Acceptability of injectable cabotegravir versus daily oral TDF/FTC for PrEP: Lesson from HPTN 084

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BACKGROUND

HPTN 084, a multisite, double-blind, randomized Phase 3 trial, compared the safety and efficacy of injectable cabotegravir (CAB) administered 8-weekly to daily oral TDF/FTC for prevention of HIV-1 in uninfected African women. Initiated in November 2017, the study enrolled >3,200 sexually active women aged 18-45 who were randomized to receive one active (CAB or TDF/FTC) and one placebo product and participated in a 5-week oral run-in before moving into an injection phase.

Like a similar trial in men-who-have-sex-with-men and transgender persons (HPTN 083), the trial was stopped early for demonstrating superiority of CAB over TDF/FTC in preventing HIV. Participants in both trials have been "unblinded" (e.g., informed about which active product they were using), and are currently being followed on the product of their choice (or no product)[1]. The shortened timeline of these two trials has expedited the need to consider introduction strategies for different populations.

We examine qualitative data from the initial phase of a four-country sub-study nested within HPTN 084 to better understand acceptability of these two PrEP methods and considerations for CAB access among African women at risk of HIV.

Take home message:
Women's desire for privacy and ease of use outweighed other injectable concerns, resulting in a strong preference for Injectable PrEP. Concerns about cost and accessibility will need to be addressed by implementation programs.

METHODS

In January 2020, we initiated a prospective qualitative sub-study with a maximum of 104 women from 4 sites [Lilongwe, Malawi; Johannesburg, South Africa; Kampala, Uganda; Harare, Zimbabwe]. Up to 3 in-depth interviews (IDIs), spanning participation in the blinded trial, the unblinded phase and transition to the open-label extension are planned to assess the acceptability of and preferences for various PrEP options, as well as PrEP access considerations for women.

This analysis focuses on the first IDI, conducted during the blinded clinical trial, during which participants described their household and partner contexts, reasons for trial participation, and initial experiences using study products.

Sample 10-16 continuing participants (CP) per site selected from randomly generated lists of participants by period of enrollment (2018, 2019 and 2020) for repeated IDIs.

In addition, up to 10 special cases (SP) who became pregnant, experienced product holds or sero-converted were also invited to participate.

Analysis The research teams followed a four-step process to 1) read transcripts for emerging themes (e.g., Sexual History, Product-related Acceptability, Adherence, Pregnancy, PrEP Use, and Clinical Trial Experiences); 2) develop a codebook and apply codes in NVivo to transcripts with intermittent interrater reliability checks; 3) develop memos identifying sub-themes and illustrative contexts for main codes; and 4) summarize information in Excel matrices to explore differences across risk categories related to product acceptability and other themes.

Table 1 provides an overview of sub-study participants, by country.

	All (n=63)	Malawi (n=17)	South Africa (n=15)	Uganda (n=15)	Zimbabwe (n=16)
Age (mean)	26.3	26.3	24.5	26.3	28.1
Marital status (#/%):					
Married/cohabitating	21 (33)	6 (35)	0 (0)	7 (47)	8 (50.0)
Divorced/separated	14 (22)	7 (41)	0 (0)	0 (0)	7 (44)
Single	28 (44)	4 (24)	15 (100)	8 (53)	1 (6)
Participant category:					
Continuing Participant	45 (71)	10 (59)	12 (80)	10 (67)	13 (81)
Pregnancy Special Case	10 (16)	1 (6)	2 (13)	4 (27)	3 (19)
Seroconversion	6 (10)	5 (29)	1 (7)	0 (0)	0 (0)
Product Discontinuation	2 (3)	1 (6)	0 (0)	1 (7)	0 (0)
Sexual risk category:					
Self-declared sex work	12 (19)	3 (20)	0 (0)	5 (33)	4 (25)
Transactional sex	12 (19)	4 (23. 5)	3 (20)	4 (27)	1 (6)
Multiple, romantic partners	15 (24)	4 (23.5)	7 (47)	4 (27)	0 (0)
Monogamous	24 (38)	6 (35)	5 (33)	2 (13)	11 (69)

FINDINGS

Sub-study participants' risks contexts varied across sites, and their motivations to join HPTN 084 were multiple. Over a third of women reported being monogamous, either married, cohabitating or in committed relationships. Others described multiple, sequential, or concomitant partners – some relationships were more transactional, and about 1/5 described themselves as sex workers (Table 1). Across contexts, women wanted to gain access to HIV prevention products, either due to concern about their own risk behaviors or because they suspected their partner's behaviors. Women also sought access to free long-acting contraception, HIV testing or new experiences.

To varying degrees, participants' perceptions of injectable and oral PrEP options, and their thoughts about PrEP access and use post-trial differed by risk category.

Injectable PrEP

By far, women liked the ease and convenience of a long-acting formulation. Injectable PrEP did not require daily remembering and fit better into women's lifestyles, especially for women who traveled or had unpredictable work:

> *I joined this study because when my marriage ended, I was promiscuous and when I heard that there is a study where there is a product that prevents HIV, I decided to join. During that time, with the nature of my work, I thought I was being protected because I was having unprotected sex with multiple sexual partners. Sure. So, there was a certain month when I was reckless because I went away for a long time, and I stopped taking my pills…. I had more confidence in the injection and although I missed the oral pills, I had the feeling that the injection would protect me because it is long acting. (Malawi, 29 divorced sex worker)*

Regardless of risk category, women liked the injectable's privacy from husbands, boyfriends, sexual clients or just "nosey people". Of note, few women in any category reported disclosing study participation to partners, but were more likely to have disclosed to other family members or friends. Disclosure was at times necessary when a household member found a woman's study pills.

The potential effectiveness of injectable PrEP was mentioned by some women, more often among women in higher risk categories.

The **main disadvantage of injectable PrEP** was pain. Almost all women described some level of pain, but descriptions varied widely. For some, the initial injection was painful, but they got used to it over time. Others attributed the level of pain to the skill of the clinic staff, while for some pain continued to be intense with each injection.

> *That one… It is painful! It is better here but when you go home, the buttock is very painful and even when the partner touches you on the injection site you scream! It is painful. It is painful. You really feel numbness on the leg. AH… It is painful. (Malawi, 28-year-old, monogamous married participant)*

> *The Depo injection is more painful… Aah as for this one, it is not painful. I would not know if it is the one which is not painful (e.g., placebo), or it's the people who make it painless. (Zimbabwe, 24-year-old divorced sex worker)*

A small number of women complained of other side effects from injectable PrEP, including injection site swelling and itchiness, or post-injection dizziness. Several worried about potential longer-term health effects, especially on the unborn baby.

Oral PrEP

About 1/3 of participants found oral PrEP easy to take and mentioned low side effects. But, more than half worried about forgetting to take oral pills. Some referenced prior mishaps, including unintended pregnancies, when taking oral contraceptive pills. Pill attributes – size, taste and smell were disliked by some.

> *HOW DID IT APPEAR TO YOU WHEN YOU FIRST SAW IT? I thought I would not be able to swallow it. I have always detested pills. That is why I never took family planning tablets because I detest pills. [Laughs} (Zimbabwe, 33-year-old divorced participant, monogamous)*

Additionally, most participants described encountering some problems with study pill adherence. For some, adherence was challenging early in the study as they figured out the best timing to take pills. Forgetting to take their pills due to late night work, when travel unexpectedly came up, or after heavy drinking was mentioned mostly by women who acknowledged sex work or engaged in transactional sex.

> *I had just started participating, I would forget. HOW MANY DAYS DID YOU FORGET? I won't lie to you, they were a bit many. I think about a week but of course not consecutively, you would forget today but you take it the following day, like that. (Uganda, 22-year-old, single participant, monogamous)*

Less frequently (but more often than for injections), women listed an array of side effects they attributed to oral PrEP use. These included: hunger pains, dizziness, nausea, headache, diarrhea, sleepiness, or sweating. Participants often stated that these side effects subsided over time.

PrEP Preferences

Most women preferred injections to daily pills, with strongest preferences appearing to be related to risk category.

> *The injection is painful, but I will choose it. MAY YOU TELL ME WHY? [Be]cause it's a one-time thing. You just have to remember the date, but after that it's over. AND IF MAYBE WE FOUND THAT THE PILL WORKS BETTER, WOULD YOU STILL PICK THE INJECTION? No, I'll go for the pill. A pill is not bad, hey, the part of having to remember every day. (South Africa, 28-year-old single participant, transactional sex)*

> *Aah all things have advantages and disadvantages. …For those who forget the pills, if they have the injection, it will be easier for them. but for those who find the injection painful they would rather have the pills then it also becomes easy for them. So, a person will make a choice. (Zimbabwe, 23-year-old, married, monogamous participant who preferred pills)*

PrEP Access Beyond the Trial

Only a third of women said they knew of ways to access PrEP in their communities. Most referred generically to clinics, several specifically mentioned clinics for sex workers. A few participants believed that PrEP might be available at pharmacies or the hospital, although few women had previously sought PrEP or knew someone who had. Cost was often mentioned as a potential barrier to PrEP access. Other barriers included eligibility (e.g., not high-risk), poor services or being lazy.

DISCUSSION

Our qualitative data support the hypothesis that injectables are preferred over pills because they are discreet, and easier to adhere to – particularly for women with busy lives. However, no data exist yet to indicate how well women will adhere to and/or persist on CAB outside the trial setting. For example, the degree to which pain will be a disincentive to persist on PrEP is unknown. This analysis includes women on CAB or a placebo (Intralipid 2%) injection; shown to have different pain profiles[2]. Women often compared their experience with the study injection to contraceptive injections, as either less or more painful. Women's familiarity with injectable contraception may increase acceptability and potentially tolerability of injectable PrEP.

As with contraception, women recognized the potential for choice among a range of alternatives for HIV prevention to suit their different lifestyles. Women in higher-risk categories were more likely to mention effectiveness as influencing method choice. Other factors, shared by all women, included convenience, side effects, access, and cost.

LIMITATIONS

Our analysis included only the first of several repeat interviews. However, because participants were at different stages of follow-up, we did obtain a range of use experiences over time. In this analysis, we remain blinded to participants' study arm so unable to assess whether experience of pain or dislike of pill attributes related to overall delivery format or the study drug. Furthermore, though many sub-study participants were motivated to join the trial to access PrEP, they may still differ in important ways from those who might access PrEP outside of a trial setting – either more or less likely to seek CAB.

[1]Sinead Delaney-Moretlwe, James P Hughes, Peter Bock et al (2022). Cabotegravir for the prevention of HIV-1 in women: results from HPTN 084, a phase 3, randomized clinical trial. LANCET.
[2]Elizabeth E Tolley, Sahar Z Zangeneh, Gordon Chau et al (2020). Acceptability of Long-Acting Injectable Cabotegravir (CAB LA) in HIV-Uninfected Individuals: HPTN 077. AIDS & Behavior.

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