff Initials	
Date	

Guardian Consent Form for the Pluspills study

LEGAL GUARDIAN CONSENT FORM

LEGAL GUARDIAN CONSENT FORM FOR SCREENING AND ENROLMENT

Study Title: 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.

Study Number: DAIDS ES ID 11931

Study Sponsor: Desmond Tutu HIV Foundation

Principal Investigator	**Prof Linda-Gail Bekker**
Site Address	**Desmond Tutu HIV Foundation**
	Guinea Fowl Road
	Masiphumelele

Site Telephone Number **021 785 5454**

To the potential participant: *This consent form may contain words that you do not understand. To help you understand these words we have included simpler words in brackets after complex ones. Please ask the study doctor or the study staff to explain any words or information that you do not clearly understand. You may take home* ***an unsigned copy of this consent*** *form to think about or discuss with family or friends* ***before making your decision.***

INTRODUCTION

The Desmond Tutu HIV Foundation is doing a study of young people and a medication called Truvada, and you and your child are being invited to take part.

Before agreeing to be screened for enrolment into the study, it is important that you read and understand the following explanation of the purpose (reason for) of the study, the study procedures (what will happen during the study), benefits, risks, and you and your child's right to withdraw from the study at any time.

This form has information to help you decide if you want your child to participate. If you decide for your child to take part you will sign this form because your child is younger than 18 years. Your child will also need to sign a form. If your child turns 18 while she/he is participating in the study she/he will sign another form because she/he will be able to consent without your permission.

ABOUT THE STUDY

South African adolescents are at risk for HIV infection. Rates of HIV infection, mostly through sexual transmission, among adolescents are increasing rapidly. Therefore, prevention methods to lower HIV risk among adolescents are urgently needed.

This is part of a bigger project called The CHAMPS (Choices for HIV Adolescent Methods of Prevention in South Africa) project. In this project we are assessing whether an HIV prevention "menu" can be developed for adolescents in South Africa. What we mean by this is that it may mean that people can apply different prevention tools to their lives, e.g. Condoms as well as PrEP. The CHAMPS project is comprised of three pilot studies rolled out as a series of small, focused, interrelated protocols and will help us understand how your child may choose to use various prevention tools when they know what tools are on offer.

The purpose of this research study is to find out whether adolescents will use the medication called Truvada as an HIV prevention tool. Truvada is a type of antiretroviral (ARV) medication that is commonly used to treat HIV when used in combination with another drug. Truvada is not effective when used alone in the treatment of HIV infection in HIV positive individuals. Truvada is now also being tested as a pre-exposure prophylaxis or PrEP. PrEP is an experimental approach

that uses ARVs to prevent HIV infection in HIV-negative people—it is used by HIV negative persons to protect them against possible infection with HIV.

We do not know the effects of PrEP in adolescents between the ages of 15 and 19 years, and we do not know if it protects adolescents from getting HIV. Because of this, the South African Medicines Control Council (MCC) has not yet approved Truvada for preventing HIV infection in adolescents. The MCC however, has given permission for a study to be conducted to establish how safe it is for adolescents to use Truvada and whether they would find it acceptable to use the medication as instructed.

A number of studies have been conducted to show that Truvada is safe in HIV uninfected men and women over 18 years of age. Four studies, whose results were announced in 2010, 2011 and 2013, showed that HIV infection among adult men and women can be prevented by taking Truvada daily. These adult studies involved adult males and females, men who have sex with men (in South Africa) and sero-discordant couples (where one partner is HIV positive and the other is HIV negative) as well as people who inject drugs. Adult studies have shown that even though the risk of HIV was reduced, HIV infections still occurred. We do not know whether it is safe yet nor can we say whether it can stop some HIV infections in adolescents between the ages of 15 and 19 years.

We will enroll 75 adolescents aged 15 to 19 years at the Masiphumelele Clinic in Cape Town and 75 adolescents at the Perinatal HIV Research Unit (PHRU) site which is based in Kliptown, located near Soweto, close to Johannesburg. We want to answer several questions during the study:

- Will adolescents use the study medication (Truvada) in the way in which they have been told to take it?
- What helps young people adhere to, or keep taking, the study medication?
- How do young people's relationships, attitudes, and sexual behaviour change over time, while taking this medication?

- Is the study medication (Truvada) safe for young people 15-19 years old?

To see if your child can join this study, there are a number of screening procedures we need to do. These include:

- Interview questions
- Urine tests
- Blood tests
- Physical examination

Your child can **not** participate in this study if they are:

- HIV positive
- Hepatitis B positive
- Currently taking part in another HIV prevention study that involves medication
- (For females) Pregnant or planning on becoming pregnant or breastfeeding
- Has a job or other obligations that would require long absences from the area (> 4 weeks at a time)

SCREENING PROCEDURES

In order to find out if your child is eligible to participate in the study, you and your child will be asked to consent to some screening tests, once they are fully explained to both of you. These tests may take more than one visit and may take 1-2 hours to complete. All screening tests must be done within 40 days. If all tests are not done within 40 days, and you and your child still want to find out if your child is eligible for the study, you will both have to be re-consented and your child must begin the screening tests again.

The following procedures will occur at the screening visit:

- An identification number will be assigned to your child.

- Your child will be counseled about HIV before having an HIV test. We will take some blood from your child's finger (about a drop) for the HIV test. Your child will be told their result as soon as it is available at this visit. Your child will talk with the study staff about the meaning of their result and how they feel about it.

- If the test shows that your child has HIV, they cannot continue with the screening nor take part in the study. Your child will receive counseling and referral for HIV care and treatment. Your child will be encouraged to share their results with an adult whom they trust. If their test results show that your child does not have HIV, they may continue with the screening.

- A trained medical staff member will conduct a full physical examination of your child.

- Your child will also need to answer questions about themself, which will include where they live, their health and medical history, and personal questions about their relationships and sexual behaviour. Your child cannot take part in this study if they are not sexually active. You will therefore be aware that your child is sexually active if they do take part.

- If your child is female, the study doctor and/or study nurse will ask your child to give some urine for a pregnancy test. Your daughter will be required to take a low dose hormonal birth control (the pill or injection) during the study, which we will provide. She can receive information about contraception and access to contraceptives without your consent, and we will counsel her to practice safer sex. If she is pregnant, she cannot take part in the study. We will not tell you but will encourage her to tell an adult she can trust. We will counsel her about her options in relation to her pregnancy.

- We will take one tube, about 5 mls (about 1 teaspoon) of blood with a needle from your child's arm to check how well their kidneys and liver are working as well as checking their general health.

- We will take two tubes, about 10 mls (about 2 teaspoons) of blood to check for Hepatitis B infection. Hepatitis B is a virus that causes inflammation of the liver. This infection is spread in a similar way as the HIV virus, that is, from mother to child, through contaminated blood, and in some cases through sexual transmission. Tenofovir, one of the active ingredients in the study medication, can be used to treat both Hepatitis B and HIV. The blood will be sent to a laboratory for testing and your child will be provided with their test results. If we find that your child has Hepatitis B infection, they may not participate in the study. Your child will receive appropriate counselling and referrals. If we find that your child does not have Hepatitis B infection, the study staff will vaccinate your child (give your child three separate injections) that will prevent this disease in the future.

- Your child will be tested for, and counseled about, other infections that may be passed on to them during sex, including herpes (HSV-2), chlamydia, and gonorrhea, which are sexually transmitted infections (STIs). If your child is having health problems that may be due to these infections, we will help them get the appropriate medical care.

    - Chlamydia, and gonorrhea are bacterial infections. If a person takes medicines, they will go away completely. We will test your child for chlamydia and gonorrhea at screening, at Month 3, and at their final study visit.

    - Herpes is a virus which may cause painful sores in the genital area. However, herpes may cause no symptoms at all. If painful sores from herpes arise, they can be treated with medicine. The herpes

virus always stays with a person and may be spread to their sexual partners. We will test your child for herpes at screening, month 3 and at their final study visit. If you child has sores, we will help them get medicine to help the sores go away.

- Your child will be asked about medications they are currently taking, previous medical problems they may have had, and will have a physical examination. Your child should be open with their study doctor or study nurse regarding their health history, since by not disclosing all the information about their health, they may put themselves at risk by participating in this study. They will be given appropriate feedback and access to care, should these procedures reveal important information about their health.
- If all the tests show that your child is eligible to participate in the study, we will explain the study to you and your child again and check that you both are still willing for your child to continue in the study and answer any questions you have.
- Your child may be given a vaccine injection to protect against Hepatitis B, if they have not been previously vaccinated.
- If you and your child are in agreement and decide for your child to be enrolled in the study, you will be asked to sign this document to confirm your understanding of and participation in the study. You will be given a copy of this Guardian Consent Form for Screening and Enrolment Version 3.0 dated 24 July 2015 to keep.
- After reading this document, the study doctor and/or study nurse will ask your child to complete a short quiz in order to make sure that you understand what you have consented to for enrolment. If your child gets enough of the answers right, your child will be able to continue with enrolment. Your child has three chances for this. If after three chances your child has still not got enough answers right, your child will not be

able to continue in the study. This is to make sure that you are making an informed decision about taking part.

- Both you and your child need to be in agreement in order for your child to be enrolled. Your child will also be asked to read or will have an information form read to them. If they agree, they will be asked to sign a copy and will be given a copy to take home. You will also need to complete the test to ensure that you understand what you are consenting to when your child takes part in the study.
- Even though you must give consent for your child to be enrolled in the study, your child will be giving their own assent to take part and will consent independently for tests that we will perform and treatment that she/he may receive during the study. We will tell you more about these tests in the next sections.
- Your child's decision to continue in the study or to withdraw will not affect your child's regular care or harm your child's relationship with the study doctor and/or study nurse.

ENROLMENT VISIT

This visit may take about 3 hours to complete. In addition to the above procedures, the following will happen:

- Study staff will provide your child with any test results received since the screening visit(s).
- Study staff will ask your child to provide information on their health history and any medical events that have taken place since the screening visit.
- Study staff will take some blood from your child's finger (about a drop) for the HIV test. Your child will be told their result as soon as it is available at this visit. Your child will receive pre- and post-test counseling, which will include risk reduction counseling.

- Female participants will be asked to give some urine at each visit for a pregnancy test. Study staff will talk with your child about her choices and will ask about her use of contraception at each study visit.
- Your child will also need to answer personal questions about their relationships, attitudes, and sexual behaviour.
- Study staff will ask your child to update the information on where you live and on how they can keep in contact with you and your child.
- We will provide your child with enough condoms until the next study visit and discuss how to use them and how your child can protect himself/herself from becoming infected with HIV.
- Your child may be given a vaccine injection to protect against Hepatitis B, if they have not been previously vaccinated.
- Your child will be asked to take the study medication "Truvada" – one pill every day of the week for the next month. They will be given enough pills for 30 days.
- Your child will be counseled about the need for adherence.Throughout the study your child will also have blood taken to test how much Truvada there actually is in your child's blood. This result will be available at the next study visit. Your child will be asked whether he/she wishes to receive this result or whether they prefer to be counseled without this result. Research staff will give the results and counsel your child accordingly. Those who choose not to get these results will still receive standard counseling on how and why they should take the pills.

FOLLOW-UP VISITS

Your child will complete monthly follow-up visits (approximately every 30 days) during the first three months of the study, after he/she enrols. These follow-up visits will take about 60 to 90 minutes and the following will occur:

- Study staff will take some blood from your child's finger (about a drop) for the HIV test. Your child will be told their result as soon as it is available at this visit. Your child will talk with the study staff about the meaning of their result and how they feel about it. Your child will receive pre- and post-test counseling, which will include risk reduction counseling.
- Female participants will be asked to give some urine at each visit for a pregnancy test. If your daughter becomes pregnant, it is necessary that she stops using the medication. Study staff will talk with your child about her choices and will ask about her use of contraception at each study visit.
- Your child will also need to answer personal questions about their relationships, attitudes, and sexual behaviour.
- Study staff will ask your child to update the information on where they live and on how staff can keep in contact with both of you.
- We will provide your child with enough condoms until the next study visit and discuss how to use them and how they can protect themselves from becoming infected with HIV.
- Should your child have any symptoms that cause concern, they will be asked to have a physical examination. Every 3 months, your child will receive a full physical examination.
- Your child will be given study medication (Truvada) and asked to take a pill a day every day until the next scheduled visit. They will be re-issued with medication at every scheduled visit for 3 months.
- Study staff will ask your child about how well they have taken the medication and any side effects or difficulties that may have occurred.
- Study staff will also collect some blood, approximately 5 mls (1 teaspoon) from your child to check their general health and to determine the amount of study medication in their blood. Results from some of these

blood tests will be given to participants who wish to hear these results, in order for the research team to understand if that affects their usage of the study medication.

FOLLOW-UP VISITS (MONTHS 4-12)

At the 3-month visit, your child will be offered study medication, but will be allowed to choose whether they prefer to continue with it or stop it. It is your child's choice whether or not to take this medication. Your child may decide that they do not want to take study medication, or your child may choose to take the study medication at a later time. Your child will be asked about their choice every 3 months by the study staff.

If your child chooses not to take the study medication at any time, your child can still remain in the study and will be asked to attend all visits.

At the end of month 3, your child will begin 3 monthly visits, approximately every 90 days for the remaining 9 months.

Participants will receive blood tests throughout the study that measure the amount of study medication in their blood. These tests are called Dried Blood Spots and involve pricking your child's vein, taking a small amount of their blood, and drying a blood spot on a special piece of paper. These tests will occur at all study visits, and at the next visit , your child will be shown the result of the test if they wish to receive this – it is their choice. Either way, they will be counseled about the use of the Truvada pills.

For study participants who agree to take the study medication, the following procedures will also be conducted during follow up visits during Month 4-12:

- Study staff will take some blood from your child's finger (about a drop) for the HIV test. Your child will be told their result as soon as it is available at this visit. Your child will talk with the study staff about the meaning of their result and how they feel about it. Your child will receive pre- and post-test counseling, which will include risk reduction counseling.

- Your child will have urine testing
- Female participants will be asked to give some urine at each visit for a pregnancy test. If your child becomes pregnant, it is necessary that she stops using the medication. Study staff will talk with her about her choices and will ask about her use of contraception at each study visit.
- Your child will also need to answer personal questions about their relationships, attitudes, and sexual behaviour.
- Study staff will ask your child to update the information on where they live and on how they can keep in contact with your child.
- Your child will be given enough study medication until the next study visit and instructed about how to take it.
- We will remind your child to use their study medication daily by SMS (if they choose to receive it) and ask your child if they are experiencing any problems using the medication.
- Your child must bring back all unused study medication to the study staff.
- We will provide your child with enough condoms until the next study visit and discuss how to use them and how your child can protect themselves from becoming infected with HIV.
- Should your child have any symptoms that cause concern, they will be asked to have a physical examination. For the rest of the study, your child will receive a full physical examination every 3 months.
- Study staff will also collect some blood, approximately 5 mls (1 teaspoon) to check your child's general health and to determine the amount of study medication in their blood. Results from some of these blood tests will be given to those who wish, in order for the research team to understand if that affects their usage of the study medication.

- Every three months, your child will be asked by a study staff member again about whether or not h/she wishes to take the study medication. Your child can either stop or start the study medication at these visits.
- At each adherence counseling session your child will be asked whether they wish to receive blood drug level results. This is voluntary. We will ask your child why he/she has made the choice they do.
- Your child will be asked about any social harms or benefits they have experienced as a result of participating in the study.

SECOND FINAL STUDY VISIT

These procedures will also be done at an early discontinuation visit

- Your child's second final study visit will be at Month 12 (Week 48).
- Study staff will take some blood from your child's finger (about a drop) for the HIV test. You child will be told their result as soon as it is available at this visit.
- Urine testing in your child will be performed.
- Female participants will be asked to give some urine at each visit for a pregnancy test.
- Study staff will test your child for herpes (HSV-2), chlamydia, and gonorrhea.
- Study staff will ask your child personal questions about their relationships, attitudes, sexual behavior, and opinions about the study medication.
- Study staff will also collect some blood, approximately 5 mls (1 teaspoon) to check your child's general health and to determine the amount of study medication in their blood.

FINAL STUDY VISIT (week 52)

- Study staff will ask your child some personal questions about your child's relationships, attitudes, sexual behavior and opinions about the study medication.
- All final and outstanding blood results will be returned.

FOCUS GROUPS

- Between Month 11 and 12, some participants will be randomly selected to attend a focus discussion group about their experiences with taking the medication, their likes, dislikes, where they would like to access it if it is licensed and how they think they would use it. Your child may be asked to participate. This is voluntary – your child may decline.

LEAVING THE STUDY

Tell us if you or your child decides to leave the study or if your child stops taking the medication.

You and/or your child are free to leave/withdraw consent from the study at any time and for any reason. Your child's care at this clinic and their legal rights will not be affected, but it is important for you to let us know.

We will ask your child to come back to the clinic one last time. We may ask to take some blood and urine samples. We will also ask about any personal problems or benefits your child has experienced from being in the study and ask them to complete a questionnaire about why they want to leave the study.

IF YOUR CHILD BECOMES INFECTED WITH HIV DURING THIS STUDY

It is important to identify people with HIV early so that they can get the services that they need.

If the HIV test result is positive, your child will receive counseling from study staff. They will be encouraged to share their test results with an adult they trust. This does not have to be their parent/legal guardian. Your child will also be referred for appropriate care and support services in the community. Your child may be asked to join other studies that may be going on at this study clinic.

Following another pretest information session, a blood sample for CD4 count will be obtained. These tests will provide the doctor with more information about their health, immunity, and the nature of the disease. When your child returns to the clinic for the next interim visit, results of the CD4 count will be discussed and a referral letter to a Primary Health Care facility will be prepared. Your child will be followed up for one year beyond sero-conversion and will have a CD4 at 3 monthly intervals to ensure that initial care is well-managed.

If your child becomes infected with HIV during this study, and this has been confirmed with the procedures described above, your child will be told to stop using the study medication because we are not sure about the effects of the study medication in HIV infected people. Your child will be invited to continue with the remainder of the study visits, and will be supported with disclosure to a trusted adult. A genotype test will be performed on the HIV Virus from your child's blood to help with management.

AT ANY TIME DURING THE STUDY

Your child will be asked to tell the study staff about medical problems your child may have during the study. You or your child can also contact the study staff between regular visits to report these problems. The study staff will examine your child as needed and will either provide or refer your child for medical care that they may need.

If your child is having health problems that may be caused by infections passed during sex, they will be given a physical examination. Your child will get treatment for curable infections passed on to them during sex if they need it. If your child has any infections that their partner may also have, they can bring him or her to the trial site for treatment that may be needed. This will be at no cost to them or their partner.

Your child can have extra counseling and testing for HIV if needed between regular visits. If they wish, their partner can have HIV counseling and testing with them.

Your child or the study staff may request an interim study visit at any time.

During this study your child may also be asked to participate in other sub-studies (studies related to this one). Your child does not have to participate in any sub-studies if they do not want to. You and your child will be given aseparate consent to sign for each sub-study that they wish to participate in.

While your child is in this study, we ask that they please:

- Do not share their study medication with anyone else or use study medication that doesn't belong to them.
- Do not participate in any other study involving other HIV prevention medication - this is important for their own safety:
    - If your child uses other study medication from different studies at the same time and then has a problem that requires medical attention, we will not know which medication has caused the problem.
    - If your child is using study medication from different studies at the same time, we cannot assess which study medication is working.
- Remember that the medication that we are testing has not been proven for safety in adolescents and we do not know if it can prevent HIV infection, so it is important that your child continues to use male and female condoms, and engages in other safer sex behaviours.

CONTACT

Once you and your child join the study, it is very important for us to stay in touch with you and find out how you and your child are doing. We will ask for your name, address, phone number, and other contact information at your child's first study visit. We also will ask for the names and contact information of people whom we may contact if we cannot reach you.

We will ask your child to update this information at each study visit. We will use your contact information to remind your child of scheduled study visits. If your

child misses a visit, we may call you with your permission or send letters or visit your home to find you and your child. We will also try to reach you through the contact people that you list for us. If we talk to these people, we will not tell them why we are trying to reach your child.

RISKS AND/OR DISCOMFORTS OF STUDY PARTICIPATION

Risks of blood draws:

In this study, we will take some blood samples. Blood draws can cause bruising, pain, fainting, soreness, redness, swelling, itching, and (rarely) infection where the needle was put in.

Personal problems/discrimination:

Some participants report personal problems or discrimination because of being in a study. This could happen to your child. Family or friends may worry, get upset or angry, or assume that your child is infected with HIV and treat them badly as a result. If you or your child has bad things happen because of the study, please tell us. We will try to help.

Embarrassment/anxiety:

Your child may feel embarrassed when we ask personal questions about relationships, attitudes, and sex. Your child may feel nervous or scared waiting for their study test results. Your child could feel worried if their test results show that they are infected with HIV, herpes, chlamydia or gonorrhoea. If they are feeling this way, we will try to help her / him feel better.

Risks of someone finding out your personal information:

We will protect you and your child's personal information. The risk of someone seeing your child's personal information, when they should not have done so, is very low. However, if that happened, you both could feel upset and embarrassed. Someone could use the information to treat you and your child badly. We can tell you more about how we will protect your personal information if you would like it.

Side effects from the study medication:

Your child may have side effects from taking the study medication. The most common risks and side effects from the study drug include dizziness, fatigue, difficulty sleeping, depression, strange dreams, diarrhea, nausea (upset

stomach), vomiting, headache, rash and gas. Skin discoloration (small spots or freckles) may also occur.

Less common but more serious risks may include:

- Liver problems
- Kidney problems
- Inflammation of the pancreas
- Anemia (low red blood cells)
- 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)
- Metabolic disorders (changes to lipid and sugar levels in your blood)
- Changes in bone mineral density (thinning bones). This may be made worse if your child is also using injectable hormonal methods of family planning, e.g. nur isterate IMI.
- 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;
- If your child is infected with hepatitis B virus, flare-ups of this infection may occur. We will minimise this risk by screening your child for Hepatitis B and vaccinating them if they are not yet vaccinated or infected.

- Resistance: if your child becomes infected with HIV and is taking Truvada, there is a risk that the HIV virus in your child's blood may change its make up and become resistant to this antiretroviral medication. This means your child would not be able to use this medication for treatment of their HIV. We will try to minimise this risk by making sure your child is not HIV infected when s/he starts the treatment and also by testing her / him for HIV frequently.

- The study medication is investigational (experimental) and there may be other risks or side effects which are unforeseen or unknown. You or your child should immediately contact the study doctor or study nurse if any side effects occur throughout their participation in this study.

We will try to minimize any side effects and/or risks to your child's safety and well-being. Tests will be done to carefully monitor your child's physical and mental health, including their kidney and liver functioning. The study doctor or study nurse will ask your child about any side effects they have experienced at every visit and a full physical exam will be conducted as needed or every 3 months. Your child will be provided with information about how to prevent HIV and will have access to counseling, support, and other social and health-related services as needed.

EARLY TERMINATION/DISCONTINUATION

There are some situations where we would need to stop your child from taking Truvada. These are as follows:

- Toxicity related to Truvada
- Your child needs to take medication that cannot be taken while they are taking Truvada
- Your child becomes HIV infected
- Your child is pregnant/breastfeeding
- Your child has completed the study

- Your child has requested to stop taking Truvada
- Any conditions or clinical reasons that will threaten your child's safety and well-being

There are certain situations where we may discontinue your child's participation in the study. These are as follows:

- We are unable to contact your child after a number of attempts
- Your child is repeatedly not taking Truvada as prescribed
- Your child is pregnant/breastfeeding
- Your child requests to be withdrawn from the study
- You no longer thinks the study is in your child's best interests
- Your child is 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 him/herself or seriously interfere with the validity of study results
- At the discretion of the Independent Ethics Committee, Medicines 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.

BENEFITS OF STUDY PARTICIPATION

- We will give your child condoms and show them how to use them, and counsel them on how to prevent HIV, and provide them with referrals for male circumcision, Post Exposure Prophylaxis or PEP (a medication that someone can take after they might have been exposed to HIV), and reminders that STI treatment may assist in the prevention of HIV.
- Your child will have physical examinations and some lab tests over the course of the study. This may help them to identify health problems that they did not know about. If we find medical problems during these

procedures, we will provide your child with treatment if it is provided at this clinic or we will refer your child to another clinic or services.

- Your child will get counseling and testing for HIV and if they are infected with HIV, they will be referred for medical care, counseling, and other services available to them.
- Your child will receive treatment if they show any symptoms of STIs.
- You and your child's participation in this study will contribute to medical knowledge that may help prevent other adolescents from developing HIV.

PREGNANCY AND CONTRACEPTION (For female participants only)

The risks of the study medication to an unborn baby are not known. Adolescent girls who are pregnant or breastfeeding may not participate in this study. Adolescent girls who become pregnant during the study will remain in the study but will be instructed to stop using the study medication while they are pregnant. Your child must confirm that they are not pregnant now, and that they do not intend to become pregnant during the study. If your child suspects that they have become pregnant during this research study they must notify the study doctor or study nurse immediately.

ALTERNATIVE TREATMENT/METHODS FOR HIV PREVENTION

There are no medications proven to prevent HIV infection in adolescents although medical male circumcision has been shown to reduce infection in young men as young as 15 years. The only known way to prevent HIV infection during sex is to use a condom every time you have sex. Treating STI's may also help. It may also help to give someone post-exposure prophylaxis after they might have been exposed to HIV. That is, if there is a chance that they might have been infected with HIV e.g. during rape, they can be treated afterwards with medication. In order for PEP to work, it needs to be taken within 72 hours of becoming exposed.

There may also be other research studies that are testing ways to prevent HIV infection in this area that your child may be eligible for. However, if your child

agrees to participate in an alternative study on HIV prevention that involves an experimental study medication, your child will not be eligible for participation in this study.

RIGHTS AS A PARTICIPANT IN THIS STUDY

Your child's participation in this study is entirely voluntary and your child can refuse to participate, or stop at any time, without stating any reason. Your child's withdrawal will not affect their access to other medical care. If you or your child chooses to withdraw from this study, your child does not waive any of their legal rights as a patient or a research participant at this site. You and your child will be informed of any trial related new information in case it may impact your willingness for your child to participate.

COSTS AND REIMBURSEMENT FOR STUDY PARTICIPATION

You and your child will not be paid for taking part in this study. However the study specific visits, study medication and laboratory tests related to this study will be at no extra cost to you or your child. Your child will however be reimbursed to cover the costs of transport to and from the clinic and to compensate them for time spent at the clinic. This will be R50 per visit. We will not be able to reimburse your child for visits that are not part of the regular visit schedule.

INSURANCE

The sponsor has taken out insurance from SHA in the event of a trial-related injury, i.e. harm suffered as a result of participation in the trial. The sponsor agrees to pay all reasonable medical expenses in accordance with the Association of the British Pharmaceutical Guidelines (ABPI) in the event of an injury or side-effect resulting directly from your child's participation in the trial. The ABPI guidelines recommend that the sponsor of the study should pay, without you having to prove that the sponsor is at fault, for any injury resulting from your child getting the study medication or from other procedures carried out in accordance with the protocol for this study. The sponsor will not be liable for any

loss, injuries and/or harm that your child may sustain where the loss is caused by the use of unauthorized medicine or substances during the study; any injury that results from your child not following the protocol requirements or the instructions that the study doctor may give your child; any injury that arises from any action or lack of action to deal adequately with a side effect or reaction to the study medication; an injury that results from negligence on your child's part. By agreeing to participate in this study, you do not give up your right to claim compensation for injury where you can prove negligence. In particular, your right to pursue such a claim in a South African court in terms of South African law must be ensured.

You must notify the study doctor or nurse immediately of any complications, side effects and/or injuries during the study and the nature of the expenses to be covered. Contact information is provided below.

The insurance does not cover and the study will not pay for:

- Medical treatment of other injuries or illnesses.
- Injury caused by not following the research protocol
- Per DAIDS policy DWD-POL-CL-02.00, the US NIH does not have a mechanism to provide direct compensation for research-related injury.

CONFIDENTIALITY

We will do our best to protect your child's private information. Your child's study records will be kept secure. We use a code number in place of your child's name on most records. We will not share your child's name unless someone working on or reviewing the study needs to know it. This may include the research staff, ethics committee members, members of the MCC, FDA, study sponsor (NIAID), and other related agencies.

We will keep the information listed below, private and will not share this information with you:

- Your child's attitudes towards sexual behaviour and reasons for staying in the study.
- Your child's answers to questions about sexual behaviour and whether they are having sex.
- Any birth control information we talk about and your child's access to contraceptives if they choose.
- The results of tests (including pregnancy and STIs) and treatment that your child has consented to without the help of an adult.

To protect your child from harm, we will encourage them to tell a trusted adult (not necessarily their parents/legal guardian) about certain situations. We will help and support them when they tell others about these difficult situations:

- If they become pregnant or have a termination of pregnancy.
- If they have a positive HIV test result.

Also, the law requires us to tell authorities if your child is being sexually or physically abused. The law also requires us to report sexual offenses like rape to the authorities. We will tell your child if we are going to inform the authorities.

Furthermore, if your child is in a relationship with someone who is very much older than s/he and who seems to be using your child in an unfair way, the study staff will give your child support and help. They will encourage your child to talk to a trusted adult, so that they might help your child deal with this situation.

WHO HAS REVIEWED THE STUDY

These screening and enrolment procedures are part of an overall study. We sent the protocol for the whole study to the University of Cape Town Human Research Ethics Committee. This is an independent committee established to help protect the rights of research participants at the Desmond Tutu HIV Foundation research sites.

We also sent it to the South African Medicines Control Council. Both these institutes have given their approval for us to run the study.

We are following ethical guidelines when we run this study. These are the South African Department of Health Clinical Trial Guidelines 2006, and DOH (2004) and ICH/GCP Guidelines and the Declaration of Helsinki (last updated October 2013). These guidelines recommend ways to protect the welfare of research participants. Please ask us for a copy of these guidelines if you would like to see them.

The study doctor does not have any financial or personal interests with this organisation that may bias his/her actions.

If you want any information regarding your or your child's **rights as a research participant, or complaints regarding this research study**, you may contact Professor Marc Blockman at the University of Cape Town Human Research Ethics Committee, which is an independent Committee established to help protect the rights of research participants on telephone number 021 406 6338.

After you have consulted with the study doctor and/or Ethics Committee and if they have not provided you with answers to your satisfaction, you should write to the South African Medicines Control Council (MCC) at:

The Registrar

South African Medicines Control Council

Department of Health

Private Bag X828

PRETORIA

0001

Fax: 012 395 9201

Email: gouwsj@health.gov.za and mogobm@health.gov.za

EMERGENCY CONTACT

If your child requires emergency care, or if hospitalisation is required at any time during the study or up to 30 days after taking the last dose of study medication,

please tell the treating doctor that your child is/was enrolled in this research study and that your child's study doctor and/or study nurse must be informed.

If you or your child has questions or problems at any time during your participation in this study, use the following important contacts.

If you have questions about this study or want to leave this study, contact Cleopatra Jaars 021 785 5454.

If your child has any symptoms that you think may be related to this study, contact Katherine Gill 021 785 3121.

If you have questions about your rights as a research participant, or problems or concerns about how you are being treated in this study, contact Linda-Gail Bekker at 021 650 6959 .

INFORMED CONSENT/SIGNATURES

You will be given a signed copy of this Guardian Consent Form for Screening and Enrolment Version 3.0 dated 24 July 2015 to keep.

- I confirm that I have received and read or have had read to me and understood this Guardian Consent Form for Screening and Enrolment Version 3.0 dated 24 July 2015 for this research study and have had the opportunity to discuss the study and ask questions. My questions have been answered to my satisfaction and I have had time to decide whether I wish my child to take part.

□

- I understand that sections of any of my child's medical notes may be looked at by responsible individuals associated with the study, study monitors, or from Regulatory Authorities where it is relevant to my child taking part in this research study. I give permission for these individuals to have access to my child's records.

□

- I understand that my child's participation is voluntary and that s/he is free to withdraw at any time without giving any reason, without her / his medical care or legal rights being affected.

□

- I agree to my data and the results of the study being published and submitted to Desmond Tutu HIV Foundation's offices, the US National Institutes of Health/Division of AIDS, and the South African Medicines Control Council
- I give permission for my child's personal doctor about my child's participation in the study, if applicable
- I authorise the collection, transfer and processing of my child's study data.

□

*** FOR ANY IMPARTIAL WITNESS**

I have received and read this Guardian Consent Form for Screening and Enrolment Version 3.0 24 July 2015 and any other written information provided to the participant.

□

I have attended all verbal discussions between the investigator/study coordinator or designee and participant about the study.

□

By signing, I attest that the information provided was accurately explained to and apparently understood by the participant and that informed consent was freely given.

□

Printed Name of Guardian

_____ _____

Guardian Signature Date and time

OR

Participant thumbprint _____

---

* Printed Name of Witness

_____ _____

* Signature of Witness Date and time

---

* Printed Name of Person Conducting Consent

(If other than Investigator)

_____ _____

Signature of Person Conducting Consent Date and time

(If other than Investigator)

Printed Name of Investigator

_____ _____

Signature of Investigator Date and time

I hereby verify that consent was obtained from the above mentioned person.

The participant's guardian has been informed about the risks and the benefits of this study, understands the risks and benefits and gave consent for their child to participate without coercion, undue influence or inappropriate incentives.

Acceptability, safety, and patterns of use of oral tenofovir disoproxil fumarate and emtricitabine for HIV pre-exposure prophylaxis in South African adolescents: an open-label single-arm phase 2 trial

Katherine Gill, Leigh Johnson, Janan Dietrich, Landon Myer, Rebecca Marcus, Melissa Wallace, Tanya Pidwell, Eve Mendel, Lauren Fynn, Kai Jones, Lubbe Wiesner, Catherine Slack, Ann Strode, Hans Spiegel, Sybil Hosek, James Rooney, Glenda Gray, Linda-Gail Bekker

Summary

Background HIV incidence among adolescents in southern Africa remains unacceptably high. Pre-exposure prophylaxis (PrEP) is an effective HIV prevention intervention but there are few data on its implementation among adolescents. We aimed to investigate the safety, feasibility, and acceptability of PrEP with oral tenofovir disoproxil fumarate and emtricitabine as part of a comprehensive HIV prevention package in an adolescent population in South Africa.

Methods This open-label single-arm phase 2 study (PlusPills) was done in two research clinics in Cape Town and Johannesburg, South Africa. Adolescents aged 15–19 years were recruited into the study through recruitment events and outreach in the community. Potential participants were eligible for enrolment if they reported being sexually active. Exclusion criteria were a positive test for HIV or pregnancy at enrolment, breastfeeding, or any relevant co-morbidities. Participants were given oral tenofovir disoproxil fumarate and emtricitabine for PrEP to take daily for the first 12 weeks and were then given the choice to opt in or out of PrEP use at three monthly intervals during scheduled clinic visits. Participants were invited to monthly visits for adherence counselling and HIV testing during the study period. The primary outcomes were acceptability, use, and safety of PrEP. Acceptability was measured by the proportion of participants who reported willingness to take up PrEP and remain on PrEP at each study timepoint. Use was defined as the number of participants who continued to use PrEP after the initial 12-week period until the end of the study (week 48). Safety was measured by grade 2, 3, and 4 laboratory and clinical adverse events using the Division of AIDS table for grading the severity of adult and paediatric adverse events, version 1.0. Dried blood spot samples were collected at each study timepoint to measure tenofovir diphosphate concentrations. This trial is registered with ClinicalTrials.gov, NCT02213328.

Findings Between April 28, 2015, and Nov 11, 2016, 244 participants were screened, and 148 participants were enrolled (median age was 18 years; 99 participants [67%] were female) and initiated PrEP. PrEP was stopped by 26 of the 148 (18%) participants at 12 weeks. Cumulative PrEP opt-out, from the total cohort, was 41% (60 of 148 participants) at week 24 and 43% (63 of 148 participants) at week 36. PrEP was well tolerated with only minor adverse events (grade 2) thought to be related to study drug, which included headache (n=4, 3%), gastrointestinal upset (n=8, 5%), and skin rash (n=2, 1%). Two participants (1%) experienced grade 3 weight loss, which was deemed related to the study drug and resolved fully when PrEP was discontinued. Tenofovir diphosphate concentrations were detectable (>16 fmol/punch) in dried blood spot samples in 108 (92%) of 118 participants who reported PrEP use at week 12, in 74 (74%) of 100 participants at week 24, and in 22 (59%) of 37 participants by the study end at week 48.

Interpretation In this cohort of self-selected South African adolescents at risk of HIV acquisition, PrEP appears safe and tolerable in those who continued use. PrEP use decreased throughout the course of the study as the number of planned study visits declined. Adolescents in southern Africa needs access to PrEP with tailored adherence support and possibly the option for more frequent and flexible visit schedules.

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Introduction

Sub-Saharan Africa carries the largest burden of HIV globally, with an estimated 1·1 million new infections annually.[1,2] HIV incidence among young people in the region remains disproportionately high, with girls accounting for three of four new infections among individuals aged 15–19 years.[3,4] The importance of HIV prevention strategies for adolescents in tackling the epidemic worldwide is increasingly recognised, with a global target from UNICEF to reduce new adolescent HIV infections by 75% by 2020.[5,6]

Adolescent susceptibility to HIV infection is due to a complex interplay between structural, economic,

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linda-gail.bekker@hiv-research.org.za

Research in context

Evidence before this study

We searched the electronic databases Medline, Embase, PubMed, African Index Medicus, and the Cochrane database of systematic reviews to identify studies of PrEP in adolescents in which the primary outcomes were safety and acceptability. We included studies published up to Sept 1, 2019, in any language. Our search included keywords "PrEP" or "Pre-exposure prophylaxis" or "tenofovir/emtricitabine" and "safety" or "acceptability" and "adolescent" or "young" and "Africa". We screened abstracts to retrieve full text articles for assessment of eligibility and checked reference lists of relevant studies and reviews for additional references. Although there was plenty of evidence for the safety and acceptability of PrEP in adult populations and a few studies in adolescent men who have sex with men (MSM) in North America, we were unable to find any studies meeting our search objectives in an African adolescent context. The Adolescent Trials Network 113 and 110 studies have been reported. These studies tested the acceptability, safety, and adherence of PrEP among 78 MSM aged 15–17 years and 200 MSM aged 18–24 years respectively. The studies showed that although acceptability to oral PrEP use was high, there was lower adherence among these young people than among adults. Furthermore, adherence to oral PrEP waned over time in these studies. The use of oral PrEP to prevent HIV in younger people might be viewed as a time-limited strategy that could bridge the developmental period between sexual debut and adulthood. However, several questions regarding the use of PrEP in young people still need to be addressed, including acceptability and adherence in different at-risk populations.

Added value of this study

PlusPills is the first study to investigate the safety and acceptability of oral PrEP within an African adolescent population. The study provides safety, acceptability, and adherence data, which builds on the sparse but growing evidence from adolescent and young adult populations. The study was also designed to replicate real-world PrEP use and to understand patterns of uptake and use in a population particularly at risk for HIV.

Implications of all the available evidence

This study supports the hypothesis that oral PrEP is safe and acceptable for adolescents. It also underscores the view that adherence is challenging for young people. PrEP roll out in South Africa is being prioritised to groups most at risk for HIV, including sex workers, MSM, and most recently, adolescent girls. An evidence base for this roll-out will inform policy makers and practitioners on how to best implement and promote an oral PrEP regimen for African adolescents.

sociocultural, and biological factors during a developmental phase when behaviours associated with HIV acquisition and sexual and reproductive health seeking are initiated.[4,7] The multidimensional susceptibility of adolescents and youth to HIV is particularly manifested in South Africa, where young women aged 15–24 years accounted for almost 40% of new HIV infections in 2017.[8–10] Despite the importance of HIV prevention efforts to support access to testing and treatment for young people, there are few interventions that have shown reduction in HIV infection risk among this group in South Africa and other resource-poor settings.[11–14] CHAMPS (Choices for HIV Adolescent Methods of Prevention in South Africa) is a programme made up of three independent protocols designed to explore different HIV prevention options in adolescents in South Africa, including medical male circumcision and different modes of pre-exposure prophylaxis (PrEP) delivery. The PlusPills study is the protocol under CHAMPS designed to explore feasibility, safety, and uptake of oral PrEP.

PrEP has been shown to be efficacious in various contexts and populations.[15–17] PrEP studies have largely focused on adults with subsequent inadequate youth representation and minimal data specifically applicable to adolescents and young people in southern Africa.[18] Although data are emerging on the use of PrEP in youth at risk of HIV in the USA,[19] these data might not be broadly applicable to a younger African heterosexual population. The challenge of daily PrEP adherence in younger people (<25 years) in all settings is recognised, with a strong correlation between inadequate adherence to PrEP and reduced efficacy.[20–22] Given the HIV incidence rates among adolescents in southern Africa, oral PrEP for this group is likely to have an effect on population-level HIV incidence.[9,10,23] To help inform PrEP implementation strategies, we designed the PlusPills study.

Methods

Study design

The PlusPills study was an open-label phase 2 clinical trial designed to assess the acceptability, use, adherence to, and safety of daily oral PrEP (tenofovir disoproxil fumarate and emtricitabine) for HIV prevention among 150 male and female participants between 15 and 19 years old in two research clinics in Cape Town and Johannesburg, South Africa. The two research sites in Cape Town and Johannesburg provide services to peri-urban low-income communities with a substantial burden of HIV. Both sites have long-established relationships with community stakeholders, experienced study staff, adolescent responsive activities, sexual and reproductive health services, and an active adolescent Community Advisory Board. The study protocol was approved by the Institutional Review Boards of participating study sites, the South African Medicine Control Council, and the Division of AIDS at the National

Institute of Allergy and Infectious Diseases of the US National Institutes of Health. The trial was done in compliance with the guidelines from the International Conference on Harmonisation Good Clinical Practice and the South African Good Clinical practice.

Participants

Multiple recruitment methods were used to recruit participants, including community outreach at schools, youth groups, sports clubs, local clinics, transport hubs, and recruitment drives in the community. Potential participants were given recruitment materials (pamphlets, brochures, and flyers), and those expressing an interest in participating were invited to attend pre-screening information sessions at the research site. Recruitment events, materials, and information sessions were geared towards heterosexual orientations and relationships; however, participants were not asked about their sexual orientation. Participants were included if they reported being sexually active and between 15 and 19 years old. Participants had to be willing to participate in study-required procedures, including orally taking tenofovir disoproxil fumarate and emtricitabine as PrEP for the first 12 weeks of the study. Potential participants were deemed ineligible if they were pregnant, were breastfeeding, were HIV positive, or had any relevant comorbidities, namely hypophosphataemia of grade 2 or higher, acute or chronic hepatitis B infection, renal dysfunction with creatinine clearance less than 75 mL/min, or a history of unexplained bone fractures. Female participants agreed to use contraceptive methods during the study, with implantable, injectable, and oral hormonal contraception being provided by the study sites. All participants were evaluated for symptoms of acute HIV infection before enrolment. Written informed consent was given by all participants aged 18 years or older or by parental or guardian proxy for all participants younger than 18 years.

Procedures

Participants were invited to screen for this study following an HIV prevention education session at the research sites. Those determined to be eligible were requested to return for an enrolment visit at which they were asked to take PrEP for at least 12 weeks as part of a comprehensive prevention package (which also included risk reduction counselling, free condoms and condom counselling, screening and treatment for sexually transmitted infections [STIs], and counselling and referral for other HIV prevention interventions, as per national policies). During this time, participants were required to attend monthly appointments for adherence counselling and HIV testing. Results of drug concentration sampling were used as an adherence-enhancing strategy for those participants who chose to receive this information during follow-up visits. Participants who chose not to receive these results received standard motivational adherence counselling during study visits. Participants were given the option to opt out of PrEP but to remain in the study at the 12-week visit, and then every 3 months thereafter until follow-up ended at week 52 (figure 1). PrEP acceptability was recorded at every follow-up visit. The acceptability instrument (a 12-item Likert scale) assessed the usability of PrEP and the motivation for continued PrEP use. Other measures to enhance adherence included optional daily or weekly SMS reminders and periodic adherence clubs that brought adolescents together at the clinic for information and fun activities.

Intracellular tenofovir-diphosphate dried blood spot samples and tenofovir plasma samples were collected at weeks 4, 8, 12, 24, 36, and 48. Tenofovir diphosphate concentrations were measured in dried blood spots at the University of Cape Town using a validated liquid chromatography tandem mass spectrometry (LC/MS/MS) assay, originally developed and validated at the University of Colorado, CO, USA.[20] Plasma tenofovir was measured with a validated LC/MS/MS assay at the University of Cape Town. Intracellular tenofovir diphosphate in dried blood spot was used as an objective measure of product adherence with a detectable concentration of more than 16 fmol/punch and a threshold level for high adherence of 500 fmol/punch at 4 weeks and 700 fmol/punch thereafter, on the basis of the time for intracellular tenofovir diphosphate concentrations to reach steady state.[21,20,22] Plasma tenofovir drug concentrations were an alternative measure of product adherence with a cutoff of 10 ng/ml

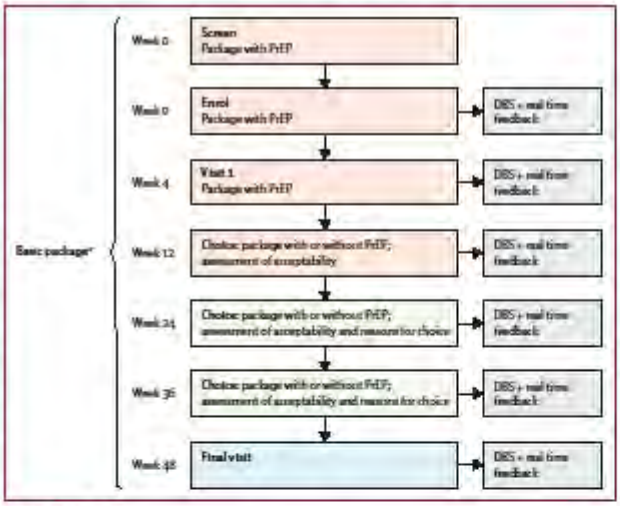

Figure 1: Study design

PrEP=pre-exposure prophylaxis. DBS=dried blood spots. *Included PrEP, and voluntary risk reduction counselling, free condoms and condom counselling, screening and treatment for sexually transmitted infections, and counselling and referral for other HIV prevention interventions.

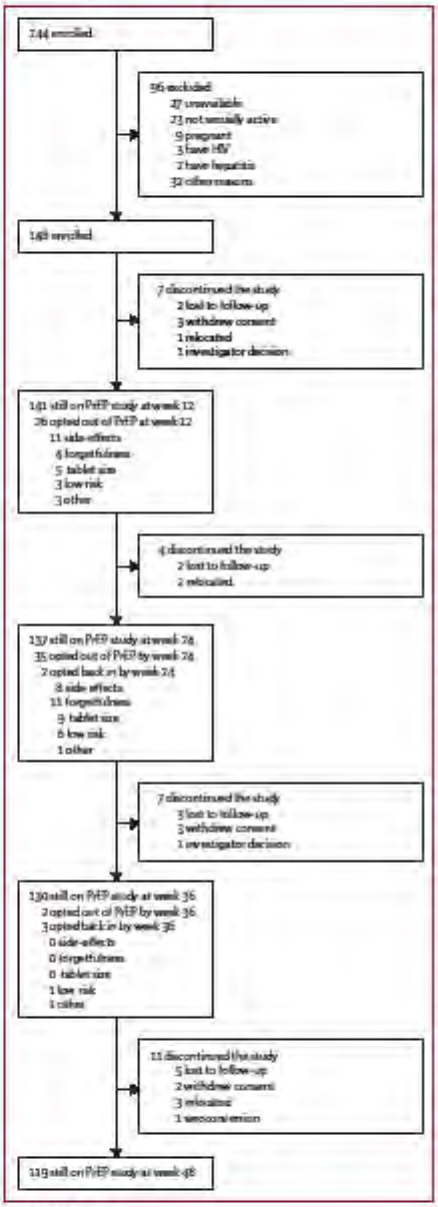

Figure 2: Trial profile

to indicate any use (a detectable level) and 40 ng/ml as adherent use.[8]

Pregnancy testing, HIV and hepatitis B testing, and safety blood testing (full blood count, creatinine, phosphate, alanine aminotransferase, aspartate aminotransferase, urine dipstick) were done at screening. HIV and pregnancy tests were taken at enrolment and at weeks 4, 8, 12, 24, 36, and 48. HIV rapid testing was done in parallel using Determine HIV-1/2 Ag/Ab Combo and Uni-Gold Recombigen HIV-1/2. If the rapid HIV test was reactive, an HIV-1 RNA qualitative assay (Abbot) was done. A positive test was confirmed with a second blood sample collected a week later. Self-collected vaginal swabs (female participants) and urine (male participants) were collected and tested for *Chlamydia trachomatis* and *Neisseria gonorrhoeae* using GeneXpert (Sunnyvale, CA); furthermore, Herpes simplex virus type 2 testing (Kalon) was done. The testing of these three sexually transmitted diseases was done at screening, and at weeks 12 and 48, with appropriate treatment provided.

Safety and tolerability were assessed during the study. Proteinuria, creatinine clearance, glycosuria, and liver enzymes were monitored regularly, and all adverse events were graded, recorded, and assessed. Neurological side-effects such as headaches and dizziness, gastrointestinal side-effects, and social harms were recorded. Participants who tested positive for HIV at screening or throughout the study were referred for ongoing HIV care and management. Expedited adverse event reporting followed standard reporting requirements as defined in the DAIDS Manual for Expedited Reporting of Adverse Events version 2.0, March, 2011, and adverse events were discussed contemporaneously with the Protocol Safety Team. An external Data and Safety Monitoring Board reviewed study safety data on three occasions at 6-month intervals during trial implementation and recommended that the study continued to completion.

Outcomes

The primary outcomes were acceptability, use, and safety of PrEP, as a part of an HIV prevention package. Acceptability was measured by the proportion of participants who reported willingness to use the study regimen, take up PrEP, and remain on PrEP at each 3-month study timepoint. Use was defined as the number of participants who continued to use PrEP after the initial 12-week period until the end of the study (week 48). PrEP discontinuation was defined as participants who attended a visit and refused PrEP. Safety was measured by laboratory and clinical adverse events of grades 2, 3, and 4, using the Division of AIDS table for grading the severity of adult and paediatric adverse events, version 1.0. Further study outcomes outlined in the protocol will be discussed in another paper.

The secondary outcomes were adherence to PrEP, sexual risk behaviours, HIV, and sexually transmitted

infections (STIs). Adherence was measured by self report, pill count, and the proportion of participants on PrEP with detectable plasma and dried blood spot drug concentrations. Sexual activity was defined as a minimum of one act of self-reported vaginal sex in the past 12 months. Sexual risk behaviours included the number of regular and casual sex partners and details of partners. In addition, we collected information on substance use and condom use, captured by participant responses to interviewer-administered questionnaires. Incidence of HIV and herpes simplex virus type 2 was measured as the number of infections per person time at risk. STI prevalence was measured as the proportion of participants with STIs at the 12-week and 48-week visits.

Statistical analysis

The sample size calculation was based on the ability to measure the primary objectives of acceptability and use in the participant population. The sample size of 150 was estimated to detect non-acceptability end points occurring in 10% of participants with approximately 5% precision and an estimated loss to follow-up of 10%.

Demographic and other baseline characteristics were summarised using appropriate descriptive statistics (including medians and IQRs) for continuous variables. Youth who were adherent to PrEP (tenofovir diphosphate ≥700 fmol/punch) and youth who were non-adherent to PrEP were compared on factors affecting adherence, using a logistic regression with mixed effects modelling. Statistical analyses of the baseline data were done using STATA version 14 (StataCorp). This trial is registered with ClinicalTrials.gov, NCT02213328.

Role of the funding source

The role of Gilead Sciences in this study was restricted to providing the study drug and reviewing the manuscript. Gilead Sciences had no role in data collection, data analysis, and data interpretation. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Between April 28, 2015, and Nov 11, 2016, 244 participants were screened and 148 participants enrolled across both sites (figure 2). The most common reason for ineligibility was being unavailable for all trial visits and procedures (n=27), followed by not being sexually active (n=23), pregnancy (n=9), HIV seropositivity (n=3), and hepatitis B surface antigen positivity (n=2). Table 1 shows the cohort characteristics at enrolment. The median age of participants was 18 years (IQR 17–19). 99 (67%) of the 148 participants were female and 49 (33%) were male, with female participants aged 18 and 19 years comprising 42% of the cohort. 28 participants were prematurely discontinued from the study with reasons for non-completion shown in figure 2. Overall study retention was 81%.

	Female participants (n=99)	Male participants (n=49)	All participants (n=148)
Age, years	18 (16–19)	18 (17–18)	18 (17–19)
Ethnicity: Black African	99 (100%)	49 (100%)	148 (100%)
Location			
Cape Town	52 (53%)	23 (47%)	75 (51%)
Soweto	47 (47%)	26 (53%)	73 (49%)
School attendance	72 (73%)	39 (80%)	111 (75%)
Highest completed grade*	10 (10–12)	10 (9–11)	10 (9–12)
Attending tertiary education	9 (9%)	6 (12%)	15 (10%)
Living with mother or father, or both	82 (83%)	37 (76%)	119 (80%)
Consistent condom use in the past year	70 (71%)	30 (61%)	100 (67%)
Condom use (last sexual act)	70 (71%)	38 (78%)	108 (73%)
Any positive test of sexual transmitted infection	50 (51%)	10 (20%)	60 (41%)
Multiple partners in past year	22 (22%)	27 (55%)	49 (33%)
Had a partner at least 5 years older in past year	24 (24%)	6 (12%)	30 (20%)
Transactional sex in past year	3 (4%)	1 (2%)	5 (3%)

Data are median (IQR) or n (%). *There are 12 grades in the school system in South Africa. Going to school up to grade 9 is compulsory.

Table 1: Baseline demographic characteristics

PrEP was stopped by 26 of the 148 (18%) participants at 12 weeks (figure 2). 35 (24%) of the 148 participants chose to opt-out of PrEP at the 24-week visit, and two (1%) further participants chose to opt-out of PrEP at the 36-week visit. In total, 63 (43%) of the 148 participants chose to stop taking PrEP at any point during the study. At week 12, 121 (82%) participants had not opted out of PrEP use. Side-effects were the most commonly cited reason for choosing to stop (19 of 63 participants, 30%). Other reasons included forgetting to take medication (15 of 63 participants, 24%), tablet size (14 of 63 participants, 22%), and decreased perception of risk (ten of 63 participants, 16%). Five (8%) of the 63 participants chose to start taking PrEP again after stopping, citing increased risk as the reason.

At week 12, 104 (83%) of 126 participants indicated that they "liked" or would "like to continue" taking PrEP on the Likert scale and 100 (79%) of 126 participants collected their PrEP prescription at the study site. At week 12, 123 (98%) of 126 participants taking PrEP indicated that they "liked" PrEP as they felt protected from HIV. This preference remained constant throughout the study.

Regarding safety and tolerability, 16 (11%) of the 148 participants experienced either grade 2 or grade 3 transient adverse health events (appendix). The most common grade 2 events were headaches and dizziness (n=4), and nausea and vomiting (n=4). Participants also reported abdominal pain (n=2), diarrhoea (n=2), and skin rash (n=2). Two participants experienced grade 3 weight

See Online for appendix

	Female participants			Male participants			All participants		
	Baseline (n=99)	Week 12 (n=82)	Week 48 (n=58)	Baseline (n=49)	Week 12 (n=42)	Week 48 (n=33)	Baseline (n=148)	Week 12 (n=124)	Week 48 (n=91)
Chlamydia	38 (38%)	18 (22%)	23 (40%)	7 (14%)	3 (7%)	1 (3%)	45 (30%)	21 (17%)	24 (26%)
Gonorrhoea	6 (6%)	8 (10%)	6 (10%)	1 (2%)	0 (0%)	0 (0%)	8 (5%)	8 (6%)	6 (7%)
Herpes	20 (20%)	20 (24%)	18 (31%)	4 (8%)	5 (12%)	5 (18%)	24 (16%)	25 (20%)	23 (25%)
Any*	50 (51%)	29 (35%)	29 (50%)	10 (20%)	6 (14%)	6 (18%)	60 (41%)	35 (28%)	37 (41%)

Data are n (%). *Any of the examined sexually transmitted infections (chlamydia, gonorrhoea, or herpes).

Table 2: Prevalence of sexually transmitted infection

loss, which was deemed related to the study drug and resolved fully when PrEP was discontinued. No bone fractures and no PrEP interruptions occurred because of renal impairment. Four participants experienced a grade 3 or 4 serious adverse event that was deemed unrelated to the study drug. One participant overdosed on study medication in a parasuicide attempt unrelated to study participation following an argument with her mother. She received support from the site, was referred for psychological support, and made a full recovery. Side-effects were cited as a reason for stopping PrEP in 19 (13%) of the participants. One incident of social harm was attributed to study participation: one participant was assaulted by her partner after he found the tablets and assumed she had been concealing her HIV status. The participant was assisted to report the incident to the police, was referred for counselling, and withdrew from the study. One 14-year-old participant was inadvertently enrolled and exited from the study following a discussion with the safety team and Ethics Committee.

Median age at sexual debut was 15 (IQR 14–16). 49 (33%) of the participants reported multiple sexual partners in the past year and 30 (20%) reported age-disparate relationships (sexual partners are at least 5 years older than participant; table 1). 48 (32%) of participants gave a history of inconsistent condom use at baseline with no significant differences between the sexes (p=0·5). Ten (7%) participants reported previous anal intercourse . 83 (56%) participants reported alcohol use in the preceding 12 months. 25 (17%) participants had used recreational drugs in the preceding 12 months, with marijuana as the most commonly reported drug used (n=23/148, 16%).

Table 2 shows STI prevalence during the study stratified by sex. The prevalence of sexually transmitted infections was high at baseline with 60 (41%) participants testing positive for at least one STI. 51% (ie, 50 of 99) of the female participants had at least one STI at baseline versus 20% (ie, 10 of 49) of male participants (p=0·001). STI prevalence remained high throughout the study despite treatment, counselling, and partner treatment. Chlamydia trachomatis was the most frequently occurring infection, occurring in 45 (30%) of 148 participants at baseline, 21 (17%) of 124 participants at week 12, and 24 (26%) of 91 participants at study end. Herpes simplex virus type 2 was the second most common infection with 24 (16%) of 148 participants testing seropositive at baseline, and an overall incidence of 8·3 per 100 person-years (95% CI 4·31–16·11). There were no incident pregnancies reported during study follow up. There was one reported HIV seroconversion in a 19-year-old female participant who had stopped PrEP 24 weeks before diagnosis. The overall HIV incidence was 0·76 cases per 100 person-years (95% CI 0·1–4·3) and 1·16 cases per 100 girl-years (95% CI 0·2–6·29).

Dried blood spot tenofovir concentrations indicated that 141 (95%) of the 148 participants had a detectable drug concentration during the study, with seven (5%) participants not having used PrEP at all. Plasma tenofovir concentrations similarly showed that 121 (82%) participants had a detectable drug concentration at any time during the study.

Drug concentrations were relatively constant in the first 12 weeks with 105 (94%) of 112 participants having detectable tenofovir diphosphate concentrations at week 4, 107 (94%) of 113 participants at week 8, and 108 (92%) of 118 at week 12. In contrast, 79 (71%) of 112 participants had detectable plasma tenofovir concentrations at week 4, 76 (67%) of 113 participants at week 8, and 64 (54%) of 118 participants at week 12.

There was also a decline in tenofovir diphosphate concentrations from the visit at week 24, with detectable concentrations seen in 74 (74%) of 100 participants who chose to continue PrEP. Plasma tenofovir concentrations declined to detectable plasma concentrations in 41 (41%) of 100 participants who chose to continue PrEP. This percentage concentration remained constant over the following 24 weeks with 22 (59%) of 37 participants on PrEP having a detectable concentration according to dried blood spot samples at the visit at week 48 and 17 (46%) of 37 participants on PrEP having a detectable level according to plasma samples at the visit at week 48. Table 3 shows a mixed-effects logistic regression model for factors predicting adherence. The only statistically significant predictors of adherence were time (week 4, 8, 12, 24, 36, and 48; adjusted odds ratio [OR] 0·89, 95% CI 0·86–0·92, p=0·001) and age (15–17 years and 18–19 years; adjusted OR 0·57, CI 0·40–0·82, p=0·003). The most common reasons given for poor adherence were that participants forgot, lost, or ran out

of tablets (41%). Other reasons given included being worried about potential side-effects (6%), being too busy (5%), or being away from home (5%). Figure 3 shows tenofovir diphosphate concentrations by week.

Plasma tenofovir and tenofovir diphosphate drug concentration results were correlated and reached agreement in 425 (77%) of 552 samples. 73 (13%) of the 552 samples had high plasma tenofovir with low tenofovir diphosphate, suggesting a dose taken before the study visit but otherwise poor adherence in the preceding month. 54 (10%) of the 552 samples had low plasma tenofovir with high tenofovir diphosphate, suggesting good adherence in the preceding month but no dosing before the study visit.

Discussion

PlusPills is the first oral PrEP study in an adolescent, presumed heterosexual population in Africa and provides important safety and adherence data for young people in South Africa and in the region. Oral PrEP was safe and relatively well tolerated by participants; reported side-effects were temporary and similar to those described in adult PrEP studies.[16–17] Acceptability of PrEP and study participation remained high throughout the study.

This study demonstrated the feasibility of enrolment and retention of young men and women who appear to be at substantial risk of HIV acquisition. The substantial number of STIs both at baseline and during the study, together with self-reported sexual risk behaviours, suggest a population suitable for PrEP use, obviating the need for complex risk assessment tools for selection of a target population.

HIV incidence was low, with a single HIV seroconversion occurring in one participant who had opted out of PrEP earlier in the study. The HIV incidence rate of 0·76 cases per 100 person-years found in our study is 73% lower than the HIV incidence rate that is estimated nationally for sexually active adolescents aged 15–19 years (which is 2·81 cases per 100 person-years if assuming that a third of the population is male and two thirds are female, as in our study population).[21] Although this study was not powered to measure HIV incidence or designed as an efficacy study, the low incidence rate, relative to the national average, suggests a possible benefit from PrEP. The STI prevalence and incidence throughout the study indicates that young people in South Africa remain engaged in sexual risk behaviours even within a context of supportive and adolescent-responsive health services. Incorporating PrEP as an added measure into adolescent sexual and reproductive services would allow for holistic and targeted care for young people during this susceptible period.

The rationale for offering PrEP opt-in and opt-out at intervals during the PlusPills study was to replicate real-world PrEP use according to periods of HIV risk.[18–19] A possible explanation for the low HIV incidence in this study despite high prevalence of STIs suggesting condomless sex is that participants identified their own risk periods and successfully used PrEP during these times. This possibility warrants further study. Implementation programmes should aim to support and empower the adolescent to use PrEP for specified periods of anticipated HIV exposure instead of relying on traditional adherence messaging and measures such as pill counts, which is still used in some clinics offering antiretroviral therapy in resource-poor settings. Using PrEP according to a specified period of risk should be recognised as different to event-based PrEP. The ADAPT (HPTN 067) study,[20] also done in Cape Town albeit in a slightly older group of women, found that daily oral PrEP was more successful than intermittent use in terms of number of sex acts that were covered by drug exposure. More research into dosing and dosing schedules is urgently required among young heterosexual people. It is probable that an individualised and non-judgmental approach to PrEP is likely to improve uptake and adherence. Another consideration is that PlusPills required parental proxy consent for

	Univariate model		Multivariate model	
	OR (95% CI)	p value	Adjusted OR (95% CI)	p value
Consistent condom use	1·32 (0·66–2·67)	0·42	..	..
Transactional sex	1·34 (0·5–3·59)	0·56	..	..
Anal sex	0·32 (0·07–1·4)	0·13	..	..
Sexually transmitted infection at baseline	0·64 (0·33–1·27)	0·22	..	..
Sexual debut, years	0·99 (0·92–1·06)	0·84	..	..
More than one sex partner	1·33 (0·76–1·53)	0·21	..	..
Time, weeks	0·91 (0·87–0·94)	0·001	0·89 (0·86–0·92)	0·001
Age, years	0·65 (0·53–0·85)	0·002	0·57 (0·40–0·82)	0·003
Gender (male)	0·73 (0·36–1·53)	0·39	0·55 (0·30–1·07)	0·13
Site (Soweto)	1·36 (0·69–2·68)	0·38	1·52 (0·62–3·91)	0·34

OR=odds ratio.

Table 3: Univariate factor model and multivariable mixed effects logistic regression model for high adherence (tenofovir diphosphate concentrations ≥700 fmol/punch)

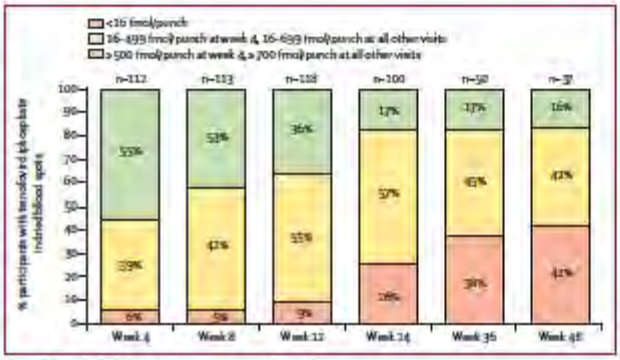

Figure 3: Tenofovir diphosphate concentrations by week

participation of adolescents younger than 18 years. This practice probably led to the lower numbers of younger people in the cohort and could also have contributed to recruitment of individuals with lower HIV incidence.

Daily PrEP adherence is a considerable challenge for younger populations (<25 years), as seen in this study and in PrEP studies with North American adolescents and young adults. In particular in the Adolescent Trials Network 110 study[19,20] and the Adolescent Trials Network ATN 113 study,[19,21] tenofovir diphosphate concentrations in blood samples declined as the frequency of study visits were reduced per protocol. Adherence also decreased with increasing age, which might reflect increased familial support in the younger participants who needed parental consent to participate. In PlusPills, a third of the population was younger than 18 years. Fewer than 60% of participants had detectable tenofovir diphosphate concentrations by week 48, and 40% of the study population had chosen to discontinue PrEP by week 36, although participants were retained in the study and continued to receive the range of adolescent-friendly sexual and reproductive health services offered. This finding underlines the importance of integrating PrEP into sexual and reproductive health services so that PrEP can be offered regularly to young people attending health services. Young people on PrEP might benefit from more frequent PrEP visits to augment and support adherence as appropriate. Work is needed to identify successful adolescent-specific strategies to address adherence, including mobile technology to enhance clinic contact frequency, adherence support groups, peer mentors, and cash incentives.

Drug concentrations measured in plasma and dried blood spots correlated reasonably well, indicating that in this population either could be used to provide objective measures of PrEP use. In PlusPills, the recommendation to participants was that they take the oral PrEP daily, and these measures provide some additional information in understanding patterns of PrEP use. In those individuals who choose to use PrEP intermittently according to sexual exposure risk, the interpretation of these measures of adherence will remain challenging.

This study supports the hypothesis that oral PrEP is safe and acceptable for young people although it also reinforces the view that adherence is challenging for young people. PrEP roll out in South Africa is being prioritised to groups most at risk, including sex workers, men who have sex with men, and most recently, adolescent girls. Prioritising PrEP for young women at risk can be cost-effective considering that there could be costly obstacles to initiating treatment for young people with HIV using the same drug.[3,22] Oral PrEP in combination with other proven HIV prevention interventions should be offered to South African adolescents and young people in a tailored fashion, including developmentally appropriate support for effective PrEP use.

Contributors

L-GB, LM, MW, LJ, CS, AS, SH, HS, GG, and JD all played a role in the conceptualisation and design of the study. L-GB and KG put the first draft together. LJ and LM contributed to the analysis. All authors were involved in the interpretation of the data and finalisation of the manuscript. All authors signed off on the final version.

Declaration of interests

JR is an employee and stockholder of Gilead Sciences. All other authors declare no competing interests.

Data sharing

De-identified data that underlie the results in this Article will be made available on request.

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Title: An Open Label, phase II, Demonstration Study to Assess the Acceptability, Safety and Patterns of Use of oral Pre-exposure Prophylaxis of tenofovir disoproxil fumarate/emtricitabine to prevent HIV in Healthy, South African Adolescents.

Dear Professor Bekker,

I am pleased to tell you that your submission, An Open Label, phase II, Demonstration Study to Assess the Acceptability, Safety and Patterns of Use of oral Pre-exposure Prophylaxis of tenofovir disoproxil fumarate/emtricitabine to prevent HIV in Healthy, South African Adolescents., has been accepted for publication in The Lancet Child & Adolescent Health.

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- Designated authors should meet all four criteria for authorship in the ICMJE Recommendations
- All authors, and all contributors (including medical writers and editors), should specify their individual contributions at the end of the manuscript
- We encourage collaboration and coauthorship with colleagues in the locations where the research is conducted
- The Lancet Group takes a neutral position with respect to territorial claims in institutional affiliations

ICMJE Recommendations
http://www.icmje.org

Author statement form
https://www.thelancet.com/for-authors/forms?section=tlchild-author-sag

ICMJE COI form
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Joint ICMJE statement
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- When choosing coauthors, we ask lead authors to be mindful of the benefits of diversity in authorship and to consider inviting coauthors who reflect diversity in every sense, including (but not limited to) background, career stage, gender, geography, and race
- *The Lancet Child & Adolescent Health* will not publish any paper unless we have the signatures of all authors
- We suggest you use the author statement form and upload the signed copy with your submission
- Please include written consent of any cited individual(s) noted in acknowledgments or personal communications
- Those forms should only be supplied if your paper is selected for peer review. You will receive instruction from the editorial team when to send these documents
- If a collaborator or study group has been used and they wish to be indexed on PubMed, please provide a separate word document including a table of first initials and surnames of all members

Forms and signatures

For Reviews, Viewpoints, Comments, and Correspondence, we require you to upload your forms at submission. For original research (Articles), we will request these forms after peer review. The following signed statements are required:

- Authors' contributions
- Conflicts of interest statements (ICMJE forms)
- Statements of role, if any, of medical writer or editor
- Acknowledgments—written consent of cited individual
- Personal communications—written consent of cited individual
- Use of copyright protected material signed permission statements from author and publisher

These statements can be scanned and submitted electronically with your submission. Please note that *The Lancet* journals will accept hand signed and electronic (typewritten) signatures.

Declaration of interests

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- *All authors are required to provide a Conflict of Interest Statement* and should complete a standard form, which is available at https://www.thelancet.com/for-authors/forms?section=icmje-coi. The form has been modified by the ICMJE following consultation with authors and editors. Further information is available in a joint ICMJE statement published on July 1, 2010. For more information see *Lancet* 2009; 374: 1395–96.
- For any Review or Viewpoint, *The Lancet Child & Adolescent Health* will not publish the manuscript if an author, within the past 3 years, and with a relevant company or competitor, has any stocks or shares, equity, a contract of employment, or a named position on a company board; or has been asked by any organisation other than *The Lancet Child & Adolescent Health* to write, be named on, or to submit the paper (see *Lancet* 2004; 363: 2–3)
- For any Review or Viewpoint, the use of medical writers is not permitted unless they have been paid and instructed directly by an author, or their institution, and their role is purely technical (eg, editing a first draft for language and grammar). If you are contemplating use of a medical writer, please contact the journal immediately to ensure it complies with our policies

Role of the funding source (to be included only with Articles)

- All sources of funding should be declared as an acknowledgment at the end of the text
- At the end of the Methods section, under a subheading "Role of the funding source", authors must describe the role of the study sponsor(s), if any, in study design; in the collection, analysis, and interpretation of data; in the writing of the report; and in the decision to submit the paper for publication
- If there is no Methods section, the role of the funding source should be stated as an acknowledgment. If the funding source had no such involvement, the authors should so state
- The corresponding author should confirm that he or she had full access to all the data in the study and had final responsibility for the decision to submit for publication

Role of medical writer or editor

- If a medical writer or editor was involved in the creation of your manuscript, we need a signed statement from the corresponding author to include their name and information about funding of this person
- This information should be added to the Acknowledgments and/or Contributors section
- We require signed statements from any medical writers or editors declaring that they have given permission to be named as an author, as a contributor, or in the Acknowledgments section

Patient and other consents

- Appropriate written consents, permissions, and releases must be obtained where you wish to include any case details, personal information, and/or images of patients or other

individuals in *The Lancet Child & Adolescent Health* in order to comply with all applicable laws and regulations concerning privacy and/or security of personal information. Studies on patients or volunteers need approval from an ethics committee and informed consent from participants. These should be documented in your paper.

- Do not use "blackout" bars or similar devices to anonymise patients in clinical images: if you have taken consent appropriately masking is not needed.
- Since the consent form needs to comply with the relevant legal requirements of your particular jurisdiction, we do not provide sample forms; this is your responsibility. Your affiliated institution should be able to provide an appropriate form.
- For the purposes of publishing in *The Lancet Child & Adolescent Health*, a consent, permission, or release should include, without limitation, publication in all formats (including print, electronic, and websites), in sublicensed and reprinted versions (including translations), and in other works and products.
- To respect your patient's and any other individual's privacy, please do not send signed forms to *The Lancet Child & Adolescent Health*. Please instead complete the patient consent section of the Author Statements while retaining copies of the signed forms in the event they should be needed.
- If consent, permission, or release is made subject to any conditions, *The Lancet Child & Adolescent Health* must be made aware in writing of all such conditions before publication.
- For more information about our policy, please visit http://www.elsevier.com/about/company-information/policies/patient-consent.

Types of article and manuscript requirements

Please ensure that anything you submit to *The Lancet Child & Adolescent Health* follows the guidelines provided for each article type. For instruction on how to format the text of your paper, including tables, figures, panels, and references, please see our Formatting guidelines. Please note *The Lancet Child & Adolescent Health* does not publish case reports in any format.

Red section (Articles and Meta-analyses)

Articles

- *The Lancet Child & Adolescent Health* prioritises reports of original research that are likely to change clinical practice or thinking about paediatrics, or child or adolescent health and wellbeing
- We invite submission of all clinical trials, whether phase 1, 2, 3, or 4 (see *Lancet* 2006; 368: 827–28). For phase 1 trials, we especially encourage those of a novel substance for a novel indication, if there is a strong or unexpected beneficial or adverse response, or a novel mechanism of action
- We require registration of all interventional trials, whether early or late phase, in a primary register that participates in WHO's International Clinical Trial Registry Platform (see *Lancet* 2007; 369: 1909–11) or in ClinicalTrials.gov, in accord with ICMJE recommendations. We also encourage full public disclosure of the minimum 21-item trial registration dataset at the time of registration and before recruitment of the first participant (see *Lancet* 2006; 367: 1631–35. The registry must be independent of for-profit interest
- Reports of trials must conform to CONSORT 2010 guidelines, and should be submitted with their protocols
- All reports of randomised trials should include a section entitled Randomisation and masking, within the Methods section. Please refer to *The Lancet*'s formatting guidelines for randomised trials
- Cluster-randomised trials must be reported according to CONSORT extended guidelines
- Randomised trials that report harms must be described according to extended CONSORT guidelines
- Studies of diagnostic accuracy must be reported according to STARD guidelines
- Observational studies (cohort, case–control, or cross-sectional designs) must be reported according to the STROBE statement, and should be submitted with their protocols
- We encourage the registration of all observational studies on a WHO-compliant registry (see *Lancet* 2010; 375: 348)
- Genetic association studies must be reported according to STREGA guidelines
- Reports of studies of global health estimates should be reported according to the GATHER statement (see *Lancet* 2016; 388: e19–23)
- To find reporting guidelines see http://www.equator-network.org
- Please be aware it is *The Lancet Child & Adolescent Health*'s standard practice to commission an independent Comment to accompany all published Articles and Meta-analyses to add context and insight

All Articles should, as relevant:

- Be up to 3500 words (4500 for randomised controlled trials) with 30 references (the word count is for the manuscript text only)
- Include an abstract (semistructured summary), with five paragraphs (Background, Methods, Findings, Interpretation, and Funding), not exceeding 300 words. Our electronic submission system will ask you to copy and paste this section at the "Submit Abstract" stage
- For randomised trials, the abstract should adhere to CONSORT extensions: abstracts (see *Lancet* 2008; 371: 281–83)
- When reporting Kaplan-Meier survival data, at each timepoint, authors must include numbers at risk, and are encouraged to include the number of censored patients.
- For intervention studies, the abstract should include the primary outcome expressed as the difference between groups with a confidence interval on that difference (absolute differences are more useful than relative ones). Secondary outcomes can be included as long as they are clearly marked as secondary and all such outcomes are reported
- Use the SI system of units and the recommended international non-proprietary name (rINN) for drug names. Ensure that the dose, route, and frequency of administration of any drug you mention are correct
- Use gene names approved by the Human Gene Organisation. Novel gene sequences should be deposited in a public database

CONSORT 2010 guidelines
http://www.consort-statement.org/consort-2010

Formatting guidelines for randomised trials
https://www.thelancet.com/for-authors/forms?section=rct

CONSORT extended guidelines
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STREGA guidelines
http://www.equator-network.org/reporting-guidelines/strobe-strega/

GATHER statement
http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(16)30388-9/fulltext

To find reporting guidelines, see
http://www.equator-network.org

Human Gene Organisation
http://www.genenames.org/

WHO's International Clinical Trial Registry Platform
http://www.who.int/ictrp/network/trds/en/index.html

Clinical trials
http://clinicaltrials.gov

ICMJE recommendations
http://icmje.org/recommendations/browse/publishing-and-editorial-issues/clinical-trial-registration.html

(GenBank, EMBL, or DDBJ), and the accession number provided
Authors of microarray papers should include in their submission the information recommended by the MIAME guidelines. Authors should also submit their experimental details to one of the publicly available databases: ArrayExpress or GEO

MIAME guidelines
http://fged.org/projects/miame/
Array and GEO
http://www.ebi.ac.uk/microarray-as/aer/
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- Include any necessary additional data as part of your EM submission
- All accepted Articles should include a link to the full study protocol published on the authors' institutional website (see *Lancet* 2009; 373: 992 and *Lancet* 2010; 375: 348).
- We encourage researchers to enrol women and ethnic groups into clinical trials of all phases, and to plan to analyse data by sex and by race
- For all study types, we encourage correct use of the terms sex (when reporting biological factors) and gender (when reporting identity, psychosocial, or cultural factors). Where possible, report the sex and/or gender of study participants, and describe the methods used to determine sex and gender. Separate reporting of data by demographic variables, such as age and sex, facilitates pooling of data for subgroups across studies and should be routine, unless inappropriate. Discuss the influence or association of variables, such as sex and/or gender, on your findings, where appropriate, and the limitations of the data.

Putting research into context

- All research papers (including systematic reviews/meta-analyses) submitted to any journal in *The Lancet* family must include a panel putting their research into context with previous work in the format outlined below (see *Lancet* 2014; 384: 2176–77, for the original rationale). This panel should not contain references. Editors will use this information at the first assessment stage and peer reviewers will be specifically asked to check the content and accuracy.
- The Discussion section should contain a full description and discussion of the context. Authors are also invited to either report their own, up to date systematic review or cite a recent systematic review of other trials, putting their trial into context of the review

MENDELEY data
https://data.mendeley.com

Research in context

Evidence before this study

This section should include a description of all the evidence that the authors considered before undertaking this study. Authors should briefly state: the sources (databases, journal or book reference lists, etc) searched; the criteria used to include or exclude studies (including the exact start and end dates of the search), which should not be limited to English language publications; the search terms used; the quality (risk of bias) of that evidence; and the pooled estimate derived from meta-analysis of the evidence, if appropriate.

Added value of this study

Authors should describe here how their findings add value to the existing evidence.

Implications of all the available evidence

Authors should state the implications for practice or policy and future research of their study combined with existing evidence.

Research in context panels should not contain references; key studies mentioned here should be referenced in the main text.

PRISMA guidelines
http://www.prisma-statement.org/
Formatting guidelines for meta-analyses
https://www.thelancet.com/for-authors/forms?section=meta-analysis

Data sharing

From July 1, 2018, all submitted reports of clinical trials must contain a data sharing statement, to be included at the end of the manuscript. Data sharing statements must indicate:

- Whether data collected for the study, including individual participant data and a data dictionary defining each field in the set, will be made available to others ("undecided" is not an acceptable answer);
- What data will be made available (deidentified participant data, participant data with identifiers, data dictionary, or other specified data set);
- Whether additional, related documents will be available (eg, study protocol, statistical analysis plan, informed consent form);
- When these data will be available (beginning and end date, or "with publication", as applicable);
- Where the data will be made available (including a complete URL or email addresses if relevant);
- By what access criteria data will be shared (including with whom, for what types of analyses, by what mechanism—eg, with or without investigator support, after approval of a proposal, with a signed data access agreement—or any additional restrictions).

See table for examples. Clinical trials that begin enrolling participants on or after Jan 1, 2019, must include a data sharing plan in the trial's registration. If the data sharing plan changes after registration, this should be reflected in the statement submitted and published, and updated in the registry record. For reports of research other than clinical trials, data sharing statements are encouraged but not required. Mendeley Data is a secure online repository for research data, permitting archiving of any file type and assigning a permanent and unique digital object identifier (DOI) so that the files can be easily referenced. If authors wish to share their supporting data, and have not already made alternative arrangements, a Mendeley DOI can be referred to in the data sharing statement.

Meta-analyses

- In general, these should follow the PRISMA guidelines. Please refer to *The Lancet*'s formatting guidelines for systematic reviews and meta-analyses.
- Manuscripts should be structured around five sections: Summary, Introduction, Methods, Results, and Discussion
- Aim for a maximum length of about 3000 words and 75 references
- Meta-analyses should also contain a semistructured summary as described previously for Articles

Blue section (Comment, Correspondence, etc)

Editorial

- Editorials are the voice of *The Lancet Child & Adolescent Health*, and are written in-house by the journal's editorial-writing team and signed "The Lancet Child & Adolescent Health"

Comment

- This section contains commentaries that accompany papers

published in *The Lancet Child & Adolescent Health* or on issues of wide-reaching concern in paediatric, or child or adolescent health. Most commentaries are commissioned, and linked to specific research Articles to add context, but unsolicited commentaries (no more than 750 words, ten references, and one figure, panel, or small table) are also welcome. Unsolicited commentaries may be peer reviewed.

- At the Editor's discretion, commentaries may be shortened in the interests of space
- The place to respond to something we have published is in our **Correspondence** section
- See **Conflicts of Interest** guidelines for comments

Correspondence

- We welcome correspondence on content published in *The Lancet Child & Adolescent Health* or on other topics of interest to our readers
- Letters for publication in the print journal must reach us within 8 weeks of publication of the original item and should be no longer than 400 words
- Letters of general interest, unlinked to items published in the journal, can be up to 400 words long
- Correspondence letters are not usually peer reviewed, but we might invite replies from the authors of the original publication, or pass on letters to these authors
- Only one table or figure is permitted, and there should be no more than five references and five authors
- All accepted letters are edited, and proofs will be sent out to authors before publication

Corrections

- Any substantial error in any article published in *The Lancet Child & Adolescent Health* should be corrected as soon as possible. Blame is not apportioned; the important thing is to set the record straight
- *The Lancet* journals have a policy for types of errors that we do and do not correct. We will always correct any error affecting a non-proprietary drug name, dose, or unit, any numerical error in the results, or any factual error in interpretation of results
- Other corrections are at the Editor's discretion

For *The Lancet* journals' policy on correction of errors see https://www.thelancet.com/for-authors/forms?section=correction

Green section (Reviews, Viewpoints, Clinical Pictures, Commissions)

Reviews

Most reviews are commissioned, but unsolicited short outlines (300–400 words) can be directed to the Editor. If you have already written the paper, please submit it for consideration via our online system

Online System www.editorialmanager.com/thelancetchildadol

- Reviews should be either a definitive overview of a major topic connected with pediatrics, or child or adolescent health or an update of knowledge in a somewhat narrower field of current interest
- Manuscripts will be assessed in-house and those judged suitable will be peer reviewed before an editorial decision is made
- Reviews should be no more than 4500 words, with a maximum of 75 references
- References selected for publication should be chosen for their importance, ease of access, and for the "further reading" opportunities they provide; citations to papers published in non peer reviewed supplements are discouraged. In addition to references, authors should consider supplying a short list of useful websites where readers can find further information on the subject
- A 150-word unstructured summary should be included. Use of up to 5–6 illustrations is encouraged to aid the reader
- Complete transparency about the choice of material included is important to any Review paper. Therefore, all Reviews should include a brief section entitled "Search strategy and selection criteria" stating the sources (including databases, MeSH and free text search terms and filters, and reference lists from journals or books) of the material covered, and the criteria used to include or exclude studies. Citations to papers published in non-peer-reviewed supplements are discouraged. Since these papers should be comprehensive, we encourage citation of publications in non-English languages. An example is shown below

Search strategy and selection criteria

References for this Review were identified through searches of PubMed with the search terms "young onset", "early onset", "presenile", and "dementia" from 1995 until April, 2019. Articles were also identified through searches of the authors' own files. Only papers published in English were reviewed. The final reference list was generated on the basis of originality and relevance to the broad scope of this Review

- Systematic reviews should be prepared according to the PRISMA guidelines

Viewpoints

- These should be 2000–4000 words in length, with a maximum of 75 references
- These opinion pieces may reflect an individual perception, involvement, or contribution to pediatrics, or child or adolescent health, and should be prepared in a similar way to a Review. Unsolicited contributions are welcome, although please contact the Editor before submission to ensure that the proposed topic is within the remit of the journal

Clinical Pictures

- The ideal Clinical Picture provides visual information that will be useful to other clinicians. Clinical Pictures should be interesting, educational, and respectful of the patient. *The Lancet Child & Adolescent Health* is less interested in pictures that simply illustrate an extreme example of a medical condition, a unique response, or first use of a new intervention
- Each Clinical Picture must be accompanied by text that puts the image in context. This text should include a brief patient history, and should explain what the Clinical Picture shows and why it is of interest to the general reader. Maximum text length is 300 words, with no references

- All Clinical Picture submissions must be accompanied with a challenging clinical question related to the case along with four possible answers. This quiz will be peer-reviewed and will be used on the journal's website to encourage users to read the underlying article
- Authors must obtain signed, informed patient consent. Do not use "blackout" bars or similar devices to anonymise patients if you have taken consent appropriately, masking is not necessary

Commissions

- Topics for *The Lancet Child & Adolescent Health* Commissions are selected by our editors, who work with academic partners to identify the most pressing issues in science, medicine, and global health with the aim of producing recommendations to change public policy or improve practice. Projects usually last 2–3 years, and author groups will represent a broad range of international expertise. All *The Lancet Child & Adolescent Health* Commissions are academic publications and are subject to the same rigorous peer review process as all other research papers published in our journals. *The Lancet Child & Adolescent Health* does not provide direct financial support to Commissioners for the research or writing of the reports. Funding is sought directly by authors, with oversight from our editors.

Index Medicus
http://www.nlm.nih.gov/

Formatting guidelines

Language

- Manuscripts should be submitted in English. Authors writing in Chinese, Portuguese, or Spanish may wish to use the Webshop (http://webshop.elsevier.com/languageservices) to provide an English translation of their manuscript for submission

Title page

- A brief title, author name(s), preferred degree (one only), affiliation(s), and full address(es) of the authors must be included. The name and address of the corresponding author should be separately and clearly indicated along with email and telephone details

Formatting guidelines for text, tables, and figures
Guidelines on formatting of text, tables, and figures can be found at https://www.thelancet.com/pb/assets/raw/Lancet/authors/artwork-guidelines.pdf

Formatting of text

- Type a single space at the end of each sentence
- Do not use bold face for emphasis within text
- Do not worry about type of font or point size
- We use a comma before the final "and" or "or" in a list of items
- Type decimal points midline (ie, 23·4, not 23.4) To create a midline decimal on a PC hold down ALT key and type 0183 on the number pad, or on a Mac: ALT shift 9
- Numbers one to ten are written out in words unless they are used as a unit of measurement, except in figures and tables
- Use single hard-returns to separate paragraphs. Do not use tabs or indents to start a paragraph
- Do not use the automated features of your software, such as hyphenation, endnotes, headers, or footers (especially for references) Please use page numbering
- Guidelines on formatting tables are available in the artwork guidelines

References

- Cite references in the text sequentially in the Vancouver numbering style, as a superscripted number after any punctuation mark. For example
  "...as reported by Saito and colleagues.[1]"
- Two references are cited separated by a comma, with no space. Three or more consecutive references are given as a range with an en rule. To create an en rule on a PC hold down CTRL key and minus sign on the number pad, or on a Mac: ALT hyphen
- References in tables, figures, and panels should be in numerical order according to where the item is cited in the text
- Here is an example for a journal reference (note the use of tab, bold, italic, and the en rule or "long" hyphen):

  "...15[tab]Saito N, Ebara S, Ohotsuka K, Kumeta J, Takaoka K Natural history of scoliosis in spastic cerebral palsy. *Lancet* 1998; **351**: 1687–[en rule]92."

- Give any subpart to the title of the article Journal names are abbreviated in their standard form as in Index Medicus
- If there are six authors or fewer, give all six in the form: [surname] [initials]
- If there are seven or more give the first three in the same way, followed by et al
- For a book, give any editors and the publisher, the city of publication, and year of publication
- For a chapter or section of a book, also give the authors and title of the section, and the page numbers
- For online material, please cite the URL, together with the date you accessed the website
- Online journal articles can be cited using the DOI number
- Do not put references in the Summary

Figures

Our in-house illustrators redraw most figures into Lancet style. The quality of the files we receive from authors has a direct effect on the accuracy and time taken to prepare figures that are suitable for publication.

We have different criteria for photographic and illustrative files, the following notes are a summary of our ideal requirements, but a detailed description is in the artwork guidelines

- For images (photographs or photographic images) that are used as part of illustration or image composite figures we require a file that is no less than 300 dpi when set at its final printed size. Ideal file formats are TIF or JPG
- For trial profiles, study profiles, and CONSORT diagrams, please supply as an editable flow diagram in Word (.doc) or PowerPoint (.ppt) file
- For illustrations (all non photographic line work and general drawing) we require editable vector files that contain selectable geometry and fonts (editable text). The editability of files depends on the package they were created in, but as a rule we would prefer to receive any of the following: Adobe Illustrator (.ai) file, Adobe Illustrator or generic .eps files exported from a graphics program, vector based PDF, PowerPoint, or Word file, or SVG file. If authors are unable to supply files in any these formats, our in-house

illustrators can offer guidance on whether it is more economical to export or convert the file into another format, or to redraw from scratch. When files are exported to eps files, we would prefer text to be exported "as text" rather than "as objects", which is especially crucial for files such as forest plots in which there is a lot of text

- If your figures are annotated, please supply two copies of each of these figures as separate files (one annotated copy and one non annotated and editable copy). Our in-house illustrators will annotate according to journal style using the annotated figures as a guide. For multi part figures, please supply the individual parts as well as a combined version to be used as a guide for our illustrators to recreate the files
- Images that have been published previously should be accompanied by a statement indicating permission to reproduce the image. If required, further assistance can be obtained from the editorial team. If you have used previously published images, you must obtain permission from the copyright holder of the paper, which might be the authors or the publisher. If all the figures are your own and have not been published before, then this requirement does not apply

Guidelines for supplementary material

All material should be submitted as one PDF (with numbered pages) with the paper and will be peer reviewed. Material will be published at the discretion of *The Lancet* journals' editors. For clinical trials, we encourage authors to include a copy of the study protocol. All material should be provided in English.

Text

- Main heading for the web extra material should be in 12 point Times New Roman font BOLD
- Text should be in 10 point Times New Roman font, single spaced
- Headings should be in 10 point BOLD

Tables

- Main table heading should be in 10 point Times New Roman font BOLD
- Legends should be in 10 point, single spaced
- Tables should be in 8 point Times New Roman font, single spaced
- Headings within tables should be in 8 point BOLD

Data

- SI units are required
- Numbers in text and tables should always be provided if % is shown
- Means should be accompanied by SDs, and medians by IQR
- p values should be given to two significant figures, unless p<0·0001

Drug names

- Recommended international non proprietary name (rINN) is required
- We encourage use of neuroscience based nomenclature for psychotropic drugs

References

- Vancouver style—eg,

—Smith A, Jones B, Clements S. Clinical transplantation of tissue-engineered airway. Lancet 2008; 372: 1201–09.

—Hourigan P. Ankle injuries. In: Chan D, ed. Sports medicine London: Elsevier, 2008: 230–47.

- Numbered in order of mention in Webappendix and numbered separately from references in the full paper

Figures

- All images must have a minimum resolution of 300 dpi, width 107 mm
- Main figure heading should be in 10 point Times New Roman font BOLD
- Legends should be in 10 point, single spaced

Audio/video material

- The paper to which the audio or video clip relates should be mentioned in the recording
- Audio clip and video files should be accompanied with brief text explaining the content of the audio, names of interviewers/interviewees, date of recording, and place of recording if relevant
- Written consent from all parties must be supplied at submission

Audio

- Audio material submitted as an mp3 file, no larger than 50 Mb
- Your paper may be selected for a podcast. If so, the Web Editor will contact you to arrange a pre-recorded interview to discuss your paper. For more information, see **Audio**

Video

- Video material should be submitted in .mp4 format with aspect ratio of 16:9, and be no larger than 50 Mb
- We welcome your videos and invite you to submit any video material (reports, interviews, scans, imaging) for consideration in the online journal. Please ensure that all those featured in the video have given permission for publication (see also the previous section on **Patient and other consents**)
- All video files can be submitted alongside your article in EM

Disclosure of results before publication

- Presentation of data at a scientific meeting, as a poster, abstract, orally, on a CD, or as an abstract on the web, or on a preprint server does not conflict with submission to the *Lancet* journals. As a member journal of the International Committee for Medical Journal Editors, *The Lancet Child & Adolescent Health* does not regard results that are posted in the same clinical trials registry in which primary registration resides as a previous publication, if the results are presented in the form of a brief structured abstract or table
- The *Lancet* journals operate an embargo system, whereby journalists are given access to papers and press releases ahead of publication, allowing them a protected window to develop their stories. We believe that this window can help encourage

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Drug names
For more on neuroscience based nomenclature see http://www.thelancet.com/pdfs/journals/lancet/PIIS2215-0366(17)30098-6.pdf

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