

**AN EVALUATION OF THE INTEGRATION OF ORAL PRE-EXPOSURE
PROPHYLAXIS (PREP) AS STANDARD OF CARE FOR HIV PREVENTION IN
CLINICAL TRIALS IN SOUTH AFRICA**

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Declaration

I, Ivana Beesham, declare that this thesis is my own work. It is being submitted for the Degree of Philosophy at the University of the Witwatersrand, Johannesburg, South Africa. It has not been submitted before for any degree or examination at any other University.



_____ (signature)

Date: 04 May 2023

Dedication

I dedicate this thesis to my family.

My dad, Aroonkumar, a professor in applied mathematics, inspired me to pursue a career in research and of course, to publish. I remain in awe of your knowledge and greatness, and more importantly, your humility.

My mother, Nirupa, a pillar of strength and guidance, always celebrated my achievements along this journey. I thank you for cheering me on for every presentation, publication, and scholarship.

My dear sisters, Kashmiri and Aditi consistently encouraged and supported me. Kashmiri, I will always be grateful for our conversations on health, energy, philosophy, and spirituality. Aditi, I have always been able to rely on you, and admire your work ethic and efficiency, which have motivated me to progress with my tasks throughout my PhD. I also thank you for being a great listener.

My darling nephew, Kaelin, I thank you for your keen interest in my research, and for listening eagerly as I practiced many oral presentations. I recall fondly your excitement and delight upon seeing a new poster I designed for a conference, or a manuscript that was recently published.

My son, Nitai, was around 7 years old when I started this journey. You are my biggest fan and words cannot express how much joy you bring to me. I thank you for your unconditional love. It amazes me that at this young age, you enquire about HIV, PrEP, and other aspects of my research, and try to understand the meaning of my work.

My husband, Hiresh, has been by my side for longer than this PhD journey, and at times may have questioned my desire to continue studying after six years of medical school and three postgraduate diplomas. I thank you for your love, commitment, and encouragement.

Finally, my helper Joyce, I thank you for taking care of my household, thereby giving me more time to pursue this degree. You have become family and I am so grateful for all you do.

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Firstly, I would like to thank my PhD supervisors, Dr Leila Mansoor and Prof Mags Beksinska for their guidance, dedication, availability, and academic support throughout this project. I have learned so much from both of you. I recall approaching Leila in 2019, with an idea for a PhD project when I discovered a scholarship opportunity that was being offered by the South African Medical Research Council (SAMRC). Leila shared my enthusiasm and together we developed my idea of exploring the use of oral pre-exposure prophylaxis (PrEP) as standard of care for HIV prevention in clinical trials in South Africa. Thereafter, I approached Mags and requested for Wits MatCH Research Unit (WMRU) to support me for the duration of my PhD project, and for her to co-supervise me. Together, the three of us worked on the scholarship application and a few months later, the scholarship was awarded by the SAMRC. I was delighted and registered soon after for a PhD. However, my entry into research began prior to my PhD interest – in 2015, as a young naïve doctor with no prior research experience, I applied for a medical officer position at WRMU, and Prof Jenni Smit along with a panel of interviewers, had interviewed me for a clinician position for the Evidence for Contraceptive Options and HIV Outcomes (ECHO) Trial. At the time, I did not conceive that this would be the start of a long and exciting journey in research, including completing a PhD thesis. It was in fact Jenni who had motivated and guided me to write my first research study on reasons for contraceptive implant removals.

Secondly, I thank my colleagues Busi Maphumulo (project manager on the ECHO Trial), Shannon Bosman (clinician on the ECHO Trial), and the rest of the ECHO Trial team at the Durban, WMRU trial site for their contributions to the ECHO Trial, which included oral PrEP integration into the trial, as well as supporting several of my ancillary studies. I recall fondly discussing my ancillary study ideas with Busi and Shannon. I thank Cecilia Milford who played a fundamental role in teaching me about qualitative research and making herself available to review my transcripts, coding, themes, and manuscript drafts. I also acknowledge the rest of the ECHO Trial team including the management committee, site investigators, data team, and other members of the ECHO Trial consortium for their support. I thank my dear friend Tricia Smith for regularly checking in on my PhD progress, celebrating every poster and publication, and for her positive energy and unconditional support always.

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Presentations from this thesis

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2. **Beesham I**, Welch J, Heffron R, et al. Integrating oral PrEP into a large HIV endpoint-driven clinical trial in Eastern and Southern Africa: The ECHO Trial experience. 10th IAS Conference on HIV Science (IAS 2019), *21-24 July 2019*, Mexico City, Mexico (media briefing).
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Publications from this thesis

1. **Beesham I**, Welch JD, Heffron R, et al. Integrating oral PrEP delivery among African women in a large HIV endpoint-driven clinical trial. *J Int AIDS Soc*. 2020;23(5):e25491. doi:10.1002/jia2.25491 (published manuscript).
2. **Beesham I**, Heffron R, Evans S, et al. Exploring the Use of Oral Pre-exposure Prophylaxis (PrEP) Among Women from Durban, South Africa as Part of the HIV Prevention Package in a Clinical Trial. *AIDS Behav*. 2021;25(4):1112-1119. doi:10.1007/s10461-020-03072-0 (published manuscript).
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6. **Beesham I**, Milford C, Smit J, et al. Post-trial access to and use of pre-exposure prophylaxis in Durban, South Africa. *BMC Public Health*. (manuscript under review).

Publication statement and physical contribution of the candidate to the study

The candidate, Dr Ivana Beesham, is the first author on all six manuscripts that have been developed as part of this thesis. Five manuscripts have been published in peer-reviewed journals and the final manuscript is under review in a peer-reviewed journal. All co-authors have agreed to the use of papers within the thesis. The contribution of the candidate to each paper is provided in Table 1.

Table 1: Contribution of PhD candidate to writing of each multi-authored paper

Title of Paper	PhD candidate contribution
Integrating oral PrEP delivery among African women in a large HIV endpoint-driven clinical trial	Drafted the initial manuscript. Contributed to integration of oral PrEP in the ECHO Trial. Read the manuscript, provided critical review and approved the final manuscript.
Exploring the Use of Oral Pre-exposure Prophylaxis (PrEP) Among Women from Durban, South Africa as Part of the HIV Prevention Package in a Clinical Trial	Conceptualised the study and drafted the initial manuscript. Read the manuscript, provided critical review and approved the final version.
Daily Oral Pre-exposure Prophylaxis (PrEP) Continuation Among Women from Durban, South Africa, Who Initiated PrEP as Standard of Care for HIV Prevention in a Clinical Trial	Conceptualised the study and drafted the initial manuscript. Analysed the data. Approved the final version of the manuscript.
Quantifiable Plasma Tenofovir Among South African Women Using Daily Oral Pre-exposure Prophylaxis During the ECHO Trial	Conceptualised the study and drafted the initial manuscript. Analysed the data. Read the manuscript, provided critical review, and approved the final version
Key stakeholders' perspectives on providing oral pre-exposure prophylaxis as HIV prevention standard of care in clinical trials in South Africa	Conceptualised the study, conducted interviews, developed the codebook, analyzed the data (coding and thematic analysis), wrote the first draft of the manuscript and approved the final version.
Post-trial access to and use of pre-exposure prophylaxis in Durban, South Africa	Conceptualised the study, conducted the interviews, transcribed, and coded the interviews, conducted thematic analysis, wrote the first draft of the paper and approved the final draft.

Dr Ivana Beesham was the clinician for the Evidence for Contraceptive Options and HIV Outcomes (ECHO) Trial, from 2015 to 2018, at the Wits MatCH Research Unit (WMRU) trial sites. During the ECHO Trial, she was responsible for the clinical management and safety of trial participants. In addition, she was involved in ethics submissions, project management, clinical assessment and management of study participants, adverse event reporting, quality control processes (including data cleaning, response to queries on case report forms and

quality management) and dispensing of medication. She also presented at participant events, community advisory board meetings, and investigator meetings.

She was instrumental in the implementation of oral PrEP as standard of care for HIV prevention, particularly the integration of onsite oral PrEP provision as part of the trial HIV prevention package at the South African trial sites. As the study clinician, she initiated and managed women who used oral PrEP during the trial, at her trial site. This included counselling, side effect management, case report form completion, and PrEP dispensation. Dr Beesham conceptualised and developed an ancillary PrEP study to collect additional data on oral PrEP use among women enrolled at the Durban, South Africa, ECHO Trial site. She developed informed consent forms, data collection tools, and conducted interviews with women as part of this ancillary study. She conceptualised a second ancillary study that quantified plasma tenofovir at the final trial visit among women enrolled at eight of the South African ECHO Trial sites, which provided an objective measure of oral PrEP adherence. She obtained funding for the tenofovir testing. Finally, Dr Beesham was responsible for conceptualising both qualitative studies – the interviews among key stakeholders from research sites in South Africa, as well as interviews with participants who had exited the ECHO Trial and were continuing oral PrEP at trial exit. For these studies, she designed the consent forms and data collection tools, conducted the interviews, and coded and analysed the data.

Signatures

 Student signature	Date: 04 May 2023
 Supervisor 1 signature	11th May 2023 Date:
 Supervisor 2 signature	Date: 11 May 2023

ABSTRACT

Background: Oral tenofovir-based pre-exposure prophylaxis (PrEP) is an effective biomedical HIV prevention option. In 2015, the World Health Organization (WHO) recommended oral PrEP for those at substantial risk of HIV infection, and several countries have since adopted oral PrEP into their national guidelines. In the context of trials, HIV endpoint-driven trials frequently enrol individuals who are at elevated risk of acquiring HIV. Ethical guidelines recommend that study sponsors and investigators should provide access to a package of HIV prevention methods to trial participants, as recommended by WHO, including adding new prevention methods as these are validated. In 2017, the South African Medical Research Council recommended that oral PrEP be provided in HIV prevention trials. The Evidence for Contraceptive Options and HIV Outcomes (ECHO) Trial was ongoing at the time and incorporated oral PrEP into the trial's HIV prevention package, including the onsite provision of oral PrEP at the South African trial sites during the last eight months of the trial. The ECHO Trial, conducted from 2015 to 2018, enrolled women aged 16-35 years, from 12 research sites in four African countries, and assessed the effect of three contraceptives on HIV incidence. In 2019, when this PhD project was conceptualised, there was a lack of data on the integration of oral PrEP as part of the HIV prevention package in HIV endpoint-driven trials. To address this gap, I evaluated the integration of oral PrEP as standard of care for HIV prevention in clinical trials in South Africa.

Objectives:

1. To describe the process of implementing oral PrEP provision, the uptake of oral PrEP and the characteristics of women who initiated (versus those who did not initiate) oral PrEP during the ECHO Trial.
2. To evaluate oral PrEP adherence and factors associated with adherence by conducting plasma tenofovir (TFV) drug level testing using stored blood samples among a subset of women from South Africa who reported current oral PrEP use at the final ECHO Trial visit.
3. To describe the experiences of women who initiated oral PrEP at the Durban, South Africa, ECHO Trial site.
4. To explore post-trial access to oral PrEP, and barriers and enablers to post-trial oral PrEP access, among a subset of women from the Durban, South Africa, ECHO Trial site.
5. To review the current status of oral PrEP as standard of care for HIV prevention in clinical trials in South Africa.

Methods: This was a mixed methodology study, conducted from 2019 to 2022, and both qualitative and quantitative methods were utilized. I describe the process undertaken by the ECHO Trial team to incorporate oral PrEP delivery into the trial's HIV prevention package, including the onsite provision of oral PrEP by ECHO Trial staff at the South African trial sites. Characteristics between women who ever initiated oral PrEP versus those who had access to but did not initiate oral PrEP, were assessed using Chi-squared/Fisher's exact tests for categorical variables and t-tests for continuous variables. HIV seroincidence comparisons between participants who never versus ever initiated oral PrEP were modelled using exact Poisson regression.

To objectively measure adherence to oral PrEP, plasma samples collected at the final ECHO Trial visit, from a subset of women enrolled at the South African ECHO Trial sites, who reported ongoing PrEP use, were tested for TFV. Bivariate logistical regression was used to evaluate participant characteristics associated with quantifiable TFV at the final ECHO Trial visit.

To understand experiences of women who used oral PrEP and patterns of oral PrEP use, we conducted questionnaires with women who initiated oral PrEP onsite at the Durban, South Africa, ECHO Trial site. Face-to-face questionnaires were conducted approximately three months following oral PrEP initiation, and explored reasons for using and discontinuing oral PrEP, side effects experienced, oral PrEP adherence and disclosure of oral PrEP use. I also evaluated factors associated with oral PrEP continuation at the final ECHO Trial visit using univariate and multivariate logistical regression. Among women continuing oral PrEP at ECHO Trial exit, telephonic follow-up was conducted 4-6 months later, to briefly explore oral PrEP access and ongoing use following study exit.

Additional face-to-face, participant in-depth interviews were conducted in 2021 with a subset of women from the Durban, South Africa, ECHO Trial site, who reported ongoing oral PrEP use at ECHO Trial exit and who were given a 3-month PrEP supply at study exit. The interviews explored barriers and enablers to post-trial oral PrEP access.

Finally, telephonic in-depth interviews were held with key stakeholders from research sites across South Africa known to conduct HIV endpoint-driven clinical trials to explore their perspectives on providing oral PrEP as HIV prevention standard of care in clinical trials in South Africa. Participant and stakeholder interviews were audio-recorded and transcribed, and thematic analysis was facilitated using NVivo.

Results: Our key findings indicate that it was feasible to integrate oral PrEP as standard of care for HIV prevention in the ECHO Trial. PrEP uptake was 17.2% (622/3626) among those eligible for oral PrEP when it became available. Women who initiated oral PrEP were more likely to be unmarried, not living with their partner, having multiple partners; and less likely to be earning their own income and receiving financial support from partners (all $p < 0.05$). There were 37 HIV seroconversions among women who had access to oral PrEP but did not initiate oral PrEP, and 2 seroconversions among women who initiated oral PrEP (HIV incidence 2.4 versus 1.0 per 100 person-years; Incidence Risk Ratio = 0.35; 95% confidence interval (CI) = 0.04 to 1.38). Among the 260 plasma samples from the eight South African ECHO Trial sites that were available for TFV testing, plasma TFV was quantified in 36% of samples (94/260). Women >24 years old had twice the odds of having TFV quantified compared to younger women (Odds Ratio (OR) = 2.12; 95% CI = 1.27 to 3.56). Women who reported inconsistent/no use of condoms had lower odds of TFV quantification (age-adjusted OR = 0.47; 95% CI = 0.26 to 0.83). The ancillary study conducted at the Durban, South Africa ECHO Trial site found that onsite oral PrEP uptake was high (43%, 138/324). Almost all women who initiated oral PrEP at the trial site agreed to participate in the ancillary study (96%, 132/138). Of these, 88% reported feeling at risk of acquiring HIV. Most women (>90%) heard of oral PrEP for the first time from trial staff. Oral PrEP continuation via self-report was 87% at month-1, 80% at month-3, and 75% elected to continue using oral PrEP at trial exit and were referred to off-site facilities for ongoing access. Disclosure of oral PrEP use was associated with five-fold increased odds of continuing oral PrEP at trial exit (adjusted OR = 4.98; 95% CI = 1.45 to 17.13; $p = 0.01$). At telephonic follow-up 4-6 months after women exited the ECHO Trial, >50% reported discontinuing PrEP. Qualitative interviews conducted with a subset of women from the Durban, South Africa ECHO Trial site identified several barriers to post-trial oral PrEP access at facilities such as long queues, facilities being located far from women's homes, unsuitable clinic operating hours, negative attitudes from providers, and oral PrEP being unavailable at some clinics. Interviews with key stakeholders from research sites in South Africa found that most stakeholders reported incorporating oral PrEP provision as part of the HIV prevention package offered to participants in HIV endpoint-driven trials. Stakeholders identified barriers to oral PrEP

uptake, adherence, persistence, and post-trial access. Demand creation, and education and counselling about oral PrEP were reported as factors that facilitated uptake.

Conclusion: The ECHO Trial provides evidence that it was feasible to successfully integrate oral PrEP provision as part of the trial's HIV prevention package offered to study participants. Other HIV endpoint-driven trials can utilize our findings as a model to integrate oral PrEP provision into the HIV prevention package offered in a trial. The ancillary study findings on PrEP uptake, adherence and persistence can be utilized to guide oral PrEP trials and implementation programs. While post-trial oral PrEP access was concerning and several barriers were identified, it is possible that with the scale-up of oral PrEP in the public sector in South Africa after the ECHO Trial was completed, participants exiting trials and desiring to continue oral PrEP could have better access.

Table of Contents

Declaration	2
Dedication	3
Acknowledgments	4
Presentations from this thesis	5
Publications from this thesis	6
Publication statement and physical contribution of the candidate to the study	7
Abstract	9
List of figures	13
List of tables	13
Abbreviations and acronyms	14
Chapter One	15
Chapter Two	42
Appendices	

List of Figures

Figure 1: PrEP cascade

Figure 2: Oral PrEP phased implementation in South Africa from 2016 to 2021

Figure 3: An overview of the ECHO Trial host countries and research sites

List of Tables

Table 1: Contribution of PhD candidate to writing of each multi-authored paper

Table 2: Summary of HIV endpoint-driven trials and PrEP implementation / demonstration projects

Table 3: Summary of study objectives, data sources, and analyses

Table 4: PrEP uptake/initiation and use in the ECHO Trial

Abbreviations and acronyms

AGYW	Adolescent girls and young women
ARV	Antiretroviral
AVAC	Aids Vaccine Coalition Network
BARC	Bio Analytical Research Corporation
CAB-LA	Long-acting injectable cabotegravir
DBS	Dried blood spots
DREAMS	Determined, Resilient, Empowered, AIDS-free, Mentored, and Safe
DoH	Department of Health
ECHO	Evidence for Contraceptive Options and HIV Outcomes
FDA	Food and Drug Administration
FTC	Emtricitabine
GPP	Good Participatory Practice
HIV	Human Immunodeficiency Virus
HPTN	HIV Prevention Trials Network
HREC	Human Research Ethics Committee
MSM	Men who have sex with men
MRU	MatCH Research Unit
NDoH	National Department of Health
OLE	open label extension
PrEP	Pre-exposure Prophylaxis
SA	South Africa
SAMRC	South African Medical Research Council
STI	Sexually transmitted infection
TDF	Tenofovir disoproxil fumarate
TDF-FTC	Tenofovir disoproxil fumarate and emtricitabine
TFV	Tenofovir
TFV-DP	Tenofovir diphosphate
TGW	Transgender women
UNAIDS	Joint United Nations Programme on HIV/AIDS
WHO	World Health Organization

CHAPTER ONE

INTRODUCTION AND LITERATURE REVIEW

This section provides an introduction and literature review, identifies knowledge gaps in the field and the rationale for this study, and describes the aims and objectives of this thesis.

Oral pre-exposure prophylaxis (PrEP) for HIV prevention refers to the use of antiretroviral (ARV) medication by people not living with HIV, to prevent HIV acquisition¹. One of the first clinical trials to demonstrate oral PrEP effectiveness was the iPrEx study which was conducted among men and transgender women, who have sex with men. The iPrEx study found a 44% reduction in HIV incidence among those using oral PrEP containing tenofovir disoproxil fumarate and emtricitabine (TDF-FTC) compared to placebo². Subsequent oral PrEP studies targeting heterosexual HIV transmission included the TDF2 study which showed a 62% reduction in HIV incidence among heterosexual men and women from Botswana³, and the Partners PrEP study which showed a 75% reduction in HIV incidence among HIV-serodifferent couples from Kenya and Uganda⁴. Following these and several other studies that demonstrated oral PrEP effectiveness among different populations in many countries, in 2015, the World Health Organisation (WHO) recommended that oral PrEP containing TDF be offered as an additional prevention choice for people at substantial risk of HIV infection⁵. However, not all studies demonstrated oral PrEP effectiveness – the FEM-PrEP and VOICE trials, which were conducted among African women found no significant reduction in HIV incidence, likely due to low levels of drug adherence^{6,7}.

Following the WHO recommendation that oral PrEP be offered to those at substantial risk of HIV infection, with substantial risk being defined as an HIV incidence greater than 3 per 100 person-years in the absence of PrEP⁵, several countries began incorporating oral PrEP into national guidelines as a component of HIV prevention⁸. Globally, as of September 2022, cumulative oral PrEP initiations were around 2.8 million⁸, however, the Joint United Nations Programme on HIV/AIDS (UNAIDS) target of 3 million oral PrEP initiations in low- and middle-income countries by 2020 was not reached, with only 28% of the target achieved⁹.

The need for HIV prevention options is paramount, both globally and particularly in sub-Saharan Africa. Globally, in 2021, there were 1.5 million new HIV infections, and 670,000 of these occurred in eastern and southern Africa¹⁰. In sub-Saharan Africa, women and girls accounted for almost two-thirds of new HIV infections in 2021¹⁰. In South Africa, the country with the largest HIV epidemic in the world, in 2021, 7.5 million people were living with HIV, with a prevalence of 18% among adults aged 15 to 49 years, and 200,000 adults aged 15 years and over were newly infected with HIV¹¹.

In a clinical trial context, the provision of oral PrEP as part of HIV prevention standard of care in HIV prevention trials, as the AIDS Vaccine Advocacy Coalition (AVAC) reported in late 2017, is complex, and needs to take into consideration ethics, trial design issues and mechanisms by which the intervention is provided¹². Additional considerations include community involvement and assessing oral PrEP availability and rollout in countries where trials are being conducted¹². According to the UNAIDS ethics guidance document, which was updated in 2021, researchers and trial sponsors need to ensure access to a package of prevention methods recommended by WHO during the trial, including adding new prevention methods that are validated and recommended by WHO, on consultation with relevant stakeholders¹³. The HIV Prevention Trials Network (HPTN) ethics guidance document recommends that researchers partner with key stakeholders to provide effective, comprehensive, and sustainable prevention services to participants, but recognizes that it

might be practically and ethically challenging to determine the content of the prevention package¹⁴. The Good Participatory Practice (GPP) guidelines discuss the ethical obligation of researchers to assist trial participants reduce their risk of HIV acquisition, and the importance of collaboration between researchers and stakeholders in determining the components of the HIV prevention package offered in a trial¹⁵. The HIV prevention package provided to study participants in HIV prevention efficacy trials usually consists of risk-reduction counselling, provision of condoms and lubricants, referral for medical male circumcision, sexually transmitted infection (STI) testing and treatment, and counselling and more recently referral for oral PrEP¹⁶.

A key meeting that influenced oral PrEP provision in HIV endpoint-driven trials in South Africa was a summit held by the South African Medical Research Council (SAMRC) in 2017, on the standard of care in both HIV treatment and prevention trials, in low-middle income settings¹⁷. At this meeting, advocates and community members highlighted the need for interventions that prevent HIV to be made available timeously. However, it was recognized that oral PrEP availability in South Africa was limited at the time, with only 7,000 persons using oral PrEP, and that oral PrEP was not widely available in the public sector. Furthermore, oral PrEP at the time was not standard of care, but rather the aspirational standard of care for high-risk men and women. Despite these limitations, it was recommended that a fund be established to support the provision of oral PrEP at trial sites for the duration of the trial, and participants be made aware that it was not possible to provide post-trial access due to limited funding. HIV prevention trial investigators were also advised to work together with the South African Department of Health (DoH) PrEP technical working group to support oral PrEP demonstration projects close to research sites. Finally, the manner in which oral PrEP was to be provided, referral versus onsite provision by trial staff, was to be decided by trial sites together with the surrounding communities.

While there was clearly an ethical imperative to include oral PrEP as part of the prevention package offered in HIV endpoint-driven trials^{13,14}, there were also concerns related to the provision of PrEP. These include that the provision of PrEP within trials could create undue incentives for participation in research and it could result in inequities between participants and surrounding communities^{12,14}. Post-trial PrEP access upon study termination could be challenging especially in communities where PrEP programmes are nascent or unavailable, or where eligibility criteria for access are not congruent with trial criteria¹⁷. Operational factors such as provider training, drug availability and supply, and PrEP-related laboratory testing are also important considerations.

Clinical trial design and study outcomes are additional factors that need to be considered with the provision of oral PrEP as part of the HIV prevention package in HIV efficacy trials¹⁶. Design considerations are complex and include whether oral PrEP is being used as an active comparator arm to evaluate new prevention products such as injectable PrEP drugs, or whether new HIV prevention products are being compared to placebo as in some of the HIV vaccine studies¹⁶. In instances where oral PrEP is offered as part of the prevention package, the uptake of oral PrEP by study participants might change over time as oral PrEP becomes more widely available, for example, oral PrEP uptake in HVTN 505, which was conducted from 2009 to 2013 was only 5%, while in HVTN704/HPTN085, which was conducted from 2016 to 2020, oral PrEP uptake was 40%¹⁸. Additional considerations include non-inferiority versus superiority studies, run-in periods, crossover between arms and estimating sample size¹⁹. One example of where a new prevention modality is being compared to placebo is the MOSAICO study which enrolled participants who were not using oral PrEP at study entry and who expressed a desire not to use oral PrEP at study screening/enrolment¹⁸.

One of the first clinical trials that considered the inclusion of oral PrEP as part of the trial HIV prevention package was the HVTN 505 study, which raised important considerations of whether, when and/or how oral PrEP should be offered to study participants²⁰. HVTN 505 was a phase IIb HIV vaccine efficacy trial that enrolled men who have sex with men (MSM) and transgender women (TGW) at high-risk for HIV acquisition at sites in the United States. It was during the course of this trial that the United States Food and Drug Administration (FDA) approved the use of Truvada® for HIV prevention²¹, following three large trials that demonstrated efficacy²⁻⁴. At that time, oral PrEP was not widely used in any country and the inclusion of oral PrEP in a clinical trial would go beyond available clinical care in most settings. The trial considered the following four domains when contemplating the inclusion of oral PrEP in the trial: 1) researchers' obligations to study participants and communities; 2) effects on study design; 3) health policy considerations, and 4) stakeholders' opinions²⁰. After extensive consultation, the trial team elected to provide information and education about oral PrEP to participants, and referrals to providers for those participants interested in initiating oral PrEP, which would be provided at no cost to participants²⁰.

A large clinical trial conducted in South Africa that included oral PrEP as part of the HIV prevention package was the HVTN 702 vaccine efficacy trial²². The trial, conducted between 2016 and 2019, enrolled adults between the ages of 18 and 35 years. Oral PrEP was made available to all study participants at no cost during the trial, however the uptake of oral PrEP by participant self-report was only 3%, and tenofovir diphosphate (TFV-DP) measured in dried blood spots (DBS) was detected in 2% of all samples tested. The vaccine did not show any efficacy in preventing HIV and HIV incidence in the trial was high – 3.4 per 100 person-years in the vaccine arm and 3.3 per 100 person-years in the placebo arm²². Of concern, HIV incidence among women was greater than 4 per 100 person-years, highlighting the need for HIV prevention options among this group.

As discussed earlier, following the FDA approval for oral PrEP and the WHO recommendation that oral PrEP be offered to those at substantial risk of HIV acquisition, several countries incorporated oral PrEP into their HIV prevention guidelines. This posed novel challenges for oral PrEP delivery and scale-up including how to promote oral PrEP and create demand, particularly as oral PrEP was being offered in general to otherwise healthy persons²³. Suggestions to create demand for oral PrEP include clear concise messaging, addressing stigma, user and community education and awareness, and emphasizing the positive benefits of oral PrEP in increasing user confidence and empowerment²⁴. Data also suggest that demand creation is needed both prior to, and after national guidelines are implemented, and the need for increasing oral PrEP availability²⁴.

Adherence to oral PrEP can be challenging and studies have been conducted in different settings such as trials, including open label extension (OLE) trials, and demonstration projects, to measure adherence. Adherence as measured by drug levels was 51% in the iPrEx trial, 71% in the iPrEx OLE, 82% in the Partners PrEP trial, and lower in the VOICE and FEM-PrEP trials – 28-29% and 37% respectively²⁵. Some demonstration projects have found high levels of adherence to oral PrEP, for example, in the Partners Demonstration project, adherence was 82%²⁵. Reasons for reduced or non-adherence to oral PrEP are multifactorial. In the FEM-PrEP trial, reasons for non-adherence included concerns about the investigational nature of the drug being tested, side effects, and HIV-related stigma²⁶. Additional barriers to oral PrEP adherence identified in other studies include forgetting to take tablets, disclosure-related issues, challenges with discrete storage of oral PrEP and not having PrEP pills with when travelling²⁷⁻²⁹. It is also worth noting that unlike antiretroviral therapy (ART) which is lifelong and needs to be taken regularly, oral PrEP may be taken

during periods of risk for HIV exposure and can be stopped and restarted as needed, and this is known as prevention-effective adherence³⁰.

Studies have found that oral PrEP continuation rates decrease over time, and many users discontinue early, within the first few months of use. A systematic review and meta-analysis which included trials, OLE studies, demonstration projects and implementation programmes, that were conducted in several countries including Africa, found that 66% continued oral PrEP at month-1³¹. Data from the Determined, Resilient, Empowered, AIDS-free, Mentored, and Safe (DREAMS) Initiative in Kenya showed that 57% of adolescent girls and young women (AGYW) persisted with oral PrEP at month-1 and 37% at month-3³². Similarly, the implementation science POWER study conducted in Kenya and South Africa among AGYW, found that 31% continued oral PrEP at month-1 and 20% through 6 months³³.

Oral PrEP access and availability in South Africa has expanded over time (Figure 2). Oral PrEP was first rolled out by the South African DoH in 2016 to sex workers³⁴ and expanded in 2017 to include MSM and university students³⁵. In 2018, AGYW were eligible for oral PrEP³⁵. In 2020, South Africa updated its oral PrEP guidelines to include additional populations such as those with more than one sex partner, those with recent STIs, serodifferent couples, and those who requested to use oral PrEP³⁶. A further update in 2021 included the provision of oral PrEP to at risk pregnant and lactating women³⁷. In 2016, when oral PrEP rollout had begun in South Africa, oral PrEP was available at 13 sites, and 771 were initiated on PrEP³⁵. In contrast, in 2021, when oral PrEP was expanded widely to include public sector facilities, 2,700 sites were offering oral PrEP and there were 268,068 initiations³⁵. Overall, as of December 2021, more than 450,000 people had initiated oral PrEP in South Africa³⁵.

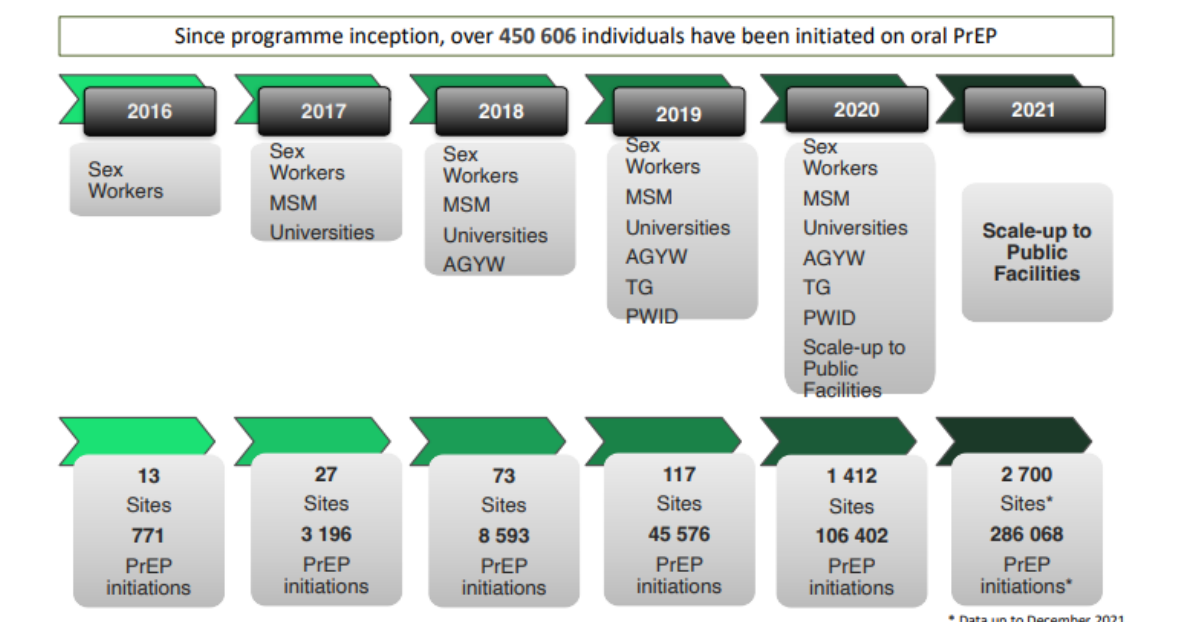


Figure 2: Oral PrEP phased implementation in South Africa from 2016 to 2021

Source: <https://bhakisisa.org/wp-content/uploads/2022/04/PrEP-updated-18-March-2022.pdf>

A summary of HIV endpoint-driven trials and demonstration / implementation studies that were being conducted in Africa, particularly in South Africa, at the time of this PhD project are summarised in Table 2 below.

Table 2: Summary of HIV endpoint-driven trials and PrEP implementation / demonstration projects

Name of study	Study design	Country	Study population	Year of study	PrEP uptake, continuation	PrEP adherence measures	Comments
The Partners Demonstration Project ³⁸	Open-label evaluation of integrated delivery of PrEP and ART	Kenya, Uganda	HIV Sero-discordant couples	2012-2016	PrEP uptake: 97% Median duration of PrEP use – 12 months	MEMS Cap: 71% took ≥80% of doses. TFV detected in 81% of plasma samples.	High PrEP uptake and adherence among sero-discordant couples
HVTN702 ²²	Phase 2b-3 trial – HIV vaccine efficacy. (placebo controlled).	South Africa	Adults (males and females)	2016-2020	PrEP uptake was 3% via self-report.	TFV-DP in DBS was detected in 2% of all samples tested.	Oral PrEP was offered as part of the trial HIV prevention package.
DREAMS – Kenya ³²	Package of behavioral, biomedical, economic and social HIV prevention interventions.	Kenya	AGYW	2017	PrEP continuation at Month-1: 57% Month-2: 46% Month-3: 37% Median persistence: 56 days	PrEP refills.	PrEP persistence evaluated using survival analysis and programmatic PrEP refill data.
PlusPills ³⁹	Open-label single-arm phase 2 study	South Africa	15-19 years (males and females)	2015-2016	PrEP continuation: 82% at week-12, and 76% at week-24, and 59% at week-24.	Plasma TFV was detected in 54% of samples at week-12. TFV-DP in DBS: 92% had detectable TFV-DP levels at week-12, and 74% at week-24.	

POWER study ³³	Implementation science study	South Africa, Kenya	AGYW	2017-2020	PrEP uptake: 94% Refill at Month-1: 37% Among those with 6-month follow-up, 20% continued PrEP	TFV-DP levels indicated that 47% took an average of ≥ 4 doses/week	
HPTN 082 ⁴⁰	Open-label PrEP demonstration study	South Africa, Zimbabwe	AGYW	2016-2018	PrEP uptake: 95% 55% persisted with PrEP through month-12.	PrEP refills: 55% had uninterrupted refills through 12 months. TFV-DP: 84% had detectable TFV-DP levels at month-3, 57% at month-6, and 31% at month-12.	

In 2019, when my PhD project was conceptualized, very little was known about integrating oral PrEP into the HIV prevention package in HIV endpoint-driven trials. While ethical guidelines at the time had spoken to the obligation of trialists to provide access to state-of-the-art HIV risk reduction methods to participants in HIV prevention biomedical trials, including adding on new HIV risk reduction methods as these are scientifically validated and approved⁴¹, data on the feasibility and logistics of integrating oral PrEP as HIV prevention standard of care in trials, was scarce. There were several unanswered questions at the time which included:

- What would the uptake of oral PrEP by young African women enrolled in HIV endpoint-driven trials be when PrEP is offered as part of HIV prevention standard of care?
- Which participants would opt to initiate oral PrEP?
- Would women adhere to oral PrEP during the trial?
- What are the experiences of women who initiate oral PrEP during the trial?
- Would women who elect to continue using oral PrEP after exiting the study be able to access oral PrEP post-trial exit?
- What are the barriers and enablers to post-trial oral PrEP access?
- What are the experiences of South African researchers in including oral PrEP as part of the HIV prevention package in HIV endpoint-driven trials? What are the facilitators and challenges?

The Evidence for Contraceptive Options and HIV Outcomes (ECHO) Trial was one of the first HIV endpoint-driven clinical trials to provide oral PrEP onsite as part of the trial's HIV prevention package to study participants during the latter part of the trial; and provided the basis for this PhD project⁴². While the ECHO Trial provided oral PrEP to study participants in South Africa during the trial, and recorded dates of oral PrEP use, oral PrEP was not a study outcome of the trial, therefore additional data related to PrEP such as reasons for using PrEP, adherence, disclosure of PrEP use, side effects and post-trial access, were not captured. As part of my PhD project, I conceptualized and designed several ancillary studies to collect additional data on oral PrEP integration during the ECHO Trial including data on oral PrEP adherence, persistence, side effects, reasons for using oral PrEP, and post-trial access.

Several components of this PhD project such as PrEP uptake, continuation, adherence and post-trial access fit well into a PrEP cascade. Dunbar and team described the use of an intervention-centric PrEP cascade as a framework to evaluate uptake and coverage of oral PrEP among AGYW⁴³. I have adapted this framework proposed by Dunbar and team to describe PrEP access, uptake/initiation, continuation, adherence, and post-trial PrEP access (Figure 1).

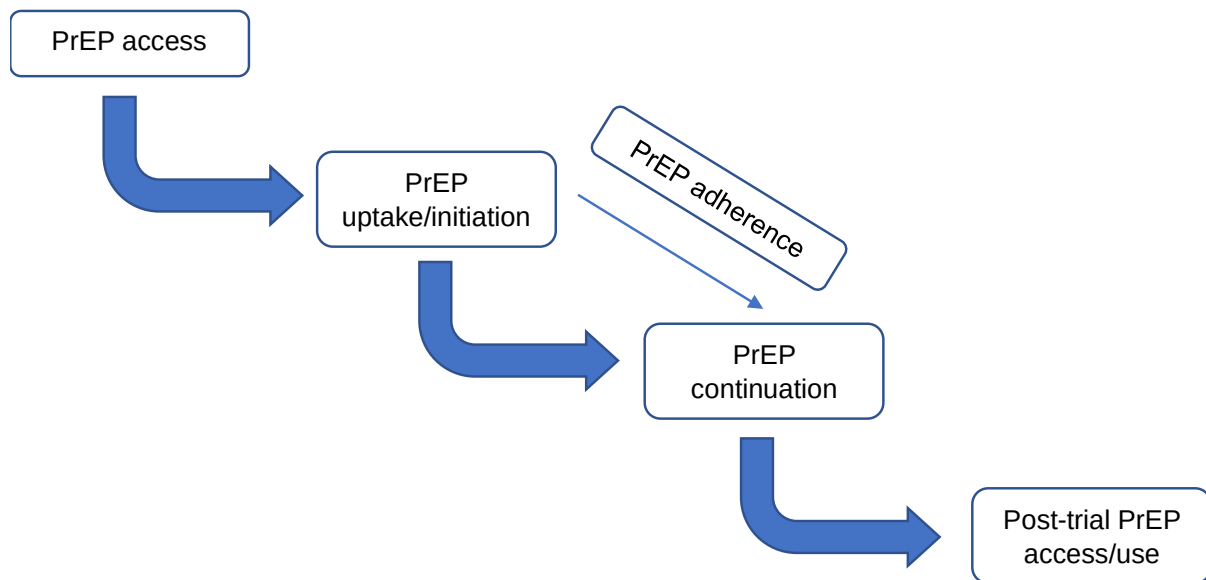


Figure 1: PrEP Cascade

AIM AND OBJECTIVES

The aim of my PhD project was to describe the process of integrating oral PrEP as standard of care for HIV prevention in the ECHO Trial and the experiences of women who initiated oral PrEP, including adherence and post-trial access to oral PrEP.

My objectives were:

1. To describe the process of implementing oral PrEP provision, including the uptake of oral PrEP and the characteristics of women who initiated (versus those who did not initiate) oral PrEP during the ECHO Trial.
2. To evaluate oral PrEP adherence and factors associated with adherence by conducting plasma TFV drug level testing using stored blood samples among a subset of women from South Africa who reported current oral PrEP use at the final ECHO Trial visit.
3. To describe the experiences of women who initiated oral PrEP at the Durban, South Africa, ECHO Trial site.
4. To explore post-trial access to oral PrEP, and barriers and enablers to post-trial oral PrEP access, among a subset of women from the Durban, South Africa, ECHO Trial site.
5. To review the current status of oral PrEP as standard of care for HIV prevention in clinical trials in South Africa.

METHODS

This section summarizes my methodology. I provide an overview of the ECHO Trial, and thereafter describe the methods utilized for each study objective. This is a mixed methodology PhD project and both qualitative and quantitative methods have been utilized. Additional methodology details are available in each of the manuscripts in Chapter 2 of this thesis.

Overview of the ECHO Trial: The ECHO Trial was an open-label, randomized trial that assessed the effects of three contraceptives (intramuscular depot medroxyprogesterone acetate, a copper intrauterine device, and a levonorgestrel implant) on HIV incidence⁴⁴. The trial was conducted at 12 trial sites in Eswatini, Kenya, South Africa and Zambia (Figure 3), between 2015 and 2018. In total, 7829 HIV-negative, sexually active women, aged 16 to 35 years and seeking contraception were enrolled into the trial. Follow-up was 12-18 months. Women were seen a month after enrolment, then in two months, and thereafter quarterly. Detailed ECHO protocol and trial procedures, including inclusion and exclusion criteria, as well as the outcome of the trial have been published elsewhere^{44,45}. Overall, HIV incidence in the ECHO Trial was 3.8 per 100 person-years (95% confidence interval (CI) 3.45 to 4.21), and there was no substantial difference in HIV acquisition risk among the three contraceptive methods⁴⁴. Women signed written informed consent to participate in the ECHO Trial.

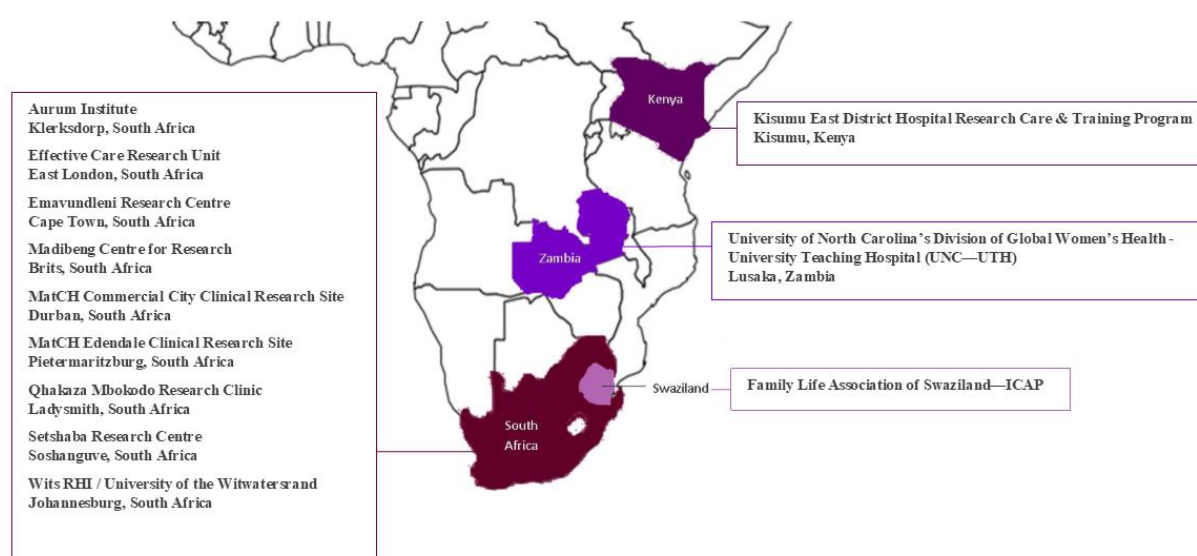


Figure 3: An overview of the ECHO Trial host countries and research sites

Source: <http://echo-consortium.com/wp-content/uploads/2018/09/map-of-sites-2018-1.png>

For objective 1, we described in detail the process undertaken by the ECHO Trial team to incorporate oral PrEP delivery as part of the HIV prevention package provided during the trial. The HIV prevention package provided to study participants at each follow-up visit included HIV risk reduction counselling, HIV counselling and testing, screening and treatment of STIs, provision of condoms, partner HIV counselling and testing either onsite or via referral, counselling on ART for risk reduction, and referral for ART for serodiscordant couples. When the ECHO Trial began recruitment in 2015, oral PrEP was not yet considered standard of care for HIV prevention in the host countries. The ECHO Trial protocol allowed for women to use oral PrEP at any time, and for the offering of oral PrEP onsite as part of the trial prevention package if oral PrEP was incorporated into national HIV prevention policies in the host countries. The four ECHO Trial host countries incorporated oral PrEP into their national policies in different ways and times. We described how each country incorporated oral PrEP provision to trial participants during the trial. For the ECHO Trial, oral PrEP was made available to trial participants through two mechanisms: 1) onsite as part of

the HIV prevention package and 2) off-site via referral. At the nine South African ECHO Trial sites, oral PrEP was made available onsite to study participants from March 2018 and was available at all South African trial sites by June 2018. Women who initiated oral PrEP onsite were seen a month after initiation and thereafter 3-monthly. In addition, PrEP visits were aligned with regular study visits where feasible. Baseline and follow-up investigations such as Hepatitis B and creatinine testing were conducted as per South African DoH PrEP guidelines³⁴.

Additional considerations for the onsite PrEP provision at the South African ECHO Trial sites included stakeholder and community consultation, staff training, drug procurement and management, laboratory testing, costs, availability of resources, policy framework and local PrEP guidelines. Prior to the onsite provision of PrEP, each trial site had to complete a readiness checklist to ensure that all components needed for provision for PrEP were available including having a standard operating procedure in place. Sites were only permitted to initiate onsite PrEP provision once approved by the ECHO site liaison.

During the ECHO Trial, quantitative data were collected using case-report forms that were faxed to a central database. A thorough quality control system was in place both at the trial site by study staff, and at the central data management centre. All data were cleaned during the study. Data collected during the ECHO Trial included demographics, behavioural characteristics, contraceptive method use, presence of STIs, HIV test results and dates of oral PrEP use.

Characteristics between women who ever initiated oral PrEP versus those who had access to but did not initiate oral PrEP, were assessed using Chi-squared tests (or Fisher's exact tests for uncommon characteristics) for categorical variables and t-tests for continuous variables. HIV seroincidence comparisons between participants who never versus ever initiated oral PrEP were modelled using exact Poisson regression. This analysis was conducted by an ECHO Trial statistician.

Objective 1 incorporates PrEP access, PrEP uptake/initiation, and PrEP continuation from the PrEP cascade.

For objective 2, we tested stored plasma samples that were collected at the final study visit for women who reported ongoing oral PrEP use at this visit. This analysis was limited to women enrolled at eight of the nine South African ECHO Trial sites – Brits, Durban, East London, Edendale, Johannesburg, Klerksdorp, Ladysmith, and Soshanguve. We tested samples from women enrolled at these sites who: 1) initiated oral PrEP during the trial (either onsite or off-site), 2) reported ongoing oral PrEP use at the final study visit, and 3) consented to long-term sample storage and future testing at enrolment into the trial. The list of samples for testing was generated by the ECHO data centre. During the trial, samples that were collected from women at trial sites at the final visit, were processed and then transported to Bio Analytical Research Corporation (BARC) laboratory in Johannesburg, South Africa. At BARC, samples were stored in freezers at minus 80 degrees Celsius. Samples were retrieved from storage and then transported to the University of Cape Town (UCT) for testing. TFV in plasma was analysed with a liquid chromatography tandem mass spectrometry assay developed at the Division of Clinical Pharmacology, UCT. Samples were processed with a protein precipitation extraction method using TFV-d6 as internal standard followed by high performance liquid chromatography with tandem mass spectrometry detection using an AB SCIEX API 5500 instrument. Gradient chromatography was performed on a Waters Atlantis T3 (C18, 3 µm, 100 mm X 2.1 mm) analytical column. The mobile phase consisted of 0.1% formic acid in water and 0.1% formic acid in acetonitrile and was delivered at a flowrate of 300 µL per minute. The analyte and internal standard were

monitored at mass transitions of the protonated precursor ions m/z 288.1 and m/z 294.0 to the product ions m/z 176.2 and m/z 182.0 for TFV and TFV-d6, respectively⁴⁶. Quantification of TFV above 10ng/mL was defined as quantifiable.

Bivariate logistical regression was used to evaluate participant characteristics associated with quantifiable TFV at the final trial visit. Each factor significant at $p \leq 0.05$ in a bivariate model was then adjusted for age in independent models. Results were presented as crude and adjusted odds ratios (OR) with 95% confidence intervals (CI) and p-values. Analyses were conducted using Stata version 14.1. I conducted this analysis under supervision.

Plasma TFV results were not provided to study participants as testing was conducted retrospectively and all participants had exited the trial prior to testing of samples. Furthermore, it was unlikely that the results would be of value to participants as testing was conducted in 2021. We chose to test plasma TFV samples (as opposed to intracellular TFV-DP in red blood cells) because we had retrospectively initiated testing of stored study samples and whole blood samples were not collected/available.

Objective 2 incorporates PrEP adherence from the PrEP cascade.

To answer objective 3, I conducted an ancillary oral PrEP study at a single ECHO Trial site in Durban, South Africa to collect additional data on oral PrEP use. This ancillary study was conducted from April 2018 to April 2019. Women who initiated oral PrEP onsite at the Durban trial site were invited to complete a structured interviewer-administered questionnaire, in English or isiZulu, approximately three months after initiating oral PrEP. Written informed consent was obtained to participate in the ancillary study. The questionnaire probed experiences with using trial provided oral PrEP, including reasons for initiating and discontinuing oral PrEP, side effects experienced, perceived HIV risk, reported adherence to oral PrEP and disclosure of oral PrEP use. In addition, data were also collected at the final ECHO Trial visit on whether oral PrEP was being continued, and reasons for discontinuation. Among women who elected to continue using oral PrEP at the final study visit, telephonic follow-up was conducted approximately four to six months after exiting the trial to briefly explore post-trial oral PrEP access and continued use. Women were asked whether they were still using oral PrEP, if they had any problems accessing oral PrEP after the trial had ended. If women discontinued oral PrEP, reasons for discontinuation were probed. For the phone-based interviews, women were asked to confirm their name and surname, and were asked a study specific question to verify that they were the correct participant in the study. Interviews were arranged at a time that was suitable for the woman. Data for this study were entered onto the REDCap® electronic data capture tools hosted at the University of the Witwatersrand⁴⁷, and analysed using Stata version 14 (StataCorp, College Station, USA). Descriptive analyses were conducted for the purpose of this study.

I evaluated factors associated with oral PrEP continuation at study exit among women who initiated oral PrEP onsite at the Durban, South Africa, ECHO Trial site, using univariate logistical regression models. Factors associated with oral PrEP continuation at $p < 0.05$ were included in the multivariate analysis in which I adjusted for a priori confounders (age and relationship status). Results are presented using crude and adjusted ORs with 95% CIs. All statistical analyses were conducted using Stata version 14.1 and were conducted under supervision.

Objective 3 incorporates PrEP uptake/initiation, PrEP continuation, and briefly post-trial PrEP access from the PrEP cascade.

For objective 4, I conducted face-to-face interviews with 13 women who had initiated oral PrEP onsite at the Durban, South Africa, ECHO Trial site, and had continued using oral

PrEP at ECHO Trial exit in 2018. I recruited women who had provided written informed consent to be contacted for future studies. Women were contacted by telephone and invited to participate in a one-time, in-depth interview. Women who agreed were interviewed from November to December 2021, which was approximately three years after all participants had been exited from the ECHO Trial. The semi-structured interview guide explored reasons for initiating oral PrEP during the trial, oral PrEP use following study exit, barriers and enablers to oral PrEP access post-trial, reasons for oral PrEP discontinuation, and suggestions to improve oral PrEP services for women. Each interview lasted approximately 15 to 30 minutes. Interviews were conducted at the research site in a quiet, private room to ensure confidentiality. Women were informed that I was conducting this research as part of my PhD project.

Interviews were audio recorded and transcribed verbatim. Field notes were taken. Interviews were coded, and analysis was facilitated using NVivo, version 10. Coding was inductive and deductive, and the code list was modified as additional transcripts were coded. Thematic analysis was conducted.

Objective 4 incorporates post-trial PrEP access from the PrEP cascade.

To answer objective 5, qualitative methods were used. Fifteen semi-structured, one-time, in-depth interviews were conducted via telephone with key stakeholders, who were working at research organizations in South Africa that were known to conduct HIV prevention and endpoint-driven clinical trials. Key stakeholders recruited to participate in the interviews were employed in job categories that included site directors, principal investigators, clinicians, and other senior staff with experience in HIV prevention research. The sampling techniques utilized to identify key stakeholders were purposive and snowball sampling. Potential participants were contacted via email to request participation in the study. The email provided details about the study which included an information sheet. Those who responded and were agreeable to participate signed written informed consent. Interviews were conducted by myself, in English, from August 2020 to May 2021. The interview guide explored contents of the HIV prevention package provided to study participants in clinical trials, whether oral PrEP was provided and how it was provided (onsite versus off-site referrals), experiences in providing oral PrEP to study participants, facilitators and barriers to oral PrEP provision, and post-trial oral PrEP access. Each interview was approximately 30 to 40 minutes. Interviews were audio-recorded and transcribed, and analysis was facilitated using NVivo version 10. Inductive and deductive methods were used to derive codes. Thematic analysis was conducted.

Objective 5 incorporates all the steps from the PrEP cascade.

A summary of my methodology and analyses are provided in Table 3.

Table 3: Summary of study objectives, data sources, and analyses

Objective	Data source(s)	Data analyses
1. To describe the process of implementing oral PrEP provision, the uptake of oral PrEP and the characteristics of women who initiated (versus those who did not initiate) oral PrEP during the ECHO Trial.	Main ECHO Trial data. Includes all 12 ECHO Trial sites.	Descriptive Chi-squared/Fisher's exact tests for categorical variables and t-tests for continuous variables Poisson regression
2. To evaluate oral PrEP adherence and factors associated with adherence by conducting plasma TFV drug level testing using stored blood samples among a subset of women from South Africa who reported current oral PrEP use at the final ECHO Trial visit	Stored plasma samples. Main ECHO Trial data. Includes 8 of the 9 ECHO Trial sites in South Africa.	Descriptive Logistical regression
3. To describe the experiences of women who initiated oral PrEP at the Durban, South Africa, ECHO Trial site.	Ancillary study questionnaires. Main ECHO Trial data. Includes one ECHO Trial site (Durban, South Africa).	Descriptive Logistical regression
4. To explore post-trial access to oral PrEP, and barriers and enablers to post-trial oral PrEP access, among a subset of women from the Durban, South Africa, ECHO Trial site.	In-depth interviews with participants who exited the ECHO Trial. Includes one ECHO Trial site (Durban, South Africa).	Thematic analysis (facilitated with NVivo)
5. To review the current status of oral PrEP as standard of care for HIV prevention in clinical trials in South Africa.	In-depth interviews with key stakeholders from research sites in South Africa.	Thematic analysis (facilitated with NVivo)

Ethics: The ECHO Trial was approved by research ethics committees for each of the study sites, the FHI360 Protection of Human Subjects Committee, and the WHO ethics committee. The ECHO ancillary study was approved by the University of the Witwatersrand Human Research Ethics Committee (Wits HREC) (Reference: 141112). This PhD project, which included the plasma tenofovir testing, as well as the in-depth interviews with key stakeholders and with study participants was approved by Wits HREC (Reference: M191155).

Participant confidentiality: Participant data for the main ECHO Trial, ancillary studies and in-depth interviews were de-identified and collected using participant identification numbers. Identifying information such as informed consent forms and link logs were stored in lockable cabinets in access-controlled areas, and separately from the study coded documents. Transcripts from the in-depth interviews were password protected. Access to study documents were restricted to research staff, PhD supervisors and ECHO Trial monitors.

Data storage and destruction: All data collected for the ECHO Trial and the rest of this PhD project were stored in lockable cabinets, secure storage units (post-study closure), and/or online databases which were password protected. Data, including interview recordings, will be destroyed as per the research unit's guidelines which are South African Good Clinical Practice compliant.

RESULTS

This section summarizes the main results of my PhD project. Six manuscripts have been developed, five of which have been published in peer-reviewed journals, and the final manuscript has been submitted to a peer-reviewed journal and is under review. The published and submitted papers are presented in Chapter 2.

Objective 1: To describe the process of implementing oral PrEP provision, including the uptake of oral PrEP and the characteristics of women who initiated (versus those who did not initiate) oral PrEP during the ECHO Trial

The published manuscript, titled, "Integrating oral PrEP delivery among African women in a large HIV endpoint-driven clinical trial" describes the process of implementing oral PrEP provision, the uptake of oral PrEP, and characteristics of women who initiated (versus those who did not initiate) oral PrEP during the ECHO Trial. We described the availability of oral PrEP in the four ECHO host countries – Eswatini, Kenya, South Africa and Zambia, and thereafter describe how oral PrEP was integrated into the ECHO Trial at each of the host countries. We found that oral PrEP access in the ECHO Trial started in Kenya through public availability in May 2017 (Table 3). In Eswatini and Zambia, oral PrEP was available via government-sponsored demonstration projects which began in 2017. In South Africa, oral PrEP was available in 2016, but limited to sex workers, and guidelines were later updated to include MSM, sero-different couples, and AGYW. Following the statement made by the SAMRC that recommended that oral PrEP be made available to participants in HIV endpoint-driven clinical trials, the ECHO Trial team together with the support of the community advisory board, explored how to make oral PrEP available to ECHO Trial participants. For women in Eswatini, Kenya and Zambia, access to oral PrEP was via referral to off-site facilities. For the South African trial sites, oral PrEP was made available onsite via provision by trial staff, in addition to off-site referrals where available.

Table 4: PrEP uptake/initiation and use in the ECHO Trial

Characteristic	N or N (%) or median or date
Number (N) enrolled and followed in the ECHO Trial (all sites)	7829
Date when PrEP became available at trial sites: South Africa ECHO Trial sites Eswatini Kenya Zambia	March – June 2018 December 2017 May 2017 November 2017
Number (N) in follow-up who had access to PrEP when PrEP became available (all sites)	3626
PrEP uptake / initiation (N, %) All ECHO Trial sites (n=12) South Africa ECHO Trial sites (n=9) Eswatini Kenya Zambia	622 (622/3626), 17.2% 559 (559/2069), 27.0% 11 (11/363), 3.0% 45 (45/889), 5.1% 7 (7/305), 2.3%
Median duration of PrEP use in days from initiation to trial exit (all sites)	85 days
PrEP continuation at trial exit among all sites (N, %)	414 (414/622), 66.6%

We found that 3626 of the 7829 women (46.3%) enrolled in the ECHO Trial were still in study follow-up when oral PrEP became available, and of these, 17.2% (n=622) initiated oral PrEP. Of the 622 women who initiated oral PrEP, 559 (89.9%) were from the South African trial sites, and only 49 (8.8%) of these women had initiated oral PrEP at off-site facilities, prior to onsite PrEP provision. The uptake of oral PrEP at the South African trial sites was 27%. Overall, those who initiated oral PrEP were older, more likely to be unmarried, not living with their partner, having multiple partners; and less likely to be earning their own income and receiving financial support from partners (all $p < 0.05$). There was no statistically significant difference in oral PrEP initiation across randomized contraceptive groups ($p = 0.7$). Two-thirds of women reported they were continuing oral PrEP at study exit. There were 37 HIV seroconversions among women who had access to oral PrEP but did not initiate oral PrEP, and 2 seroconversions among women who initiated oral PrEP (HIV incidence 2.4 versus 1.0 per 100 person-years, Incidence Risk Ratio = 0.35, 95% CI = 0.04 to 1.38).

Overall, we found that it was feasible to integrate PrEP into the ECHO Trial with regards to operational requirements, logistics and costs. Furthermore, PrEP was successfully integrated into the trial as indicated by PrEP uptake and continued use at trial exit.

Objective 2: To evaluate oral PrEP adherence and factors associated with adherence by conducting plasma TFV drug level testing using stored blood samples among a subset of women from South Africa who reported current oral PrEP use at the final ECHO Trial visit

The published brief report, titled, “Brief Report: Quantifiable Plasma Tenofovir Among South African Women Using Daily Oral Pre-exposure Prophylaxis During the ECHO Trial” describes oral PrEP adherence and factors associated with adherence by conducting plasma TFV drug level testing using stored blood samples, in a subset of women, who reported oral PrEP use at the final study visit. For this paper, we included women from eight

of the nine South African trial sites. In total, 465 women had initiated oral PrEP at the eight trial sites and 260 (56%) plasma samples from the final study visit were tested for TFV. The remaining 205 women did not have TFV testing performed because of declining long-term sample storage (n=19) or not using oral PrEP at the final study visit (n=186). Of the 260 women included, about half were ≤ 24 years and 22% were diagnosed with *Chlamydia trachomatis* at enrolment into the ECHO Trial. At oral PrEP initiation, 68% reported inconsistent/no use of condoms. The median duration of oral PrEP use was 90 days. TFV was quantified in 36% (n=94) of samples. Women >24 years old had twice the odds of having TFV quantified compared to younger women (OR = 2.12; 95% CI = 1.27 to 3.56). Women who reported inconsistent/no use of condoms had lower odds of TFV quantification (age-adjusted OR = 0.47; 95% CI = 0.26 to 0.83).

Objective 3: To describe the experiences of women who initiated oral PrEP at the Durban, South Africa, ECHO Trial site.

The published manuscript titled, “Exploring the Use of Oral Pre-exposure Prophylaxis (PrEP) Among Women from Durban, South Africa as Part of the HIV Prevention Package in a Clinical Trial” describes the experiences of women who initiated oral PrEP at the Durban, South Africa, ECHO Trial site. We found that of the 324 women eligible for oral PrEP when it became available onsite, 42.6% (n=138) initiated oral PrEP. In total, 132 women consented to participate in this study. Of these, the mean age at ECHO Trial enrolment was 24 years old and 82 women (62.1%) were ≤ 24 years. The main reasons that women cited for initiating oral PrEP were to prevent or protect against HIV (n=98, 74.2%); and partner-related reasons (n=50, 37.9%) such as distrust of the partner, the partner being unfaithful previously and having a partner whose HIV status was unknown. Almost a quarter of the women (n=28, 21.2%) initiated oral PrEP due to inconsistent or no condom use. Majority of women had heard of oral PrEP for the first time by trial staff (n=120, 90.9%), and most had disclosed oral PrEP use (n=119, 90.2%). About a third of women (38/102, 37.3%) reported not missing taking their oral PrEP within the last 30 days. Of the remaining women (n=64), reasons for missing doses included being away from home when oral PrEP needed to be taken (n=33, 51.6%), and forgetful to take oral PrEP (n=33, 51.6%). Overall, 100 women (75.8%) had decided to continue oral PrEP at the ECHO study exit visit and 32 (24.2%) had discontinued oral PrEP either during study follow-up or at the final study visit. At follow-up four to six months post-trial exit, more than 50.0% of women reported discontinuing PrEP, and barriers relating to oral PrEP access emerged.

A second published manuscript titled, “Daily Oral Pre-exposure Prophylaxis (PrEP) Continuation Among Women from Durban, South Africa, Who Initiated PrEP as Standard of Care for HIV Prevention in a Clinical Trial” describes oral PrEP continuation during the ECHO Trial up to study exit, reasons and timing for oral PrEP discontinuation, and factors associated with oral PrEP continuation at study exit. This paper included women enrolled at the Durban, South Africa, ECHO Trial site. I found that of the 132 women included in this study, 87% (n=115) reported continuation of oral PrEP at month 1, 80% (n=106) at month 3, and 75% (n=99) continued using oral PrEP at their final trial visit and were referred to off-site facilities for ongoing oral PrEP access. The median duration of oral PrEP use was 91 days. Among women discontinuing oral PrEP (n=32), $>50\%$ discontinued within the first month, and the most frequent reason for discontinuation was reporting side effects. Women who disclosed their oral PrEP use to someone had increased odds of continuing oral PrEP at trial exit (adjusted OR = 4.98; 95% CI = 1.45 to 17.13; p=0.01). Women who reported >1 sex partner and those who felt they would probably or definitely get infected with HIV had

reduced odds of continuing oral PrEP at trial exit (adjusted OR = 0.24; 95% CI = 0.06 to 0.97; $p=0.05$ and adjusted OR = 0.21; 95% CI = 0.08 to 0.55; $p<0.01$ respectively).

Objective 4: To explore post-trial access to oral PrEP, and barriers and enablers to post-trial oral PrEP access, among a subset of women from the Durban, South Africa, ECHO Trial site.

The submitted manuscript, entitled, “Post-trial access to and use of pre-exposure prophylaxis in Durban, South Africa” explores post-trial access to oral PrEP, and barriers and enablers to post trial PrEP access, in a subset of women from the Durban, South Africa, ECHO Trial site. I interviewed 13 women who reported continuing oral PrEP at the final study visit. I found that women experienced several barriers to oral PrEP access after exiting the trial which limited their continued use of oral PrEP. These included long queues at facilities, facilities being located far from women’s homes, being unable to afford transport costs to access clinics, unsuitable clinic operating hours, negative attitudes from providers, and oral PrEP being unavailable at some facilities. Facilitators to PrEP access and use included clinics being located close to women’s homes, quality information and counselling provided by oral PrEP providers, oral PrEP demand creation and having a referral letter from the research site to collect oral PrEP refills. Only one woman was still using oral PrEP at the time of the interview. Most women who were not on oral PrEP expressed a desire to use oral PrEP again, particularly if barriers to access could be removed.

Objective 5: To review the current status of oral PrEP as standard of care for HIV prevention in clinical trials in South Africa

This published manuscript, titled, “Key stakeholders’ perspectives on providing oral pre-exposure prophylaxis as HIV prevention standard of care in clinical trials in South Africa” reviews the current status of oral PrEP as standard of care for HIV prevention in clinical trials in South Africa. I interviewed 15 key stakeholders from research sites across South Africa known to conduct HIV prevention and HIV endpoint-driven clinical trials. Most stakeholders reported that they had incorporated oral PrEP provision as part of the HIV prevention package in HIV prevention and endpoint-driven clinical trials. Key stakeholders reported that the decision to provide oral PrEP in clinical trials was influenced by the SAMRC summit on the standard of care in clinical trials, the rollout of oral PrEP by the South African DoH, ethical considerations, and by trial funders. Barriers identified to oral PrEP uptake and use among participants included challenges with daily pill taking, side effects, stigma, a lack of demand creation, limited knowledge and education about oral PrEP in communities, and personal preferences for other modes of PrEP delivery such as injectables. Barriers to oral PrEP uptake frequently overlapped with reasons for poor adherence and oral PrEP discontinuation. Demand creation, and education and counselling about oral PrEP, facilitated uptake. Most stakeholders felt that oral PrEP could be factored into trial calculations and analyses, and therefore were not concerned that oral PrEP use would affect study outcomes. Several barriers to post-trial oral PrEP access were identified, such as long queues and inconvenient operating hours at PrEP facilities, distance, and oral PrEP being unavailable at some facilities.

DISCUSSION

In this section, I discuss the key findings from my PhD project, and compare and contrast my findings with other studies, and to the HIV prevention field. Each manuscript in Chapter 2 provides a more detailed discussion on my research.

Our findings indicate that it was possible to successfully integrate oral PrEP as standard of care for HIV prevention in a large multicentre HIV endpoint-driven trial, with almost one in five women who were eligible for oral PrEP, opting to initiate it. At the South African trial sites, where oral PrEP was provided onsite during the final eight months of the trial, we found that 49 women initiated oral PrEP prior to onsite provision, and more than 500 had initiated oral PrEP when it became available onsite. This suggests that onsite PrEP provision might be important in stimulating greater uptake in clinical trials⁴².

HIV prevention and endpoint-driven trials enrol individuals at heightened risk for HIV acquisition. In the ECHO Trial, HIV incidence overall was 3.8 per 100 person-years⁴⁴, in the HVTN 702 trial, HIV incidence was greater than 3 per 100 person-years overall, and among women, HIV incidence exceeded 4 per 100 person-years²². Baseline characteristics among participants enrolling in these trials include multiple risks for HIV acquisition such as high prevalence of bacterial STIs, high rates of intimate partner violence, having older partners, uncertainty about their partner's HIV status, and condomless sex^{23,29,48}. This underscores the need for access to state-of-the-art HIV prevention methods for participants enrolling in HIV prevention and endpoint-driven trials. Ethical guidelines recommend access to prevention methods including new prevention methods as they become validated¹³, together with partnering with key stakeholders to provide an HIV prevention package that is effective, comprehensive and sustainable¹⁴, and the importance of local community involvement¹⁵. In a South African context, the SAMRC made a recommendation to provide oral PrEP as part of the HIV prevention package in HIV prevention and endpoint-driven trials in 2017¹⁷ (17). At the time, PrEP access in South Africa was rather limited¹⁷, and there were concerns that the provision of PrEP within trials would create perverse incentives for participation in research, however, in the case of the ECHO Trial, enrolment had been completed prior to the onsite availability of oral PrEP as part of the trial's HIV prevention package.

The manner in which oral PrEP was integrated into the ECHO Trial differed from the HVTN 505 study, which was conducted from 2009 to 2013²⁰. In HVTN 505, participants were provided with information and education about oral PrEP and then referred for oral PrEP initiation, while in the ECHO Trial, oral PrEP was made available onsite at the South African trial sites during the latter part of the trial. Similar to the ECHO Trial, the HVTN 702 vaccine efficacy trial provided oral PrEP onsite to study participants at no cost²², however the uptake of oral PrEP was much higher in the ECHO Trial compared to HVTN 702, 17% versus 3.2% respectively. Both the HVTN 704/HPTN 085 and the HVTN 703/HPTN 081 trials, which tested the efficacy of neutralizing antibodies to prevent HIV infection, provided counselling on oral PrEP and unrestricted access at no cost to participants⁴⁹. The HVTN 704/HPTN 085 trial was conducted among cisgender men and transgender persons, who have sex with cisgender men or transgender persons, in the Americas and Europe, and the HVTN 703/HPTN 081 trial enrolled heterosexual women from sub-Saharan Africa. The uptake of oral PrEP in these studies was 39% and 3.8% respectively, as measured by detectable TFV-DP. Notably, oral PrEP uptake was very low among women in the neutralizing antibody study compared to men and transgender persons.

Several other studies have assessed oral PrEP uptake among African women, many of which have found a high uptake of oral PrEP. The CAPRISA 082 study, conducted between 2016 and 2018, in KwaZulu-Natal, South Africa, found that 62% of young women aged 18 to 30 years initiated oral PrEP⁴⁸. Uptake was higher in the HPTN 082 study, conducted from

2016 to 2018, which enrolled women aged 16 to 25 years from South Africa and Zimbabwe – here the uptake of oral PrEP was 95%⁴⁰. Similarly, the POWER study which enrolled women aged 16 to 25 years from South Africa and Kenya found that the uptake of oral PrEP was 94%³³. However, these studies were designed specifically to study oral PrEP compared to the ECHO Trial where oral PrEP was offered as part of the HIV prevention package and the main aim of the study was to assess the effect of three contraceptives on HIV incidence.

In the ECHO Trial, oral PrEP provision was integrated with contraceptive provision and care during the trial. Some studies have looked at integrating oral PrEP provision with contraceptive services⁵⁰⁻⁵², as these could serve as ideal entry points for women to access HIV prevention. In Kenya, a real-world PrEP implementation program called PriYA, found that it was feasible to integrate oral PrEP delivery among women at risk for HIV acquisition, in routine family planning clinics⁵⁰. The uptake of oral PrEP in this setting was 22%. A study in Cape Town, South Africa that looked at mobile oral PrEP delivery integrated with sexual and reproductive health services (SRHS), found AGYW highly valued the integration of oral PrEP with SRHS⁵².

Some of the early oral PrEP studies among African women found low levels of adherence to oral PrEP. In the VOICE trial, TFV was quantified in approximately 30% of samples⁷, and in the FEM-PrEP trial, less than 40% of HIV-uninfected women had TFV quantified⁶. In the ECHO Trial, we found that TFV was quantified in 36% of samples at the final study visit among women reporting ongoing PrEP use. Differences between the ECHO Trial and the two trials described above include that the former trials were placebo-controlled trials of an unproven product, while in the ECHO Trial, oral PrEP was a recommended intervention to prevent HIV. In the ECHO Trial, we measured plasma TFV, which provides a measure of adherence over a few days^{53,54}. A longer-term measure of adherence is TFV-DP in DBS which has a half-life of 17 days and provides a measure of adherence over weeks⁵⁵. Quantifiable TFV in our study was higher than CAPRISA 082 which found that TFV-DP was only quantified in 13% of samples⁴⁸, and lower than HPTN 082, where TFV-DP was quantified in 84% of women at month 3 and 57% at month 6⁴⁰. However, both these studies measured TFV-DP while the ECHO Trial measured TFV. Of interest, despite only about a third of women in the ECHO Trial having TFV quantified at the final trial visit, we found that among all women who initiated oral PrEP in the trial, only two women had seroconverted at HIV incidence rate of 1.0 per 100 person-years, which was much lower than the overall HIV incidence in the trial⁴⁴. Furthermore, additional analyses that were conducted among the South Africa ECHO Trial sites found that onsite access to oral PrEP was associated with a halving of HIV incidence⁵⁶. These study findings may be useful to future trials of HIV prevention that integrate PrEP as part of the trial HIV prevention package⁵⁶.

While many PrEP trials conducted among African women found high uptake of oral PrEP, PrEP persistence, measured by participant self-report and/or drug levels declined over time. In the DREAMS initiative in Kenya, in 2017, PrEP persistence among AGYW at month-3 was 37%³². In the CAPRISA 082 study, three-quarters remained on oral PrEP at month-3, 64% at month-6, and about 50% persisted through 12 months⁴⁸. In the PriYA programme, 41% of women returned for a PrEP refill post initiation⁵⁰. In the ECHO Trial, where the median duration of oral PrEP was about 85 days prior to trial exit, we found that two-thirds of women continued oral PrEP at trial exit⁴². In the ancillary PrEP study conducted at the Durban, ECHO Trial site, we found high rates of oral PrEP persistence with 87% of women persisting at month-1, and 80% at month-3. However, in both the ECHO Trial, and the ancillary study, PrEP persistence was limited by follow-up remaining for participants in the trial. We postulate that the high rates of PrEP continuation observed in the ECHO Trial could be attributed to the integration of oral PrEP with contraceptive provision and care, the provision

of oral PrEP at no cost to participants, aligning PrEP study visits with the main trial visits where feasible, and quality education and counselling provided by trial staff which included allowing participants to explore their own risk profile and which HIV prevention options would be suitable for them. Additional factors to consider include that the study population was research literate and received reimbursement for study participation which differs from real-world settings.

Our ancillary PrEP study, which was conducted at the Durban, South Africa, ECHO Trial site provided insights into women's use of oral PrEP as part of the HIV prevention package during the trial. We found that more than 90% of women had heard about oral PrEP for the first time from trial staff, hence, trials may serve as an entry point to provide information and education about oral PrEP and other prevention options. Qualitative research from the POWER study indicated that PrEP awareness was very low in the communities in which participants lived, and that AGYW primarily heard about PrEP for the first time at the clinic where the POWER study took place²⁹. One of the early lessons learned from oral PrEP implementation projects among young African women was the importance of awareness and demand creation to motivate young women to consider initiating PrEP²⁴. We found that most women in our study had disclosed oral PrEP use. Qualitative research suggests that disclosure can result in support for oral PrEP use, for example with pill reminders, however, disclosure may also result in stigma such as the assumption that PrEP pills are ART, or accusations of infidelity by partners^{29,57}. Notably, in our study we found that women who disclosed oral PrEP use had almost five times the odds of continuing oral PrEP at the final trial visit compared to those who did not disclose oral PrEP use. Reasons for oral PrEP discontinuation in our study have been consistent with findings in other studies^{29,48,50}, and in our study, perceived side effects related to oral PrEP use were the most frequent reason for oral PrEP discontinuation during the trial.

We found that women from the Durban, South Africa, ECHO Trial site experienced several barriers to accessing oral PrEP after exiting the ECHO Trial in 2018, and this frequently resulted in oral PrEP discontinuation. These barriers included long queues, inconvenient operating hours, distance, inability to afford transport costs to collect PrEP refills, and PrEP being unavailable at some clinics. One contributing factor was the phased rollout of oral PrEP in South Africa, which began in 2016 and was initially limited to sex workers³⁴, thereafter gradually expanding to include additional populations³⁷. It was only in 2021 when oral PrEP access was upscaled to include thousands of public sector facilities in the country³⁵. Barriers to oral PrEP access such as being unable to collect oral PrEP refills due to school/work commitments, lacking transport to get to PrEP facilities, unsuitable facility operating hours, long waiting queues and negative attitudes of health care workers have been found in other studies in Africa^{29,58,59}. Recently, there has been a shift to simplified PrEP delivery and the latest WHO PrEP guidelines (2022) emphasize the importance of differentiated and simplified PrEP delivery⁶⁰. These include models of oral PrEP integration into family planning clinics⁵⁰, pharmacies⁶¹, antenatal and postnatal care^{62,63} and community models of delivery such as mobile clinics⁵² and community-based platforms⁶⁴. Many of these models have shown success in delivering oral PrEP by removing access-related barriers to oral PrEP delivery.

A novel contribution of this PhD project was the exploration of stakeholders' perceptions and experiences in offering and/or providing oral PrEP as part of the HIV prevention package in clinical trials in South Africa. Barriers to oral PrEP use as reported by stakeholders such as challenges with daily pill taking, a lack of oral PrEP awareness and demand creation, perceived and experienced side effects, and preferences for other methods of PrEP delivery are similar to barriers reported by participants in several studies^{24,29,59,65}. The impact of oral

PrEP use on study outcomes was also explored in the stakeholder interviews – this is an area that has received much discussion and debate over recent years. Considerations for HIV efficacy trials include the trial population that will be enrolled, the standard of prevention offered during the trial, the control group and whether a placebo will be used, the intervention arm, the primary endpoint and whether it will be HIV acquisition versus a surrogate endpoint, and whether the trial will be a superiority or a non-inferiority design¹⁶. Stakeholders interviewed in our study generally felt that oral PrEP use could be factored into study calculations and analyses by trial statisticians, and therefore would unlikely impact study outcomes. Of concern, many stakeholders reported multiple barriers to post-trial oral PrEP access, and this finding was also observed in our participant interviews on post-trial oral PrEP access and use. As discussed earlier, differentiated and simplified models of PrEP delivery⁶⁰, as well as increased availability of oral PrEP (35) may alleviate some of the challenges with post-trial access.

Finally, a discussion about oral PrEP and the HIV prevention field would be incomplete without discussing long-acting drugs for HIV prevention – these include implants, rings, injectables and extended-release oral preparations⁶⁶. The ASPIRE trial which enrolled African women aged 18 to 45 years, found a 27% reduction in HIV incidence among women randomized to the dapivirine vaginal ring compared to placebo⁶⁷. In 2022, the South African Health Products Regulatory Authority approved the use of the dapivirine vaginal ring⁶⁸. Long-acting injectable cabotegravir (CAB-LA) has been shown to be very effective in preventing HIV in MSM and TGW, as well as women. In HPTN 083, CAB-LA was found to be superior to TDF-FTC in preventing HIV infection among MSM and TGW⁶⁹, and similarly in HPTN 084, CAB-LA was superior to TDF-FTC in preventing HIV infection in women⁷⁰. Long-acting PrEP drugs may help alleviate some challenges with PrEP adherence and continuation, particularly among young women, which was found in our study and several other studies^{31-33,71}. Another long-acting injectable drug for HIV prevention that is currently being evaluated in the PURPOSE clinical trials is subcutaneous lenacapavir, which is given 6-monthly⁷². The addition of long-acting HIV prevention drugs to the HIV prevention toolbox will allow users to choose which options are suitable for them, and could increase uptake, adherence and persistence of PrEP, ultimately reducing HIV incidence. While some lessons from this PhD project may be utilized among trials of long-acting PrEP methods, it is worth noting that several trials evaluating long-acting PrEP methods have active control arms.

Recent innovations in the HIV prevention field include MATRIX, which is a USAID project, funded by USAID and PEPFAR, that aims to advance the research and development of innovative HIV prevention drugs including multi-purpose technologies such as combined contraceptive and HIV prevention products, and is conducting studies in South Africa, Kenya and Zimbabwe⁷³. Another project, MOSAIC, is a PEPFAR funded global project via USAID, which aims to prevent HIV infections among AGYW by accelerating the introduction and scale-up of new biomedical prevention products in several African countries⁷⁴.

My PhD project has some limitations. While the ECHO Trial encouraged, facilitated, and documented the use of oral PrEP as part of a combination HIV prevention package, the ECHO Trial was not explicitly designed to study oral PrEP, therefore data on oral PrEP adherence, reasons for choosing to use PrEP or not, and reasons for discontinuing PrEP were not collected as part of the main ECHO Trial. The ancillary study conducted at the Durban, South Africa ECHO Trial site did collect data on some of these factors, however, data are limited to a single trial site, and therefore generalizability is limited. Oral PrEP was introduced relatively late into the ECHO Trial; hence our findings are applicable to early PrEP use. As many studies have shown, oral PrEP adherence and persistence may change over time. Plasma TFV quantification was limited to eight of the nine South Africa ECHO

Trial sites and was collected at one time-point and not consecutively. Measures of adherence such as TFV-DP in DBS would have been useful to assess longer-term oral PrEP adherence. Interviews with participants to explore post-trial oral PrEP access were conducted approximately 3 years after participants had exited the ECHO Trial. Oral PrEP access and availability in South Africa have increased considerably since the ECHO Trial till now, thereby alleviating some of the access-related barriers reported by stakeholders and participants in this study.

CONCLUSION

Participants enrolling in HIV endpoint-driven trials are frequently at heightened risk for HIV acquisition, and researchers and trial implementers have an ethical obligation to help participants reduce their risk for HIV acquisition. The ECHO Trial was one of the first trials to successfully integrate oral PrEP as standard of care for HIV prevention during the trial, providing evidence that it is practical and feasible to integrate oral PrEP provision into the HIV prevention package provided in clinical trials. Other trials with HIV endpoints can utilize our findings as a model for integrating oral PrEP provision into the HIV prevention package offered to participants. My study findings provide insights on reasons for using oral PrEP, patterns of oral PrEP use, oral PrEP adherence and persistence. I identified several barriers to post-trial oral PrEP access, however, the scale-up of oral PrEP in South Africa will hopefully enhance PrEP access for participants who desire to continue using PrEP upon trial termination.

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CHAPTER TWO

Paper 1: Integrating oral PrEP delivery among African women in a large HIV endpoint-driven clinical trial (published)

Paper 2: Quantifiable Plasma Tenofovir Among South African Women Using Daily Oral Pre-exposure Prophylaxis During the ECHO Trial (published)

Paper 3: Exploring the Use of Oral Pre-exposure Prophylaxis (PrEP) Among Women from Durban, South Africa as Part of the HIV Prevention Package in a Clinical Trial (published)

Paper 4: Daily Oral Pre-exposure Prophylaxis (PrEP) Continuation Among Women from Durban, South Africa, Who Initiated PrEP as Standard of Care for HIV Prevention in a Clinical Trial (published)

Paper 5: Post-trial access to and use of pre-exposure prophylaxis in Durban, South Africa (under review)

Paper 6: Key stakeholders' perspectives on providing oral pre-exposure prophylaxis as HIV prevention standard of care in clinical trials in South Africa (published)

RESEARCH ARTICLE

Integrating oral PrEP delivery among African women in a large HIV endpoint-driven clinical trial

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Clinical Trial Number: Clinicaltrials.gov NCT02550067.

Abstract

Introduction: Global guidelines emphasize the ethical obligation of investigators to help participants in HIV-endpoint trials reduce HIV risk by offering an optimal HIV prevention package. Oral pre-exposure prophylaxis (PrEP) has increasingly become part of state-of-the-art HIV prevention. Here we describe the process of integrating oral PrEP delivery into the HIV prevention package of the Evidence for Contraceptive Options and HIV Outcomes (ECHO) Trial.

Methods: ECHO was an open-label randomized clinical trial that compared HIV incidence among women randomized to one of three effective contraceptives. In total, 7830 women aged 16 to 35 years from 12 sites in four African countries (Eswatini, Kenya, South Africa and Zambia) were enrolled and followed for 12 to 18 months, from 2015 to 2018. Part-way through the course of the trial, oral PrEP was provided to study participants either off-site via referral or on site via trained trial staff. PrEP uptake was compared between different contraceptive users using Chi-squared tests or t-tests. HIV seroincidence rates were compared between participants who never versus ever initiated PrEP using exact Poisson regression.

Results: PrEP access in ECHO began through public availability in Kenya in May 2017 and was available at all sites by June 2018. When PrEP became available, 3626 (46.3%) eligible women were still in follow-up in the study, and of these, 622 (17.2%) initiated PrEP. Women initiating PrEP were slightly older; more likely to be unmarried, not living with their partner, having multiple partners; and less likely to be earning their own income and receiving financial support from partners (all $p < 0.05$). PrEP initiation did not differ across study randomized groups ($p = 0.7$). Two-thirds of PrEP users were continuing PrEP at study exit.

Conclusions: There is a need for improved HIV prevention services in clinical trials with HIV endpoints, especially trials among African women. PrEP as a component of a comprehensive HIV prevention package provided to women in a large clinical trial is practical and feasible. Provision of PrEP within clinical trials with HIV outcomes should be standard of prevention.

Keywords: pre-exposure prophylaxis; clinical trials; standard of care; women; HIV

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1 | INTRODUCTION

Within the context of clinical trials in which incident HIV infection is a primary study outcome, global guidelines emphasize an ethical imperative to assist participants reduce HIV risk by offering state-of-the-art prevention packages [1-4]. Guidelines do not detail a specific set of recommended HIV prevention interventions, and best practices for HIV prevention have evolved over time. Risk-reduction counseling, HIV counseling and testing, and provision of condoms have been commonly provided, and more recent trials have included testing and treatment for sexually transmitted infections (STIs),

HIV and STI testing of partners, voluntary medical male circumcision for HIV-uninfected men, and initiation of antiretroviral therapy (ART) for partners living with HIV [1]. Importantly, the components of prevention packages should reflect community and stakeholder involvement in making decisions about what constitutes an optimal HIV standard of prevention, tailored to the context of each locality, trial and changing expectations about effective prevention services.

In 2015, the World Health Organization (WHO) issued a global recommendation that antiretroviral-based pre-exposure prophylaxis (PrEP) become a component of combination HIV prevention [5]. Many countries have since incorporated oral

PrEP into their national HIV prevention strategies [6-8]. Incorporating PrEP into standard of care HIV prevention services for trials with HIV outcomes has emerged as an important component of trial design and operational plans [9]. How to incorporate new prevention interventions into the standard prevention package of clinical trials comes with ethical, operational and scientific complexities, and this area is currently an active topic of ethical, advocacy and research discussion [4,10].

The Evidence for Contraceptive Options and HIV Outcomes (ECHO) Trial was an open-label, randomized clinical trial testing the relative effects of three effective contraceptive methods on HIV acquisition risk, with incident HIV as the primary study endpoint [11]. The ECHO Trial protocol called for a comprehensive HIV prevention package to be provided to all participants, including PrEP as it became a part of national prevention policies in the host countries and as national recommendations for PrEP emerged during the trial period. Despite the provision of a comprehensive HIV prevention package to women during the ECHO Trial, the HIV incidence was 3.8 per 100 women-years [12]. Here, we describe the process undertaken by the trial team to incorporate oral PrEP delivery as part of the ECHO Trial HIV prevention package.

2 | METHODS

2.1 | Design and follow-up

The ECHO Trial was conducted between December 2015 and October 2018 and followed 7829 women at twelve study sites in four African countries (Eswatini, Kenya, South Africa and Zambia) (Clinicaltrials.gov NCT02550067). Women desiring contraception were randomized in a 1:1:1 ratio to depot medroxyprogesterone acetate by intramuscular injection (DMPA-IM), a copper intrauterine device (IUD), or a levonorgestrel (LNG) implant. Follow-up was quarterly for up to 18 months. Incident HIV infection was the primary study endpoint. Rapid HIV testing was done at baseline, quarterly and if clinically indicated or requested by a participant [11]. Participants signed written informed consent. Approval was obtained from Research Ethics Committees (RECs) associated with each trial site and the Protection of Human Subjects Committee [12].

The trial's community engagement was informed by Good Participatory Practice (GPP) guidelines including developing a GPP plan at each site that detailed community engagement activities and establishing a platform to discuss technical support for GPP [2]. A Global Community Advisory Group (GCAG) was established to provide a forum for civil society, advocates and other stakeholders to engage with the ECHO team about the trial conduct and discuss how broader issues related to HIV prevention and contraceptive use might impact the trial and policies globally.

2.2 | HIV prevention in the ECHO Trial and PrEP availability

The ECHO Trial protocol specified that all participants would be provided a standard HIV prevention package at all visits that included risk reduction counseling, provision of HIV testing and screening, STI testing and treatment, offering condoms, partner HIV counseling and testing, and counseling on ART for HIV risk reduction, and referral for ART in HIV

serodiscordant couples [12]. When ECHO launched participant recruitment in 2015, PrEP was not yet considered standard of care in the host countries. A key consideration in the decision to provide PrEP was accessing PrEP through local means available which would be more sustainable over time. The protocol allowed for women to use PrEP at any time, and for the offering of PrEP on site if it was incorporated into national HIV prevention policies.

The four ECHO Trial host countries incorporated PrEP into national policies in different ways and times. In South Africa, HIV prevention policies were updated in 2016 to include PrEP for all persons with substantial HIV risk but public PrEP programmes were initially restricted to select clinics and demonstration projects for sex workers, eventually expanding to include men who have sex with men, serodiscordant couples and adolescent girls and young women [8]. Kenya introduced PrEP guidance in 2016 and national rollout in May 2017 with universal access to all people with substantial HIV risk [13]. In Eswatini and Zambia, PrEP pilots in government-sponsored demonstration projects began in 2017. In November 2017, the South African Medical Research Council (SAMRC) held a stakeholder meeting, attended by members of the ECHO GCAG, about the evolving PrEP standard of care and issued a recommendation that PrEP should be made available to research participants in clinical trials with HIV endpoints in South Africa [14]. With the support of the GCAG, the ECHO Trial team explored the opportunity to make PrEP available on site at all twelve ECHO sites through trial funds. For women from Kenya and Zambia, it was determined that there was sustainable access to PrEP at referral centres that would continue post-trial. For women from Eswatini, the research site was not part of the country's demonstration project programme, and the site used referral to relevant sites for PrEP access. For the nine sites in South Africa, the ECHO team proceeded to take the steps necessary to make PrEP available at the research sites.

PrEP was made available to ECHO Trial participants through two mechanisms: (1) on site as part of the HIV prevention package and (2) off-site via referral.

2.3 | Process of PrEP integration at the South African ECHO Trial sites

All nine South African ECHO sites began offering PrEP between March and June 2018 following relevant consultation, training and determination of operational readiness. The SAMRC guidance recognized that discussion and input from the local community stakeholders and RECs was essential to ensure meaningful implementation of PrEP [14], and these groups were included in the decision-making process. The decision to provide PrEP on a voluntary basis was supported by the overseeing REC's.

Training of site staff was conducted during the first quarter of 2018 at each trial site. For the training, components were adapted from the South African standardized PrEP training package, and the South African National Department of Health (NDoH) PrEP Guidelines [15]. In addition, field-tested material developed by the Southern African HIV Clinicians Society, the NDoH, and an Optimizing Prevention Technology Introduction on Schedule were used [16]. Training was coordinated with the South African NDoH guidelines to ensure alignment with the national plan. The training also

incorporated provider sensitization, the provision of PrEP as part of an optimal combination HIV prevention package for ECHO Trial participants, the importance of participants exploring their own risk profile and risk reduction options, and adherence to and effective use of PrEP. An important component of the training included communication with participants about post study access to PrEP. Where possible, participants who started PrEP on site would be referred to demonstration projects and public facilities to access PrEP at study exit. The entire site staff teams were included in the training, including cadres representative of the pharmacists, counselors, and outreach, administrative, clinical and quality assurance staff. Additional targeted training was designed for the different staff roles, including in-depth training on informational resources, materials and referrals with each site's community and outreach team. Separate educational workshops and presentations on PrEP were also conducted with each research site's Community Advisory Boards (CABs).

Operational aspects of PrEP readiness focused on costs, commodities and logistical aspects of PrEP delivery: South African national PrEP guidelines include laboratory testing (HIV, pregnancy, creatinine and hepatitis B virus testing) prior to initiation; the PrEP drug (generic emtricitabine/tenofovir disoproxil fumarate) needed to be procured and distributed; and hepatitis B vaccination would be offered. PrEP visits were scheduled according to South African national guidelines, and visits were generally aligned where possible with ECHO Trial study visits. PrEP was offered to participants as part of the HIV prevention package on a voluntary basis in women who were eligible under national PrEP clinical guidelines. PrEP was only offered to participants who were still in active follow-up and had at least one month remaining in the trial. Participants who had initiated PrEP on site and desired to continue PrEP were given a three-month supply of PrEP at their final trial visit and referred to facilities providing PrEP where available.

2.4 | Process of PrEP integration at the non-South African sites

Participants from sites in Eswatini, Kenya and Zambia were counselled on PrEP by trial staff, and those who were interested were referred to facilities off-site. Site investigators and community liaison officers established linkages to off-site facilities providing PrEP where participants could receive PrEP, such as government-approved demonstration sites.

2.5 | PrEP data collection

At each study visit, participants were asked a standardized question about whether she had used PrEP since the last study visit and the dates of PrEP use were recorded. Because PrEP was not a research component of the trial, additional data specific to PrEP were not captured (e.g. reasons for refusal, side effects, laboratory test results specific to PrEP, adherence).

2.6 | Data analysis

2.6.1 | Access to PrEP

For each participant, we defined the date PrEP became available as the earlier of (1) the date when their ECHO site

began offering PrEP (South African sites only) or PrEP became widely available per national programme rollout (Kenyan site only), or (2) the self-reported date of PrEP initiation at an off-site facility (Eswatini and Zambia). Participants who could have initiated PrEP were defined as those who either met the on-site criteria for being offered PrEP (i.e. attended a study visit after PrEP was available, had at least one month remaining in study follow-up, were HIV-uninfected, and at sites in South Africa and Zambia, were not pregnant or breastfeeding), or who were ascertained to have received PrEP off-site. PrEP was not recommended for pregnant and breastfeeding women in South Africa and Zambia as per country guidelines at the time.

2.6.2 | PrEP use

PrEP medications and dates of use were obtained through on-site records of PrEP use using case report forms that were completed by study clinicians on dispensing PrEP and via participant self-report. We defined PrEP use as continuing at study exit if the participant had previously initiated PrEP, attended her final scheduled follow-up visit, and at her final scheduled follow-up visit either received PrEP on site or self-reported ongoing use of PrEP received off-site.

2.7 | Statistical analysis

Comparisons of characteristics between PrEP groups were assessed using Chi-squared tests (or Fisher's exact tests for uncommon characteristics) for categorical variables and t-tests for continuous variables. HIV seroincidence comparisons between participants who never versus ever initiated PrEP were modeled using exact Poisson regression and included covariates that were both significantly different between the never versus ever PrEP users in Table 1.

3 | RESULTS

Of the 7829 women followed in the ECHO Trial, 3626 (46.3%) had access to PrEP prior to exiting the study and 622 (17.2% of those with access) initiated PrEP (Figure 1). Of the 622, 11 initiated in Eswatini (11 of 363 with access, 3.0%), 45 in Kenya (45 of 889, 5.1%), 559 in South Africa (559 of 2069, 27.0%) and 7 in Zambia (7 of 305, 2.3%). For those in South Africa, 49 women had initiated PrEP prior to on-site provision at the South African sites.

The median age of women who initiated PrEP was 24 years (IQR 21 to 27). Women who initiated PrEP compared to those who did not were slightly older, more likely to be unmarried, not living with their partner, having more than one partner and less likely to be earning their own income and receiving financial support from partners (Table 1). Women who initiated PrEP also had a higher VOICE modified risk score (median = 5, IQR 4 to 7) [17] compared to those who did not initiate PrEP (median = 4, IQR 2 to 6). The prevalence of *Chlamydia trachomatis* at enrolment was higher in women who initiated PrEP ($p = 0.005$). Condomless sex at the time of PrEP access was high both in women who did not initiate PrEP as well as women who initiated PrEP with just over half of women in both groups reporting that the last vaginal sex

Table 1. Participant characteristics and association with PrEP initiation

Participant Characteristics: N (%) or median (IQR)			
Characteristic	Had access to but did not initiate PrEP (N = 3004)	Ever initiated PrEP (N = 622)	p-value
Baseline characteristics			
Age group (years)			<0.0001
16 to 17	57 (1.9%)	4 (0.6%)	
18 to 20	820 (27.3%)	129 (20.7%)	
21 to 24	1082 (36.0%)	218 (35.0%)	
25 to 30	815 (27.1%)	200 (32.2%)	
31 to 35	230 (7.7%)	71 (11.4%)	
Never married	1999 (66.5%)	558 (89.7%)	<0.0001
Lives with partner	1194 (39.7%)	134 (21.5%)	<0.0001
Partner provides financial/material support	2188 (72.8%)	277 (44.5%)	<0.0001
Education			<0.0001
None	27 (0.9%)	2 (0.3%)	
Primary (any)	530 (17.6%)	27 (4.3%)	
Secondary (any)	1974 (65.7%)	496 (79.7%)	
Post-secondary (any)	473 (15.7%)	97 (15.6%)	
Earns own income	800 (26.6%)	107 (17.2%)	<0.0001
Number of partners in the past three months			0.006
0	12 (0.4%)	0 (0%)	
1	2840 (94.6%)	573 (92.1%)	
≥2	151 (5.0%)	49 (7.9%)	
Condom use with last vaginal sex			<0.0001
Yes	1331 (44.3%)	317 (51.0%)	
No, had condomless sex	1486 (49.5%)	294 (47.3%)	
No, no vaginal sex	174 (5.8%)	11 (1.8%)	
No, no partner	12 (0.4%)	0 (0%)	
Chlamydia trachomatis	475 (15.8%)	127 (20.4%)	0.005
Neisseria gonorrhoeae	121 (4.0%)	33 (5.3%)	0.15
Voice modified risk score category ^a			<0.0001
0 to 4	1719 (57.6%)	224 (36.1%)	
5 to 8	1267 (42.4%)	396 (63.9%)	
Characteristics at PrEP access date (if did not initiate PrEP) or PrEP initiation date (if ever initiated PrEP)			
Number of partners in the past three months			<0.0001
0	92 (3.1%)	12 (1.9%)	
1	2815 (93.8%)	561 (90.6%)	
≥2	93 (3.1%)	46 (7.4%)	
Condom use with last vaginal sex			0.009
Yes	1177 (39.2%)	262 (42.3%)	
No, had condomless sex	1550 (51.7%)	326 (52.7%)	
No, no vaginal sex	180 (6.0%)	19 (3.1%)	
No, no partner	92 (3.1%)	12 (1.9%)	

^aThe VOICE risk score is composed of demographic and behavioural characteristics, with higher values reflecting greater expected HIV incidence [17].

act was without a condom. Most women reported having one sexual partner at the time of PrEP access (>90%), and 46 (7.4%) women who initiated PrEP reported two or more partners at the visit when PrEP was initiated.

There was no significant difference in uptake of PrEP by randomized contraceptive group with 188 women randomized

to DMPA-IM, 216 randomized to copper IUD and 218 randomized to LNG implant initiating PrEP ($p = 0.75$). Findings were similar when analysed by contraceptive method in use at the time of PrEP initiation: 194 DMPA-IM, 189 copper IUD and 212 LNG implant ($p = 0.68$). Among women who initiated PrEP, the median duration of PrEP use was 85 days prior to

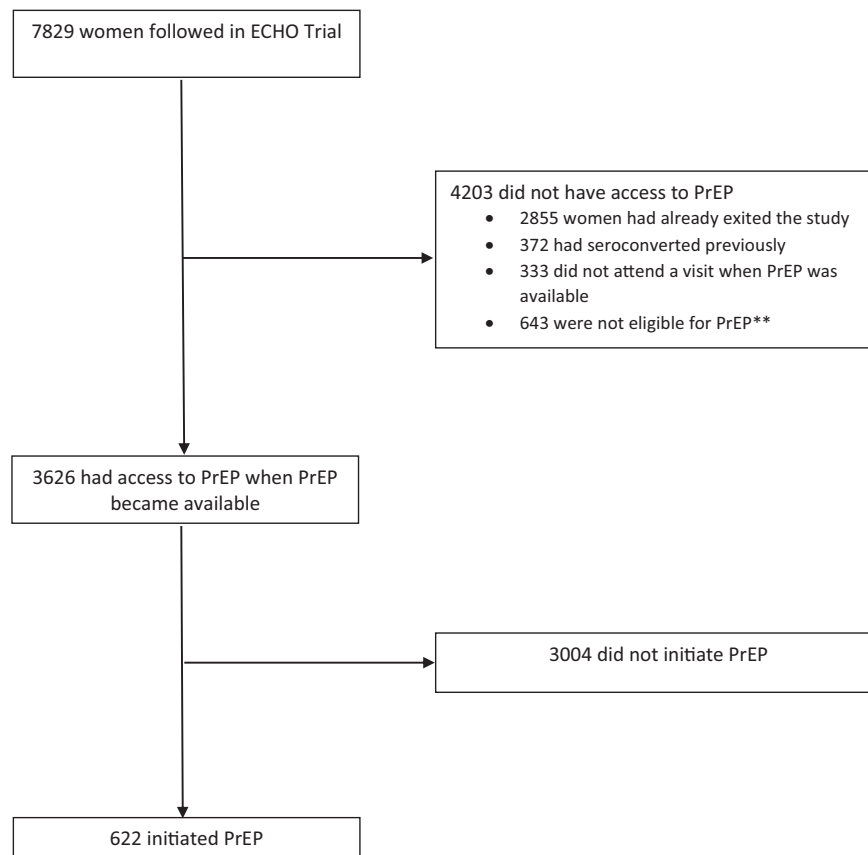


Figure 1. PrEP eligibility and initiation in the ECHO Trial.

**Of the 643 women who were not eligible, 128 had less than 28 days of follow up at sites that were providing PrEP on-site and 515 were either pregnant (26) or breastfeeding (489) at all follow up visits when PrEP was available (in sites other than Kenya and Eswatini). PrEP access was defined as beginning in May 2017 for the site in Kenya, in November 2017 for the site in Zambia, in December 2017 for the site in Eswatini, and between March 2018 and June 2018 for the nine sites in South Africa. ECHO, Evidence for Contraceptive Options and HIV Outcomes; PrEP, pre-exposure prophylaxis.

study exit (IQR 40 to 96), and two-thirds of women (66.6%) were continuing PrEP at study exit.

There were 37 HIV seroconversions among women who had access to PrEP but did not initiate PrEP and 2 seroconversions among women who initiated PrEP (HIV incidence 2.4 versus 1.0 per 100 person-years, IRR 0.35, 95% CI 0.04 to 1.38). Of the two women who seroconverted after starting PrEP, one had stopped PrEP approximately two months prior to seroconversion. The other woman reported continuous PrEP use for 28 days, followed by a two-day break in use, and then continuous use for 52 days until the date of seroconversion. She tested negative on rapid HIV testing both at baseline when initiating PrEP and 30 days later at her first follow-up visit post PrEP initiation.

4 | DISCUSSION

The ECHO Trial provided PrEP as a component of a comprehensive HIV prevention package. In other trials with HIV as the primary endpoint, HIV prevention packages provided to participants have included risk-reduction counselling, free condoms, referral for or provision of male medical circumcision, testing and treatment of STIs, and counselling and referral for

post-exposure prophylaxis. In recent years, substantial discussion has focused on the ethical, logistical and scientific considerations regarding incorporation of oral PrEP into clinical trials with HIV as the primary endpoint, as part of a standard prevention package or an active comparator for new PrEP agents [4,10]. The ECHO Trial represents one of the first trials with incident HIV as a primary study outcome to successfully incorporate PrEP into a standard HIV prevention package, provided on site, and could be used as a model for future trials as PrEP becomes part of standard prevention services.

Almost one in five women with access to PrEP initiated it, and women who initiated PrEP had characteristics suggesting an increased risk for acquiring HIV. Other HIV prevention trials have found similar characteristics among participants, such as a high prevalence of *C. trachomatis* and inconsistent condom use [18,19]. Recent studies have found good uptake of PrEP among young women in Africa [20].

For South Africa, there was a substantial difference in the uptake of PrEP prior to the on-site provision with only 49 women initiating PrEP prior to on-site provision but > 500 initiating after PrEP was available on site. In addition, nearly 90% of those who initiated PrEP were from the South African sites. Together, these suggest that on-site provision of PrEP might be important for stimulating greater uptake in trial settings like this.

There were similar ratios of PrEP uptake among women by randomized contraceptive method and current contraceptive method in use. Theoretically, it was possible that women using DMPA-IM would be more likely to initiate PrEP due to concerns about the possible increased risk of acquiring HIV with DMPA-IM use, as women were extensively counselled about this potential risk when enrolling into the study and during follow-up as a result of updating WHO guidance about the change of progestogen-only injectables among women at high risk for HIV from a WHO MEC category 1 to category 2 which occurred during the course of the trial [21]. However, we did not find greater uptake of PrEP in women using DMPA-IM compared to the other contraceptive methods.

We found that two women who had initiated PrEP had seroconverted compared to 37 women who did not initiate PrEP. Of the two women who had seroconverted, one of these had stopped PrEP two months prior to HIV detection. Our trial was not designed to collect detailed data about PrEP use and directly assess PrEP efficacy, which has been demonstrated in more rigorous and well-powered studies already [6].

The well-being of trial participants is the highest priority for clinical investigators and every effort should be made to help prevent HIV infection in clinical trials with HIV endpoints. It is likely that the provision of PrEP for persons at high risk for HIV will reduce the rate of HIV seroconversions, therefore affecting the study power in HIV endpoint trials. In ECHO, PrEP was offered late into the trial and thus would not be expected to have a significant impact on the total number of HIV infections in the trial. Nevertheless, this potential limitation should not be a barrier to providing oral PrEP in future trials. It is still possible to obtain study outcomes but it might take a longer period of time to achieve these; and the provision of PrEP should be factored into study power calculations. Novel trial designs and analyses are being considered in response to effective HIV prevention provision to all participants [10]. Not all women who are offered PrEP will initiate it, and not all women who initiate PrEP will continue using it or remain adherent to achieve optimal levels of protection. For example, in the recent HPTN 082 study, despite an uptake of PrEP in 95%, detectable plasma tenofovir concentrations declined from 65% at three months to 25% at twelve months [22].

A key limitation of this analysis is that even though the ECHO Trial encouraged, facilitated and documented the use of PrEP as part of a combination HIV prevention package, the trial was not explicitly designed to study PrEP, therefore data on PrEP adherence, reasons for choosing to use PrEP or not, and reasons for discontinuing PrEP were not collected. One of the considerations for the provision of PrEP was participants' post-study access to PrEP. Participants in the ECHO Trial who commenced PrEP on site in the South African sites were counselled about the availability of PrEP and post-study access to PrEP, and where possible, participants were referred to demonstration projects and other sites that were providing PrEP. Post-study access is important not just for PrEP but also for other trial benefits such as contraception and other forms of HIV prevention. We hope that the positive response to the uptake of PrEP in this trial will provide supportive information to governments, policymakers and regulatory bodies that can lead to policies improving public access to PrEP.

Women in Africa and in particularly South Africa are at high risk of acquiring HIV [23]. In the ECHO Trial, HIV incidence was 3.8 per 100 women-years overall and 4.5 per 100 women-years for the nine South African sites [12]. Similar HIV incidence rates have been found in both the FEM-PrEP and VOICE trials [18,19]. WHO recommends that offering PrEP should be a priority for populations with an HIV incidence of about 3 per 100 person-years or higher [5]. HIV prevention trials are conducted among communities and populations at high HIV risk in order to be able to evaluate the efficacy of new interventions. Thus, PrEP provision in such trials must be a priority. PrEP may not be acceptable for all women but it can be offered as an option that is part of an optimal HIV prevention package and women can be given a choice about whether they want to initiate PrEP or not, after being provided with the necessary information and counselling to make an informed decision.

The successful delivery of PrEP in ECHO demonstrates the feasibility of including PrEP in the standard prevention package offered within clinical trials. Barriers to access diminished when PrEP was offered on site, and the number of accepters was high. Our experience shows that with coordinated planning, research sites can quickly train staff, obtain PrEP medication and initiate PrEP services; these lessons are applicable to other clinical trials with HIV as a primary endpoint. The high proportion of women who accepted PrEP during ECHO demonstrates there is a demand for PrEP by this population. Moreover ECHO's integration of PrEP within a study primarily focused on contraceptive services suggest these services are an ideal entry point for HIV prevention.

5 | CONCLUSIONS

There was a high HIV incidence in the ECHO Trial and women who initiated PrEP had characteristics suggesting higher HIV risk. The provision of PrEP as part of HIV prevention standard of care in the ECHO Trial was logistically feasible, and it was possible to provide PrEP in a manner that was aligned with host countries' policies and guidelines. Other clinical trials with incident HIV as a primary study outcome can and should plan to offer PrEP as part of a standard HIV prevention package.

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COMPETING INTERESTS

None were declared.

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IB and JDW drafted the initial manuscript. LK and DD analysed the data. IB, JDW, RH, MP, LK, TP, KA, DB, EAB, CL, TDM, JS, JRB, MM, VCB, MB, DD and

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Quantifiable Plasma Tenofovir Among South African Women Using Daily Oral Pre-exposure Prophylaxis During the ECHO Trial

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Background: HIV endpoint-driven clinical trials provide oral pre-exposure prophylaxis (PrEP) as HIV prevention standard of care. We evaluated quantifiable plasma tenofovir among South African women who used oral PrEP during the Evidence for Contraceptive Options and HIV Outcomes (ECHO) Trial.

Methods: ECHO, a randomized trial conducted in 4 African countries between 2015 and 2018, assessed HIV incidence among

HIV-uninfected women, aged 16–35 years, randomized to 1 of 3 contraceptives. Oral PrEP was offered onsite as part of the HIV prevention package at the South African trial sites. We measured tenofovir in plasma samples collected at the final trial visit among women reporting ongoing PrEP use. We used bivariate and multivariate logistical regression to assess demographic and sexual risk factors associated with plasma tenofovir quantification.

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I.B. conceptualized the study and drafted the initial manuscript. I.B. analyzed the data under the supervision of D.J.D. M.B., L.E.M., J.M.B., and D.J.D. reviewed and revised the first drafts. L.W. was involved in the testing and analysis of samples. I.B., L.E.M., D.J.D., T.P., J.S., K.A., P.S., C.L., M.S., P.K., R.H., L.W., U.M.P., H.R., J.M.B., and M.B. have read the manuscript, provided critical review, and approved the final version.

Access to data from the ECHO study may be requested through submission of a research concept to icrc@uw.edu. The concept must include the research question, data requested, analytic methods, and steps taken to ensure ethical use of the data. Access will be granted if the concept is evaluated to have scientific merit and if sufficient data protections are in place. As of the time of publication, data access applications are in process with the governing institutional review boards of the ECHO study to make deidentified data publicly available.

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Results: Of 260 women included, 52% were ≤ 24 years and 22% had *Chlamydia trachomatis* at enrollment. At PrEP initiation, 68% reported inconsistent/nonuse of condoms. The median duration of PrEP use was 90 days (IQR: 83–104). Tenofovir was quantified in 36% ($n = 94$) of samples. Women > 24 years had twice the odds of having tenofovir quantified vs younger women (OR = 2.12; 95% confidence interval = 1.27 to 3.56). Women who reported inconsistent/nonuse of condoms had lower odds of tenofovir quantification (age-adjusted OR = 0.47; 95% confidence interval = 0.26 to 0.83).

Conclusions: Over a third of women initiating PrEP and reporting ongoing use at the final trial visit had evidence of recent drug exposure. Clinical trials may serve as an entry point for PrEP initiation among women at substantial risk for HIV infection with referral to local facilities for ongoing access at trial end.

Clinical trial number: NCT02550067.

Key Words: HIV prevention, women, plasma tenofovir, oral PrEP, clinical trials, Africa

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INTRODUCTION

In 2020, 63% of new HIV infections in sub-Saharan Africa occurred in women and girls¹ and 140,000 South African women aged 15–49 years acquired HIV,² highlighting an urgent need for HIV prevention options in this setting. Oral pre-exposure prophylaxis (PrEP) containing tenofovir disoproxil fumarate (TDF) is recommended by the World Health Organization (WHO) as an HIV prevention option for persons at substantial risk of HIV³ and is approved for use in South Africa (SA).⁴ Adherence to oral PrEP is important for adequate levels of protection against HIV acquisition. Subjective measures of adherence such as participant self-report may be subject to bias and lead to an overestimation of adherence,⁵ whereas objective measures provide greater accuracy. Adherence to oral PrEP as measured by plasma tenofovir has varied in studies.⁶ In studies enrolling African women using oral TDF/emtricitabine (FTC), plasma tenofovir was quantified in 29% of samples in the VOICE trial,⁷ in $< 40\%$ of samples in the FEM-PrEP study,⁸ and in 68% of samples in HPTN 067.⁹

Although several trials have assessed adherence to oral PrEP using plasma tenofovir,^{7–9} data on adherence to oral PrEP where oral PrEP was offered as part of the HIV prevention package in a trial are lacking. The objective of this analysis was to evaluate the frequency and factors associated with the quantification of plasma tenofovir among women from SA who elected to use daily oral PrEP (hereafter referred to as PrEP) as part of the HIV prevention package in the Evidence for Contraceptive Options and HIV Outcomes (ECHO) Trial.¹⁰

METHODS

ECHO Trial Procedures

The design, procedures, and outcomes, including the integration of PrEP in the ECHO Trial (ClinicalTrials.gov NCT02550067), have been previously described.^{10,11} In brief, the ECHO Trial, conducted between 2015 and 2018, assessed HIV incidence among HIV-uninfected women, aged 16–35

years, who were randomized to 1 of 3 contraceptives (intramuscularly injected depot medroxyprogesterone acetate, the copper intrauterine device, or levonorgestrel implant). Testing for sexually transmitted infections (STIs; *Chlamydia trachomatis* and *Neisseria gonorrhoeae*) was conducted at enrollment and exit. Follow-up was quarterly for 12–18 months.

PrEP Access and On-Site Availability

Initially, PrEP access during the trial was through referral to off-site facilities where PrEP was available. During the latter 8 months of the trial (March to October 2018), daily oral PrEP containing TDF/FTC was provided on-site by trial staff at the SA trial sites. All eligible women remaining in study follow-up were offered PrEP as an additional HIV prevention option. PrEP was dispensed for a month at initiation, and subsequently, 3-monthly supplies were provided. Eligibility criteria for on-site PrEP initiation included having at least 1 month of follow-up remaining in the trial.

Data Collection

Demographic data (age, education, marital status, cohabitation with partner, income, and partner support) were collected at enrollment. Sexual risk behaviors were collected at the PrEP initiation visit. Demographics, sexual risk behaviors, and PrEP use dates were collected with standardized questionnaires in face-to-face interviews by trained study staff and recorded using case report forms. To ascertain PrEP use, women were asked at each study follow-up visit whether they had used PrEP since their previous visit, and if PrEP was used, start and stop dates were recorded. Where PrEP was provided on-site, clinicians documented dates of use. Additional adherence data, such as pill counts and on/off-site PrEP dispensation, were not collected as PrEP was provided as standard of care, not as a research component of the trial.

Sample Collection and Testing

For this analysis, we retrospectively tested stored plasma samples that were collected at the final ECHO study visit for women reporting ongoing PrEP use at this visit. This analysis is limited to women enrolled at 8 SA trial sites (Brits, Durban, East London, Edendale, Johannesburg, Klerksdorp, Ladysmith, and Soshanguve) who had initiated oral PrEP, reported ongoing use at the final study visit, and provided consent to long-term sample storage and testing. We included women who initiated PrEP on-site at the trial sites and women who obtained PrEP off-site. Samples collected from women at study sites were processed and then transported to a central laboratory (BARC; Bio Analytical Research Corporation) in Johannesburg, SA, where the samples were stored in freezers at -80°C . Samples were then transported to the University of Cape Town (UCT) for tenofovir testing. Tenofovir in plasma was analyzed with a validated liquid chromatography tandem mass spectrometry assay developed at the Division of Clinical Pharmacology, UCT.¹² Quantification of tenofovir above 10 ng/mL was defined as quantifiable. Quantifiable plasma tenofovir indicates recent PrEP use over a few days.^{13,14}

Statistical Methods

Bivariate logistical regression was used to evaluate participant characteristics associated with quantifiable tenofovir at the final trial visit. Each factor significant at $P \leq 0.05$ in a bivariate model was then adjusted for age in independent models. Results are presented as crude and adjusted odds ratios (ORs) with 95% confidence intervals (CIs) and P values. All statistical analyses were conducted using Stata v14.1.¹⁵

Ethics

Women signed written informed consent to participate in the ECHO Trial, which included consent for sample storage and future research testing. Approval for the additional tenofovir testing was obtained from the University of the Witwatersrand Human Research Ethics Committee (reference M191155).

RESULTS

In total, 465 women initiated PrEP at the 8 SA trial sites and 260 (56%) plasma samples from the final study visit were tested for tenofovir. The remaining 205 women did not have tenofovir testing performed because of declining long-term sample storage ($n = 19$) or not using PrEP at the final study visit ($n = 186$). Among the 260 women who had samples available for testing, approximately half were ≤ 24 years ($n = 136$, 52%) and most were unmarried ($n = 253$, 97%) and unemployed ($n = 215$, 83%) (Table 1). About 1 in 5 women ($n = 56$, 22%) had *C. trachomatis* and more than two-thirds reported inconsistent or nonuse of condoms ($n = 178$, 68%). The median duration of PrEP use was 90 days (IQR: 83–104 days).

Tenofovir was quantified in over a third of samples ($n = 94$, 36%). Older women (>24 years) had double the odds of having tenofovir quantified compared with younger women [odds ratio (OR) = 2.12; 95% confidence interval (CI): 1.27 to 3.56]. Women who reported inconsistent or nonuse of condoms had lower odds of having tenofovir quantified compared with women who reported always using condoms (adjusted OR = 0.47; 95% CI: 0.26 to 0.83). Similarly, women who reported not using a condom at last sex had reduced odds of having tenofovir quantified compared with those who reported using a condom at last sex (adjusted OR = 0.50, 95% CI: 0.29 to 0.86). Women who had >1 sex partner in the past 3 months had higher odds of quantifiable tenofovir (OR = 2.70, 95% CI = 0.99 to 7.36), although not statistically significant when adjusted for age (adjusted OR = 2.44; 95% CI = 0.88 to 6.75).

DISCUSSION

In this analysis, we found that tenofovir was quantified in over a third of SA women who reported PrEP use at the final study visit in the ECHO Trial. Women >24 years and those who reported multiple sex partners had a greater likelihood of having tenofovir quantified, whereas women who used condoms inconsistently or did not use condoms had a reduced likelihood of having tenofovir quantified. The novelty of this study includes that PrEP was provided as part

of an HIV prevention package and integrated with contraceptive provision and care.

The proportion of women with quantifiable tenofovir in our study was similar to the VOICE trial that enrolled women from 3 African countries, where tenofovir was quantified in around a third of samples⁷; however, women in our study were younger (18–35 vs. 18–45 years) and from SA only. Furthermore, the VOICE trial was a blinded, placebo-controlled trial of an unproven product, whereas PrEP in ECHO was of a now recommended intervention. Quantifiable tenofovir in our study was lower than HPTN 067 that enrolled women from Cape Town, SA, where tenofovir was quantified in just over two-thirds of samples, but in HPTN 067, women were directly observed dosing for 5 weeks and thereafter assigned to either daily or nondaily oral PrEP regimens.⁹ Although we measured plasma tenofovir in the ECHO Trial, other studies have measured tenofovir-diphosphate (TFV-DP) in dried blood spots (DBS),^{16,17} which has a half-life of 17 days and provides a measure of adherence over weeks.¹⁸ In HPTN 082 that enrolled women from 2 African countries, TFV-DP in DBS was quantified in 84% of women at month 3 and 57% at month 6,¹⁶ and a PrEP implementation study that enrolled women from maternal child health and family planning clinics in Kenya found TFV-DP in DBS quantified in 61% of samples at a median of 5 weeks after PrEP initiation.¹⁷

An additional consideration when evaluating adherence to PrEP is the “effective use of PrEP” which takes into account that some PrEP users might have periods or “seasons” of risk and therefore will require PrEP during these times and use might not be continuous.¹⁹ Despite only about a third of women having quantifiable tenofovir in our study, among all women who had initiated PrEP in the ECHO Trial, only 2 had seroconverted at an incidence rate of 1.0 per 100 person-years compared with 3.81 per 100 person-years in the overall study.¹⁰ Furthermore, HIV incidence in ECHO dropped by about 50% after on-site access to PrEP.²⁰ We found that 40% of women discontinued PrEP before the final visit in our study, and this was consistent with findings from a large systematic review and meta-analysis where about a third discontinued PrEP within the first month.²¹

In our study and the VOICE trial, older age was associated with quantifiable tenofovir.⁷ The VOICE trial also found that being married and earning an income were associated with quantifiable tenofovir; however, when adjusting for age, we did not find similar associations. Age ≥ 24 years was also associated with quantifiable TFV-DP in DBS in a real-world PrEP implementation program in Kenya.¹⁷ Notably, we found that women who used condoms inconsistently or did not use condoms were less likely to have tenofovir quantified, and this reflects the complex interplay of condom use with factors such as HIV risk perception and partner risk.

Our study has some limitations. Plasma tenofovir provides an indication of PrEP use over the previous few days; therefore, biomarkers such as TFV-DP that measure longer-term adherence to PrEP would have been useful to assess longer-term PrEP use. It is also possible that even among women with quantifiable tenofovir at the final visit, PrEP use might not have been consistent. PrEP was introduced relatively late in the ECHO Trial, and testing was conducted at 1 time point and not

TABLE 1. Participant Characteristics and Factors Associated With Quantifiable Tenofovir Among Oral PrEP Users in the ECHO Trial

Variable	Total, N	Tenofovir Quantified, N (%)	Tenofovir Not Quantified, N (%)	OR, 95% CI	P	OR, 95% CI (Adjusted for Age)	P (Adjusted for Age)
Baseline participant characteristics (at enrollment into the ECHO trial)							
Age							
18-24	136	38 (27.9)	98 (72.1)	Ref			
25-35	124	56 (45.2)	68 (54.8)	2.12 (1.27 to 3.56)	0.004		
Marital status							
Never married	253	88 (34.8)	165 (65.2)	Ref			
Married/previously married	7	6 (85.7)	1 (14.3)	11.25 (1.33 to 94.93)	0.03	8.04 (0.94 to 68.92)	0.06
Does not live with partner/no partner	224	82 (36.6)	142 (63.4)	Ref			
Lives with partner	36	12 (33.3)	24 (66.7)	0.87 (0.41 to 1.82)	0.70		
Partner provides financial/material support							
No/no partner	164	59 (36.0)	105 (64.0)	Ref			
Yes	96	35 (36.5)	61 (63.5)	1.02 (0.60 to 1.72)	0.94		
Does not earn own income	215	72 (33.5)	143 (66.5)	Ref			
Earns own income	45	22 (48.9)	23 (51.1)	1.90 (0.99 to 3.64)	0.05	1.71 (0.88 to 3.31)	0.11
Education*							
Secondary (any)	222	84 (37.8)	138 (62.2)	Ref			
Postsecondary	37	9 (24.3)	28 (75.7)	0.53 (0.24 to 1.17)	0.12		
Sexually transmitted infections							
<i>Chlamydia trachomatis</i> not detected	204	77 (37.7)	127 (62.3)	Ref			
<i>C. trachomatis</i> detected	56	17 (30.4)	39 (69.6)	0.72 (0.38 to 1.36)	0.31		
<i>Neisseria gonorrhoeae</i> not detected	246	89 (36.2)	157 (63.8)	Ref			
<i>Neisseria gonorrhoeae</i> detected	14	5 (35.7)	9 (64.3)	0.98 (0.32 to 3.01)	0.97		
Participant characteristics at PrEP initiation visit†‡							
Number of sex partners in the past 3 mo							
0/1	243	84 (34.6)	159 (65.4)	Ref			
≥2	17	10 (58.8)	7 (41.2)	2.70 (0.99 to 7.36)	0.05	2.44 (0.88 to 6.75)	0.09
No new sex partner/no partner	245	85 (34.7)	160 (65.3)	Ref			
New sex partner	15	9 (60.0)	6 (40.0)	2.82 (0.97 to 8.20)	0.06		
Condom use in the past 3 months§							
Always used condoms	69	33 (47.8)	36 (52.2)	Ref			
Did not use/inconsistent use	178	55 (30.9)	123 (69.1)	0.49 (0.28 to 0.86)	0.01	0.47 (0.26 to 0.83)	0.01
Condom use at last vaginal sex§							
Yes	121	52 (43.0)	69 (57.0)	Ref			
No, had condomless sex	126	36 (28.6)	90 (71.4)	0.53 (0.31 to 0.90)	0.02	0.50 (0.29 to 0.86)	0.01
HIV status of primary sex partner							
Negative/unknown	248	88 (35.5)	160 (64.5)	Ref			
Positive	9	4 (44.4)	5 (55.6)	1.45 (0.38 to 5.56)	0.58		
Do you feel your primary sex partner had sex with anyone else beside you in the past 3 months?							
No/do not know	225	76 (33.8)	149 (66.2)	Ref			
Yes	32	16 (50.0)	16 (50.0)	1.96 (0.93 to 4.13)	0.08		

Bold values = $P \leq 0.05$

*One woman reported no school education.

†Three women reported not having a primary sex partner over the past 3 months

‡None of the women reported having anal sex over the past 3 months

§Thirteen women had no sex partner/did not have vaginal sex.

prospectively. Some studies have shown that adherence to PrEP might change over time, aligning with relationship dynamics and life situations. Although we recorded dates of PrEP use, we did not collect additional adherence data on patterns of PrEP use, including reasons for not taking or discontinuing PrEP. As more clinical trials and rollout programs begin to provide oral PrEP onsite as part of HIV prevention standard of care, additional research is needed to explore patterns of PrEP use, including the use of PrEP during periods of risk, barriers to PrEP adherence, and linkage of study participants to publicly available PrEP sources at trial completion. Finally, longer-acting PrEP agents such as injectables, rings, and implants might address some barriers to oral PrEP adherence.

CONCLUSIONS

We found that over a third of South African women who initiated PrEP as an HIV prevention option during the ECHO Trial and reported ongoing PrEP use at the final trial visit had evidence of recent use on testing. Younger women and those who reported inconsistent or nonuse of condoms had lower odds of having tenofovir quantified. Clinical trials can potentially be used as an entry point for PrEP initiation among persons at substantial risk for HIV infection with referral for continuing PrEP access to local facilities on trial termination.

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Exploring the Use of Oral Pre-exposure Prophylaxis (PrEP) Among Women from Durban, South Africa as Part of the HIV Prevention Package in a Clinical Trial

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Abstract

HIV endpoint-driven clinical trials in Africa enroll women who are at heightened risk of acquiring HIV. In 2017, the South African Medical Research Council recommended the provision of oral pre-exposure prophylaxis (PrEP) in HIV prevention trials, at which time the Evidence for Contraceptive Options and HIV Outcomes trial was ongoing and began to provide PrEP on-site at some trial sites. We interviewed 132 women who initiated PrEP on-site at the Durban, South Africa trial site to explore PrEP use, and conducted phone-based interviews 4–6 months post-trial exit to explore post-trial PrEP access. PrEP uptake was high (42.6%). Among women initiating PrEP on-site, 87.9% felt at risk of acquiring HIV. Most women (> 90%) heard of PrEP for the first time from study staff and three-quarters who initiated PrEP on-site continued at trial-exit. PrEP use declined post-trial exit with more than 50% of women discontinuing PrEP, and barriers relating to access emerged.

Keywords Oral pre-exposure prophylaxis · Clinical trials · HIV prevention · Women

Introduction

South Africa (SA) has the largest HIV epidemic in the world [1]. In 2018, there were 7.7 million people living with HIV and 240,000 new infections, with women more disproportionately affected than men, and more than double the number of new infections occurring in young women (15–24 years) compared to men in the same age group [2]. Increased HIV prevention efforts are needed to combat the HIV epidemic. In 2015, the World Health Organization

(WHO) made the recommendation that daily oral pre-exposure prophylaxis (PrEP) containing tenofovir disoproxil fumarate (TDF) should be used as a prevention choice for people at substantial risk of HIV infection as part of combination prevention approaches [3]. SA began its PrEP roll-out to select sex worker sites in 2016, and later expanded to include additional key populations, including men who have sex with men (MSM), serodiscordant couples, and adolescent girls and young women [4]. Recently, since 2018, access to PrEP in SA has expanded and PrEP is currently available in public sector health facilities within the country [5], in addition to demonstration projects and observational studies [6].

In the context of clinical trials, ethical guidelines recommend that appropriate counselling and access to “state-of-the-art” HIV risk reduction methods are provided to participants in biomedical HIV prevention trials [7]. In SA, the national policy on PrEP which was released in 2016, recommends that the provision of PrEP be framed in a human-rights-based approach ensuring the rights to dignity, non-discrimination, privacy, confidentiality, and the right to services are upheld [8]. The HIV Prevention Trials Network (HPTN) guidance states that in partnership with key stakeholders, HPTN should establish a package of effective,

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comprehensive and locally sustainable prevention services to be offered to participants [9]. In November 2017, the South African Medical Research Council (SAMRC) recognised the limited availability of PrEP in SA and recommended the provision of PrEP in HIV prevention trials, along with the support of ethical committees, and community consultation and involvement [10]. Biomedical prevention trials have taken different approaches regarding PrEP that have included the provision of information only, the provision of information and referral for PrEP, and on-site provision of PrEP [11].

In this study, we collected data on PrEP use among women who initiated PrEP on-site as part of the HIV prevention package during the Evidence for Contraceptive Options and HIV Outcomes (ECHO) trial. The ECHO trial was conducted between 2015 and 2018, and enrolled 7830 HIV negative women, aged 16 to 35 years, from 12 sites in four African countries [12]. Women desiring contraception were randomized to intramuscular depot medroxyprogesterone acetate (DMPA-IM), a copper intrauterine device (IUD), or a levonorgestrel (LNG) implant, and followed for 12–18 months. The primary ECHO trial outcome was HIV incidence, which was 4.5 per 100 woman-years at the SA trial sites [13]. During the ECHO trial, all women were counselled about PrEP and those who were interested in PrEP were referred to off-site facilities such as demonstration projects where available, to access PrEP. The ECHO trial was ongoing at the time of the SAMRC recommendation and shifted from offering PrEP via referral to off-site facilities where available, to on-site provision at the SA study sites, in addition to referral. The integration of PrEP delivery into the ECHO trial has been described previously [14]. Here, we present data on the uptake of PrEP, reasons for initiating and discontinuing PrEP, side effects experienced, perceived HIV risk, self-reported adherence to PrEP, disclosure of PrEP use and post-trial access to PrEP among women at one study site in Durban, SA.

Methods

This ancillary study was nested within the ECHO trial (ClinicalTrials.gov, NCT02550067) [12]. The HIV prevention package provided to all women during the ECHO trial included HIV risk reduction counselling; HIV counselling and testing; sexually transmitted infection (STI) testing, treatment and partner notification of STIs; condom provision; partner HIV counselling and testing, and referral for antiretroviral therapy (ART) in discordant couples. At the SA trial sites, women were initially referred to off-site facilities such as demonstration sites and public sector facilities providing PrEP where available, and during the latter part of the trial, PrEP was provided on-site from March 2018. For the Durban ECHO trial site, prior

to on-site PrEP provision, a link had been established in September 2017 with a non-governmental organization (NGO) located in close proximity to the research site, that was providing PrEP at no cost. Women were actively referred to this site for PrEP, if interested from October 2017. Women who were HIV negative, not pregnant or breastfeeding, and who perceived themselves to be at substantial risk for acquiring HIV were eligible. Following the on-site provision of PrEP from March 2018, all women in study follow-up who wanted to initiate PrEP, had requested to do so on-site. Women who initiated PrEP on-site and desired to continue PrEP at the final study visit were given a 3-month supply of PrEP and referred to NGO's, demonstration projects and public-sector facilities providing PrEP. In addition, women who were interested in initiating PrEP at the final study visit were referred.

The ECHO trial captured minimal information on PrEP use since PrEP was part of the comprehensive HIV prevention package and not a separate research procedure. To collect additional information on PrEP use, we conducted an ancillary study from April 2018 to April 2019 among women who chose to initiate PrEP on-site at the Durban, SA ECHO trial site. All women who chose to initiate PrEP on-site were invited to participate in a structured interviewer-administered questionnaire, in their language of choice, approximately 3 months after initiating PrEP on-site. The questionnaire, which was completed during study follow-up or at the final study visit, explored PrEP use, including reasons for initiating and discontinuing PrEP, side effects experienced, perceived HIV risk, reported adherence to PrEP and disclosure of PrEP use. Among women initiating PrEP on-site, data were also collected at the final ECHO study visit on whether PrEP was being continued, and reasons for discontinuation. In addition, women initiating PrEP on-site who elected to continue using PrEP at the final study visit, and who consented to telephonic follow-up, were contacted via telephone 4 to 6 months after their trial exit to explore post-trial access and continued use of PrEP. Women were asked questions on whether they were still using PrEP, if they had any problems accessing PrEP after the trial had ended, and if they had discontinued using PrEP, reasons for discontinuation. In addition, we collected limited information from source notes on women who initiated PrEP off-site from 2017. Here, we collected data on the number of women referred, the number who initiated PrEP, and the timing of PrEP initiation. Data were entered onto the RED-Cap® electronic data capture tools hosted at the University of the Witwatersrand [15] and analysed using Stata version 14 (StataCorp, College Station, USA). Descriptive analyses were conducted for the purpose of this study.

Data that were collected during the ECHO trial such as demographics and behavioral risk factors (using case report forms), and STIs (STI testing was conducted at the

enrolment and final study visit using PCR Gene Expert testing on provider-collected endocervical swabs) were also included. In addition, we collected data on the number of women who were referred for off-site PrEP provision, and the proportion of these women who had initiated PrEP. Eligibility for on-site PrEP provision included being HIV negative, not pregnant or breastfeeding (as per local guidelines at the time), with at least one month of follow-up remaining in the trial, and attended a study visit from March 2018.

Additional written informed consent was obtained to conduct the ancillary study questionnaire and the follow-up phone calls. For the phone-based interviews, women were asked to confirm their name and surname, and were asked a study specific question to verify that they were the correct participant in the study. Women were also asked if it was a suitable time, and they were in a suitable place (quiet and confidential) to conduct the interview. The interviewers conducted the interviews in a private room that was conducive to conducting phone-based interviews. This study was approved by the University of Witwatersrand Human Research Ethics Committee (Wits HREC) (Reference 141112). For the ECHO trial, participants completed written informed consent, and approval was obtained from Wits HREC and the FHI360 ethics review board.

Results

Of the 324 women eligible for PrEP when it became available on-site, 138 (42.6%) initiated PrEP. An additional 17 women had initiated PrEP off-site. In total, 132 (132 of 138, 95.7%) women who initiated PrEP on-site consented to participate in the ancillary study. At baseline, the mean age was 24 years (range 18–35 years) and 82 (62.1%) women were ≤ 24 years. A quarter (33, 25.0%) had *Chlamydia trachomatis* and three (2.3%) had *Nisseria gonorrhoeae* detected at enrolment into the ECHO trial. At the time of the questionnaire, most women (116, 87.9%) reported feeling at risk of acquiring HIV. Of these 116 women, 97 (83.6%) women reported inconsistent condom use, 57 (49.1%) women felt that their partner had other sexual partners and approximately one in five women (24, 20.7%) did not know their partner's HIV status (Table 1).

The main reasons that women cited for initiating PrEP ($n = 132$) were to prevent or protect against HIV (98, 74.2%); and partner-related reasons (50, 37.9%) such as distrust of the partner, the partner being unfaithful previously and having a partner whose HIV status was unknown (Table 2). Almost a quarter (28, 21.2%) of the women initiated PrEP due to inconsistent or no condom use.

Over a third of women ($n = 53$, 40.2%) reported experiencing side effects since starting PrEP, but only four of the 53 (7.5%) women had ongoing side effects at the time

Table 1 Reasons women provided for feeling at risk of acquiring HIV

Reason(s) for feeling at risk of acquiring HIV ^a (N = 116)	N (%)
I don't always use a condom when having sex	97 (83.6)
I think my partner has other sexual partners beside me	57 (49.1)
I don't know my partner's HIV status	24 (20.7)
I don't trust my partner	17 (14.7)
I have been diagnosed or treated for an STI	17 (14.7)
I have more than one sexual partner	5 (4.3)
Non-sexual HIV exposure	4 (3.4)
Fear of condoms breaking during sex	4 (3.4)
My partner's status is HIV positive	1 (0.9)

^aMultiple responses allowed

of the questionnaire. Common side effects perceived to be related to PrEP ($n = 53$) included nausea or vomiting (26, 49.1%), headaches (17, 32.1%), and drowsiness or dizziness (9, 17.0%). The four (7.5%) women who had ongoing side effects reported increased appetite and weight gain; headache, nausea and vomiting; nausea and bad dreams; and vomiting.

Most women had heard about PrEP for the first time from study staff ($n = 120$, 90.9%). Among the 12 (9.1%) women who had heard about PrEP previously, four (33.3%) heard of PrEP from a public health facility, two (16.7%) from friends, two (16.7%) from the internet, and five (41.7%) from other sources (a poster at a clinic, at an HIV counselling and testing course, from a teacher at high school, from other study participants and at a research event). Most women had disclosed PrEP use ($n = 119$, 90.2%) including about two-thirds who disclosed to a family member (81, 68.1%), just over a third to their partner(s) (46, 38.7%), and just over a third to a friend (44, 37.0%).

Self-reported adherence to PrEP was collected over the prior seven, and prior 30 days at the time of the questionnaire. About half of the women (54 of 96, 56.3%) reported no missed doses within the past 7 days, and about one-third (38 of 102, 37.3%) reported no missed doses in the last 30 days (Fig. 1). The main reasons for missing doses in the last 30 days ($n = 64$) were being away from home when tablets needed to be taken (33, 51.6%), and forgetful to take tablets (33, 51.6%) (Table 3).

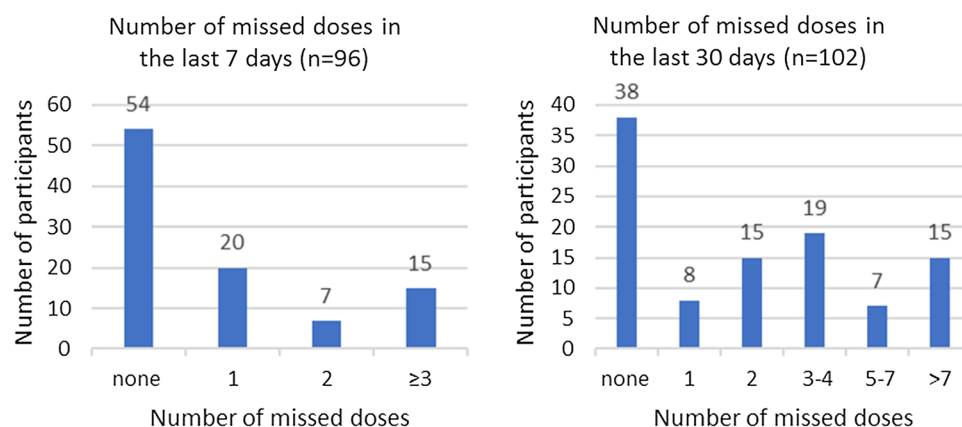
In total, 100 (75.8%) women had decided to continue PrEP at the ECHO study exit visit and 32 (24.2%) women had discontinued PrEP either during study follow-up or at the final study visit. Of the 32 women who discontinued PrEP, 12 (37.5%) stopped due to side effects, five (15.6%) due to partner or family influence, four (12.5%) due to forgetfulness to take PrEP, two (6.3%) were scared of potential side effects and three (9.4%) were unable to return to the research site for a refill. Side effects ($n = 12$) that led to PrEP being discontinued were nausea or vomiting (7, 58.3%),

Table 2 Reasons for initiating PrEP

Reason(s) for initiating PrEP ^a (N = 132)	N (%)
To prevent HIV or protect against HIV/feel “safe”/felt at risk for acquiring HIV	98 (74.2)
Partner-related reasons (distrust of partner/partner was unfaithful/partner’s HIV status unknown)	50 (37.9)
Inconsistent or no condom use	28 (21.2)
Fear of acquiring HIV	8 (6.1)
Novelty	8 (6.1)
Fear of condom breaking during sex/previously experienced broken condom during sex	6 (4.5)
Other people in my family have HIV	3 (2.3)
Fear of being raped/previously raped	3 (2.3)
Method “I could use myself”	2 (1.5)
Having sex under the influence alcohol	2 (1.5)
Other ^b	3 (2.3)

^aMultiple responses allowed

^bOther reasons for initiating PrEP: counselled by staff and thought it was a good idea to use, trusts the site to give good advice so decided to use PrEP, has multiple partners and does not use condoms with all of them

Fig. 1 Missing doses in the last 7 and last 30 days**Table 3** Reasons for missed doses in the last 30 days

Reason(s) for missed doses ^a (N = 64) ^b	N (%)
I was away from home when I needed to take my tablets	33 (51.6)
I forgot to take my tablets	33 (51.6)
I did not have time	8 (12.5)
Alcohol related	5 (7.8)
I ran out of tablets	4 (6.3)
I was having side effects	3 (4.7)
Work related	3 (4.7)
Unable to return to site for a refill	3 (4.7)
I needed a break	2 (3.1)
I did not feel I was at risk anymore	2 (3.1)
Being away from home for long periods and did not take tablets with	2 (3.1)

^aMultiple responses allowed

^b102 women were using PrEP in the last 30 days, 38 of these reported none missed doses. Reasons for missed doses among the remaining 64 women are presented

increased appetite (3, 25.0%), fatigue (3, 25.0%), headache (2, 16.7%), weight gain (1, 8.3%), weight loss (1, 8.3%), dizziness (1, 8.3%), diarrhoea (1, 8.3%), sweating (1, 8.3%) and itchiness of the skin (1, 8.3%).

The following reasons were provided for discontinuing PrEP due to partner or family influence. One participant reported her mother found her PrEP pills and had lots of questions and said to her, “*Are you sure they are not giving you the pills to make you get HIV easily? Ever since I was born I never heard of such a thing.*” A second participant reported that her mother was not happy about her taking PrEP and told her that she should stop. The participant said, “*I don’t think she understands these things.*” A third participant reported her partner said that there was no need for her to take PrEP and disposed of her tablets. A fourth reported she told her mother about PrEP upon initiating PrEP, but her mother was still unable to understand even after she explained, and her mother said, “*these stupid pills*” of yours

and that the participant should not take the tablets. Finally, a fifth participant reported that her mother felt she is too young to be taking pills.

Of the 100 women continuing PrEP at study exit, 87 (87.0%) women were contacted telephonically 4 to 6 months post study exit and 41 (47.1%) of these women reported ongoing PrEP use. Among the 41 women, 13 (31.7%) women accessed PrEP from a facility (public sector or NGO) providing PrEP and the remaining 28 (68.3%) reported having leftover tablets from the ECHO trial. Reasons for discontinuing PrEP ($n=46$) after the study had ended included “not knowing” or being unable to find a facility providing PrEP (11, 23.9%), feeling that the facility was located too far away from the participants home (7, 15.2%), and not having enough money for transport to get to a facility providing PrEP (6, 13.0%) (Table 4).

A total of 61 women were referred off-site to access PrEP prior to the on-site availability of PrEP provision. Of these, about a quarter (17, 27.9%) were started on PrEP at the off-site facility. Eighteen (29.5%) of these women who were referred for PrEP had not initiated PrEP off-site but returned to the study site to initiate PrEP on-site when it became available.

Discussion

To our knowledge, the ECHO trial was one of the first trials to provide PrEP on-site as part of the HIV prevention package [12]. We observed a high uptake of PrEP at the Durban, SA site, with almost one in two eligible women initiating PrEP, and nearly all on-site. Women who initiated PrEP felt that they were at high risk of acquiring HIV. Surprisingly, most women (> 90%) had heard about PrEP for the first time

from trial staff. Both the use of PrEP and access to PrEP had declined post-trial exit.

High rates of PrEP uptake have been seen in other studies among African women where PrEP has been integrated into youth-friendly clinics, family planning clinics and mobile clinics [16]. While PrEP uptake in the FEM-PrEP and VOICE trials was low (20–30%) [17, 18], the uptake of PrEP in HPTN 082 was 95% [19]. However, these studies were designed to study PrEP, while in the ECHO trial, PrEP was offered as part of the HIV prevention package and not specifically as a research question. On the other hand, in HVTN 702, where PrEP was provided as part of HIV standard of prevention during the trial, PrEP use (monitored by self-report and laboratory testing) was low, with only 0.9% of participants reporting PrEP use, and detectable TFV-DP found in only 2.2% of samples [20]. In a “real-world” implementation program in family planning clinics in Kenya, the uptake of PrEP was 22% [21]. Almost 90% of women felt at risk of acquiring HIV and half of these felt their partner had other sexual partners in our study. In HPTN 082, approximately 30% felt their partner had other sexual partners, and both in our study and HPTN 082, over 20% of women did not know their partners HIV status and inconsistent condom use was high [19]. Similar rates of baseline STI infections (*Chlamydia trachomatis* and *Nesseria gonorrhoeae*) were observed in HVTN 702 [20].

In our study, 90% of women had disclosed PrEP use to family members, partners and friends. This contrasts with HPTN 082 where only about 40% of women planned to disclose PrEP use [19]. Stigma has been associated with having a negative influence on both the disclosure of PrEP use and continuation [22]. Five women in our study discontinued PrEP due to the influence of the partner or their mother. This is an important consideration in the planning

Table 4 Reasons for discontinuing PrEP post study exit

Reason(s) for discontinuing PrEP ^a (N=46)	N (%)
Did not know the facility providing PrEP/unable to find the facility providing PrEP	11 (23.9)
Facility providing PrEP was too far away	7 (15.2)
Did not have the time to go to a facility to access PrEP	7 (15.2)
Lost referral letter	6 (13.0)
Did not have enough transport money to get to facility providing PrEP	6 (13.0)
Relocated out of Durban	5 (10.9)
No longer felt at risk for acquiring HIV	4 (8.7)
Unable to go because of work	4 (8.7)
Went to another facility that did not provide PrEP	2 (4.3)
Stopped because “got tired” of taking tablets	2 (4.3)
Other ^b	6 (13.0)

^aMultiple responses allowed

^bOther reasons for discontinuing PrEP post study exit: joined another study, was hospitalised, partner wanted me to stop, it was the festive season and I was forgetful to take tablets, I was temporarily away from home for a funeral, and I didn't feel I needed the tablets

and execution of clinical trials providing PrEP, and PrEP delivery programs, and highlights the need for broader community education and engagement. In the context of clinical trials, clinicians, counsellors and other study staff should be aware of these factors and be able to employ strategies that can assist participants with disclosure of PrEP use where needed. Community outreach teams and advisory boards can play a role in community education and awareness of HIV prevention methods available, including PrEP. Study staff were found to be vital in the delivery of PrEP in the ECHO trial, and we found that > 90% of participants had heard about PrEP for the first time from study staff. PrEP awareness and demand creation are essential components of PrEP provision [16]. In contrast, a study done in SA primarily among female sex workers and MSM found that only a third of participants had never heard of PrEP [23].

An important consideration in PrEP provision in clinical trials is the issue of post-trial access. The SAMRC noted that post-trial PrEP access could not be supported due to limited funding [10]. In the ECHO trial, we provided a 3-month PrEP supply at exit and other trials providing PrEP should similarly plan to bridge women to publicly available PrEP programs by providing a supply of PrEP at study exit. We found less than half of the women reported ongoing PrEP use after exiting the ECHO trial, and only a third of these had accessed a facility providing PrEP. Of concern is that many women reported having “leftover” tablets from the ECHO trial implying that PrEP adherence might wane over time, or that PrEP use might be intermittent, and this is an area that needs exploration in future research studies. In HPTN 082, detectable plasma tenofovir dropped from 65% at month 3, to 47% at month 6, and only 25% at month 12 [19]. Of the women that discontinued PrEP post-ECHO trial exit, PrEP continuation was limited by structural factors such as poverty and access. A contributing factor could also be the changes experienced by women in accessing PrEP in a trial setting compared to an NGO or public facility. These structural factors are crucial as large-scale rollout of PrEP is considered in SA, and facilities should be located close to where potential clients reside thus reducing barriers like distance and transport costs. The integration of PrEP into existing community facilities e.g. family planning clinics might also eliminate some barriers to access. Furthermore, the number of public sector facilities providing PrEP in SA has recently expanded, thereby increasing access.

Several women reported missing doses of PrEP with more than 50% of participants reporting missing ≥ 2 doses over the prior 30 days, implying protection might have been inadequate as at least 6 doses a week are required for adequate protection in non-rectal HIV exposure [24]. Reasons for missing doses because participants forgot, were busy, and feared or experienced side effects have been documented in other studies [25]. One strategy to foster PrEP adherence

and persistence has been to integrate PrEP refills with other reproductive health services e.g. contraception [16]. In the ECHO trial, PrEP follow-up visits were aligned with study follow-up visits where possible. This might have contributed to more women continuing PrEP for the duration of the study. Reasons for stopping PrEP in other studies have included low perceived HIV risk, access, side effects, not wanting to take a daily pill and stigma [26] which were similar to what we found in our study. Overall, adherence (as measured by plasma TFV) has varied in other studies ranging from 24% in FEM-PrEP to 81% in the Partners PrEP Study [27].

This study has some limitations. PrEP was introduced relatively late in the trial, therefore, the maximum follow-up time each woman had with on-site PrEP use was limited to approximately 6 months and some data, e.g. persistence on PrEP is limited by follow-up time. We used a structured questionnaire which was administered at one study site in Durban, therefore our findings might not be applicable to different geographical settings and sites. Additional in-depth information is needed to better understand dynamics of PrEP use, including post-trial access. Objective markers of adherence would have been useful to enhance our understanding of adherence as well as greater data on the impact of PrEP use for the women in the trial. However, our study has several strengths. The ECHO trial was one of the first studies to successfully provide PrEP on-site and this is one of the first studies to explore the voluntary use of PrEP by interviewing women who initiated PrEP on-site. There was a high uptake of PrEP. Reasons for starting and stopping PrEP can be of use to other clinical trials providing PrEP, as well as PrEP implementation programs. It is well documented that participants might over-report adherence, however in our study we found that many women reported missing doses and provided reasons that could be useful for PrEP implementation programs and adherence counselling.

Conclusions

Our study findings strongly support offering PrEP on-site as part of HIV prevention in clinical trials with HIV endpoints. We found that there was a high uptake of PrEP by women who perceived themselves to be at high risk for HIV acquisition and study staff were vital in increasing awareness of, and delivering PrEP. However, we found that > 50% of women discontinued PrEP after exiting the study with barriers relating to PrEP access emerging.

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Compliance with Ethical Standards

Conflict of interest The authors declares that they have no conflict of interest.

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Daily Oral Pre-exposure Prophylaxis (PrEP) Continuation Among Women from Durban, South Africa, Who Initiated PrEP as Standard of Care for HIV Prevention in a Clinical Trial

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Abstract

HIV incidence among women in Eastern and Southern Africa remains unacceptably high, highlighting the need for effective HIV prevention options, including pre-exposure prophylaxis (PrEP). The Evidence for Contraceptive Options and HIV Outcomes trial offered daily oral PrEP to participants during the latter part of the clinical trial as an additional HIV prevention choice. We explored daily oral PrEP continuation at trial exit among women enrolled from Durban, South Africa who initiated oral PrEP at the trial site. Of the 132 women initiating oral PrEP, 87% reported continuation of oral PrEP at month 1, 80% at month 3, and 75% continued using oral PrEP at their final trial visit and were referred to off-site facilities for ongoing oral PrEP access. The median duration of oral PrEP use in trial participants who used oral PrEP was 91 days (IQR 87 to 142 days). Women who disclosed their oral PrEP use to someone had increased odds of continuing oral PrEP at trial exit. Women who reported > 1 sex partner and those who felt they would probably or definitely get infected with HIV had reduced odds of continuing oral PrEP at trial exit. Of those discontinuing oral PrEP (n = 32), > 50% discontinued within the first month, and the most common reason for discontinuation was reporting side effects. The high rates of oral PrEP continuation in our study are encouraging and our findings can be utilized by other clinical trials providing oral PrEP as standard of care for HIV prevention and by oral PrEP implementation programmes.

Keywords Oral pre-exposure prophylaxis (PrEP) · PrEP continuation · HIV prevention · Women · Clinical trials · South Africa

Introduction

Over the last decade, substantial progress has been made in reducing HIV infections in Eastern and Southern Africa, with a 38% decline in new infections since 2010, however, adolescent girls and young women (AGYW) continue to account for over one-quarter of incident HIV infections in the region [1]. In South Africa, in 2019, the HIV prevalence among women aged 15 to 49 years was 25%, and 120,000 women aged 15 years and older became infected with HIV [2]. The main mode of transmission of HIV in this setting is via heterosexual sex [3]. Daily oral pre-exposure prophylaxis (PrEP) is a single pill consisting of tenofovir disoproxil fumarate and emtricitabine that reduces the risk of HIV transmission during sex by about 99% when taken daily [4]. In 2015, the World Health Organization (WHO) included daily oral PrEP as an additional prevention choice for those at substantial risk of HIV infection as part of combination prevention

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[5]. Globally, almost a million people had initiated oral PrEP by the end of 2020, with over 100,000 people in South Africa [6].

Despite progress in the uptake of oral PrEP, studies have shown that many users discontinue oral PrEP within 1 to 3 months, and continuation rates have been low [7–10]. A systematic meta-analysis that included clinical trials, demonstration projects and real-world settings on oral PrEP continuation found that on average 65% continued oral PrEP at month 1 [7]. Other studies in sub-Saharan Africa found even lower rates of oral PrEP continuation, for example, in the DREAMS study among AGYW in Kenya, 37% of women continued oral PrEP at 3 months [8]; in the PRIYA programme in Kenya, 41% continued at month 1, and 24% at month 3 [9]; and in the POWER study conducted among AGYW in Kenya and South Africa, 30% continued at month 1 and 21% through 6 months [10]. Reasons for oral PrEP discontinuation have included side effects (perceived and/or experienced), difficulties with a daily pill regimen, stigma, a lack of social support, disapproval from family and sexual partners, a reduction in HIV risk and challenges in accessing oral PrEP [11–13].

In the context of clinical trials, current global ethical guidelines advise that researchers and trial sponsors in HIV prevention studies should, at minimum, provide the recommended package of HIV prevention methods as stipulated by WHO, which includes oral PrEP for those at substantial risk of HIV [14]. In addition, in 2017, the South African Medical Research Council (SAMRC) recommended that oral PrEP be provided as HIV prevention standard of care at clinical trial sites conducting HIV prevention research [15]. The aim of this study was to describe oral PrEP continuation, the timing and reasons for oral PrEP discontinuation, and factors associated with oral PrEP continuation, among women from Durban, South Africa who were enrolled in the Evidence for Contraceptive Options and HIV Outcomes (ECHO) trial. The ECHO trial was a multi-centre randomized clinical trial conducted between 2015 and 2018, at 12 sites in four African countries, and the primary outcome was HIV incidence among women randomized to one of three contraceptives [16]. The ECHO trial was one of the first HIV endpoint-driven clinical trials in Africa to incorporate oral PrEP as part of the HIV prevention package provided to study participants. During the latter 8 months of the ECHO trial, oral PrEP was provided onsite to women as part of a comprehensive HIV prevention package. Given that HIV endpoint-driven clinical trials enrol persons at high risk for HIV acquisition and many oral PrEP users discontinue oral PrEP early, data on oral PrEP continuation when oral PrEP is provided as standard of care in clinical trials is important for current and future HIV endpoint-driven clinical trials.

Methods

Study Population and Procedures

HIV-negative, sexually active women, aged 18 to 35 years, desiring contraception, and willing to receive any of the three study contraceptives (intramuscularly injected depot medroxyprogesterone acetate, the copper intrauterine device or levonorgestrel implant) with no contraindications to any of the methods were enrolled into the ECHO trial at the Durban, South Africa trial site. Follow-up was quarterly for 12–18 months. The ECHO trial was conducted from December 2015 to October 2018 [16]. We conducted an ancillary study nested within the ECHO trial to collect additional data on oral PrEP use among women who initiated oral PrEP onsite at the Durban trial site and the primary results of this ancillary study have been published [17]. For this analysis, we describe oral PrEP continuation and factors associated with continuation at study exit among women who initiated oral PrEP onsite at the ECHO trial site in Durban, South Africa.

Onsite Oral PrEP Provision During the ECHO Trial

The integration of oral PrEP within the ECHO trial has been previously described [18]. Briefly, oral PrEP was provided onsite on a voluntary basis at the Durban trial site from March till October 2018 as part of a comprehensive HIV prevention package. Some women who had been enrolled earlier in the ECHO trial had been exited prior to oral PrEP being made available onsite. Women were eligible for onsite oral PrEP provision if they attended a study visit from March 2018, were HIV negative, not pregnant or breastfeeding (as per local guidelines at the time) and had at least 1 month of follow-up remaining in the trial. Staff were trained at the trial site using components that were adapted from the South African standardized PrEP training package, and the South African National Department of Health (NDoH) PrEP Guidelines [18]. Field-tested material developed by the Southern African HIV Clinicians Society, the NDoH, and an Optimizing Prevention Technology Introduction on Schedule were also used [18]. The training included provider sensitization, as well as the importance of participants exploring their own risk profile and risk reduction options, and adherence to and effective use of oral PrEP.

At the Durban site, during HIV risk-reduction counseling at each follow-up visit, counsellors discussed HIV prevention options with women, including daily oral PrEP. Those who were interested in initiating oral PrEP were referred to study clinicians for same day initiation. Women

who initiated oral PrEP were seen 1 month after initiation and thereafter every 2–3 months. Oral PrEP was dispensed onsite by trial clinicians. A 1-month supply of oral PrEP was given at initiation, and thereafter, refills were given approximately every 3 months. Women were counselled on oral PrEP adherence at initiation and follow-up visits by trial staff. Where possible PrEP visits were integrated with the main ECHO trial study visits. At the final study visit, women who desired to continue using oral PrEP were given a 3-month supply and referred to off-site facilities for oral PrEP refills, such as local demonstration projects and public sector clinics providing oral PrEP. Women were given a referral letter and details about the off-site oral PrEP facility including the physical address. In addition, where feasible, women were provided with transport from the research site to the off-site facility for the first visit if they felt they would be unable to locate the facility independently.

Women could choose to discontinue oral PrEP at any time point. Women who seroconverted discontinued oral PrEP and were referred for HIV care. HIV resistance testing was conducted among oral PrEP users that seroconverted and results were provided to women and their healthcare providers.

Oral PrEP Continuation

For this analysis, oral PrEP continuation was defined as women who had initiated oral PrEP onsite at any time during the course of the trial, prior to the final trial visit, who continued using oral PrEP at their final trial visit and were referred for off-site oral PrEP access at the final visit. We also report on oral PrEP continuation at month 1 and month 3 post PrEP initiation. The duration of oral PrEP use was limited by follow-up time remaining in the trial for each participant from the date of oral PrEP initiation.

Oral PrEP Adherence

Self-reported adherence to oral PrEP was collected over the prior 30 days among women who reported ongoing oral PrEP use (had used oral PrEP within the prior 30 days) at the time of the questionnaire. As previously reported, 37% of women reported no missed doses in the prior 30 days [17].

Data Collection

Data that were collected during the main ECHO trial such as participant demographics, sexual risk behaviours and dates of oral PrEP use were recorded using case report forms (CRFs). At each study visit, women were asked a question on whether they had used oral PrEP since the previous visit, and if they had taken oral PrEP, dates of use were recorded

on study CRFs by clinicians. If oral PrEP was discontinued, the date of discontinuation was recorded on CRFs. For the ancillary study, among women who had initiated oral PrEP on-site, an additional interviewer administered questionnaire was administered. Data collected for the ancillary study included reasons for discontinuing oral PrEP, oral PrEP disclosure, HIV risk-perception and timing of oral PrEP discontinuation. Data for the ancillary study were entered onto the REDCap® electronic data capture tools hosted at the University of the Witwatersrand [19].

Sexually Transmitted Infection (STI) Testing

STI testing was conducted at baseline via provider collected swabs and nucleic acid amplification testing for *Chlamydia trachomatis* (CT) and *Neisseria gonorrhoeae* (NG). Women who had clinical signs of STIs and/or diagnoses of STIs based on laboratory testing were treated.

Data Analysis

We evaluated baseline factors at enrolment into the ECHO trial (including age, education, relationship status, STIs, and partner HIV status), sexual behaviours at oral PrEP initiation (including the number of sexual partners and condom use), and HIV risk perception and disclosure of oral PrEP use approximately 3 months after oral PrEP initiation, using descriptive analyses. We report on frequencies and proportions for categorical variables. Continuous variables such as age, number of sex acts, and number of partners were converted into categorical variables.

We constructed univariate logistical regression models to evaluate factors associated with oral PrEP continuation at study exit. Factors associated with oral PrEP continuation at $p < 0.05$ were included in the multivariate analysis in which we adjusted for a priori confounders (age, relationship status). The model results are presented as crude and adjusted odds ratios (OR and aOR) with 95% confidence intervals (CIs). All statistical analyses were conducted with STATA v14.1 [20].

Ethics

Women signed written informed consent to participate in the ECHO trial, and additional informed consent was obtained to participate in the ancillary study. The ECHO trial was approved by the University of the Witwatersrand Human Research Ethics Committee (Wits HREC) and the FHI360 ethics review board. The ancillary study was approved by Wits HREC (Reference 141112).

Results

In total, 138 women who were enrolled in the ECHO trial initiated oral PrEP onsite at the Durban trial site. Of these, 132 (96%) consented to participate in the ancillary study. Among women enrolled in the ancillary study, the median age was 23 years (range 18–35 years) and almost two-thirds were ≤ 24 years (62%) (Table 1). Most women were unmarried (97%) and not living with their partner (92%). A quarter of the women had CT detected at baseline, and 2% had NG. At oral PrEP initiation, 7% of women reported having two sexual partners, and two-thirds (67%) reported inconsistent or non-use of condoms over the prior 3 months.

Of the 132 women who initiated oral PrEP in the trial, 87% ($n = 115$) continued using oral PrEP at month 1, and 80% ($n = 106$) at month 3 (Fig. 1). The median duration of oral PrEP use among all users during follow-up was 91 days (IQR 87 to 142 days). Overall, 75% of women ($n = 99$) had elected to continue using oral PrEP at their final trial visit. Among the 32 women who had discontinued oral PrEP, three-quarters ($n = 24$, 75%) had discontinued within the first 3 months. The most frequent reason for discontinuing oral PrEP was reporting side effects ($n = 12$, 38%), and half of the women who discontinued due to experiencing side effects, had done so within the first 30 days of starting oral PrEP (Table 2). Other reasons for discontinuing included being influenced by a partner or family member to stop (16%) and forgetting to take oral PrEP (13%). Fewer than 10% of women discontinued oral PrEP because they no longer felt at risk of acquiring HIV.

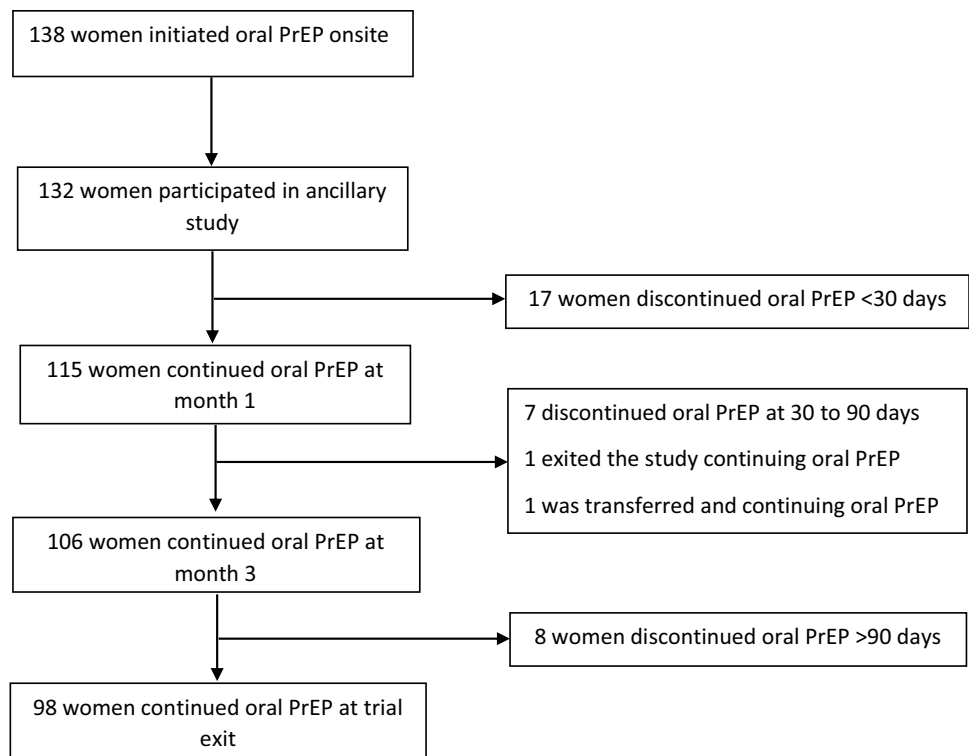
Among women who disclosed oral PrEP use to family members, partners and/or friends ($n = 118$), 79% (93 of 118) continued using oral PrEP at the final visit. Women who disclosed oral PrEP use had almost five times the odds of continuing using oral PrEP at the final study visit compared to those who did not disclose that they were taking oral PrEP (aOR 4.98; 95% CI 1.45, 17.13; $p = 0.01$), adjusted for age and relationship status (Table 3). Women who had more than one sex partner ($n = 9$, 7%) had lower odds of continuing oral PrEP compared to those who had one sex partner (aOR 0.24; 95% CI 0.06, 0.97; $p = 0.05$), adjusted for age and relationship status. Among women who reported that they felt they would probably or definitely get infected with HIV ($n = 30$), over half (57%) continued using oral PrEP at the final trial visit. Women who felt they would probably or definitely get infected with HIV had lower odds of continuing oral PrEP compared to women who felt they would definitely or probably not get infected with HIV (aOR 0.21; 95% CI 0.08, 0.55; $p < 0.01$), adjusted for age and relationship status.

Less than half of the women who did not disclose oral PrEP use (6 of 13, 46%) continued oral PrEP at the final

Table 1 Participant characteristics at baseline and oral PrEP initiation visit ($n = 132$)

Characteristic	n (%)
<i>Baseline characteristics</i>	
Age	
18–24	82 (62)
25–30	41 (31)
31–35	9 (7)
Education	
Secondary (incomplete)	49 (37)
Secondary (complete)	46 (35)
Post-secondary	37 (28)
Marital status	
Married	3 (2)
Never married	128 (97)
Separated	1 (1)
Lives with partner	
Yes	9 (7)
No	122 (92)
No partner	1 (1)
Earns an income	
Yes	22 (17)
No	110 (83)
STI diagnosis	
Chlamydia trachomatis	33 (25)
Neisseria gonorrhoea	3 (2)
Partner HIV status	
Positive	0 (0)
Negative	112 (85)
Unknown	20 (15)
<i>Characteristics at PrEP initiation visit</i>	
Number of sexual partners in last 3 months	
0	1 (1)
1	122 (92)
2	9 (7)
No of sexual acts in the last 3 months ^a	
0	8 (6)
1–3	42 (32)
4–6	36 (27)
7–9	14 (11)
10–12	14 (11)
13–20	8 (6)
> 20	9 (7)
Condom frequency during the last 3 months	
Never	23 (17)
Rarely	2 (2)
Sometimes	53 (40)
Often	11 (8)
Always	34 (26)
No sex partner/did not have sex	9 (7)

^aApplies to participants who had a sexual partner in the last 3 months ($n = 131$)

Fig. 1 Oral PrEP continuation during study follow-up**Table 2** Timing and reasons for oral PrEP discontinuation up to the final trial visit (n=32)

Reasons for oral PrEP discontinuation ^a	n (%)
<i>Discontinued oral PrEP < 30 days</i>	
Side effects for example, nausea, vomiting	6 (19)
Influenced by the partner/family to stop using oral PrEP	4 (13)
Afraid of potential side effects related to oral PrEP use	2 (6)
Was unable to return to study site for a refill	2 (6)
Decided to use condoms instead	1 (3)
Forgetful to take oral PrEP	1 (3)
Was going away from study site for more than a month and felt she would run out of tablets	1 (3)
Stopped due to religious reasons	1 (3)
<i>Discontinued oral PrEP at 30 to 90 days</i>	
Side effects for example headaches, vomiting	5 (16)
Forgetful to take oral PrEP	1 (3)
No longer at risk (no partner)	1 (3)
<i>Discontinued oral PrEP > 90 days</i>	
Forgetful to take oral PrEP	2 (6)
No longer at risk (no partner/partner is going away for a few months)	2 (6)
Does not have time to attend clinic for oral PrEP refills	1 (3)
Influenced by partner/family to stop using oral PrEP	1 (3)
Does not want to take a daily pill	1 (3)
Does not want a high pill burden (on oral tablets for a medical condition)	1 (3)
Side effects (fatigue)	1 (3)

^aMultiple reasons allowed

Table 3 Factors associated with self-reported oral PrEP continuation at the final study visit (median of 3 months) among 131 women

Characteristic	Total n (%)	Oral PrEP continuation at the final trial visit (median = 91 days) n (%)		Odds ratio (OR) (95% confidence interval [CI])	p value	Adjusted OR (95% CI) ^a	p value
		Yes	No				
Age > 24 years	50 (38)	40 (40)	10 (31)	1.49 (0.64, 3.48)	0.36		
Age ≤ 24 years (ref)	81 (62)	59 (60)	22 (69)				
Education (secondary level or higher)	82 (63)	62 (63)	20 (63)	1.01 (0.44, 2.29)	0.99		
Education (secondary level—incomplete) (ref)	49 (37)	37 (37)	12 (38)				
Relationship status					0.35		
Lives with partner	9 (7)	8 (8)	1 (3)	2.76 (0.33, 22.92)			
Does not live with partner (ref)	121 (93)	90 (92)	31 (97)				
Earns an income	22 (17)	18 (18)	4 (13)	1.56 (0.48, 4.99)	0.46		
Does not earn an income (ref)	109 (83)	81 (82)	28 (88)				
STI diagnosis at enrolment							
Chlamydia trachomatis detected	32 (24)	22 (22)	10 (31)	0.63 (0.26, 1.52)	0.30		
Chlamydia trachomatis not detected (ref)	99 (76)	77 (78)	22 (69)				
Neisseria gonorrhoea detected	3 (2)	3 (3)	0 (0)	—	—		
Neisseria gonorrhoea not detected (ref)	128 (98)	96 (97)	32 (100)				
Unknown partner HIV status	20 (15)	14 (14)	6 (19)	0.71 (0.25, 2.04)	0.53		
Partner is HIV-negative (ref)	111 (85)	85 (86)	26 (81)				
More than 1 sex partner	9 (7)	4 (4)	5 (16)	0.23 (0.06, 0.91)	0.04	0.24 (0.06, 0.97)	0.05
Has 0/1 sex partner (ref)	122 (93)	95 (96)	27 (84)				
> 12 sex acts in the last 3 months	17 (14)	13 (14)	4 (14)	1.02 (0.30, 3.40)	0.97		
≤ 12 sex acts in last 3 months (ref)	105 (86)	80 (86)	25 (86)				
Any unprotected sex in last 3 months	88 (72)	67 (72)	21 (72)	0.98 (0.39, 2.49)	0.97		
No unprotected sex (always used condoms) (ref)	34 (28)	26 (28)	8 (28)				
HIV risk perception						0.21 (0.08, 0.55)	< 0.01
I will probably/definitely get infected with HIV	30 (25)	17 (18)	13 (48)	0.24 (0.10, 0.60)	< 0.01		
I will probably/definitely not get infected with HIV (ref)	90 (75)	76 (82)	14 (52)				
Disclosed oral PrEP use	118 (90)	93 (94)	25 (78)	4.34 (1.34, 14.07)	0.01	4.98 (1.45, 17.13)	0.01
Did not disclose oral PrEP use (ref)	13 (10)	6 (6)	7 (22)				

Bold values indicate $p \leq 0.05$

^aFactors associated with oral PrEP continuation at $p < 0.05$ are included in the multivariate analysis in which we adjust for a priori confounders (age (continuous) and relationship status)

trial visit. Among women who reported that they felt they would probably or definitely not get infected with HIV ($n = 90$), 76 (84%) continued oral PrEP at the final study visit.

One woman who initiated oral PrEP seroconverted. She reported discontinuing oral PrEP approximately 2 months prior to seroconversion.

Discussion

In this ancillary PrEP study, where daily oral PrEP was offered onsite as part of HIV prevention standard of care during the latter part of the ECHO trial, we found that oral PrEP continuation during the trial and at the final trial visit, among women enrolled at the Durban trial site was high, with 87% of women continuing oral PrEP at month 1, 80% at month 3, and 75% electing to continue using oral PrEP at trial exit. Of the 25% of women who reported discontinuing oral PrEP, three-quarters had discontinued within the first 3 months, and side effects were the most frequent reason for oral PrEP discontinuation. Women who disclosed oral PrEP use continued oral PrEP more than those who did not disclose, whilst women who reported having more than one sexual partner and those who felt that they had a high risk of HIV infection had reduced odds of continuing oral PrEP at the final study visit. As reported previously, 43% of women who were eligible for oral PrEP when it became available, had initiated oral PrEP onsite [17].

We found that the proportion of women continuing oral PrEP at month 1 and month 3 in our study was higher than in some studies conducted among AGYW in South Africa and Kenya [8, 10] such as the DREAMS study in Kenya, where only 37% of AGYW who initiated oral PrEP, persisted with PrEP use at month 3 [8]. Similarly, in a real-world implementation programme in Kenya (PriYA), where oral PrEP was integrated into family planning clinics in Kenya, less than half of the women who initiated oral PrEP had returned for a PrEP refill at month 1 [9]. A recent study conducted in South Africa among pregnant women who initiated oral PrEP during pregnancy found higher rates of oral PrEP continuation where three-quarters of women continued at month 1 and 62% at months 3 [21]. In this study among pregnant women, factors associated with an increased odds of continuing oral PrEP at month 3 included having a partner who was living with HIV or of unknown serostatus, and reporting intimate partner violence [21]. In the HPTN 082 study which enrolled AGYW from Zimbabwe and South Africa and had good retention (~90% at month 3), 84% of women had detectable levels of tenofovir-diphosphate at month 3 [22]. Oral PrEP continuation in this study might have been facilitated by weekly 2-way text messaging, adherence counselling, and voluntary participation in monthly adherence clubs.

The high rates of oral PrEP continuation reported by participants in our study could be attributed to several factors. First, oral PrEP was offered and provided as part of a comprehensive HIV prevention package in the ECHO trial and was integrated with contraceptive provision and care. Where possible, PrEP study visits were aligned with regular study

follow-up visits. Second, oral PrEP was provided onsite, at no cost to participants, and this removed several barriers to oral PrEP access. Third, oral PrEP use was facilitated by trial staff. Staff received training on oral PrEP provision, including the importance of participants exploring their own risk profile and risk reduction options, and adherence to and effective use of oral PrEP. Oral PrEP information and materials were readily available to study participants, and separate workshops and presentations on oral PrEP were conducted with study community advisory boards [18].

Reasons for oral PrEP discontinuation in our study are consistent with other published studies [9, 12, 22]. An important consideration when assessing oral PrEP use is the use of oral PrEP during periods of risk and stopping oral PrEP when no longer at risk, and recently, there has been much discussion on “prevention-effective” adherence [23, 24]. In our study, we found that some women discontinued using oral PrEP as they no longer felt at risk for acquiring HIV. Among women who discontinued oral PrEP, almost 40% had done so due to side effects and this highlights the need for ongoing counselling and effective management of side effects among oral PrEP users, especially during the first few weeks of oral PrEP use. As oral PrEP was offered relatively late into the trial, overlapping side effects from contraceptives and oral PrEP were less of a concern, as contraceptive use had been established in most women.

In our study, most women who initiated oral PrEP (90%) had disclosed oral PrEP use to family members, partners and/or friends, and those who had disclosed oral PrEP use had almost five times the odds of continuing oral PrEP at trial exit compared to women who did not disclose. However, even among those who discontinued oral PrEP ($n = 32$), almost 80% had disclosed oral PrEP use. A study conducted among AGYW in South Africa found that disclosure can be a facilitator or barrier to oral PrEP use—supportive disclosures could provide instrumental adherence support such as pill reminders, however, unsupportive disclosures could undermine oral PrEP adherence and subject women to stigma, and in some cases, result in oral PrEP discontinuation [25]. An additional consideration is who a person discloses to, and the study among AGYW found that partners and parents provided the most support to participants who disclosed oral PrEP use [25]. Stigma was also found to be a barrier to oral PrEP continuation among pregnant women in South Africa [26]. We found that women who felt they would probably or definitely get infected with HIV had reduced odds of continuing oral PrEP at the final study visit. This might be related to the timing of the questionnaire, as it was administered approximately 3 months after oral PrEP initiation, and women might have felt less at risk because of using daily oral PrEP. Alternatively, it is possible that women who felt at increased risk for HIV acquisition experienced additional challenges and barriers to oral PrEP

continuation such as partner-related issues (i.e., difficulties with disclosure of oral PrEP use and issues relating to trust and/or fidelity in the relationship) or stigma (fear that others may think that oral PrEP is treatment for HIV) [26]. Surprisingly, women who had more than one sex partner had reduced odds of continuing oral PrEP, and this is an area that requires further exploration. However, this finding was limited to a small number of women who reported more than one sex partner ($n = 9$).

One of the strengths of this study was that all women who had initiated oral PrEP onsite remained in the ECHO trial until oral PrEP discontinuation, transfer to another study site or trial exit, therefore, we do not have missing data on women who did not return for an oral PrEP refill. Limitations of this study include that oral PrEP was introduced relatively late during the ECHO trial, therefore, the duration of oral PrEP use and continuation rates were limited by study follow-up time. Continuation rates beyond this time would have been useful to understand longer term oral PrEP use, including stopping and restarting oral PrEP. We enrolled women from one study site only and our sample size was small, hence, our findings may not be generalizable to other populations and settings. Furthermore, this was a clinical trial population who were research literate and being reimbursed for study participation, hence our findings might not be generalizable to oral PrEP users in real-world settings such as oral PrEP demonstration and implementation projects. In addition, we reported on oral PrEP continuation via participant self-report, and this might not correlate with adherence to oral PrEP as we did not conduct any objective measures of adherence such as measuring tenofovir drug levels. Finally, in-depth interviews would have been useful to gain deeper insights into reasons for oral PrEP continuation among clinical trial participants.

Conclusions

The high rates of oral PrEP continuation among women participating in the ECHO trial in Durban, South Africa who initiated oral PrEP are encouraging. Three-quarters of women who discontinued oral PrEP had discontinued within 3 months of initiating oral PrEP. This highlights the importance of providing additional support, counselling and side effect management especially during the first few months of oral PrEP use. Disclosure of oral PrEP use was positively associated with oral PrEP continuation, however overall disclosure rates were high in our study population, and this is an area that requires further exploration. Additional research exploring HIV risk perception both at oral PrEP initiation and subsequently, is needed to better understand oral PrEP use. Our findings can be used by other clinical trials

providing oral PrEP as standard of care for HIV prevention, and importantly, may inform oral PrEP programmes as oral PrEP is being scaled up in South Africa, and other countries in sub-Saharan Africa.

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Author Contributions IB conceptualised the study and drafted the initial manuscript. IB analysed the data, under the supervision of DLJD. DLJD, MB, SB, JS and LEM have read the manuscript and provided critical review. All authors approved the final version of the manuscript.

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Data Availability Access to data from the ECHO Study may be requested through submission of a research concept to icrc@uw.edu. The concept must include the research question, data requested, analytic methods, and steps taken to ensure ethical use of the data. Access will be granted if the concept is evaluated to have scientific merit and if sufficient data protections are in place. As of the time of publication, data access applications are in process with the governing institutional review boards of the ECHO Study to make de-identified data publicly available.

Code Availability Not applicable.

Declarations

Conflict of interest The authors have none to declare.

Ethical Approval The ECHO trial was approved by University of Witwatersrand Human Research Ethics Committee (Wits HREC) and the FHI360 ethics review board. This ancillary study was approved by Wits HREC (Reference 141112).

Consent to Participate Informed consent was obtained from women to participate in the ECHO trial, and additional informed consent was obtained to participate in this ancillary study.

Consent for Publication Not applicable.

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Title Page

Post-trial access to and use of pre-exposure prophylaxis in Durban, South Africa

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Abstract (349 words)

Background: HIV endpoint-driven clinical trials increasingly provide oral pre-exposure prophylaxis (PrEP) as standard of prevention during the trial, however, among participants desiring to continue using PrEP at trial exit, little is known about post-trial access PrEP access and continued use.

Methods: We conducted one-time, semi-structured, face-to-face, in-depth interviews with 13 women from Durban, South Africa, from November to December 2021. We interviewed women who initiated oral PrEP as part of the HIV prevention package during the Evidence for Contraceptive Options and HIV Outcomes (ECHO) Trial, elected to continue using PrEP at study exit, and were given a 3-month PrEP supply and referred to facilities for PrEP refills at the final trial visit. The interview guide probed for barriers and enablers to post-trial PrEP access, and current and future PrEP use. Interviews were audio-recorded and transcribed. Thematic analysis was facilitated using NVivo.

Results: Of the 13 women, six accessed oral PrEP post-trial exit, but five later discontinued. The remaining seven women did not access PrEP. Barriers to post-trial PrEP access and continued use included PrEP facilities having long queues, inconvenient operating hours, and being located far from women's homes. Some women were unable to afford transport costs to collect PrEP. Two women reported visiting their local clinics and requesting PrEP but were informed that PrEP was unavailable at the clinic. Only one woman was still using PrEP at the time of the interview. She reported that the PrEP facility was located close to her home, staff were friendly, and PrEP education and counselling were provided. Most women not on PrEP reported wanting to use it again, particularly if barriers to access could be alleviated and PrEP was easily available at facilities.

57 **Conclusions:** We identified several barriers to post-trial PrEP access. Strategies to
58 enhance PrEP access such as a reduction in waiting queues, convenient facility
59 operating hours, and making PrEP more widely available and accessible are
60 needed. It is also worth noting that oral PrEP access has expanded in South Africa
61 from 2018 till now and this could improve access to PrEP for participants exiting
62 trials who desire to continue PrEP.

63 Keywords: oral pre-exposure prophylaxis, post-trial access and use, young women,
64 South Africa

Background

Recently, several HIV prevention and endpoint-driven clinical trials have provided tenofovir-based oral pre-exposure prophylaxis (PrEP) to study participants as a component of their standard package of HIV prevention (1-3). This has been driven partly by ethical guidelines that recommend that participants enrolling in HIV prevention research should be provided with a package of HIV prevention methods recommended by the World Health Organization (WHO), but also that prevention services should be effective, comprehensive and sustainable (4). This is of importance as prevention research trials frequently enrol populations who are at elevated risk of HIV acquisition, including adolescent girls and young women (AGYW) (5). An additional consideration for the provision of oral PrEP in clinical trials is assessing what prevention services are available to the local community and how this differs from the prevention package provided during the trial (4). When the South African Medical Research Council (SAMRC) first recommended the provision of oral PrEP in HIV prevention trials in 2017, it recognized that at the time, oral PrEP availability was limited in South Africa with only 7,000 people accessing oral PrEP, and the importance of increasing oral PrEP access (6). Access to effective HIV prevention and treatment modalities post trial termination is important to ensure sustainability and continued use for participants who desire to continue using study drugs after exiting the trial.

In South Africa, the rollout of oral PrEP began in 2016 at select facilities that provided services to sex workers (7), expanding in 2017 to include men who have sex with men (MSM) and university students (8). In early 2018, oral PrEP was gradually rolled out to AGYW at primary health care facilities (8). PrEP guidelines in South Africa were updated in 2020 to include additional populations considered to be

at “substantial risk” for HIV infection which included, in addition to the populations described above, people with more than one sexual partner, people who inject drugs, those with recent sexually transmitted infections (STIs), serodiscordant couples, and those who recognized their own risk and requested oral PrEP (9). Finally, in 2021, further updates were made to the South African PrEP guidelines which included offering oral PrEP to pregnant and lactating women (10). As of July 2022, cumulative oral PrEP initiations in South Africa were estimated to be ~530,000 (11). Oral PrEP availability is an essential component of PrEP access, however, several other factors may impede PrEP access, such as distance and travel costs to attend clinics, having to take time off work/school for clinic appointments, long queues and inconvenient operating hours at public health facilities, stigma, eligibility criteria, and limited service delivery models (12-14).

While several studies have described oral PrEP uptake and persistence (12, 15), data on oral PrEP access and use post-trial is sparse. In this qualitative study, we describe post-trial oral PrEP access and use among women from Durban, South Africa who initiated oral PrEP at a research clinic as part of the HIV prevention package provided through the Evidence for Contraceptive Options and HIV Outcomes (ECHO) Trial (2) and elected to continue using oral PrEP at trial exit. Participants were referred to facilities for oral PrEP refills. We also describe HIV testing and family planning use post-trial, and suggestions by women to improve oral PrEP services in their communities.

Methods

ECHO Trial overview and procedures. The ECHO Trial was a randomized clinical trial, conducted from 2015 to 2018, in four African countries (Eswatini, Kenya, South Africa and Zambia). HIV-uninfected women, aged 16-35 years and desiring contraception, were enrolled and randomized to one of three effective contraceptives (2). The primary study endpoint was HIV incidence. Follow-up was quarterly for 12-18 months. Detailed ECHO Trial procedures and the primary trial results have been published elsewhere (2).

Oral PrEP provision during the ECHO Trial. During the latter eight months of the trial (March to October 2018), oral PrEP was provided onsite by trial staff at the South African trial sites (16). Women who initiated oral PrEP onsite at trial sites and requested to continue using oral PrEP at trial termination were given a three-month supply of oral PrEP at the final study visit and referred to off-site facilities for ongoing oral PrEP access.

Current study procedures. For this study, we recruited women who had participated at the trial site in Durban, South Africa, who had had initiated oral PrEP onsite during the ECHO Trial and continued using oral PrEP at trial exit. All these women had provided written informed consent to be contacted for future studies. An ancillary study was conducted at this research site to quantitatively explore PrEP use during the ECHO trial and assess PrEP use, PrEP discontinuation, and reasons for discontinuing six months after exiting the trial (17). Eligible women were contacted by telephone and invited to participate in a one-time, in-person, in-depth interview. A maximum of two follow-up telephonic calls were made to women who did not respond on the first attempt. Interviews were conducted from November to December 2021. The semi-structured interview guide explored reasons for initiating oral PrEP during the trial, oral PrEP use following study exit, barriers and enablers to

oral PrEP access post-trial, reasons for oral PrEP discontinuation if applicable, and suggestions to improve oral PrEP services for women.

Interviews were conducted in a quiet, private room at the research site to ensure confidentiality. They were conducted by a female interviewer (IB) in English. IB is a medical doctor and has 7-years of experience in conducting research. Women were informed that IB was conducting this research as part of her PhD program. IB was a study clinician in the ECHO Trial, was known to the participants, and had provided clinical care to several participants during the ECHO Trial, including the provision of oral PrEP. IB is also of a similar age group to the participants. All interviews were conducted approximately three years after the ECHO Trial had ended. Interviews lasted approximately 15 to 30 minutes.

All interviews were audio recorded and transcribed verbatim. Field notes were taken during the interview. A thematic approach was used for coding and analysis of interviews (18). Analysis was facilitated using NVivo (QSR International, version 10).

An initial code list was developed which was modified and refined as additional transcripts were coded. The code list and coding were reviewed by a qualitative researcher (CM). The codebook was developed inductively and deductively, and was informed by thematic areas outlined in the interview guide as well as participant responses. We selected representative quotes from women to highlight some of the study findings, and present these with the participant's current age (at the time of the interview).

Ethics. This study was approved by the University of the Witwatersrand's Human Research Ethics Committee (Wits HREC) (Reference: M191155). All participants signed written informed consent to participate in this ancillary study. Participants were reimbursed ZAR200 (approximately USD12) for their time and transport costs.

The ECHO Trial was approved by Wits HREC (Reference: 141112) and FHI360. All methods were carried out in accordance with the Declaration of Helsinki.

Results

We attempted to contact 26 eligible women who had elected to continue oral PrEP at ECHO Trial exit. Of these, 13 were contactable via telephone and agreed to be interviewed (50% acceptance rate), one (4%) had relocated to another province and was unable to attend an in-person interview, and 12 (46%) were not contactable via telephone. Demographics at enrolment into the ECHO Trial are presented in Table 1. At the time of the interview, the median age of women was 26 years (range: 22 to 30 years).

Reasons for initiating oral PrEP during the ECHO Trial

Women reported several reasons for electing to use oral PrEP during the ECHO Trial (Table 2). These included inconsistent or non-use of condoms, partner-related reasons such as not trusting the partner, wanting to protect oneself from acquiring HIV, and engaging in risky sexual behavior. Drivers of condom inconsistency/non-use included the partner not wanting to use condoms, using condoms with some partners but not others, and not enjoying sex when using condoms.

“The reason that [I] decide that I’m using the PrEP was just make sure my to be safe for myself ... because I don’t trust my boyfriend most of the time.” (26 years)

Disclosure of oral PrEP use

All women in our study reported disclosing oral PrEP use. Women reported disclosing to family members, friends, partners and community members. A few women reported not disclosing to their partners, even though they had disclosed to others such as family members. Reasons for withholding disclosure from the partner included losing the partner's trust in her and/or an assumption she is unfaithful; the partner's confusion that the PrEP pills are ART; and anticipating a negative reaction from the partner, for example one woman reported her partner was unhappy about her using an intrauterine contraceptive device, and upon disclosure to her partner, he insisted that she have it removed, so she felt her partner might similarly react negatively to her using PrEP. Many women reported that those to whom they had disclosed had positive reactions and/or supported their PrEP use. Few women reported experiencing negative reactions to disclosing PrEP use, however they felt that this did not impact on their PrEP use.

"I told them [cohabiting family members]. People were like, they were proud of me [for taking PrEP], they thought that I was like, that was a good thing to do and that that is a mature thing to do." (27 years)

Oral PrEP continuation and use post ECHO Trial exit

Some women reported accessing oral PrEP post-trial exit, while other women did not (Figure 1). The duration of oral PrEP use after exiting the study varied. Among women who reported not accessing PrEP post trial termination, almost all reported completing the three-month oral PrEP supply that was provided at ECHO trial exit. One woman reported starting oral PrEP after the study had ended, and then

210 discontinued PrEP after 3-4 days due to side effects. Among women who reported
211 accessing PrEP after exiting the study and then discontinuing, the frequency of oral
212 PrEP refill collection ranged from a single collection to five collections, and the
213 maximum duration of oral PrEP use post study exit was approximately one-year.
214 Finally, one woman who was still using oral PrEP at the time of the interview
215 reported continuous use of oral PrEP for more than 3 years post study.

216

217 Oral PrEP adherence post ECHO Trial

218 Most women reported missing doses while using PrEP. Reasons for missing oral
219 PrEP doses included forgetfulness, being away from home when oral PrEP needed
220 to be taken and not having PrEP pills with them, and fear of what others would think
221 of her taking PrEP.

222 “[I]t is difficult I won’t lie because sometimes you forget and sometimes ... you
223 go to work and forget them at home.” (24 years)

224 “Maybe if I’m going out with my friends ... I don’t take it [oral PrEP] sometimes
225 ... maybe I’m scared if they were saying how I’m eating [why am I taking pills]
226 ... But when I’m at home I’m actually make sure I’m drinking [taking PrEP].”
227 (26 years)

228 Women reported several different methods that facilitated adherence, and in some
229 cases, women used more than one method. These included setting an alarm as a
230 reminder to take oral PrEP, taking oral PrEP when a cohabiting family member takes
231 chronic treatment, storing PrEP pills in a visible area, support from family members
232 to take oral PrEP, and remembering to take PrEP pills when away from home.

233 “I’m not forgetting to [take] the pills ... my [family member] is HIV positive ...
234 so when they, when my [family member] take that pills and I will take mine
235 [PrEP pills].” (28 years)

236 One woman reported sharing PrEP pills with her partner and storing a bottle of oral
237 PrEP at his place.

238 “[H]e [partner] was sharing it [PrEP] ... I give him one bottle [of PrEP tablets]
239 ... When I’m going to his house, I’m using it [PrEP tablets] and he’s also using
240 it [her PrEP pills].” (27 years)

241

242 Barriers to post trial oral PrEP access and continuation among women who did not
243 access oral PrEP after exiting the ECHO Trial

244 Women identified several barriers to accessing oral PrEP after exiting the ECHO
245 Trial, resulting in discontinuation of oral PrEP use. These barriers included having to
246 spend too much time at the clinic due to long queues, clinics being located far away
247 from women’s homes, and/or being unable to afford transport costs to access clinics.

248 “The problem is that the clinic near my home ... they have long lines so ... I
249 can’t wait ... there’s a long queue to get in the clinic ... that’s why I stopped
250 taking it [oral PrEP].” (23 years)

251 “The place to take [collect] the PrEP which was far from home ... that’s why I
252 didn’t take it ... it was difficult because I had no money ... it will take 2 taxi ... I
253 think it was uh ZAR100 [approximately USD6] return.” (26 years)

254 Two women reported that they went to their local clinic and requested oral PrEP,
255 however it was not available.

256 “I stopped using PrEP after the study ended because it’s very difficult to get
257 PrEP. Most of the clinics they don’t have it.” (27 years).

258 Other barriers to oral PrEP access and continued use included being unable to
259 attend clinic visits due to work commitments, and provider-related factors such as a
260 lack of confidentiality.

261 “They [PrEP provider at clinic] don’t do their job properly ... like when I’m
262 talking to you [research staff] it’s confidential ... They [PrEP provider at clinic]
263 don’t keep that that thing, they shout, “[name of person], come here” and tell
264 you this and this and this about the patient. I’m here, that ... don’t make me
265 comfortable.” (27 years)

266

267 Facilitators and barriers to oral PrEP access among women who accessed oral PrEP
268 after exiting the ECHO Trial

269 Women who accessed oral PrEP post trial exit reported factors which facilitated their
270 oral PrEP access and use. These facilitators included that the clinics providing oral
271 PrEP were located close to their home, not having to wait in queues for their PrEP,
272 and accessing free transport from the research site to the clinic.

273 “It’s [the clinic] just a walk it’s not far you don’t have to take a taxi there.” (24
274 years)

275 “It [collecting PrEP] was quite quick, quick and easy. There wasn’t any
276 queue.” (30 years)

277 Many women also reported that the referral letter provided by the research site
278 facilitated ease of access to oral PrEP services at the clinic.

279 “Yes I did [take the referral letter to the clinic] ... other than that they [clinic
280 staff] wouldn’t accept me or what they will have to ask me some more
281 questions.” (24 years)

282 Other factors reported by a few women that facilitated oral PrEP access and use
283 included quality information and counselling provided by clinic staff, oral PrEP
284 demand creation, and friendly and welcoming clinic staff.

285 “I think PrEP is now like exposed in many clinics ... our clinic ... they give a lot
286 of information about it [PrEP]. They teach about it [PrEP], like everything.
287 Every morning if someone goes to our clinic it will be the same thing every
288 morning they update ... they always give updates about PrEP.” (24 years)

289 Despite some women accessing oral PrEP after exiting the study, many of these
290 women reported barriers to continued use. These barriers were similar to those
291 experienced by those women who had not accessed oral PrEP after exiting the main
292 study. They included oral PrEP facilities being located far from their homes, public
293 transport not utilizing routes where oral PrEP facilities were located, long waiting
294 queues, unsuitable clinic operating hours due to work commitments, and provider-
295 related factors.

296 “At the clinics they don’t attend us well ... they don’t treat us they don’t trust
297 us treat us like you do here [at the research site]. Sometimes we are not
298 comfortable sometimes the nurse will shout at you so you end up not having
299 appetite to go and fetch the uh PrEP at clinics.” (26 years)

300 “It’s hard because eh the queue is long you have to stay three hours to four
301 hours waiting for you to call you ... you had to wait three hours because you

302 are in the same queue with the people who are sick, with the people who are
303 going to do this and that.” (24 years)

304 “I work every day. I only get one [day] off and the off I get it’s on weekends the
305 clinics are closed.” (24 years)

306 One woman reported that not having a referral letter was a barrier to oral PrEP
307 access – she reported that she had decided to transfer from one PrEP facility to
308 another located closer to her home, but when she arrived at the more convenient
309 PrEP facility, clinic staff requested a referral letter.

310 “But was struggling to get it [oral PrEP] because it [PrEP facility] was far ...
311 there by [name and location of PrEP facility] ... Yes it was far for me to go
312 there when I try to go get it here when it was down here [different PrEP
313 facility] ... they said I must go and get a referral letter. So I wasn’t happy to
314 get one [referral letter] again.” (30 years)

315 Finally, one woman reported that although she had accessed oral PrEP easily at a
316 local clinic that was located close to her home, and that it was a pleasant
317 experience, she had decided to discontinue oral PrEP use without any reason.

318 “Ja it was my decision I just I decided to just stop I don’t know why.” (29
319 years)

320

321 Integration of oral PrEP with other services

322 Most of the women who accessed oral PrEP after exiting the study had utilized
323 public sector clinics. Women reported that services such as HIV testing, family

324 planning and primary health care were available at the clinics, but frequently, these
325 were not provided by the same provider or were in different locations within the same
326 facility.

327 Interviewer: "And tell me do you get all this [family planning, HIV testing,
328 primary health care services] at the same place where you get your PrEP, so
329 your family planning and your HIV test, is that done there or is it done at a
330 different place in the clinic?"

331 24-year female: "No it's done at eh eh everything has has it's door. There is a
332 door for testing, there is a door for family planning, and there is a door for pills
333 collecting."

334 Interviewer: "Okay ... So it's different people that do each of these things?"

335 24-year female: "Yes."

336

337 Family planning access post trial exit

338 Some women reported that they continued using their intrauterine devices and
339 contraceptive implants that were inserted during the ECHO Trial, and therefore, did
340 not need to access contraception after exiting the trial. Other women reported
341 accessing their local clinics for injectable contraceptives, however, oral PrEP was
342 frequently not available at facilities women used for family planning.

343

344 HIV testing post study exit

345 Most women reported accessing HIV testing after exiting the study. HIV testing was
346 most frequently accessed at clinics, but some women also reported using mobile HIV
347 testing services, hospitals and blood donor services to test for HIV. Many women

348 reported that they tested negative for HIV after exiting the trial. They reported that
349 oral PrEP was not usually discussed at HIV testing, and often, was unavailable at the
350 same facility where HIV testing was done. None of the women reported testing
351 positive for HIV after exiting the trial.

352 Interviewer: "Okay did you do HIV testing afterwards [after the study ended]?"

353 26-year female: "Yes, I did."

354 Interviewer: "Where did you test?"

355 26-year female: "At the clinic at the other side but they didn't tell me about
356 PrEP."

357

358 Future PrEP use

359 Among women not using oral PrEP at the time of the interview, almost all reported
360 they would like to use oral PrEP in future, particularly if barriers to access could be
361 removed.

362 "Yes I couldn't get transport ... So it was not easy to me to come back and go
363 there ... the transport is far so there I was stopping to eat PrEP ... but if you
364 can say I can go to fetch PrEP I can even go if there is a transport I can go to
365 fetch PrEP." (26 years)

366

367 Suggestions to improve PrEP services

368 Women provided several suggestions on ways to improve oral PrEP services and
369 make these more accessible (Table 3). These included increasing knowledge and
370 awareness on oral PrEP among oral PrEP users, their family members,

communities, and healthcare providers. Women also reported that oral PrEP needs to be made readily available at clinics. Some women suggested more convenient clinic operating hours for example, clinics to open for oral PrEP services over weekends, and a reduction in queues for oral PrEP refills. The integration of oral PrEP delivery with other services such as pharmacies, the provision of longer-acting PrEP methods, and the provision of oral PrEP in a trial/research setting were also suggested as potential ways of improving oral PrEP services and use for women.

Discussion

In our study which explored post trial oral PrEP access and use among women from Durban, South Africa who elected to continue using oral PrEP at ECHO study exit, we found that women experienced several barriers which limited their continued use of PrEP. Barriers included long queues at PrEP facilities, facilities being located far from women's homes, being unable to afford transport costs to access clinics, unsuitable clinic operating hours, negative attitudes from providers, and oral PrEP being unavailable at some facilities. Conversely, women reported facilitators to oral PrEP access and use, such as clinics being located close to their homes, quality information and counselling provided by PrEP providers, oral PrEP demand creation and having a referral letter from the research site to collect oral PrEP refills. Despite only one woman reporting ongoing oral PrEP use at the time of the interview, most women expressed a desire to use oral PrEP again, particularly if barriers to access could be removed. To our knowledge, our study is one of the first studies to report on post-trial oral PrEP access among women who used oral PrEP as standard of care for HIV prevention in a trial setting.

395 Our study findings should be interpreted in conjunction with the rollout of oral PrEP in
396 South Africa. In 2018, when study participants on oral PrEP began exiting the ECHO
397 Trial, oral PrEP in the public sector in South Africa was being rolled out to sex
398 workers, MSM, university students and AGYW, and in that year, total PrEP initiations
399 were only 8,593 and PrEP was available at only 73 sites nationally (19). This could
400 account for the limited availability of oral PrEP reported by women in our study, as
401 well as the long distances women had to travel to access oral PrEP. The scale-up of
402 oral PrEP in South Africa in primary health clinics began late in 2019, and as of April
403 2022, PrEP was available at 2,915 facilities and more than 500,000 individuals had
404 initiated oral PrEP (19). However, despite the increased availability of oral PrEP,
405 stock-outs of oral PrEP have been reported (20). Further challenges with the rollout
406 of oral PrEP in South Africa include that oral PrEP was first rolled in stigmatized
407 populations, a lack of marketing and demand creation during the early stages of
408 rollout, frequent follow-up visits and laboratory monitoring and the need for
409 specialized staff to prescribe PrEP – all of which posed barriers to increased uptake
410 and scale-up of PrEP.

411 Barriers to oral PrEP access reported in our study have been consistent with findings
412 from studies conducted in Africa (12, 21, 22). A study conducted among AGYW in
413 Kenya and South Africa found that barriers to oral PrEP persistence included being
414 unable to collect PrEP refills due to school/work commitments, and lacking transport
415 to fetch PrEP from distant clinics (12). Similarly, a study conducted in Zimbabwe
416 among clients attending a family planning clinic and a youth facility, found that
417 unsuitable clinic operating hours and being unable to afford transport costs to PrEP
418 facilities were barriers to continued PrEP use (22). In a study conducted among
419 males and females aged 13-24 years in South Africa, Uganda and Zimbabwe, long

420 waiting queues and negative attitudes of healthcare workers were perceived barriers
421 to oral PrEP uptake (21).

422 The provision of oral PrEP in a research setting does offer some benefits.
423 Participants may receive one-on-one education and counselling on oral PrEP
424 including addressing any concerns, myths and fears. Regular study follow-up during
425 the trial may facilitate the early recognition and management of oral PrEP related
426 side effects. Study reimbursement and the provision of oral PrEP at no cost to
427 participants removes financial and transport related barriers to PrEP access.
428 Furthermore, research sites are less likely to have long waiting queues and may be
429 better resourced than public sector health facilities. Therefore, while clinical trials
430 may serve as a starting point for oral PrEP initiation and early use, sustainability and
431 continued use can only be successful if participants who desire to continue using
432 oral PrEP post study are able to access oral PrEP at local healthcare facilities.

433 Several models for oral PrEP delivery have been studied and ongoing studies are
434 assessing novel and innovative methods for delivering PrEP, particularly models that
435 simplify PrEP delivery. The integration of oral PrEP into routine family planning
436 services was shown to be feasible in Kenya (23) and we found that in our study,
437 many women continued to access family planning at clinics post study termination.
438 HIV testing services may serve as an entry point for oral PrEP demand creation,
439 however, despite many women in our study reporting accessing HIV testing services
440 after exiting the study, oral PrEP was rarely discussed during HIV counselling.
441 Antenatal and postnatal services may also serve as entry points for oral PrEP
442 delivery and a study in Cape Town, South Africa found high rates of oral PrEP
443 initiation and early continuation among this population (24). In addition, differentiated
444 models that include mobile and community-based platforms for oral PrEP delivery

should be considered (14) as these might address facility-based barriers to oral PrEP access. A study in Cape Town found that delivering oral PrEP to AGYW using a community-based mobile health clinic was feasible and acceptable (25). An additional community-based HIV testing and same-day PrEP initiation study is currently underway in South Africa (26).

Our study has some limitations. We interviewed a small number of women from one study site and therefore the generalizability of our study findings may be limited. Women were interviewed in English and not in their native language (isiZulu) and were interviewed by a study clinician, both of which could potentially bias our findings. While there is potential for social desirability and power relations to influence our findings, due to women being interviewed by a study clinician, this relationship could also be a strength and result in improved rapport. PrEP access and availability in South Africa have increased substantially over the last five years, and this needs to be considered when interpreting our study findings. Our study findings could be utilized by current and future clinical trials, especially as new effective HIV prevention products, such as longer acting PrEP products, become available. Furthermore, our findings may be useful for counselling participants in clinical trials about post-trial access and continued use of HIV prevention methods that might not yet be widely available in communities and facilities.

Conclusions

Women who had initiated oral PrEP as part of HIV prevention standard of care during the ECHO Trial reported several barriers to oral PrEP access and moderate amounts of continued use following study exit. These barriers which included

distance, transport costs, clinic operating hours, long queues, and limited oral PrEP availability frequently resulted in oral PrEP discontinuation. HIV testing services were frequently a missed opportunity to counsel and promote oral PrEP use. However, most women who had discontinued PrEP use reported wanting to use oral PrEP again, particularly if barriers to access could be alleviated or removed. The increased availability of oral PrEP in the public sector in South Africa could improve access to oral PrEP for trial participants following study termination.

List of abbreviations

AGYW	Adolescent girls and young women
ART	Antiretroviral therapy
ECHO Trial	Evidence for Contraceptive Options and HIV Outcomes Trial
HREC	Human Research Ethics Committee
MSM	Men who have sex with men
PrEP	Pre-exposure prophylaxis
SAMRC	South African Medical Research Council
STI	Sexually transmitted infection
WHO	World Health Organization

Declarations

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- Competing interests:

- The authors have none to declare

- Ethics approval:

- This study was approved by the University of the Witwatersrand's Human Research Ethics Committee (Wits HREC) (Reference: M191155). The

511 ECHO Trial was approved by Wits HREC (Reference: 141112) and
512 FHI360.
513
514 • Consent to participate:
515 ○ Written informed consent was obtained from all women to participate in this
516 study.
517
518 • Consent for publication:
519 ○ Not applicable
520
521 • Availability of data and material:
522 ○ Access to data from the ECHO Study may be requested through
523 submission of a research concept to icrc@uw.edu. The concept must
524 include the research question, data requested, analytic methods, and
525 steps taken to ensure ethical use of the data. Access will be granted if the
526 concept is evaluated to have scientific merit and if sufficient data
527 protections are in place. As of the time of publication, data access
528 applications are in process with the governing institutional review boards
529 of the ECHO Study to make de-identified data publicly available.
530 ○ Access to data from this study available upon request to
531 i_beesham@yahoo.com
532
533 • Code availability:
534 ○ Code available upon request to i_beesham@yahoo.com
535

536 • Authors' contributions:
537 ○ IB conceptualized the study, conducted the interviews, transcribed and
538 coded the interviews, conducted thematic analysis, wrote the first draft of
539 the paper and approved the final draft. CM reviewed analysis (coding and
540 codebook), revised first drafts of the paper, approved the final draft. MB
541 and LEM conceptualized the study, revised drafts of the paper and
542 approved the final draft. JS, DLJD, JMB and RH revised drafts of the
543 paper and approved the final draft.

544

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Table 1: Participant demographics at enrolment into the ECHO Trial^a

Characteristic	n (%) or median (range)
Median Age (range) (years)	22 (18 to 25)
Marital Status	
Never married	13 (100)
Education	
Secondary school (incomplete)	5 (38)
Secondary school (complete)	5 (38)
Post-secondary school	3 (23)
Lives with Partner	
Yes	1 (8)
No	12 (92)
Earns own income	
Yes	4 (31)
No	9 (69)

634 ^a Characteristics were collected at enrolment in the ECHO Trial and not repeated at
635 the time of the interview

Table 2: Reasons reported by women for initiating oral pre-exposure prophylaxis (PrEP) during the ECHO Trial

Reasons for using oral PrEP	Quotes
Condom-related Inconsistent or non-use of condoms Fear that condoms might “break” during sex	“I decide to use PrEP because most of the time when I’m doing sex with my partner we don’t use condom.” (23 years) “Uhm I decided to use PrEP because uh sometimes uhm as we are teenagers let me uh just not say we teenagers, like we [are] girls ... We don’t like condoms” (22 years) “My decision to use PrEP ... is in order to protect myself because we know that you can use your condom but it’s not 100% sure it can break.” (24 years)
Partner related Does not trust partner Partner is unfaithful	“reason that decide that I’m using the PrEP was just make sure my, to be safe for myself ... Because I don’t trust my boyfriend most of the time.” (26 years) “the reason why I decided to use PrEP it’s because they said it will prevent HIV even if your partner is not faithful” (29 years)
To prevent/protect oneself from acquiring HIV and/or to feel safe	“because I saw the whole benefit of it [PrEP] ... it help you to prevent HIV and AIDS” (26 years) “I want to be to be protected that’s why I decide to use PrEP” (23 years)
Gender stereotypes	“You cannot cannot trust anyone in this world especially mens you cannot trust them ... those people go around sleep with everyone” (PID 3160313410) “boys they playing so much ... And so I decide to take PrEP” (26 years)
Engaging in risky behavior	“I like enjoying party, so you know what happened (laughs) we got drunk ... Sometimes they new people, you know one night stand ... I sleep with maybe two ... two different guy[s] in the one day” (28 years)
Planning for pregnancy	“I think for the future reason ... I also need to prevent [HIV] ... because ... I don’t want to to infect my child once I’m get pregnant” (30 years)
Other	“Okay coz I came here [to research site] and then you’ll introduced me to PrEP and you’ll told me like the good and the bad about it, and I decided to take it coz it prevents you from being affected and it helps you ... You may never know you might get raped someday you can never plan for HIV (laughs) ... I need to make sure that like I don’t have, if I were to get affected it

	must be like not on purpose like accidentally like when we getting raped or getting like, I don't know how else you get (laughs) HIV (laughs)" (27 years)
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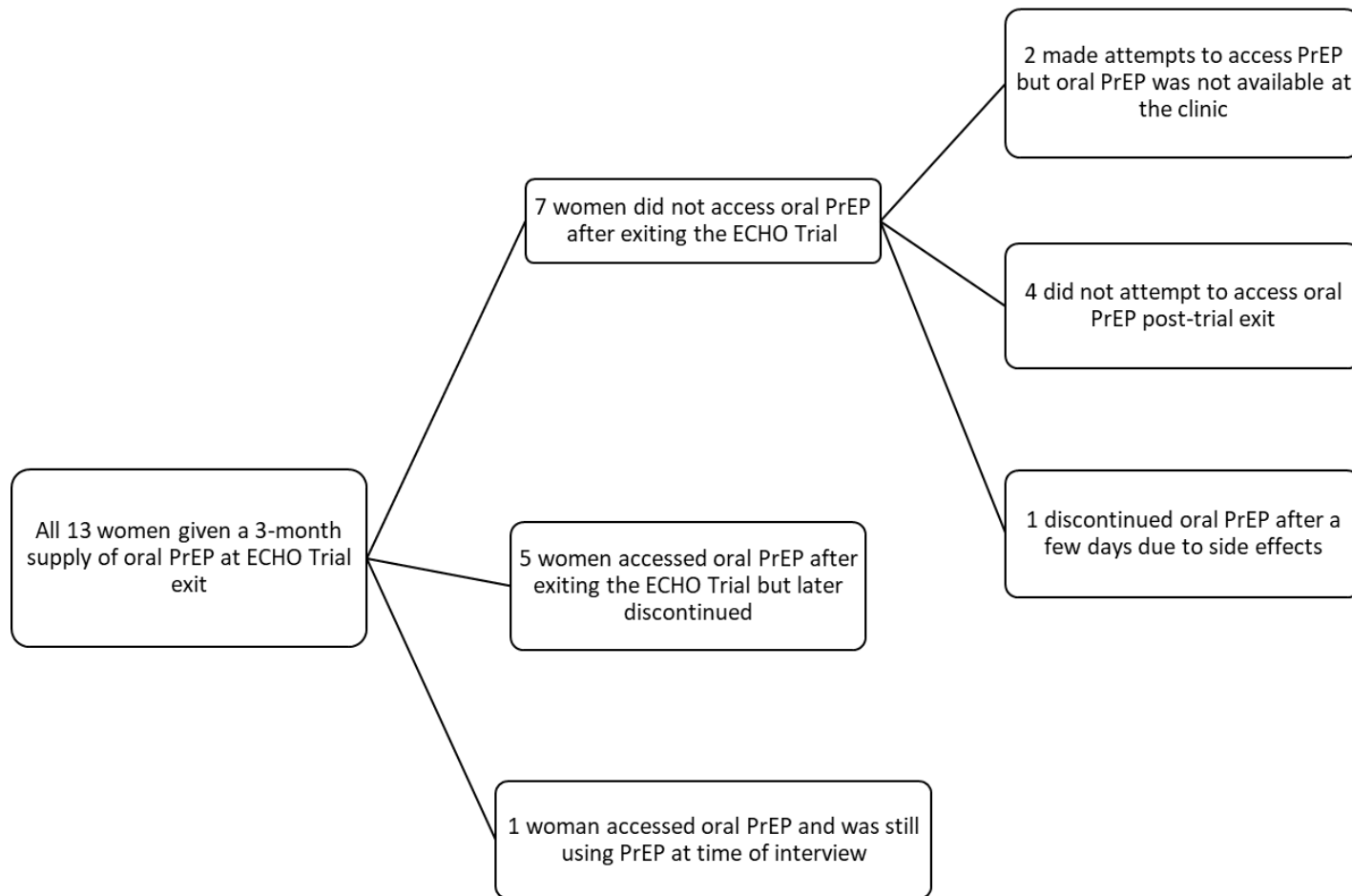


Figure 1: Post-trial oral pre-exposure prophylaxis (PrEP) access and use among women from Durban, South Africa

Table 3: Suggestions provided by women on improving pre-exposure prophylaxis (PrEP) services

Suggestion(s)	Quotes
Increasing awareness and knowledge about oral PrEP among users, and increased availability of oral PrEP	“People will get education more and more and more about it [PrEP] like I think from clinics they need to be sent the PrEP, needs to go the clinics and then those, the nurses need to tell people about it ... in the clinics they need to educate people about it ... Even old people, tell them about it, they’ll go home and they’ll tell their children and the news will go on like that like that” (27 years) “That they should like ... maybe they should tell the nurses at the clinic like that PrEP should be everywhere, educate people at the clinics. You see like condoms, every clinic has a condom. So every clinic should have uh PrEP.” (27 years)
Increasing knowledge and awareness about oral PrEP among providers	“Like there’s this like clinic, they [clinic staff] didn’t even know about it. I was like no, I had to google it, I was like “this here” [showing clinic staff]. They [clinic staff] like, “No, we, we don’t have that here.” (27 years)
Reduction in waiting queues and/or separate queues at the clinic for oral PrEP	“I think at the clinics they should provide the place if you come at the gate ... some certain like uh uh it’s uh sort of a timetable ... if you are going for PrEP you go that side, if you are going for this you go this side, so it will be easy for you if you go to the clinic if you know <i>uthi</i> (isiZulu word -says) you are supposed to [go to] that door rather than standing in one queue with the people who are go have different places with you” (24 years)
Availability of longer-acting PrEP modalities	“Maybe if they can be injections, not pills ... maybe people can more women can try ... can do PrEP because it’s hard to take a pill everyday (sighs) ... It’s hard it’s kind of hard” (29 years).
Integrating oral PrEP delivery	“Pharmacies, they can also give PrEP because it will be easy if you have a a pharmacy next to you, you can go there and look for PrEP ... even if you are at work, you you don’t have PrEP at that time, you can go to the clinic [at the pharmacy] and ask for PrEP” (24 years)
Reminders for clinic appointments	“Maybe if there could be another place that’s based on that where they gonna call and remind you, “Do you still remember you have to come and take PrEP?” Yes because sometimes we have a lot of things we that we are doing ... we go to school we are working we have to go home and all those thing maybe you even forget ... you even forget your date” (27 years)
Provision of oral PrEP in a research / trial setting	Interviewer: What do you think would make it easier for women to get PrEP when studies finish?

	27-year female: It's to continue with the study ... It's to continue with the study. That's what I can say ... Very easy and comfortable [to get oral PrEP as part of the study]. We always feel like free. Here it's, it's more like you were going to your own personal doctor. "I don't know how it can happen if we can have like, like uh study that basically for PrEP like how you [research site staff] uh get hold of us try to get hold of more women get them here make them sit down like how you sat down with us [ECHO Trial participants] and tell them about the PREP maybe it's gonna make a difference. Maybe after like uh uh three months or six months you can refer them to a clinic. Then a person is used to the se uh side effects and they know what they are doing then they can for sure you can go to the clinic this will take it when someone sat you down and told you about it. (24 years)
Clinics to provide PrEP after-hours or on weekends	"It will be easy, especially weekend time [for clinics to provide oral PrEP] ... Some people they work, they are working during week" (27 years)

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Key stakeholders' perspectives on providing oral pre-exposure prophylaxis as HIV prevention standard of care in clinical trials in South Africa

Introduction

Every day in 2021, there were an estimated 4 000 new HIV infections in adults and children globally (UNAIDS (a), 2022). Of these, 58% were in sub-Saharan Africa. In South Africa alone, there were 230 000 new HIV infections in 2020, and almost 8 million people were living with HIV (UNAIDS (b), 2021). Despite a 45% decrease in new HIV infections since 2010 in South Africa (UNAIDS (b), 2021), there remains a significant need for accelerating HIV prevention efforts in the country. Currently, there are several prevention options that can be used as part of combination HIV prevention, including oral pre-exposure prophylaxis (PrEP) (World Health Organization (WHO), 2021). In 2015, after several trials demonstrated oral PrEP effectiveness, the World Health Organization (WHO) made a recommendation that oral PrEP be provided as an additional prevention choice to those at substantial risk of HIV as part of combination HIV prevention (WHO, 2015).

In the context of HIV prevention and HIV endpoint-driven clinical trials, ethical guidelines have been developed that provide guidance on the standard of prevention that should be provided to trial participants. The HIV Prevention Trials Network (HPTN) guidance states that prevention researchers should provide a package of effective, comprehensive, and sustainable prevention services to participants (Brown et al., 2020). The recently revised Joint United Nations Programme on HIV/AIDS (UNAIDS) and WHO ethical guidance document states that researchers and sponsors should at minimum ensure access to the package of HIV prevention methods recommended by WHO for every participant throughout the trial and follow-

up (UNAIDS & WHO, 2021). Both documents emphasize the importance of stakeholder and community engagement and involvement. In 2017, the South African Medical Research Council (SAMRC) convened a summit on the standard of care in clinical trials (both treatment and prevention) in low-middle income settings and recognized the limited availability of oral PrEP in South Africa (SAMRC, 2017). A recommendation was made that oral PrEP be provided at clinical trial sites in HIV prevention trials, and a SAMRC-initiated PrEP fund be established to make available the provision of oral PrEP to trial sites (SAMRC, 2017). In South Africa, oral PrEP is approved for use, and is available via several implementation and demonstration projects, including in the public health sector with an estimated 100 000 current oral PrEP users in December 2020 (PrEP Watch, 2020).

The mechanism of delivery and uptake of oral PrEP when oral PrEP has been offered/provided in clinical trials as part of HIV prevention standard of care has varied, for example, in the HVTN 505 vaccine efficacy trial, conducted from 2009 to 2013, which enrolled men who have sex with men and transgender women, participants were provided with information about oral PrEP and referred to providers for oral Truvada – in this study, the uptake of oral PrEP was only 1% (Treatment Action Group (TAG), 2017). Subsequently, in the HVTN 702 study, which was an HIV vaccine efficacy study, conducted from 2016 to 2019, that enrolled >5000 adults from South African trial sites, it was found that approximately 3% of participants self-reported oral PrEP use (Gray et al., 2021). In HVTN 702, oral PrEP access was via referral to pilot projects or the private sector (TAG, 2017). The ECHO Trial which was an HIV endpoint-driven clinical trial, conducted from 2015 to 2018, that enrolled young women from sites in Africa, offered oral PrEP via referral to off-site facilities (Beesham et al., 2020). In addition, during the latter months of the trial, oral PrEP was provided onsite at the South African sites by trial staff. In the ECHO Trial, the uptake of oral PrEP was 17% at all trial sites, and 27% at the South African trial sites (Beesham et al., 2020).

Overall, in the context of clinical trials in South Africa, particularly HIV prevention and HIV endpoint-driven trials, there exists a lack of data on the provision of oral PrEP as part of the HIV prevention package. In order to address this gap in knowledge on the status of oral PrEP as part of HIV prevention standard of care in clinical trials in South Africa, we conducted a qualitative assessment of key stakeholders from

several research sites across South Africa to understand oral PrEP provision as part of the HIV prevention package during the trial, including barriers and enablers to oral PrEP uptake and use, mechanism of oral PrEP delivery (onsite versus off-site) and post-trial access.

Methods

In this qualitative study, we conducted 15 semi-structured in-depth interviews with key stakeholders from South Africa, working at research organizations known to conduct clinical trials, including HIV prevention research and HIV endpoint-driven clinical trials. We recruited key stakeholders from job categories that included site directors, principal investigators, clinicians, and other senior staff with experience in HIV prevention research. Purposive and snowball sampling were used to identify key stakeholders. Potential participants were contacted via email to participate in a one-time interview. A maximum of two follow-up emails were sent to those who did not respond to the first email. Potential participants were provided with an information sheet about the study, and those who replied and were agreeable to participate signed written informed consent. Interview questions were not provided in advance to study participants.

Individual interviews were conducted by a female interviewer (XX) via telephone and in English, from August 2020 to May 2021. Interviews were scheduled at a time that was suitable and convenient for the stakeholder, including after hours if needed. XX has a medical degree and six years of research experience. XX conducted this research as part of her Doctor of Philosophy Degree (PhD), and potential participants were informed of this prior to study participation. The semi-structured interview guide covered the following domains: 1) the key stakeholders' current position in their organization, and a brief description of their organization including the research they conduct, 2) contents of the HIV prevention package provided to study participants in clinical trials at their research organisation, 3) the mechanism of delivery (on-site or off-site) of HIV prevention options including oral PrEP, 4) experiences in providing oral PrEP to study participants, 5) facilitators and barriers to oral PrEP provision, and 6) post-trial oral PrEP access.

The interviews were audio recorded and transcribed verbatim by XX. Each interview was approximately 30 to 40 minutes. Field notes were taken during the interview. Transcriptions were coded, and analysis was facilitated with NVivo v10 (QSR International). Four transcripts were read and coded to derive an initial code list. Codes were both deductive and inductive, and were informed by the thematic areas outlined by the questions as well as participant responses. The code list was reviewed and discussed with a qualitative researcher (XY). The code list was modified and refined as more transcripts were reviewed and results were organized according to emergent themes. While the sample size was a pre-determined convenient sample size, data saturation was reached. Data were thematically analysed. Participant quotations are presented by participant number (PID).

The study was reviewed and approved by the University of the Witwatersrand's Human Research Ethics Committee (HREC), (Reference: M191155). Key stakeholders were not reimbursed for study participation.

Results

We contacted 34 key stakeholders via email to participate in a once off in-depth interview. Of these, eight (24%) did not respond, seven (21%) recommended interviewing another individual from the organization, two (6%) declined to participate (did not have time), one (3%) reported that their research unit did therapeutics and translational clinical trials and therefore would not be suitable for the study, one (3%) initially replied but thereafter did not respond to emails, and 15 (44%) agreed to be interviewed.

Among the 15 interviewed, most had medical degrees (n=12, 80%) and were employed in senior positions such as directors, site leaders, project managers/directors and principal investigators in their organizations (Table 1). Almost all the stakeholders were female (n=14/15). The number of studies being conducted at each research organization ranged from one to >20 studies with most organizations conducting five or more studies, and several key stakeholders reported that their organization had multiple research sites at different locations. All stakeholder respondents reported conducting clinical trials. The type of research conducted included HIV vaccine trials, HIV prevention trials, contraceptive studies,

infectious diseases research (for example, TB and viruses such as herpes simplex virus, respiratory syncytial virus and COVID-19), demonstration projects and implementation research.

We identified key themes reported by interviewees relating to the provision of oral PrEP as HIV prevention standard of care in clinical trials. These included components of the HIV prevention package provided to study participants and the rationale for including oral PrEP; uptake, adherence and persistence of oral PrEP; the impact of PrEP provision on trial outcomes, and post-trial oral PrEP access.

HIV prevention options/package

All stakeholders reported providing an HIV prevention package to clinical trial participants, and most reported that the prevention package provided included risk reduction counselling, HIV counselling and testing (HCT), condom and lubricant provision, and screening and treatment of sexually transmitted infections (STIs). These options were usually provided at the research site. In addition, many reported that laboratory testing for STIs was conducted, and where STIs were detected, participants were usually treated onsite or in some cases, referred for treatment. Additional HIV prevention options such as circumcision for HIV-uninfected males, and referral for HIV care for HIV-infected partners and/or participants who seroconverted during studies, were offered via referral to health care facilities. Some stakeholders reported offering post exposure prophylaxis (PEP) to participants either at research sites or via referral. More recently, almost all stakeholders (n=14) reported offering daily oral PrEP as part of the HIV prevention package either at the research site or via referral.

“[F]or participants that are participating in clinical trials we provide the standard of care in terms of HIV pre-test counselling we offer HIV testing and post-test counselling, ... risk reduction behavior options like condoms... test and treat STIs if needed if it's not in the protocol then we offer syndromic treatment ... anyone becomes positive [for an STI] we then immediately refer them to the local department of health for treatment ... and then over and above that for some for the HIV prevention trials in particular we offer PrEP to the participants. PrEP is offered onsite.” (PID 03)

A few stakeholders reported that the HIV prevention package offered to participants changed over time as new prevention options became available, for example in 2007/2008, the main scope of HIV prevention was condom (male and female) provision, counselling on abstinence, and diagnosing and treating STIs. Thereafter, when voluntary medical male circumcision (VMMC) became available, participants were encouraged to inform their HIV-uninfected male partners about the HIV prevention benefits of VMMC. More recently, oral PrEP was added to the HIV prevention package. Some stakeholders reported that the contents of the HIV prevention package were determined by the study sponsor and budget, and where prevention options were not provided at the research site, access was usually via referral to local health care facilities.

Reasons for providing oral PrEP as part of HIV prevention

Stakeholders reported multiple factors that influenced the decision to provide oral PrEP onsite as part of the HIV prevention package in clinical trials. Many reported that the decision to provide oral PrEP was made at a sponsor level and was driven by trial funders. The meeting held by the SAMRC on the standard of care for HIV prevention in clinical trials contributed to some sites providing oral PrEP. Other reasons for providing oral PrEP included that HIV prevention is a goal of the research organization, and that their organizations promote the use of oral PrEP. In addition, oral PrEP has been approved for use in South Africa and is being rolled out by the South African National Department of Health (NDoH), therefore it should be provided as standard of care for HIV prevention in clinical trials as well.

Some felt that oral PrEP should be provided in HIV prevention and vaccine efficacy trials as these trials enrol individuals who are at high risk of HIV acquisition.

“[I]t’s almost a requirement [to provide oral PrEP] when you doing an efficacy trial now that you offer the whole package of prevention you know because you are enrolling such high-risk people.” (PID 07)

Other stakeholders felt that it is an ethical requirement to provide oral PrEP in HIV prevention research. One stakeholder reported that their local ethics committee refused to approve an HIV vaccine study if oral PrEP was not offered to participants.

“[W]hat actually happened was we applied to do [name of study] in [name of place] and our ethics committee refused to let this study go ahead if we didn’t provide PrEP ... unless we could guarantee that we would give PrEP to the participants.” (PID 01).

Oral PrEP uptake

The uptake of oral PrEP by clinical trial participants varied between research organizations and between different research sites within the same organization. Stakeholders identified multiple barriers to oral PrEP uptake that included challenges with daily pill taking, side effects, stigma, and a lack of demand creation. Enablers to oral PrEP uptake included education and counselling about PrEP, as well as demand creation.

Challenges/barriers to oral PrEP uptake

Many stakeholders reported a poor uptake of oral PrEP that ranged from <5% to 10-15% when oral PrEP was offered onsite. Stakeholders provided multiple reasons for the generally low uptake of oral PrEP among participants. These included challenges with daily pill taking and having to take a pill when healthy.

“... [T]here was some interest but there were women who when they heard that it’s a daily tablet were like not so keen” (PID 02)

A few stakeholders reported that the uptake of oral PrEP was suboptimal because participants were concerned about potential side effects.

“... we found that the uptake was really very poor ... the interest was non-existent and participants gave several reasons ... it was mostly, most of them I think it was the concern about side effects” (PID 13)

Many stakeholders reported stigma as a barrier to oral PrEP uptake. This included concerns of the inadvertent discovery of their oral PrEP, and the assumption that they must be living with HIV because of the similarity of PrEP to ART.

“Some of them [participants] were concerned that they were taking ... antiretrovirals and so they would be misconstrued as being HIV infected if a partner or the family found the medication.” (PID 13)

Additional factors contributing to a low uptake of oral PrEP included that oral PrEP is a relatively new product, and the need for demand creation. In some cases, stakeholders felt that there wasn't a drive to promote oral PrEP use.

“... I guess when something is new there there's a lot of work that needs to go into campaigning and sort of spreading the message and counselling people to go on it, so I think with very many new things on the market or in any market you know it does take some campaigning I guess to create demand”
(PID 08)

The lack of education in communities, by the public health sector, about oral PrEP was another factor that contributed to the low uptake.

“... [G]aps are in terms of the Department of Health rolling out PrEP. Because they don't have the time or the staff to be able to educate on a large scale within the community on PrEP and the use of PrEP” (PID 03)

Stakeholders reported some perceived barriers to oral PrEP uptake that were specific to participants enrolled in HIV vaccine studies, for example, participants might enrol in vaccine studies because of a preference for injectable HIV prevention options as a method of drug delivery over a daily pill.

“I guess it's also possible ... that you [the participant] know if you signing up for a vaccine trial perhaps you doing so because the other methods are not really ideal for you or don't work for you ...” (PID 08)

“[M]aybe the oral PrEP wasn't something that that they [participants] wanted because the fact that they joined a vaccine study with injectables is already an indication that they have that as a preference. (PID 05)

Another stakeholder described the possibility of false beliefs of protection from HIV in participants in HIV vaccine studies – where they might believe they are getting some protection from the HIV vaccine being tested, and therefore do not require any additional HIV prevention methods,

“...[Participants] see it as they take a 50:50 chance in a HIV vaccine trial so they know I'm going to get a 50% chance that I'm going to be protected and when you give people that option they know that they doing something that is

going to make them more vulnerable for infections then in their eyes they will not see it as 50:50, they will say no maybe I've got a 80% chance that I'm protected by a vaccine, or maybe even a 90% chance that I'm protected ... And why should I now use another drug [oral PrEP] on top of it? ... Why should I drink now a tablet on top of it? So now I am not interested in that [PrEP] you know.” (PID 10).

Enablers to oral PrEP uptake:

Among stakeholders who reported a higher proportion of their clinical trial participants initiating oral PrEP, demand creation, and education and counselling were seen as factors that may have contributed to improved uptake. One stakeholder reported that their research organization had initiated a demand creation campaign for oral PrEP for another study prior to the HIV vaccine studies and this had contributed to about a third of women initiating oral PrEP in the HIV-vaccine studies. Education and counselling, including individual risk assessments and addressing myths and misconceptions (such as assuming oral PrEP is ART) were also reported as factors that increased oral PrEP acceptability and willingness to use oral PrEP.

“... I think if women are educated and you know are provided with adequate counselling, their acceptability and willingness to use PrEP increases ... I think awareness and understanding of the PrEP is very important and once women were made aware of the risks ... especially those women who presented with STIs (sexually transmitted infections) and they were educated that this increases risk of HIV transmission a lot of women were then more willing and you know acceptable using PrEP” (PID 06)

One stakeholder reported that although oral PrEP uptake was poor across several of their research sites, one site had a much higher oral PrEP uptake, and this was most likely due to a highly motivated counsellor who was very active in advocating for oral PrEP.

“... [B]ecause we suddenly had 30 women on PrEP and we only had 72 enrolled in the study ... and I kind of boil this down to, we had a really great counsellor ... who was just very active in in kind of advocating for it [oral PrEP]” (PID 15)

Another stakeholder reported that women were interested in oral PrEP as it made them feel empowered and in control.

“... [T]here was definitely interest ... some individuals more than others I mean ... some women really felt empowered and they were now able to take control of the situation...” (PID 04).

Gender and PrEP uptake:

While many stakeholders described oral PrEP uptake in studies that enrolled women, one stakeholder described the uptake of oral PrEP by gender and found that males had a preference to attend mobile clinics versus the research site.

“[O]ur mobile clinic would go to for example close to one of the local clinics and would park there and in the mobile clinics we actually saw a lot more males than females in the mobile clinics ... and less males coming to our sites a fixed clinic ... we saw actually that men were more open to going to the mobile clinics than to come in to site...” (PID 09)

Oral PrEP adherence and persistence

Several stakeholders reported that oral PrEP persistence decreased over time, with many participants discontinuing within the first three months of initiation. However, among those who were still on oral PrEP at month 3, many continued using it.

“... [W]e had a sharp drop off to month 1 you know when they were asked to come back at month 1 and then there was again another slight drop-off to month 3 and then it's more stabilising, those who made it to kind of month 3, continued use...” (PID 12).

A few stakeholders reported that participants used oral PrEP for the duration of the study and were then referred to off-site facilities for ongoing oral PrEP access at trial exit. Some noted that the use of oral PrEP among participants was not continuous, and that participants cycled on and off oral PrEP. One stakeholder reported that a third of participants had interrupted use.

Adherence concerns reported by some stakeholders included that in studies where PrEP adherence was objectively measured using biomarkers such as tenofovir

levels in dried blood spots (DBS), a low proportion of samples had tenofovir detected, and that participants over-reported adherence.

“But DBS was also collected which showed of course (laughs) as participants weren’t using it (oral PrEP) as they said they were using it...” (PID 06)

Stakeholder perceptions of poor adherence and oral PrEP discontinuation were frequently multiple and overlapping, and similar to barriers to oral PrEP uptake. Stigma (perceived or experienced), issues relating to disclosure, including responses from partners or family members to oral PrEP use, oral PrEP access, pill-related factors (such as storage, side effects, pill size and frequency of dosing) all contributed to perceived reasons for poor adherence and/or discontinuation. Disclosure was seen as an important factor that may affect participant adherence, where those who disclosed had better adherence.

“[I]t’s not just about do they actually want to take the PrEP, but it’s also about what the response from their partners, their families, or they have space to store it ... Some also indicated that they experienced side effects so there are multiple things that really affect their adherence ... A lot had to do with disclosure and we saw that those who disclosed frequently adhered better. Then there were other things ... it was so hard for them to access PrEP because now we [research site] were the only space they could get PrEP as soon as they would just go to a community next door you know for a bit or they would travel then they wouldn’t have access to PrEP so access was a huge barrier also for continued use and adherence. [A]nd then when it comes to the actual pill taking ... issues you know getting into pill taking fatigue, etcetera with some, but young women also practice prevention effective adherence so knowing you know how to stop and start like when their boyfriend are out of town, or if they not in a relationship at the moment, so they also practice that sometimes ... a lot of feedback from young women is that the daily pill and that size pill that Truvada is, is not working for them. They need a smaller pill, a more infrequent pill or they need an injection is something that they really ask for.” (PID 12).

“Other people didn’t feel comfortable disclosing to their partners that they taking PrEP so that also caused some challenges specifically with adherence,

like if someone is trying to hide the fact that they taking PrEP if they going to visit someone they not gonna take their pills with them, so they not going to take their pills for a couple of days ... also with partners having issues with you know their female partners now taking PrEP. The partner will say, “Oh you don’t trust me” or “You taking PrEP because you are the one that’s you know uh sleeping around” or whatever” (PID 09).

Impact of oral PrEP use on study outcomes

Most stakeholders were not concerned that oral PrEP use would affect study outcomes in HIV endpoint-driven trials. Many felt that oral PrEP use could be factored into study calculations and/or analysis by statisticians. Stakeholders reported that studies could be powered for oral PrEP use, by adjusting sample sizes, and taking into account oral PrEP uptake and adherence, therefore they were not concerned that oral PrEP use would affect study outcomes. Furthermore, some reported that the background HIV incidence was high in their communities, therefore oral PrEP use would not have an impact on study outcomes. However, many stakeholders felt that the uptake and use of oral PrEP in trials was low and/or oral PrEP was offered relatively late in the trial timeline, resulting in no effect on study outcomes.

Several stakeholders reported their role as investigators was to prevent HIV and that they had an ethical obligation to offer oral PrEP and other HIV prevention options, as preventing HIV is more important than achieving HIV outcomes in trials.

Furthermore, stakeholders compared oral PrEP with other prevention modalities such as condoms when discussing the impact on study outcomes.

“HIV incidence is important but for me if you seeing participants HIV negative is more important ... if we have fewer seroconversions then that’s okay then that just means we’re doing a good job” (PID 06).

“Our main aim is to protect participants ... it’s a very big cornerstone in all the trials that we led ... if we put that question [impact of oral PrEP on study outcomes] on the table then we should put the same question on the table for

condoms ... PrEP is just the same as all those other modalities that we put in place and should be discussed on the same level.” (PID 10)

While most key stakeholders were not concerned about study outcomes with the use of oral PrEP, one stakeholder reported that several research staff were concerned about introducing oral PrEP because the study required the enrolment of individuals who were at very high risk for HIV acquisition and in addition to being concerned about the impact of oral PrEP on study outcomes, staff members also felt confused and thought the use of oral PrEP might be contradictory.

“Staff members were like “oooo” when we were enrolling for this studies we were put under pressure to say enrol high risk ... eligibility was getting harder and tighter because they wanted high risk high risk and then when now PrEP was introduced, staff members were like “oooooh now we wonder we have been put through hell and high waters” to enrol you know the high risk and now you got the high risk here, you are giving them this and PrEP and uhm (laughs) we were just like wondering hey what they out there staff members had a lot of concerns and we were like really uhm we, are we confused, are we contradicting ourselves” (PID 11)

Post-trial oral PrEP access

Post-trial oral PrEP access varied between research sites. Some stakeholders reported that oral PrEP was easily available at local facilities such as public sector clinics which were in close proximity to the research site and/or where participants lived. Furthermore, some reported having a list of facilities/clinics known to provide oral PrEP, and that participants would be given the list so they could choose which facility they wanted to attend for ongoing oral PrEP access. A couple of stakeholders said that studies were still ongoing, therefore they had not yet exited participants who required referral for ongoing oral PrEP use. All stakeholders reported that participants who requested to continue using oral PrEP at the end of the study were given a supply of oral PrEP at trial exit, usually for three months.

Multiple challenges with post-trial oral PrEP access were identified by stakeholders. First, many facilities providing oral PrEP were located a considerable distance from

the research site, and in some cases, in different cities or towns. One stakeholder reported that the nearest facility providing oral PrEP was 250 kilometres away, another reported that it took about an hour to get to the nearest oral PrEP facility using public transport.

Second, some trial sites did not have facilities to refer participants to for ongoing oral PrEP use after exiting the study, and participants were counselled about this before initiating oral PrEP,

“We didn’t have an option for women who wanted to continue using PrEP ... there was a lot of discussion before it was introduced at our site ... about that because we knew when we started with PrEP that we weren’t going to be able to continue with it so as people exited the study they were given three months but there were there was nowhere in our area where they could access it which was, but ... we counselled women about that before we used it [PrEP]” (PID 04).

Third, despite some research sites making arrangements with organizations to provide post-trial oral PrEP access, ongoing barriers were identified by women with linking to mobile PrEP services.

“We had multiple meetings with them [name of referral organization]. We gave [name of the organization] all the spots where our mobile clinic used to go ... we also had space available for them onsite to come and see participants that who usually comes to site to get PrEP... we had quite a few participants coming back to us saying that they couldn’t get in touch with [name of the organization] saying that they couldn’t get PrEP, ... they’ve called the numbers multiple times ... but it was quite a big frustration for participants ... some participants ... would go the mobile spot because we had told [name of the organization] to be there on certain days and they would get there, there would be no one there to receive them, no one to give them PrEP ... it was very frustrating for participants” (PID 09).

Additional facility-related barriers to post-trial oral PrEP access included long queues in public sector facilities, inconvenient clinic operating hours, limited resources such as staffing, and facilities having risk criteria for oral PrEP initiation, preventing some

participants from accessing oral PrEP as they were not considered “high risk enough” to use oral PrEP,

“[W]e did have uh a few participants who came back ... saying that their local clinics mentioned that these participants were not high risk enough” (PID 06).

Discussion

To our knowledge, this study is one of the first studies in South Africa to explore the perceptions and experiences of key stakeholders in offering and/or providing oral PrEP as part of the HIV prevention package to study participants enrolled in HIV prevention and/or HIV endpoint-driven clinical trials. Key stakeholders reported that the decision to provide oral PrEP in clinical trials was influenced by the meeting held by the SAMRC on the standard of care in clinical trials (SAMRC, 2017), the rollout of oral PrEP by the SA NDoH, ethical considerations, and by trial funders. Several barriers to oral PrEP uptake by participants were identified by key stakeholders – these included challenges with daily pill taking, concerns about potential side effects, stigma, a lack of demand creation for oral PrEP, limited knowledge and education on oral PrEP in communities, and a personal preference for other modes of PrEP delivery such as injectables. Key stakeholders reported that barriers to oral PrEP uptake by trial participants were frequently multiple and overlapping with reasons for poor adherence and discontinuation. Facilitators to oral PrEP uptake included demand creation, and education and counselling about oral PrEP. Most stakeholders were not concerned that oral PrEP use would impact study outcomes and reported that oral PrEP use could be factored in study calculations and analyses by trial statisticians. Several challenges to post-trial oral PrEP access emerged such as PrEP facilities having long queues and inconvenient operating hours, PrEP sites being located a considerable distance from research sites, and some key stakeholders reported that there were no facilities to refer participants to upon study termination.

In our study, we found that most stakeholders reported providing an HIV prevention package that included oral PrEP being offered onsite to study participants. There has been considerable debate and discussion on the contents of the HIV prevention package provided to participants enrolled in HIV prevention and HIV endpoint-driven

clinical trials (Brown et al., 2020; UNAIDS & WHO, 2021; Miner et al., 2017). The summit held by the SAMRC on the standard of care in clinical research recognized the complexities in determining the standard of care for HIV prevention in clinical trials and that the context might differ from site to site, however it was clear that researchers should move towards making oral PrEP available as part of the HIV prevention package offered to study participants (Miner et al., 2017).

In our study, key stakeholders identified several barriers to oral PrEP uptake, adherence, and continuation such as a lack of demand creation, stigma, concerns about side effects and limited knowledge about oral PrEP in communities. A qualitative study that was conducted with healthcare providers from three African countries (Kenya, South Africa and Zimbabwe) who were providing oral PrEP or planning to provide oral PrEP in the future, found similar barriers to oral PrEP uptake, adherence and continuation, which included a lack of oral PrEP awareness, stigma, issues around disclosure and side effects (Lanham et al., 2021). Other studies have found a lack of PrEP awareness among healthcare providers (Zimba et al., 2018; Joseph Davey et al., 2020). In the qualitative study among healthcare providers from three African countries, providers reported that stigma was HIV-related where adolescent girls and young women (AGYW) were concerned that community members would assume that those taking oral PrEP are taking ARVs because they are living with HIV (Lanham et al., 2021). In a systematic review that looked at reasons for non-adherence to oral PrEP, in addition to barriers such as a lack of knowledge, side effects and stigma; other factors such as medication regimen (having to take a daily pill) and factors of life (being away from home, running out of medication and having a busy schedule) were identified as drivers impacting oral PrEP adherence and uptake (Sidebottom et al., 2018). Some of the early lessons that emerged from oral PrEP implementation projects among African women included the importance of oral PrEP awareness and demand creation among AGYW to motivate young women to use oral PrEP (Celum et al., 2019).

Stakeholders interviewed in our study reported that demand creation campaigns were associated with a better uptake of oral PrEP. Stakeholders also identified challenges with daily pill taking and a preference among some participants for other methods of PrEP delivery – some of these challenges may be addressed in the near

future as newer PrEP options such as injectables, longer acting oral agents, implants and vaginal rings become available.

The impact of oral PrEP use on study outcomes and trial design is an area that has received much debate and discussion. Holly Janes and colleagues (2019) described important considerations for the design of HIV prevention efficacy trials. These include the trial population (who will be enrolled), the standard of prevention (content of the HIV prevention package), the control (placebo versus active control) and intervention arms (number of interventions), the primary endpoint (HIV acquisition versus a surrogate endpoint) and efficacy objective (superiority versus non-inferiority trials).

Of concern, stakeholders identified multiple barriers to post-trial oral PrEP access for study participants, including that in some cases, it was not possible to refer participants for ongoing oral PrEP access post study exit as there were no facilities available in proximity to the research site. While ethical guidance, for example the HPTN guidance, speaks to the importance of sustainable prevention services (Brown et al., 2020), we see that practically this is not always possible. This raises important considerations such as whether oral PrEP should be provided as part of HIV prevention during a trial if post-trial access cannot be provided, but also whether it is ethical to deny at risk participants HIV prevention options that have been proven to be effective and approved for use in countries. Potential solutions to post-trial oral PrEP access include working with local governments to provide post-trial access (Singh et al., 2019) and as suggested by the SAMRC, working with the NDoH PrEP technical working group to support demonstration projects close to research sites (SAMRC, 2017). In addition, it is worth noting that oral PrEP access in South Africa has expanded over time, and access to oral PrEP has shifted from demonstration and implementation projects to availability in several public sector clinics in the country (Department of Health, 2022). Increased availability of oral PrEP, including the integration of PrEP into existing services such as family planning clinics may also improve post-trial oral PrEP access as participants can frequent these facilities at study termination. Other studies have employed innovative methods to ensure post-trial access to oral PrEP – in the Partners PrEP study, following the demonstration of PrEP efficacy, eligible participants in the placebo arm of the trial were offered PrEP and those who consented were randomized to one of the two PrEP arms in the study

(Ndase et al., 2014). In HPTN 083, post-trial access to cabotegravir was supported by trial funders as well as via an open-label extension of the study (Sugarman et al., 2021). Considering the high HIV incidence and prevalence in South Africa (UNAIDS (b), 2021), and that HIV endpoint-driven and HIV prevention trials frequently enrol participants at heightened risk of HIV infection, the need for HIV prevention options is imperative. We found that key stakeholders were supportive of oral PrEP provision in trials and discussed the importance of preventing new infections among participants. It was notable as one key stakeholder reported that an ethics committee refused to approve a study unless oral PrEP was provided.

Our study has some limitations. We interviewed key stakeholders and not study participants, hence it is possible that key stakeholders' perceptions might not fully or accurately reflect participants' thoughts and experiences. Key stakeholders were interviewed from a limited number of research sites and geographical locations in South Africa, therefore our study findings might not be generalisable across other research sites in the country or internationally. The national rollout of oral PrEP in South Africa has not been uniform and has expanded over time and this could account for differences in experiences between sites for example, some sites did not have referral options for post-trial oral PrEP access while other stakeholders reported the availability of public sector facilities providing oral PrEP that were in close proximity to research sites.

Conclusions

In summary, we found that most research sites had incorporated the provision of oral PrEP as part of the HIV prevention package offered to study participants in clinical trials, particularly, HIV prevention and HIV endpoint-driven clinical trials. However, strategies to address barriers to oral PrEP uptake and use, such as demand creation, education and counselling, addressing stigma, managing side effects and support for daily pill taking are needed. Furthermore, post-trial oral PrEP access needs to be expanded, especially in areas where facilities are not available or located a considerable distance from where participants reside, and existing facilities providing oral PrEP should be more accessible and acceptable, for example, by having convenient operating hours. Our study findings could inform other clinical

trials providing oral PrEP as part of the HIV prevention package provided to study participants, and may be useful to oral PrEP implementation and national programs.

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Daisy Maria Machado, Alexandre Machado de Sant'Anna Carvalho, Rachel Riera. "Adolescent pre-exposure prophylaxis for HIV prevention: current perspectives", Adolescent Health, Medicine and Therapeutics, 2017

Publication

<1 %

52	Dvora L Joseph Davey, Jillian Pintye, Jared M Baeten, Grace Aldrovandi et al. "Emerging evidence from a systematic review of safety of pre - exposure prophylaxis for pregnant and postpartum women: where are we now and where are we heading?", Journal of the International AIDS Society, 2020 Publication	<1 %
53	doh.gov.ph Internet Source	<1 %
54	"Sexual and Reproductive Health", Springer Science and Business Media LLC, 2022 Publication	<1 %
55	Tanuja N. Gengiah, Atika Moosa, Anushka Naidoo, Leila E. Mansoor. "Adherence challenges with drugs for pre-exposure prophylaxis to prevent HIV infection", International Journal of Clinical Pharmacy, 2013 Publication	<1 %
56	researchonline.lshtm.ac.uk Internet Source	<1 %
57	www.jiasociety.org Internet Source	<1 %
58	www.ncbi.nlm.nih.gov Internet Source	<1 %

59

"2020 STD Prevention Conference September 14-24, 2020", Sexually Transmitted Diseases, 2020

Publication

<1 %

60

John Kinuthia, Jillian Pintye, Felix Abuna, Kenneth K Mugwanya et al. "Pre-exposure prophylaxis uptake and early continuation among pregnant and post-partum women within maternal and child health clinics in Kenya: results from an implementation programme", The Lancet HIV, 2020

Publication

<1 %

61

sanac.org.za

Internet Source

<1 %

Exclude quotes On

Exclude matches < 10 words

Exclude bibliography On



R14/49 Dr Ivana Beesham

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M191155

NAME: Dr Ivana Beesham
(Principal Investigator)
DEPARTMENT: Faculty of Health Sciences
MatCH (Maternal, Adolescent and Child Health)
Research Unit (MRU) Durban
Department of Obstetrics and Gynaecology

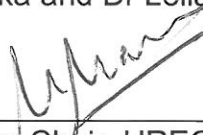
PROJECT TITLE: An evaluation of the integration of oral
pre-exposure prophylaxis (PrEP) as standard of care
for HIV prevention in clinical trials in South Africa

DATE CONSIDERED: 29/11/2019

DECISION: Approved unconditionally

CONDITIONS:

SUPERVISOR: Prof Mags Beksinska and Dr Leila Mansoor

APPROVED BY: 
Dr Nitien Naran, Co-Chair, HREC (Medical)

DATE OF APPROVAL: 07/01/2020

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary on the Third Floor, Faculty of Health Sciences, Phillip Tobias Building, 29 Princess of Wales Terrace, Parktown, 2193, University of the Witwatersrand. I/we fully understand the conditions under which I am/we are authorized

to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit the application to the Committee. **I agree to submit a yearly progress report.** The date for annual re-certification will be one year after the date of convened meeting where the study was initially reviewed. In this case, the study was initially reviewed in **November** and will therefore be due in the month of **November** each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

Principal Investigator Signature

Date

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES



R14/49 Dr Ivana Beesham

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M191155

NAME: Dr Ivana Beesham
(Principal Investigator)
DEPARTMENT: Faculty of Health Sciences
MatCH (Maternal, Adolescent and Child Health)
Research Unit (MRU) Durban
Department of Obstetrics and Gynaecology

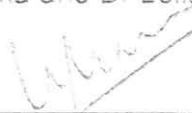
PROJECT TITLE: An evaluation of the integration of oral
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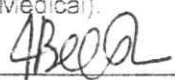
APPROVED BY: 
Dr Nitien Naran, Co-Chair, HREC (Medical)

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Principal Investigator Signature

14/01/2020
Date

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

**University
of the Witwatersrand,
Johannesburg**



Human Research Ethics Committee: (Medical)
FWA Registered No IRB 00001223

SECRETARIAT: Suite 189, Private Bag x2600, Houghton 2041, South Africa Tel: +27-11-274 9200 Fax: +27-11-274 9281

21 May 2015

FAXED & COURIERED

Dr Thesla Palanee-Phillips,
The Wits Reproductive Health & HIV Institute
Hillbrow Health Precinct, Hugh Solomon Building
Esselen Street (Cnr Klein St)
Hillbrow
2001
Fax: 086 554 1093

Dear Dr Palanee-Phillips,

PROTOCOL: FHI 360 STUDY #523201 - A MULTI CENTER, OPEN-LABEL, RANDOMISED CLINICAL TRIAL COMPARING HIV INCIDENCE AND CONTRACEPTIVE BENEFITS IN WOMEN USING DEPOT MEDROXYPROGESTERONE ACETATE (DMPA), LEVONORGESTREL (LNG) IMPLANT, AND COPPER INTRAUTERINE DEVICES (IUDS). THE EVIDENCE FOR CONTRACEPTIVE OPTIONS AND HIV OUTCOMES (ECHO) TRIAL

ETHICS REFERENCE NO: 141112

RE : FINAL ETHICS APPROVAL

This is to certify that the above-mentioned trial was reviewed by the University of the Witwatersrand, Human Research Ethics Committee (HREC), and the Protocol Review Committee (PRC) on: 28 November 2014.

The University of the Witwatersrand, Human Research Ethics Committee Approval Granted for the above mentioned study is valid for five years. Where required by Sponsor to have approval on a more frequent basis it remains the responsibility of the Sponsor and Investigator to apply for continuing review and approval, or for the duration of the Trial.

1. THIS APPROVAL IS SUBJECT TO THE FOLLOWING PROVISOS:

- * A copy of the MCC Approval and/or MCC Notification letter must be submitted to the Ethics Regulatory Office Secretariat before the study commences / or where an Amendment may be implemented (IF MCC APPROVAL / NOTIFICATION IS APPLICABLE). It remains the responsibility of the Principal Investigator and/or Sponsor to ensure that the relevant approvals are in place.
- * The study is conducted according to the protocol submitted to the University of the Witwatersrand, Human Research Ethics Committee. Any amendments to the protocol must first be submitted to the Human Research Ethics Committee for approval.
- * During the study, the University of the Witwatersrand, Human Research Ethics Committee is informed immediately of :
 - Any Unexpected Serious Adverse Events or Unexpected Adverse Drug Reactions, which, in the Investigator and/or the Sponsor's opinion are suspected to be related to the study drug. (Refer to POL-IEC-001 and SOP-IEC-005, Item 3.4).
 - Any data received during the trial which, may cast doubt on the validity of the continuation of the study .
- * The University of the Witwatersrand, Human Research Ethics Committee is notified of any decision to discontinue the study and the reason stated.
- * The Investigators authorised by this approval participate in this study. Additional Investigators shall be submitted to the University of the Witwatersrand, Human Research Ethics Committee for approval prior to their participation in the study.

* In the event of an authorised Investigator ceasing to participate in the study, the University of the Witwatersrand, Human Research Ethics Committee must be informed and the reason for such cessation given.

2. PRINCIPLES OF INFORMED CONSENT:

* The University of the Witwatersrand, Human Research Ethics Committee requires that in all studies, the Principles of Informed Consent are adhered to. This applies to volunteers as well as patients.

3. PROGRESS REPORTS:

* The University of the Witwatersrand, Human Research Ethics Committee requests that the MCC Progress Reports be submitted twice a year either in March and September or six monthly from start of study to the HREC Secretariat Office - 011 274 9281 and a report of the final results, at the conclusion of the study. (IF APPLICABLE)

4. REIMBURSEMENT TO PATIENTS FOR TRANSPORT:

* The Human Research Ethics Committee: (Medical) is in agreement that reimbursement per visit is according to the Medicines Control Council of SA and that reimbursement should be appropriate according to the situation.

5. TRANSPORT AND STORAGE OF BLOOD AND TISSUE SAMPLES IN SOUTH AFRICA:

* If blood specimens are to be stored for future analysis and is planned that such analysis will be done outside Wits, then the blood must be stored at a facility in South Africa agreed with the relevant IRB, with release of sub-samples only once projects have been approved by the local Research Ethics Committee applicable to where the analysis will be done as well as by the Wits Human Research Ethics Committee: (Medical).

6. GENETIC TESTING

* The Human Research Ethics Committee: Medical; will not approve open-ended genetic testing as this does not fit the Human Research Ethics Committee criteria.

7. GOOD CLINICAL PRACTICE

The South African Department of Health, Medicines Control Council requires Good Clinical Practice (GCP) Training for all Investigators in Clinical Trials, and that GCP training be renewed every three (3) years.

As yet, there are no National Guidelines for the content of GCP courses. Until these are available the Wits Human Research Ethics Committee (Medical) will note courses completed by Investigators without approval of the content of the individual courses.

8. THE SUPPORTING APPROVAL DOCUMENTS ARE ATTACHED:

8.1 Ethics Approval Form signed by the Chairperson of the HREC - Kindly return the copy of the Approval Form signed by the Principal Investigator / (s) per fax: 011 274 9281 for our records (this is applicable with the initial Approval).

8.2 Protocol Review Committee Approval Signature page signed by the Acting Chairperson of the PRC.

8.3 List of members present at the HREC meeting held as per INDEPENDENT ETHICS COMMITTEE APPROVAL FORM

9. WE AWAIT YOUR RESPONSES AS REQUESTED: Ensure to have these documents forwarded at the earliest for the HREC records.

* MCC Approval letter and/or letter of Notification before the above study may commence / or where an Amendment may be implemented (IF MCC APPROVAL / NOTIFICATION IS APPLICABLE). It remains the responsibility of the Principal Investigator and/or Sponsor to ensure that the relevant approvals are in place.

* Copy of Independent Ethics Declaration Approval Form signed by the Principal Investigator. (this is applicable with the initial Approval).

* Kindly forward the above to the undersigned at fax: 011 274 9281 at your earliest convenience.

Conditional Approval Noted by BEC: 'BEC 2 is approved, pending HREC approval of the study. As the application for BEC 2 was for storage only, there is no need for an MTA. Retrieval and transfer will require a separate BEC 2 application - and the MTA should be submitted then.'

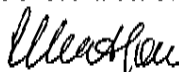
The above has been noted for the Ethics Committee information and records.

**KINDLY FORWARD TO THE RELEVANT INVESTIGATORS / CRA /
SPONSOR / STUDY CO-ORDINATORS - WHERE APPLICABLE**

Regards,

PROF PETER CLEATON-JONES

For and on behalf of the Human Research Ethics Committee: (Medical)



INDEPENDENT ETHICS COMMITTEE APPROVAL FORM



Ethics Reference No.	141112	Date of Meeting	28 November 2014
		Recertification Due	27 November 2015 (If applicable)
Principal Investigators:	Dr K Ahmed Prof GJ Hofmeyr Dr CE Louw Dr Thesla Palanee-Phillips Dr RAP Selepe Prof JA Smit	Investigators:	Dr M Bekslinska Dr Nazira Carrim-Ganey Dr KC Diphoko Dr V Edward Dr N Govender Dr C Innes Dr SS Krüger Dr M Malahleha Dr N Manzingana Dr MP Ramafalo Prof Helen Rees Dr K Sindane Dr M Singata-Madliki

Protocol Title: A Multi Center, Open-Label, Randomised Clinical Trial Comparing HIV Incidence and Contraceptive Benefits in Women using Depot Medroxyprogesterone Acetate (DMPA), Levonorgestrel (LNG) Implant, and Copper Intrauterine Devices (IUDs). The Evidence for Contraceptive options and HIV Outcomes (ECHO) Trial

DOCUMENTS REVIEWED		Tick As Appropriate	Yes	No
Protocol Number	FHI 360 Study #523201	Date:	21 October 2014	☐
Protocol	FHI 360 Study #523201 Protocol Version 1.0	Date:	21 October 2014	☒
Investigator's Brochure	ParaGard® T380A Intrauterine Copper Contraceptive - Version: 6/2013 - Dated:		☒	☐
	"Norplant® II" Levonorgestrel Implants (Jadelle®) - Version: NDA 20-544 Supplement 003 - Dated:		☒	☐
	Package Insert: Depo-Provera CI (medroxyprogesterone acetate) - Version: 4/2012 - Dated:		☒	☐
Subject Information/Consent Form	ECHO Enrollment Informed Consent Parent Comprehension Assessment Tool - Version: 1.1 - Dated: 12/Jan/2015		☒	☐
	ECHO Enrollment Informed Assent/Consent Comprehension Assessment Tool - Version: 1.1 - Dated: 12/Jan/2015		☒	☐
	ECHO Specimen Storage and Future Testing Informed Assent Form for Girls 16-17 Years of Age - Version: 1.1 - Dated: 13/Jan/2015		☒	☐
	ECHO Specimen Storage and Future Testing Parent Informed Consent - Version: 1.1 - Dated: 13/Jan/2015		☒	☐
	ECHO Participant Specimen Storage and Future Testing Informed Consent - Version: 1.1 - Dated: 13/Jan/2015		☒	☐
	ECHO Enrollment Informed Assent Form - Version: 1.1 - Dated: 13/Jan/2015		☒	☐
	ECHO Parent Enrollment Informed Consent Form - Version: 1.1 - Dated: 13/Jan/2015		☒	☐
	ECHO Participant Enrollment Informed Consent Form - Version: 1.1 - Dated: 13/Jan/2015		☒	☐
	ECHO Screening Informed Assent Form for Girls 16-17 Years of Age - Version: 1.1 - Dated: 13/Jan/2015		☒	☐
	ECHO Parent Screening Informed Consent Form - Version: 1.1 - Dated: 13/Jan/2015		☒	☐
	ECHO Participant Screening Informed Consent Form - Version: 1.1 - Dated: 13/Jan/2015		☒	☐
Advertisements				
Questionnaires	Screening Eligibility Criteria - Version: Draft 6 - Dated: 20/Oct/2014		☒	☐
	Social Harm - Version: Draft 6 - Dated: 20/Oct/2014		☒	☐
	Behaviour Assessment - Version: Draft 6 - Dated: 20/Oct/2014		☒	☐
	Contraception Side Effects (CSE) - Version: Draft 6 - Dated: 20/Oct/2014		☒	☐
	Baseline Reproductive History - Version: Draft 6 - Dated: 20/Oct/2014		☒	☐
Insurance/Compensation	Application pending - to be submitted	Valid From		To: ☒
Synopsis of Study/Trial Summary	Evidence for Contraceptive Options & HIV Outcomes		☒	☐
Other Documentation	Protocol Synopsis - Dated: 21/Oct/2014		☒	☐
	PRC Application Form - Dated: 07/Nov/2014		☒	☐
	HREC Application Form - Dated: 07/Nov/2014		☒	☐
	NHREC Trial Application ID: 3915 - Dated: 05/Nov/2014		☒	☐
	Office of International Research Ethics (OIRE) PHSC Revision Request Checklist, Dated November 20, 2014 - Dated:		☒	☐

INDEPENDENT ETHICS COMMITTEE APPROVAL FORM



Relevant Trial Hospital/(s)	Wits RHI - Reproductive Health & HIV Institute (Esselen Str)	☒	☐	☐
	Setshaba Research Centre	☒	☐	☐
	MatCH Commercial City Clinic	☒	☐	☐
	MatCH Research Centre: Edendale Lay Ecumenical Centre	☒	☐	☐
	MatCH - Maternal, Adolescent and Child Health Research, Dept of Obstetrics and Gynaecology, University of Witwatersrand	☒	☐	☐
	Madibeng Centre for Research	☒	☐	☐
	Frere Maternity Hospital	☒	☐	☐
	Cecilia Makiwane Hospital	☒	☐	☐
	Aurum Institute: Gavin J Churchyard Legacy Centre	☒	☐	☐
Syndicate and/or Research Unit	Wits RHI - Reproductive Health & HIV Institute (Esselen Str)	☒	☐	☐
	Setshaba Research Centre	☒	☐	☐
	MatCH Commercial City Clinic	☒	☐	☐
	MatCH Research Centre: Edendale Lay Ecumenical Centre	☒	☐	☐
	MatCH - Maternal, Adolescent & Child Health Research	☒	☐	☐
	Madibeng Centre for Research	☒	☐	☐
	ECRU - Effective Care Research Unit	☒	☐	☐
	Aurum Institute: Gavin J Churchyard Legacy Centre	☒	☐	☐

DETAILS OF COMMITTEE	
Name	University of the Witwatersrand Human Research Ethics Committee: (Medical)
Address	Research Office, Senate House University of the Witwatersrand, 1 Jan Smuts Avenue, BRAAMFONTEIN, Johannesburg, 2000

DETAILS OF MEETING		Yes	No
Is the Investigator a member of the committee ?		☐	☒
If "Yes" did he/she vote ?		☐	☒
Is the Committee organised and operated according to applicable laws and regulations together with ?		☒	☐
Local GCP requirements ?		☒	☐
ICH GCP requirements ?		☒	☐
FDA GCP requirements ? FWA Registered No. IRB00001223		☒	☐
Progress reports required either in March and September or six monthly from start of study ?		☒	☐

DECISION ON APPROVAL - Is approval given to conduct the trial ?		Tick As Appropriate
Yes - with no conditions		☐
Yes - with conditions		☒
Specify conditions :	Conditional Approval Noted by BEC: 'BEC 2' is approved, pending HREC approval of the study. As the application for BEC 2 was for storage only, there is no need for an MTA. Retrieval and transfer will require a separate BEC 2 application - and the MTA should be submitted then.'	

No	☐
Specify reasons	

SIGNATURES		
I confirm that the details on this form are correct:		Date
Name: Prof PE Cleaton-Jones Chair / Deputy Chair of Committee	Signature:	21 May 2015

DECLARATION OF INVESTIGATOR/(S) To be completed and ONE COPY returned to the Secretariat for the HREC at Wits Health Consortium, 8 Blackwood Avenue, Parktown, 2193 or Fax To: 011 274-9281 I/We fully understand the conditions under which I am/we are authorised to carry out and complete the above-mentioned research and I/we agree to ensure full compliance with these conditions. Should any amendment, alteration or departure be contemplated from the research procedure methodology or manner of execution, I/we will communicate with the Chairman of the Human Research Ethics Committee: (Medical) for approval prior to acting on any of the above mentioned proposed amendments, alterations or departures. I am/we are fully aware that any unauthorised amendment, alteration or departure as above will amount to misconduct and may lead to the institution of disciplinary procedures. Any approval given by the HREC is conditional upon consent being obtained by the Investigator/s from the Superintendent (or equivalent official) of the Hospital, Clinic or Institution in which the research is, in part or full, to take place. The Chairman may of course at his discretion place the matter before the full Committee. DATE: _____ SIGNATURE: _____ NAME: _____ PROTOCOL NUMBER FHI 360 Study #523201 ETHICS REF.: 141112		
--	--	--

Date Printe 21 May 2015



Wits Clinical Research

8 Blackwood Avenue, Parktown, 2193, South Africa
Tel. +27-11-274-9200, Fax: +27-11-274-9281
Postnet Sulte 189, Private Bag x2600, Houghton, 2041

FAXED & COURIERED

Dr Thesla Palanee-Phillips,

The Wits Reproductive Health & HIV Institute
Hillbrow Health Precinct, Hugh Solomon Building
Esselen Street (Cnr Klein St)
Hillbrow
2001

Fax: 086 554 1093

Dear Dr Palanee-Phillips,

PROTOCOL NO: FHI 360 Study #523201

PROTOCOL TITLE: A Multi Center, Open-Label, Randomised Clinical Trial Comparing HIV Incidence and Contraceptive Benefits in Women using Depot Medroxyprogesterone Acetate (DMPA), Levonorgestrel (LNG) Implant, and Copper Intrauterine Devices (IUDs). The Evidence for Contraceptive options and HIV Outcomes (ECHO) Trial

PRC REFERENCE NUMBER: 141112

Please be advised that your trial application was:

APPROVED

The Expert Reviewer / (s): Dr FM Conradie

Also reviewed by: Mrs J Palmer: Acting Chairperson Protocol Review Committee

Yours sincerely

A handwritten signature in black ink, appearing to read 'J Palmer'.

Acting **MRS JENNIFER PALMER**
Chairperson: Protocol Review Committee
21 May 2015

cc.

Wits RHI - Reproductive Health Dr Thesla Palanee-Phillips

Tel 011 358 5471 Cell 083 783 3574 Fax 086 554 1093



HUMAN RESEARCH ETHICS COMMITTEE MEMBERS: (MEDICAL) UNIVERSITY OF THE WITWATERSRAND

Attendance Register for the Ethics Meeting held on 28 November 2014 from 12:00 - 15:00

**Venue: EXECUTIVE COMMITTEE ROOM, Ground Floor, Phillip V Tobias Building, Cnr York Road & 29
Princess of Wales Terrace**

AFFILIATED TO THE UNIVERSITY OF THE WITWATERSRAND

Surname	Initials	Title	Discipline/s	Academic Qualifications	Gender	Present
Adam	Y	Dr	Obstetrics & Gynaecology	MB BCH; FCOG	F	Present
Cleaton-Jones	PE	Prof	Biomedical Ethics	BDS; MB BCH; PhD; DA (SA); DTM&H; DSc (Dent), FCD (SA) DPH; PhD Hon Causa, MASSAfr	M	Present
Conradie	FM	Dr	Infectious Diseases/HIV/TB	MB BCH; DTM&H; MSc; Dip HIV Man	F	Present
Cooper	PA	Prof	Paediatrics	MB BCH, PhD, DCH (SA), FCPaeds (SA)	M	Absent
Dessein	PHMC	Prof	Rheumatology	MD, FCP (SA), FRCP, PhD	M	Present
Dhai	A	Prof	Biomedical Ethics	MB ChB; FCOG; LLM; PGDiplntResEthics	F	Present
Donde	B	Prof	Radiation Oncology	MB BCH, MMed Rad (T)	M	Absent
Etheredge	H	Ms	Biomedical Ethics	MSc Med, BA	F	Present
Feldman	C	Prof	Pulmonology	MB BCH, PhD, DSc, FCP (SA), FRCP	M	Absent
Gerrand	P	Ms	Social Work	MA (Social Work)	F	Absent
Langley	G	Prof	Nursing	MSc (Nursing), PhD, MPhil (Ethics)	F	Present
Lowman	W	Dr	Clinical Microbiology	MB BCH, MMed, FC Path (SA) Micro	M	Absent
Lownie	MA	Prof	Maxillo-Facial & Oral Surgery	BDS, BA (Hons), DipMFOS, FCMFOS(SA), MEd	F	Absent
Naidoo	S	Prof	Public Health	MB BCH, DMTH, DHSM, DOH, MMED	M	Present
Naran	NH	Dr	Chemical Pathology	PhD	M	Present
Penn	C	Prof	Speech Pathology	BA (Sp&HTh), PhD, CCC SL-P, OMS	F	Present
Penny	C	Dr	Internal Medicine	BSc Hons, PhD	M	Present
Ross	M	Prof	Public Health	MB ChB, FFCH(SA), FOM(UK)	F	Absent
Sanne	IM	Prof	Infectious Diseases/HIV/TB	MB BCH, FCP (SA), DTM&H; MMed & PhD	M	Absent
Smith, Cora	C	Prof	Psychiatry	BA, BA (Hons), M.A (Clin.Psych), PhD	F	Present
Stewart	A	Prof	Physiotherapy	BSc (Physio), MSc, PhD, DPE	F	Present
Szabo	CP	Prof	Psychiatry	MB BCH, MMed, MScMed, PhD; FCPsych(SA)	M	Present
Thom	RGM	Prof	Psychiatry	MB ChB, DCH, FCPsych, PhD	F	Absent
Tsotsi	NM	Dr		BDS; MPH; MSc Med; PGDiplnt ResEthics	F	Present
Van Gelderen	CJ	Prof	Obstetrics & Gynaecology	MB BCH, FRCOG, FCOG(SA)	M	Present
Velaphi	S	Prof	Paediatrics	MB BCH, FCPaeds, MMed	M	Present
Vorster	M	Dr	Psychiatry	BA, MB BCH; MMed, FCPsych(SA), PhD PGDiplntResEthics	F	Present
Warria	A	Dr	Social Work	D Litt et Phil (SWK)	F	Absent
Willem	P	Dr	Human Genetics	MD, PhD	F	Present
Woodiwiss	AJ	Prof	Cardiovascular Pathophysiology	BSc Physiotherapy, BSc, MSc, PhD	F	Present

NOT AFFILIATED TO THE UNIVERSITY OF THE WITWATERSRAND

Surname	Initials	Title	Discipline/s	Academic Qualifications	Gender	Present
Egan	A	Father	Theology	BA (Hons), MA, MDiv, STL, PhD	M	Present
Guldozzi	Y	Adv	Lawyer	BSc (Nurs), LLB, MBA	F	Present
Ikalafeng	B	Dr	Governance	BSc (Hons), MSc, PhD	F	Absent
Myburgh	C	Prof	Educationist	BSc (Hons), MCom, DEd, HED	M	Present

Paruk	F	Prof	Anaesthesia	MB ChB, FCOG(SA), Crit Care(SA), PhD	F	Absent
Peter	JR	Adv	Lawyer	BCom; LLB; LLM	M	Absent
Poggenpoel	M	Prof	Psychiatric Nursing	RN; PhD	F	Present

RETIRED MEMBER OCCASIONALLY CO-OPTED FOR SURGICAL OPINION ON A PROJECT

Oettle	GJ	Prof	Surgery	BSc (Hons), MB BCH, FRCS	M
--------	----	------	---------	--------------------------	---

Note 1: This committee has been in continuous operation since October 1966

Note 2: The large committee size is to ensure a good attendance at meetings - size 24 core and 15 alternate members

Note 3: A Quorum is 14 members according to the 60% required by SA National Guidelines (ref 2 below)

This is to certify that the Human Research Ethics Committee: (Medical) of the University of the Witwatersrand operates according to the following guidelines of good clinical practice:

1. ICH Harmonised Tripartite Guideline for Good Clinical Practice.
2. SA National Department of Health 2006 Guidelines for Good Practice in the Conduct of Clinical Trials with Human Participants in South Africa (2006).
3. Declaration of Helsinki 2013.

The Committee's United States Federal Wide Assurance details are:

1. Country code SF.
2. FWA Number: FWA00000715.
3. University of the Witwatersrand: IORG0000862.
4. Human Research Ethics Committee: (Medical): IRB00001223.

University
of the Witwatersrand,
Johannesburg



Human Research Ethics Committee: (Medical)
FWA Registered No IRB 00001223

SECRETARIAT: Suite 189, Private Bag x2600, Houghton 2041, South Africa Tel: +27-11-274 9200 Fax: +27-11-274 9281

Mrs M Naidoo

FAXED

Maternal, Adolescent and Child Health Research Unit
40 Dr AB Xuma Street
21st Floor, Suite 2117
Commercial City Building, Durban
4000

11 April 2018

Fax: 031 301 0829

Dear Mrs Naidoo,

PROTOCOL: FHI 360 STUDY #523201 - A MULTI CENTER, OPEN-LABEL, RANDOMISED CLINICAL TRIAL COMPARING HIV INCIDENCE AND CONTRACEPTIVE BENEFITS IN WOMEN USING DEPOT MEDROXYPROGESTERONE ACETATE (DMPA), LEVONORGESTREL (LNG) IMPLANT, AND COPPER INTRAUTERINE DEVICES (IUDS). THE EVIDENCE FOR CONTRACEPTIVE OPTIONS AND HIV OUTCOMES (ECHO) TRIAL

ETHICS REFERENCE NO: 141112

RE : APPROVAL FOR AMENDMENT TO ECHO PROTOCOL (MATCH)

We acknowledge receipt of your letter dated 27 March 2018 with the following documentation pertaining to the above-captioned trial.

Amendment Date: 27-Mar-2018

Amendment Version: 1.0

Amendment Number:

Received Date: 27-Mar-2018

The following has been approved by the Wits Human Research Ethics Committee: (Medical):

- * ECHO Additional Data Collection on PrEP Use Informed Consent Form
- * PrEP Questionnaire (To be administered approximately 3 months after PrEP initiation)
- * PrEP Follow-up Questionnaire (Administered approximately 4 to 6 months after study exit)

Noted: Match will collect the data using an interviewer administered questionnaire which will take approximately 20 to 30 minutes. All participants who initiate PrEP will be asked if they are interested in answering these additional questions approximately 3 months after PrEP initiation. Participants are reimbursed R150 for scheduled ECHO study visits (as per ECHO ICF version 4.0 dated 24 April 2017, approved by the HREC on 12 May 2017) and no further reimbursement will be provided for the additional data collection. Match is also requesting approval to call participants approximately 4 to 6 months after exit to find out if the participant is still on PrEP and if there were any problems accessing PrEP after the study ended.

Ethics Approval Date: 11 April 2018

The above has been noted for the Ethics Committee information and records.

KINDLY FORWARD TO THE RELEVANT INVESTIGATORS / CRA / STUDY CO-ORDINATORS

Regards,

PROF CLEMENT PENNY

For and on behalf of the Human Research Ethics Committee: (Medical)

University
of the Witwatersrand,
Johannesburg



Human Research Ethics Committee: (Medical)
FWA Registered No IRB 00001223

SECRETARIAT: Suite 189, Private Bag x2600, Houghton 2041, South Africa Tel: +27-11-274 9200 Fax: +27-11-274 9281

15 August 2018

FAXED

Prof JA Smit,
MatCH Commercial City Clinic
Commercial City Clinic
40 Dr AB Xuma Drive
Commercial City
4000

Fax: 031 301 0829

Dear Prof Smit,

PROTOCOL: FHI 360 STUDY #523201 - A MULTI CENTER, OPEN-LABEL, RANDOMISED CLINICAL TRIAL COMPARING HIV INCIDENCE AND CONTRACEPTIVE BENEFITS IN WOMEN USING DEPOT MEDROXYPROGESTERONE ACETATE (DMPA), LEVONORGESTREL (LNG) IMPLANT, AND COPPER INTRAUTERINE DEVICES (IUDS). THE EVIDENCE FOR CONTRACEPTIVE OPTIONS AND HIV OUTCOMES (ECHO) TRIAL

ETHICS REFERENCE NO: 141112

RE : APPROVAL FOR ADDITIONAL BLOOD DRAW ON PREP

We acknowledge receipt of your letter dated 14 August 2018 with the following documentation pertaining to the above-captioned trial.

The chairperson has approved the following from MatCH:

"We received HREC approval on 11 April 2018 to collect additional data on PrEP use in the ECHO study (attached). In addition, we would like to request approval to collect an additional 4ml of blood to test for Tenofovir levels for those participants who are still on PrEP at the final visit. The additional blood volume is within the 40 ml allowed at the final visit as per ECHO ICF v4.0 dated 24 April 2017.

We will be collecting bloods at the final visit for the ECHO study and we will draw the additional blood at the same time so we will not prick the participant again. This will help us determine if participants who are given PrEP are taking PrEP. It will only apply to participants who have initiated PrEP onsite and are still currently enrolled in the study. Participants who have already exited ECHO will NOT be called back for the additional blood draw. We will request permission to collect the additional 4ml of blood using the consent form attached. Participants who come in for their final ECHO visit are reimbursed R150 and no additional reimbursement will be provided."

The following documents have been received:

- HREC approval for additional data collection on PrEP
- ECHO Additional Data Collection on PrEP Use and Blood Draw Informed Consent Form, Version 2.0 dated 06 August 2018

The above has been noted for the Ethics Committee information and records.

KINDLY FORWARD TO THE RELEVANT INVESTIGATORS / CRA / SPONSOR / STUDY CO-ORDINATORS - WHERE APPLICABLE

Regards,

A handwritten signature in dark ink, appearing to read "J. Palmer".

MRS JENNIFER PALMER

For and on behalf of the Human Research Ethics Committee: (Medical)

14 August 2019

The Chairperson
Wits Human Research Ethics Committee

RE: PERMISSION TO USE ECHO TRIAL DATA FOR DEGREE PURPOSES (PhD)

This is to confirm that Dr Ivana Beesham who was the study clinician in the ECHO Trial at the MatCH Research Unit sites (Commercial City and Edendale) has been granted permission by the ECHO Management Committee to use ECHO Trial data for degree purposes.

Dr Beesham has been very involved in the ECHO Trial from the beginning of the study and has played a big role in the implementation of PrEP as standard of care during the ECHO Trial. She has also developed an ancillary ECHO study collecting additional data on PrEP use; and blood testing for Tenofovir levels in a subset of participants at her study site at Commercial City, Durban.

Yours sincerely

Julia Welch

Julia D. Welch

ECHO Trial Project Director
FHI360
359 Blackwell Street, Durham NC 27701
jwelch@fhi360.org



**ECHO ADDITIONAL DATA COLLECTION ON PrEP USE
INFORMED CONSENT FORM**

PID: _____

STUDY NUMBER: FHI 360 Study #523201

STUDY TITLE: Evidence for Contraceptive options and HIV Outcomes (ECHO): A Multi Center, Open-Label, Randomised Clinical Trial Comparing HIV Incidence and Contraceptive Benefits in Women using Depot Medroxyprogesterone Acetate (DMPA), Levonorgestrel (LNG) Implant, and Copper Intrauterine Devices (IUDs)

SHORT TITLE FOR THE STUDY: The Evidence for Contraceptive options and HIV Outcomes (ECHO) Trial

PRINCIPAL INVESTIGATOR: Prof Jenni Smit

Good day, my name is _____ and I work for MRU (MatCH Research Unit). MRU would like to invite you to consider answering some additional questions on your experience of using Pre-Exposure Prophylaxis, also known as PrEP during and after the ECHO study.

Introduction

This form, called an Informed Consent Form will explain what additional information we want to collect. Please read this form or have it read to you. Before you decide if you want to provide the additional information, we want to explain what additional information is being collected, the potential benefits and risks, and what you will be asked to do. It is important you know the following:

- Your participation is entirely voluntary.
- You can ask questions now or at any time.
- If you agree to the additional data collection, you can change your mind later and stop at any time

Once you understand this form and if you decide to allow us to collect this additional data, you will be asked to sign this consent form, and you will be given a signed copy to keep. This process is called informed consent.

Purpose of the additional questions on PrEP

We would like to ask you questions on PrEP use as this will help us understand what influences young sexually active women to use PrEP and what women identify as risk factors for HIV acquisition. We also want to understand what post study access women have to PrEP. We hope that the information obtained can be used in the planning and implementation of PrEP services both in clinical trials and in other health care facilities.

Study procedures

If you agree to the additional data collection, we will ask you a few questions on:

- Reasons for deciding to use PrEP
- Any risk factors you feel that might put you at risk of getting HIV
- Side-effects you might have experienced since starting PrEP
- Disclosure to anyone regarding PrEP use
- Adherence to taking PrEP

The questionnaire will take an additional 20 to 30 minutes of your time and will only be asked once. We will also call you in 4 to 6 months after you exit the study, if you are agreeable, to find out if you are still on PrEP and if you were able to access PrEP after the study ended.

Possible risks

We do not expect you to have any problems by answering these additional questions. It is possible that some women might feel uncomfortable or be embarrassed discussing certain topics in the questionnaire. The information you provide in this study remains confidential.

Possible benefits

There are no direct benefits to you for answering these additional questions, but the information you provide can possibly be used in the planning of PrEP services and provide important information on the provision of PrEP in clinical trials.

Reimbursement

You will receive your R150 reimbursement for your ECHO visit today and NO additional reimbursement will be provided for answering these additional questions.

Confidentiality

All study staff will treat the information you provide with strictest confidentiality. All information will be identified only by individual participant code numbers and will be kept confidential in a locked file drawer at MRU. This information or material will be available only to study staff. Your name will never be used in any publication or presentation about this study.

Alternative to study participation

The alternative to answering these additional questions is to choose NOT to answer the additional questions. Your non-participation in answering the additional questions will not affect your participation in the ECHO study or the provision of PrEP.

Research standards and rights of participants

Your participation in answering these questions is voluntary. You may decide not to participate, or refuse to answer any question at any time.

Contact details

We appreciate the time you may take to answer the additional questions.

If you have any questions about the additional data collection or request any updates, now or in future, you can call Prof Jenni Smit, who is the MRU Principal Investigator of the ECHO study at 031 001 1941 or 082 9265 762.

The Human Research Ethics Committee of the University of the Witwatersrand has approved the recruitment of participants for this study. The Institutional Review Boards/ethics committees oversee the protection of people participating in research studies.

Informed Consent Form: Additional Data Collection on PrEP Use

If you have any questions about your rights as a research participant, or any complaints, you can contact the following person:

The Chairperson of the Human Research Ethics Committee
University of the Witwatersrand
Tel: 011 717 2301.

You now have an opportunity to ask me questions.

PERMISSION TO CONTACT PARTICIPANT TELEPHONICALLY IN APPROXIMATELY 4 TO 6 MONTHS AFTER STUDY EXIT:

In addition, we would like to know if we can contact you telephonically in approximately 4 to 6 months after your last study visit to find out if you are still on PrEP and if you had any problems accessing PrEP after the study ended.

Please sign or place your mark or thumbprint next to the option you choose:

_____ Participant signature/mark or thumbprint	Yes , I agree to be contacted telephonically
_____ Participant signature/mark or thumbprint	No , I do not agree to be contacted telephonically

Declaration of the volunteer

I understand the purpose of the additional data collection. I have read the above information, or it has been read to me. I have had the opportunity to ask questions, and any questions that I asked have been answered to my satisfaction. I consent voluntarily to answer the additional questions and understand that I have the right to stop my participation at any time.

Signature of volunteer:

Signature/mark or thumbprint		Date of signature			
			dd	MMM	yyyy
Print name		Time of signature	:		

For illiterate participants (signature of witness if applicable):

Signature of Witness		Date of signature			
			dd	MMM	yyyy
Print name		Time of signature	:		

Signature of study staff taking consent:

Signature		Date of signature			
			dd	MMM	yyyy
Print name		Time of signature	:		



ECHO ADDITIONAL DATA COLLECTION ON PrEP USE AND BLOOD DRAW INFORMED CONSENT FORM

PID: _____

STUDY NUMBER: FHI 360 Study #523201

STUDY TITLE: Evidence for Contraceptive options and HIV Outcomes (ECHO): A Multi Center, Open-Label, Randomised Clinical Trial Comparing HIV Incidence and Contraceptive Benefits in Women using Depot Medroxyprogesterone Acetate (DMPA), Levonorgestrel (LNG) Implant, and Copper Intrauterine Devices (IUDs)

SHORT TITLE FOR THE STUDY: The Evidence for Contraceptive options and HIV Outcomes (ECHO) Trial

PRINCIPAL INVESTIGATOR: Prof Jenni Smit

Good day, my name is _____ and I work for MRU (MatCH Research Unit). MRU would like to invite you to consider answering some additional questions on your experience of using Pre-Exposure Prophylaxis, also known as PrEP during and after the ECHO study.

Introduction

This form, called an Informed Consent Form will explain what additional information we want to collect. Please read this form or have it read to you. Before you decide if you want to provide the additional information, we want to explain what additional information is being collected, the potential benefits and risks, and what you will be asked to do. It is important you know the following:

- Your participation is entirely voluntary.
- You can ask questions now or at any time.
- If you agree to the additional data collection, you can change your mind later and stop at any time

Once you understand this form and if you decide to allow us to collect this additional data, you will be asked to sign this consent form, and you will be given a signed copy to keep. This process is called informed consent.

Purpose of the additional questions on PrEP

We would like to ask you questions on PrEP use as this will help us understand what influences young sexually active women to use PrEP and what women identify as risk factors for HIV acquisition. We also want to understand what post study access women have to PrEP. We hope that the information obtained can be used in the planning and implementation of PrEP services both in clinical trials and in other health care facilities.

Study procedures

If you agree to the additional data collection, we will ask you a few questions on:

- Reasons for deciding to use PrEP
- Any risk factors you feel that might put you at risk of getting HIV
- Side-effects you might have experienced since starting PrEP
- Disclosure to anyone regarding PrEP use
- Adherence to taking PrEP

The questionnaire will take an additional 20 to 30 minutes of your time and will only be asked once. We will also call you in 4 to 6 months after you exit the study, if you are agreeable, to find out if you are still on PrEP and if you were able to access PrEP after the study ended.

In addition, if you are still on PrEP at your final visit, we would like to draw an extra 4ml (less than 1 teaspoon) of blood to test and see if the PrEP drug you are using can be found in your blood. We are drawing blood for your final ECHO visit and we will collect the additional blood at the same time so we will not prick you again. We are doing this test for research purposes and will not provide you with the result.

Possible risks

We do not expect you to have any problems by answering these additional questions. It is possible that some women might feel uncomfortable or be embarrassed discussing certain topics in the questionnaire. The information you provide in this study remains confidential.

You may have some pain when we take blood from your arm. You may also feel dizzy or faint, and/or develop a bruise, swelling, or infection where the needle was inserted.

Possible benefits

There are no direct benefits to you for answering these additional questions or having the additional blood drawn, but the information you provide can possibly be used in the planning of PrEP services and provide important information on the provision of PrEP in clinical trials.

Reimbursement

You will receive your R150 reimbursement for your ECHO visit today and NO additional reimbursement will be provided for answering these additional questions and/or having the additional blood drawn

Confidentiality

All study staff will treat the information you provide with strictest confidentiality. All information will be identified only by individual participant code numbers and will be kept confidential in a locked file drawer at MRU. This information or material will be available only to study staff. Your name will never be used in any publication or presentation about this study.

Alternative to study participation

The alternative to answering these additional questions is to choose NOT to answer the additional questions. Your non-participation in answering the additional questions or having the additional blood taken will not affect your participation in the ECHO study or the provision of PrEP.

Research standards and rights of participants

Your participation in answering these questions is voluntary. You may decide not to participate, or refuse to answer any question at any time.

Contact details

We appreciate the time you may take to answer the additional questions.

If you have any questions about the additional data collection or request any updates, now or in future, you can call Prof Jenni Smit, who is the MRU Principal Investigator of the ECHO study at 031 001 1941 or 082 9265 762.

The Human Research Ethics Committee of the University of the Witwatersrand has approved the recruitment of participants for this study. The Institutional Review Boards/ethics committees oversee the protection of people participating in research studies.

If you have any questions about your rights as a research participant, or any complaints, you can contact the following person:

The Chairperson of the Human Research Ethics Committee
University of the Witwatersrand
Tel: 011 717 2301.

You now have an opportunity to ask me questions.

PERMISSION TO COLLECT ADDITIONAL BLOOD AT THIS VISIT:

_____ Participant signature/mark or thumbprint	Yes , I agree to have extra blood collected
_____ Participant signature/mark or thumbprint	No , I do not agree to have the extra blood collected / I am no longer on PrEP

PERMISSION TO CONTACT PARTICIPANT TELEPHONICALLY IN APPROXIMATELY 4 TO 6 MONTHS AFTER STUDY EXIT:

In addition, we would like to know if we can contact you telephonically in approximately 4 to 6 months after your last study visit to find out if you are still on PrEP and if you had any problems accessing PrEP after the study ended.

Please sign or place your mark or thumbprint next to the option you choose:

_____ Participant signature/mark or thumbprint	Yes , I agree to be contacted telephonically
_____ Participant signature/mark or thumbprint	No , I do not agree to be contacted telephonically

Declaration of the volunteer

I understand the purpose of the additional data collection. I have read the above information, or it has been read to me. I have had the opportunity to ask questions, and any questions that I asked have been answered to my satisfaction. I consent voluntarily to answer the additional questions and understand that I have the right to stop my participation at any time.

Signature of volunteer:

Signature/mark or thumbprint		Date of signature			
			dd	MMM	yyyy
Print name		Time of signature	:		

For illiterate participants (signature of witness if applicable):

Signature of Witness		Date of signature			
			dd	MMM	yyyy
Print name		Time of signature	:		

Signature of study staff taking consent:

Signature		Date of signature			
			dd	MMM	yyyy
Print name		Time of signature	:		

QUESTIONNAIRE

(To be administered approximately 3 months after PrEP initiation)

PID: _____

Date: _____

1. Why did you decide to use PrEP?

2. Are you currently on PrEP?

- a. Yes (**if yes, skip to Q5**)
- b. No

3. When did you stop using PrEP? (check file to confirm): dd mmm yy: _____

4. Why did you stop using PrEP? (mark all the apply)

- a. I was having side effects:
 - i. List side effects that led to PrEP being discontinued: _____
- b. My HIV test result was positive after starting PrEP
- c. My partner and I are no longer together / I don't have partner
- d. I am not sexually active
- e. Other: please describe:

5. How would you rate yourself in terms of risk of becoming infected with HIV?

- a. I will definitely not get infected with HIV
- b. I probably won't get infected with HIV
- c. I am probably going to get infected with HIV
- d. I am definitely going to get infected with HIV
- e. I am HIV positive already
- f. I don't know

6. Why do you think you are at risk of acquiring HIV? (mark all that apply)

- a. My partners status is HIV positive
- b. I don't know my partner's HIV status
- c. I have been diagnosed or treated for a sexually transmitted infection
- d. I have more than 1 sexual partner
- e. I think my partner has other sexual partners beside me
- f. I don't always use condoms when I have sex
- g. I don't know
- h. Other: please describe: _____

- i. N/A / I don't think I am at risk of acquiring HIV
- 7. Have you experienced any side effects since starting PrEP?
 - a. Yes
 - b. No (**If no, skip to Q11**)
- 8. What side effects have you ever experienced? (mark all that apply)
 - a. Headaches
 - b. Nausea / vomiting
 - c. Diarrhoea
 - d. Abdominal pain
 - e. Other: Please describe: _____
- 9. Do you have any side effects that are present now?
 - a. Yes
 - b. No (**if No, skip to Q11**)
- 10. If yes, what side effects do you have now? (List all)

- 11. Did you disclose to anyone that you are taking PrEP?
 - a. Yes
 - b. No (**If no, skip to Q13**)
- 12. If yes, who did you disclose to? (mark all that apply)
 - a. Partner(s)
 - b. Friend
 - c. Family member
 - d. Other: Please describe: _____
- 13. Before you were offered PrEP in ECHO, did you hear about PrEP from anyone or any other source?
 - a. Yes
 - b. No (**If no skip to Q15**)
- 14. If yes, where did you hear about Prep? (mark all that apply)
 - a. Media (e.g. TV, radio, internet, Facebook, Twitter) Please specify source:

 - b. Public health facility e.g. clinic or hospital
 - c. Private health facility e.g. private clinic or GP
 - d. Family
 - e. Friends
 - f. Other: Please describe: _____

Many people find it difficult to remember to take pills every day and sometimes people skip taking their medication because they have side effects, are busy, or just decide not to take the pill. We would like to understand how you are taking your PrEP tablets so will ask you some questions about

PrEP Questionnaire

missing doses. Don't worry about telling us you have missed doses as we would like to know what is really happening.

15. In the last 7 days, how often have you missed a dose of PrEP?
- a. Once
 - b. Twice
 - c. Three or more times
 - d. Never
 - e. I don't know
 - f. N/A (PrEP discontinued > 7 days ago)
16. In the past 30 days how often have you missed a dose of PrEP?
- a. Once
 - b. Twice
 - c. 3 or 4 times
 - d. 5 to 7 times
 - e. More than 7 times
 - f. Never
 - g. N/A (PrEP discontinued > 30 days ago)
17. In the past 30 days what are some of the reasons you have missed your PrEP dose? (Mark all that apply)
- a. I ran out of tablets
 - b. I was having side effects
 - c. I didn't have time
 - d. I forgot to take my tablets
 - e. I needed a break
 - f. I was concerned someone would find out I am taking PrEP
 - g. I did not feel I was at risk anymore
 - h. My PrEP tablets were lost or stolen
 - i. I was away from home at the time when I should take my tablets
 - j. Other: Please describe: _____
 - k. N/A

To extract from the Participant binder:

1. Date of PrEP initiation: (dd mmm yy): _____
2. Number of sexual partners on last BA CRF: _____
3. How often was a condom used in the last 3 months on the BA CRF? _____
4. Any evidence of previous STIs – look at screening and final visit STI result.

PrEP Follow up questionnaire

Follow up phone call 4 to 6 months post study exit for participants who are still on PrEP at study exit:

PID: _____

1. Are you still on PrEP?
 - a. Yes
 - b. No (**If no skip to Q4**)
2. If yes, where are you getting PrEP from? (write down the name of the facility):

3. Did you experience any problems accessing PrEP after the study ended?
 - a. Yes: Please describe:

b. No
END OF INTERVIEW

4. Why did you stop taking PrEP? (mark all that apply)
 - a. Having side effects
 - b. I no longer felt at risk of HIV infection
 - c. My partner wanted me to stop
 - d. I had a problem accessing PrEP after the study: Please explain: _____
 - e. Other: Please explain: _____

5. When did you stop using PrEP? (dd mmm yy) _____



STUDY INFORMATION SHEET: KEY STAKEHOLDER IN-DEPTH INTERVIEWS

An evaluation of the integration of oral pre-exposure prophylaxis (PrEP) as standard of care for HIV prevention in clinical trials in South Africa.

Study Principal Investigator: Ivana Beesham

Good day, my name is Ivana Beesham and I am currently enrolled for my PhD at the University of Witwatersrand. My PhD looks at the provision of pre-exposure prophylaxis (PrEP) in clinical trials in South Africa (SA). I would like to invite you to consider participating in a research study.

What is this study about?

I would like to learn more about your thoughts and experiences related to oral PrEP provision as standard of care for HIV prevention in studies that are conducted at your research organisation. Oral PrEP containing tenofovir disoproxil fumarate (TDF) and emtricitabine (FTC) has been proven to substantially reduce the risk of HIV infection. In November 2017, the South African Medical Research Council (SAMRC) recognised that oral PrEP was far from the Standard of Care for high risk populations in SA and recommended that oral PrEP be provided in HIV prevention clinical trials. I would like to find out about HIV prevention options that are offered at your research organisation. The interviews with staff from research organisations is a component of my PhD.

Who will be interviewed?

I plan on interviewing senior/managerial staff aged 18 years or older e.g. managers and site principal investigators at research organisations that conduct clinical trials and HIV prevention trials.

What will be involved if I take part in the study?

If you agree to be interviewed, the interview will be conducted telephonically at a time and date that is convenient to you. The interview is expected to last less than an hour.

The telephonic interview will be digitally recorded with your permission. Each digital recording will be transcribed, and all recordings will be erased within two years of publication of study findings, or if there is no publication, no later than six years after the study has ended.

The information collected will be kept confidential. You may refuse to answer any questions that make you feel uncomfortable and you can exit the interview at any time. Your name and the name of your research organisation will not be mentioned in any reports. No-one, except research staff who have permission, will have access to study material, be allowed to listen to the recording, or read the transcript of the interview.

What are the risks and benefits of participating?

Your participation in this research study poses very minimal risk to you. The main risk is a possible time inconvenience. Being in this study will not directly benefit you, but we hope that the information

provided from this PhD will help to improve PrEP implementation programmes in South Africa and guide additional implementation of PrEP in clinical trials.

Costs and reimbursement

There will be no costs or reimbursement for your participation in this study.

What is the alternative to study participation?

The alternative to participating in this study would be simply not to participate. Your non-participation in this study will not affect your rights.

What are my rights?

Your participation in this study is entirely voluntary. If you decide not to participate or if you later decide to stop participating, or refuse to answer any question, at any time, you will not lose any benefit to which you are entitled to.

What should I do if I want to participate?

For further information, or if you are interested in participating in this study, you can contact me, Dr Ivana Beesham at 076 191 7354 or email me at ibeesham@mru.ac.za.

Who should I contact if I have any concerns about my rights?

If you want any information regarding your rights as a research participant, or complaints regarding this research study, you may contact Prof. Penny, Chairperson of the University of the Witwatersrand, Human Research Ethics Committee (HREC), which is an independent committee established to help protect the rights of research participants at (011) 717 2301



INFORMED CONSENT FORM: KEY STAKEHOLDER IN-DEPTH INTERVIEWS

An evaluation of the integration of oral pre-exposure prophylaxis (PrEP) as standard of care for HIV prevention in clinical trials in South Africa.

Study Principal Investigator: Ivana Beesham

Good day, my name is Ivana Beesham and I am currently enrolled for my PhD at the University of Witwatersrand. My PhD looks at the provision of pre-exposure prophylaxis (PrEP) in clinical trials in South Africa (SA). I would like to invite you to consider participating in a research study.

Introduction

This form, called a Consent Form will explain what this study is about. Please read this form before you decide if you want to join this study or not. We want to explain the study, its risks, its potential benefits, and what you will be asked to do. You may ask questions as we discuss the study, so that you understand what the study is about. It is important you know the following:

- Your participation in this study is entirely voluntary.
- You can ask questions now or at any time during the study.
- If you agree to participate in this study, you can change your mind later and quit the study at any time.
- The information you give us will be kept confidential.

Once you understand the study, and if you decide to take part, you will be asked to sign this consent form, and you will be given/emailed a copy of it to keep. This process is called informed consent.

Purpose of this study

I would like to learn more about your thoughts and experiences related to oral PrEP provision as standard of care HIV prevention in studies that are conducted at your research organisation. Oral PrEP containing tenofovir disoproxil fumarate (TDF) and emtricitabine (FTC) has been proven to substantially reduce the risk of HIV infection. In November 2017, the South African Medical Research Council (SAMRC) recognised that oral PrEP was far from the Standard of Care for high risk populations in SA and recommended that oral PrEP be provided in HIV prevention clinical trials. I would like to find out about HIV prevention options that are offered at your research organisation. I intend on using this data for my PhD.

Study Procedures

This will involve conducting a once-off telephonic interview with you. If you agree to be interviewed, the interview will be conducted telephonically at a time and date that is convenient to you. The interview is expected to last less than an hour. With your permission, I will digitally record the interview.

Possible Risks

Your participation in this research study poses very minimal risk to you. The main risk is a possible time inconvenience.

Possible Benefits

The information you provide will not provide any direct benefits to you however it may be used to improve PrEP implementation programmes in South Africa and guide additional implementation of PrEP in clinical trials.

Reimbursement

There will be no reimbursement for participating in this study.

Confidentiality

All study staff will treat the information you provide with the strictest confidentiality. All study information or material will be identified only by individual participant code numbers and will be kept confidential in a locked file drawer at MRU. This information or material will be available only to study staff as part of routine checks to ensure that this study is being conducted in a professional way that protects your rights. Your name or the name of your organisation will never be used in any publication or presentation about this study.

People or groups that may review your records include: the research ethics committees (University of the Witwatersrand's Human Research Ethics Committee), researchers at MRU and my study supervisors. By signing the written Informed Consent Form, you authorize such access to your records. The South African Health Products Regulatory Authority and National Health Research Ethics Council, and / or other regulatory authority (ies) may also look at your study records if they have permission to do so by the National Research Ethics Council.

Digital Recoding

I will ask your permission to digitally record the telephonic interview. Each digital recording/disk will be transcribed, and all recordings/disks will be erased within two years of publication of study findings, or if there is no publication, no later than six years after the study has ended. Information from the recordings/disks may be presented at professional meetings or in written articles, in which case no names or other personal identifiers will be used.

Digital recording is a requirement for study participation, in order that we can have a true and accurate record of the discussion. If you do not want to be recorded, you will not be eligible to participate. The interview will be confidential; it will be identified only by a unique number assigned to you, and no individual names will appear on the audio file or the transcript of the interview. No one, except the researchers at MatCH Research, and my study supervisors will have access to the audio file or the transcript of the interview. You can decide to withdraw from the interview at any time. If you do not want the interview to be digitally recorded, you are not eligible to participate in the research study, since it is important that we get to listen to the digital recordings to understand exactly what is being said.

Alternatives to Study Participation

The alternative to participating in this study would be simply not to participate. Your non-participation in this study will not affect your rights as a community member or your participation in the Parent Study.

Research Standards and Rights of Participants

Your participation in this study is entirely voluntary. If you decide not to participate, or if you later decide to stop participating, or refuse to answer any question, at any time, you will not lose any benefits to which you are otherwise entitled to.

If you have a research related injury, you may contact me, Dr Ivana Beesham, at 031 001 1941 or 076 191 7354. I retain the right to withdraw you from this study if it is considered in your best interests.

Ethical approval:

The Human Research Ethics Committee of the University of the Witwatersrand has approved this study.

The study has been structured in accordance with the **Declaration of Helsinki** (last updated: October 2013), which deals with the recommendations guiding doctors in biomedical research involving human participants. A copy may be obtained from me should you wish to review it.

If you want any information regarding your rights as a research participant, or complaints regarding this research study, you may contact Prof. Penny, Chairperson of the University of the Witwatersrand, Human Research Ethics Committee (HREC), which is an independent committee established to help protect the rights of research participants at (011) 717 2301.

You will be given a copy of this consent form to keep.

You now have an opportunity to ask me questions concerning the project.

Consent to digital recording

I have been informed that the interview will be digitally recorded. I know that I can refuse to participate if I do not want to be digitally recorded. I voluntarily give permission for the interview to be digitally recorded.

Participant Signature	YES, I <i>agree</i> to digital recording of the interview
Participant Signature	NO, I <i>do not</i> agree to digital recording of the interview

Declaration of the volunteer

I understand the purpose of this study. I have read the above information, or it has been read to me. I have had the opportunity to ask questions, and any questions that I asked have been answered to my satisfaction. I consent voluntarily to participate as a participant in this study and understand that I have the right to stop my participation at any time.

Participant Print Name and Surname

Participant Signature

Date

Print Name and Surname
Person obtaining consent

Signature

Date



INFORMED CONSENT FORM: KEY STAKEHOLDER IN-DEPTH INTERVIEWS

An evaluation of the integration of oral pre-exposure prophylaxis (PrEP) as standard of care for HIV prevention in clinical trials in South Africa.

Study Principal Investigator: Ivana Beesham

Good day, my name is Ivana Beesham and I am currently enrolled for my PhD at the University of Witwatersrand. My PhD looks at the provision of pre-exposure prophylaxis (PrEP) in clinical trials in South Africa (SA). I would like to invite you to consider participating in a research study.

Introduction

This form, called a Consent Form will explain what this study is about. Please read this form before you decide if you want to join this study or not. We want to explain the study, its risks, its potential benefits, and what you will be asked to do. You may ask questions as we discuss the study, so that you understand what the study is about. It is important you know the following:

- Your participation in this study is entirely voluntary.
- You can ask questions now or at any time during the study.
- If you agree to participate in this study, you can change your mind later and quit the study at any time.
- The information you give us will be kept confidential.

Once you understand the study, and if you decide to take part, you will be asked to sign this consent form, and you will be given/emailed a copy of it to keep. This process is called informed consent.

Purpose of this study

I would like to learn more about your thoughts and experiences related to oral PrEP provision as standard of care HIV prevention in studies that are conducted at your research organisation. Oral PrEP containing tenofovir disoproxil fumarate (TDF) and emtricitabine (FTC) has been proven to substantially reduce the risk of HIV infection. In November 2017, the South African Medical Research Council (SAMRC) recognised that oral PrEP was far from the Standard of Care for high risk populations in SA and recommended that oral PrEP be provided in HIV prevention clinical trials. I would like to find out about HIV prevention options that are offered at your research organisation. I intend on using this data for my PhD.

Study Procedures

This will involve conducting a once-off telephonic interview with you. If you agree to be interviewed, the interview will be conducted telephonically at a time and date that is convenient to you. The interview is expected to last less than an hour. With your permission, I will digitally record the interview.

Possible Risks

Your participation in this research study poses very minimal risk to you. The main risk is a possible time inconvenience.

Possible Benefits

The information you provide will not provide any direct benefits to you however it may be used to improve PrEP implementation programmes in South Africa and guide additional implementation of PrEP in clinical trials.

Reimbursement

There will be no reimbursement for participating in this study.

Confidentiality

All study staff will treat the information you provide with the strictest confidentiality. All study information or material will be identified only by individual participant code numbers and will be kept confidential in a locked file drawer at MRU. This information or material will be available only to study staff as part of routine checks to ensure that this study is being conducted in a professional way that protects your rights. Your name or the name of your organisation will never be used in any publication or presentation about this study.

People or groups that may review your records include: the research ethics committees (University of the Witwatersrand's Human Research Ethics Committee), researchers at MRU and my study supervisors. By signing the written Informed Consent Form, you authorize such access to your records. The South African Health Products Regulatory Authority and National Health Research Ethics Council, and / or other regulatory authority (ies) may also look at your study records if they have permission to do so by the National Research Ethics Council.

Digital Recoding

I will ask your permission to digitally record the telephonic interview. Each digital recording/disk will be transcribed, and all recordings/disks will be erased within two years of publication of study findings, or if there is no publication, no later than six years after the study has ended. Information from the recordings/disks may be presented at professional meetings or in written articles, in which case no names or other personal identifiers will be used.

Digital recording is a requirement for study participation, in order that we can have a true and accurate record of the discussion. If you do not want to be recorded, you will not be eligible to participate. The interview will be confidential; it will be identified only by a unique number assigned to you, and no individual names will appear on the audio file or the transcript of the interview. No one, except the researchers at MatCH Research, and my study supervisors will have access to the audio file or the transcript of the interview. You can decide to withdraw from the interview at any time. If you do not want the interview to be digitally recorded, you are not eligible to participate in the research study, since it is important that we get to listen to the digital recordings to understand exactly what is being said.

Alternatives to Study Participation

The alternative to participating in this study would be simply not to participate. Your non-participation in this study will not affect your rights as a community member.

Research Standards and Rights of Participants

Your participation in this study is entirely voluntary. If you decide not to participate, or if you later decide to stop participating, or refuse to answer any question, at any time, you will not lose any benefits to which you are otherwise entitled to.

If you have a research related injury, you may contact me, Dr Ivana Beesham, at 031 001 1941 or 076 191 7354. I retain the right to withdraw you from this study if it is considered in your best interests.

Ethical approval:

The Human Research Ethics Committee of the University of the Witwatersrand has approved this study.

The study has been structured in accordance with the **Declaration of Helsinki** (last updated: October 2013), which deals with the recommendations guiding doctors in biomedical research involving human participants. A copy may be obtained from me should you wish to review it.

If you want any information regarding your rights as a research participant, or complaints regarding this research study, you may contact Prof. Penny, Chairperson of the University of the Witwatersrand, Human Research Ethics Committee (HREC), which is an independent committee established to help protect the rights of research participants at (011) 717 2301.

You will be given a copy of this consent form to keep.

You now have an opportunity to ask me questions concerning the project.

Consent to digital recording

I have been informed that the interview will be digitally recorded. I know that I can refuse to participate if I do not want to be digitally recorded. I voluntarily give permission for the interview to be digitally recorded.

Participant Signature	YES, I <i>agree</i> to digital recording of the interview
Participant Signature	NO, I <i>do not</i> agree to digital recording of the interview

Declaration of the volunteer

I understand the purpose of this study. I have read the above information, or it has been read to me. I have had the opportunity to ask questions, and any questions that I asked have been answered to my satisfaction. I consent voluntarily to participate as a participant in this study and understand that I have the right to stop my participation at any time.

Participant Print Name and Surname

Participant Signature

Date

Print Name and Surname
Person obtaining consent

Signature

Date



IN-DEPTH INTERVIEW GUIDE: KEY STAKEHOLDERS

An evaluation of the integration of oral pre-exposure prophylaxis (PrEP) as standard of care for HIV prevention in clinical trials in South Africa.

Study Principal Investigator: Ivana Beesham

PARTICIPANT ID NUMBER:	DATE (DD/MMM/YY):	START TIME:	END TIME:	INTERVIEWER INITIALS:

Thank you for agreeing to have a telephonic interview with me. You have read the information about this study and completed the informed consent form. Just to recap, I am currently enrolled for a PhD and the research I am doing focusses on pre-exposure prophylaxis (PrEP) in clinical trials in South Africa. I want to gain an understanding of the current status of PrEP as a component of HIV prevention standard of care.

A recorder will be used to capture our conversation today. In order to protect your identity we ask that you choose a pseudo-name or number. This can be any name or number that you wish to give yourself- other than your real name. This discussion will only be shared with researchers approved to work on this study and will be safely stored.

Do you have any questions before we begin?

Turn on digital recorder.

	Questions	Probes
Section 1: Description of providers' current position and organization <i>Interviewer script: I would like to start by asking you a few questions about yourself, your current job and the research your organization conducts.</i>		
1.	What is your educational background? _____	
2.	What is your current position? _____	
3.	How many people are currently employed by your organization? _____	
4.	How many studies are you currently running at your organization? _____	
5.	Please describe briefly what sort of research your organization conducts: _____	Probe for: HIV prevention trials Clinical trials

Section 2: Questions on HIV prevention options <i>Interviewer script: I would like to ask you a few questions about HIV prevention options that are offered to participants at your research organization</i>		
6.	What HIV prevention options are offered to participants at your research organization?	Probe for: Condoms, STI testing and treatment, risk reduction counselling, HIV counselling and testing, Voluntary male medical circumcision, Partner HIV testing and treatment, Initiation of ART for HIV-infected partners, oral pre-exposure prophylaxis (PrEP)
7.	How does your organization provide these options?	Probe for: Is it provided on-site or via referral? If referral, how close are these facilities? What is access like to these facilities?

Section 3: Questions on PrEP		
<i>Interviewer script:</i> I would now like to ask you a few questions specifically about pre-exposure prophylaxis or PrEP.		
8.	Does your organization offer PrEP to study participants? If yes, what do you think were some of the reasons your organization decided to offer PrEP to study participants?	Probe for: Required from study funders/protocols Was it influenced by advocates? Was it influenced by the Medical Research Council statement?
9.	For organizations that offer PrEP: Can you describe your experience in offering PrEP to study participants?	Probe for: Is it provided on-site or via referral? Who is it offered to? Which studies? Who pays for it? Study funders? If referral, how close are these facilities? What is access like to these facilities? What was the uptake of PrEP like? Were women interested in PrEP?
10.	Have you experienced any challenges regarding PrEP? If yes, can you describe any challenges that have been experienced regarding PrEP?	Probe for: Concerns regarding study outcomes Concerns regarding adherence Post-trial access

Section 4: Closing question

11.	Do you have any final thoughts that you would like to share on PrEP?	
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Thank you very much for your time. This concludes our interview. What you have told us has been very useful in understanding HIV prevention including PrEP in clinical trials.



INFORMED CONSENT FORM: In-depth Interview
**An evaluation of the integration of oral pre-exposure prophylaxis (PrEP) as
standard of care for HIV prevention in clinical trials in South Africa.**
Principal Investigator: Dr Ivana Beesham

Good day, my name is Ivana Beesham and I am a doctor working at MRU (MatCH Research Unit), of the University of the Witwatersrand, based in Durban. I am also studying towards a Doctor of Philosophy Degree at the University of Witwatersrand. I would like to invite you to consider participating in an interview today.

Introduction

This form, called an Informed Consent Form will explain what this study is about. Please read this form or have it read to you. Before you decide if you want to join this study or not, we want to explain the study, its risks, its potential benefits, and what you will be asked to do. You may ask questions as we discuss the study, so that you understand what the study is about. It is important you know the following:

- Your participation in this study is entirely voluntary.
- You can ask questions now or at any time during the study.
- If you join the study, you can change your mind later and quit the study at any time.

Before you decide whether to join this study, a member of the study staff will explain:

- The purpose of this study
- How the study may help you or others
- Any risks you may face while participating in this study
- What is expected of you during the study

Once you understand the study, and if you decide to take part, you will be asked to sign this consent form, and you will be given a signed copy of it to keep. This process is called informed consent.

Purpose of the study

If you remember, you recently participated in the ECHO (Evidence for Contraceptive Options and HIV Outcomes) trial. While you were in the ECHO trial, you had decided to start oral pre-exposure prophylaxis or PrEP to prevent HIV. At the end of the study, you were continuing to use PrEP. Today, we want to ask you some questions about PrEP use after the ECHO trial had ended, and in particular your experience in accessing PrEP after the ECHO study had ended. We also want to understand why you decided to use PrEP.

Study procedures

I plan to interview 12 to 15 women who had participated in the ECHO trial for this study. Women must be 18 years or older. I will conduct a once off interview with you that is expected to last 1 to 1.5 hours (including the consent process). I will ask you questions about your experience with using PrEP after the ECHO trial ended. I would like to understand if you wanted to continue with using PrEP after the ECHO trial ended, and if you were able to access PrEP at a facility. I would also like to understand more about your

experience in accessing PrEP after exiting the study. If you decided to stop using PrEP, I would like to understand why you decided to do so.

Possible risks

I do not expect you to have any problems participating in this interview today. However, you might feel uncomfortable or embarrassed answering some questions. You do not have to answer any questions that make you feel uncomfortable and you may stop the interview at any time if you want to.

Possible benefits

There are no direct benefits to you for participating in today's interview. However, the information you provide us can help us understand better the use of PrEP after a study has ended. This information might be beneficial to other studies that provide PrEP and could possibly be used in the planning of PrEP services.

Reimbursement

You will be reimbursed R200 for your transport costs and time for participating in the interview today.

Financial Arrangements

Neither you nor your medical scheme, if you have one, will be expected to pay for today's visit.

Confidentiality

All study staff will treat interview data with the strictest confidentiality. All study information or material will be identified only by individual participant code numbers and will be kept confidential in a locked file drawer or cupboard at MRU. This information or material will be available only to study staff, as part of routine checks to ensure that this study is being conducted in a professional way that protects your rights. Your name will never be used in any publication or presentation about this study.

People or groups that might have access to your records include my study supervisors, auditor(s), relevant ethics committee, and the regulatory authority(ies) and these parties will be granted direct access to your original records for verification of data, to the extent permitted by the applicable laws and regulations and that, by signing this consent form, you agree to authorizing such access. The National Health Research Ethics Council, and / or other regulatory authority (ies) may also look at your study records if they have permission to do so by the National Research Ethics Council.

Digital Recording

You will be asked if I can digitally record the interview, so that I can make sure that it is being carried out correctly and that I understand what is being said by participants. Each digital recording/disk will be transcribed, and all recordings/disks will be erased within two years of publication of study findings, or if there is no publication, no later than six years after the study has ended. Information from the recordings/disks may be presented at professional meetings or in written articles, in which case no names or other personal identifiers will be used.

Digital recording is a requirement for study participation, in order that we can have a true and accurate record of the discussion. If you do not want to be recorded today, you will not be eligible to participate. The interview will be confidential; it will be identified only by a unique number assigned to you, and no individual names will appear on the audio file or the transcript of the interview. No one, except the researchers at MRU, will have access to the audio file or the transcript of the interview. You can decide to withdraw from the interview at any time. If you do not want the interview to be digitally recorded, you are not eligible to participate in the

research study, since it is important that I get to listen to the digital recordings so as to understand exactly what is being said.

Alternative to study participation

The alternative to participating in this study would be simply not to participate. Your non-participation in this study will not affect your rights as community member.

Research standards and rights of participants

Your participation in this study is entirely voluntary. If you decide not to participate or if you later decide to stop participating, or refuse to answer any question, at any time, you will not lose any benefit to which you are entitled to as a community member.

If you have a research related injury, you may contact me, Dr Ivana Beesham who is the Principal Investigator of the study at 031 001 1941 or 076 191 7354.

Contact details

Please feel free to contact me about the project in the future, or to ask for any updates. I appreciate the time you may take to participate in this study.

If you have any questions about this study or study procedures now or in the future, you can call me, Dr Ivana Beesham, the Principal Investigator of this study at 031 001 1941 or 076 191 7354.

Ethical Approval:

The Human Research Ethics Committee of the University of the Witwatersrand has approved recruitment of participants for this study. The Institutional Review Board oversees the protection of people participating in research studies.

The study has been structured in accordance with the **Declaration of Helsinki** (last updated: October 2013), which deals with the recommendations guiding doctors in biomedical research involving human participants. A copy may be obtained from me should you wish to review it.

If you want any information regarding your rights as a research participant, or complaints regarding this research study, you may contact Prof. Penny, Chairperson of the University of the Witwatersrand, Human Research Ethics Committee (HREC), which is an independent committee established to help protect the rights of research participants at (011) 717 2301.

You will be given a copy of this consent form to keep.

You now have an opportunity to ask me questions concerning the project.

Consent to digital recording

I have been informed that the interview will be digitally recorded. I know that I can refuse to participate if I do not want to be digital recorded. I voluntarily give permission for the interview to be digitally recorded.

_____ Participant Signature/mark or thumbprint	YES, I agree to digital recording
_____ Participant Signature/mark or thumbprint	NO, I do not agree to digital recording

Informed Consent

PID: _____

In-depth interview

Oral PrEP provision in clinical trials in SA

Declaration of the volunteer

I understand the purpose of this study. I have read the above information, or it has been read to me. I have had the opportunity to ask questions, and any questions that I asked, have been answered to my satisfaction. I consent voluntarily to participate as a participant in this study and understand that I have the right to stop my participation at any time.

Participant Print Name and Surname
(or thumbprint if applicable)

Participant Signature

Date
Time: ____:____
 H H : M M

Print Name and Surname
Person obtaining consent

Signature

Date
Time: ____:____
 H H : M M

For participants unable to read or write

Independent Witness
Name and Surname

Signature

Date
Time: ____:____
 H H : M M



An evaluation of the integration of oral pre-exposure prophylaxis (PrEP) as standard of care for HIV prevention in clinical trials in South Africa.

Principal Investigator: Dr Ivana Beesham

IN-DEPTH INTERVIEW GUIDE

PID	
LOCATION OF INTERVIEW	
DATE (dd mmm yyyy)	
START TIME	
END TIME	
INTERVIEWER INITIALS	

[Read to participant]

Hello and thank you for agreeing to participate in this interview. My name is Ivana Beesham. Our discussion is confidential and I appreciate the time you have taken to come in today.

If you remember, you recently participated in the ECHO (Evidence for Contraceptive Options and HIV Outcomes) trial. While you were in the ECHO trial, you had decided to start oral pre-exposure prophylaxis or PrEP to prevent HIV infection. At the end of the study, you were continuing to use PrEP. Today, we want to ask you some questions about PrEP use after the ECHO trial had ended, and in particular your experience in accessing PrEP after the ECHO study had ended. Our discussion will last approximately one hour. You are the expert and so we are really eager to hear your thoughts on these questions. There are no “right” answers – just your own experience and thoughts.

Explain the ground rules for the interview:

We have just reviewed the informed consent form which tells you about the study and gives us permission to speak to you and to record the interview. You are not required to answer all of my questions, and you may skip any questions you don't want to answer. You may also end the interview at any time. Do you have any questions before we begin?

I will now switch on the digital recorder.

I am [interviewer name] interviewing [PID] on [DATE] and the start time is [time].

No	Questions	Probes
1.	During the ECHO study, you decided to use oral pre-exposure prophylaxis also known as PrEP to prevent HIV. Can you tell me about how you made the decision to use oral PrEP?	Why did you decide to use PrEP?
2	At the end of your participation in the ECHO study (remind participant of the month she exited the ECHO trial), you were continuing to use PrEP. Please tell me about your use of PrEP since exiting the ECHO study until now.	Did you stop using PrEP at any time? Why? Have you been continuously on PrEP since leaving ECHO? Were you given a referral letter to a facility to access PrEP? Did you go to this facility? Why? Why not?
3	I understand that it might not always be easy to take a tablet every day and everybody occasionally misses taking a dose now and again. I would like to learn about your experience in taking PrEP. Remember there is not right or wrong answer. I am interested to learn about your experience. Did you ever miss taking a dose of PrEP since leaving the study? If yes, what were some of the reasons for missing your doses? On the days you did remember to take your PrEP, what were some of the things that made it easier to remember?	
4	Are you taking PrEP now? If yes, can you tell me more about the place that you are getting your PrEP tablets from?	What is the name of the facility? Is it free? What made you decide to go to this place? Is it close to your home? How do you get there? How long does it take to get there? How did you hear about this place? Describe the providers who provide PrEP. Did you have any problems getting PrEP since the study ended? What other services are provided at this place?

	If no, why did you decide that PrEP was not for you?	Did you experience any problems at this facility? Why did you decide to stop using PrEP? Explore reasons - Side effects - Problems with access - Stigma/discrimination - Family / partner influence - Problems with access - Too far away / transport/no money - Lost referral letter Did you have any difficulty in accessing a place that provides PrEP? Did you go to a facility that provides PrEP? If yes, what was your experience at the facility?
5.	How do you think we can improve PrEP services for women?	
6.	Is there anything else you would like to add to our discussion? Remember, you are the expert, so we really value your opinion.	

This is the end of the interview. Thank you very much for your time.