Efficacy, safety, tolerability, and pharmacokinetics of long-acting injectable cabotegravir for HIV pre-exposure prophylaxis in transgender women: a secondary analysis of the HPTN 083 trial

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Summary

Background The HIV Prevention Trials Network (HPTN) 083 trial showed that long-acting injectable cabotegravir was more effective than tenofovir disoproxil fumarate plus emtricitabine in preventing HIV in cisgender men and transgender women who have sex with men. We aimed to characterise the cohort of transgender women included in HPTN 083.

Methods HPTN 083 is an ongoing, phase 2b/3, randomised, multicentre, double-blind, double-dummy clinical trial done at 43 sites in seven countries (Argentina, Brazil, Peru, the USA, South Africa, Thailand, and Viet Nam). HIV-negative participants were randomly assigned (1:1) to receive injectable cabotegravir or tenofovir disoproxil fumarate plus emtricitabine. The study design and primary outcomes of the blinded phase of HPTN 083 have already been reported. An enrolment minimum of 10% transgender women was set for the trial. Here we characterise the cohort of transgender women enrolled from Dec 6, 2016, to May 14, 2020, when the study was unblinded. We report sociodemographic characteristics, use of gender affirming hormone therapy, and behavioural assessments of the transgender women participants. Laboratory testing and safety evaluations are also reported. The trial is registered at ClinicalTrials.gov, NCT02720094.

Findings HPTN 083 enrolled 570 transgender women (304 tenofovir disoproxil fumarate plus emtricitabine; 266 injectable cabotegravir). Transgender women were primarily from Asia (225 [39%]) and Latin America (205 [36%]); 330 (58%) reported using gender affirming hormone therapy. Intimate partner violence was common (270 [47%] reported emotional abuse and 172 [30%] reported physical abuse) and 323 (57%) reported a history of childhood sexual abuse. 159 (28%) transgender women disagreed that they were at risk for HIV, and 142 (25%) screened positive for depressive symptoms. During study follow-up, incidence of syphilis was 16·25% (95% CI 13·28–19·69), rectal gonorrhoea was 11·66% (9·14–14·66), and chlamydia was 20·61% (17·20–24·49). Frequency of adverse events was similar between the treatment groups. Nine seroconversions occurred among transgender women during the blinded phase of the study (seven in the tenofovir disoproxil fumarate plus emtricitabine group and two in the injectable cabotegravir group); overall incidence was 1·19 per 100 person-years (95% CI 0·54–2·25): 1·80 per 100 person-years (0·73–3·72) in the tenofovir disoproxil fumarate plus emtricitabine group and 0·54 per 100 person-years (0·07–1·95) in the injectable cabotegravir group (hazard ratio 0·34 [95% CI 0·08–1·56]). Cabotegravir concentrations did not differ by gender affirming hormone therapy use.

Interpretation HIV prevention strategies for transgender women cannot be addressed separately from social and structural vulnerabilities. Transgender women were well represented in HPTN 083 and should continue to be prioritised in HIV prevention studies. Our results suggest that injectable cabotegravir is a safe and effective pre-exposure prophylaxis option for transgender women.

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Introduction

The ongoing HIV Prevention Trials Network (HPTN) 083 trial showed the superiority of injectable cabotegravir to daily oral tenofovir disoproxil fumarate plus emtricitabine for HIV prevention in cisgender men and transgender women who have sex with men (66% relative risk reduction).[1] Whereas previous HIV pre-exposure prophylaxis (PrEP) efficacy trials have not proritised transgender and gender diverse populations, including transgender women,[2,3] HPTN 083

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Research in context

Evidence before this study

Despite its successes, tenofovir-based oral pre-exposure prophylaxis (PrEP) has not homogeneously decreased HIV incidence, and transgender women continue to be disproportionately affected by HIV. Long-acting injectable cabotegravir is an integrase strand transfer inhibitor, and its superiority as compared with tenofovir-based oral PrEP has been shown in two randomised clinical trials, HPTN 083 (among gay, bisexual, and other cisgender men who have sex with men and transgender women who have sex with men) and HPTN 084 (among cisgender women). We carried out a bibliographic search of PubMed on Feb 1, 2023. The following search strategy was used: ("HIV" OR "human immunodeficiency virus") AND ("transgender women" OR "transsexual women" OR "trans women") AND ("cabotegravir") AND ("pre-exposure prophylaxis" OR "PrEP") AND ("trial"), with no restriction of publication date or language. This search retrieved only three publications, all related to HPTN 083 (one presenting the main results, another describing a cost-effectiveness analysis, and the last characterising HIV infections that occurred during the study). No publication has focused on issues specific to transgender women with respect to injectable cabotegravir.

Added value of this study

To our knowledge, this is the first report to describe characteristics, safety, behavioural, efficacy, bodyweight changes, and pharmacological data for transgender women from the phase 2b/3 HPTN 083 clinical trial. 570 (12%) of 4566 enrolled participants were transgender women, meaning that HPTN 083 had the largest cohort of transgender women included in a registrational trial to date. Transgender women were successfully enrolled and retained in HPTN 083. The adoption of a prespecified recruitment minimum for transgender women allowed a unique opportunity to evaluate injectable cabotegravir efficacy and expanded insights into tenofovir-based oral PrEP use in this population. In our analysis, we also considered gender fluidity, a topic of intense interest. Among participants included under the umbrella of transgender women, 14% self-identified as queer, gender variant, gender non-conforming, or other gender identities. The gender-fluidity discussion also emerged with the identification of 32 participants who self-identified as men who have sex with men yet reported use of gender affirming hormone therapy. Our results showed that injectable cabotegravir was a safe and effective HIV prevention strategy for transgender women and provided high levels of protection among these participants. However, transgender women had important structural vulnerabilities, such as low income and unemployment, and approximately one quarter of participants disagreed with statements about them being at risk for HIV. Finally, HPTN 083 was the first to report cabotegravir concentrations in transgender women within the context of self-reported gender affirming hormone therapy status.

Implications of all the available evidence

Adherence to tenofovir-based PrEP represents an ongoing challenge for transgender women, and injectable cabotegravir administration every 2 months is a convenient and discreet strategy that might overcome the barriers to daily oral pill-taking. Characterising the effect of injectable cabotegravir on gender affirming hormone therapy remains an important research gap. Further research will need to consider gender fluidity as it is becoming more commonly recognised as part of gender identity, and as the profile of users of gender affirming hormone therapy continues to evolve. Self-reported gender identity should be assessed longitudinally during future studies. The frequency of mental health distress, as shown by the 25% screening positive for depressive symptoms, highlights the need to address the mental health of transgender women across geographies as an urgent and pressing issue that requires special attention. HIV prevention among transgender women cannot be addressed separately from social and structural aspects. There is an essential need for a broad choice of HIV prevention strategies that are sexually congruent and acceptable to populations at risk.

set enrolment targets for the inclusion of transgender women.[1]

Transgender women are disproportionately affected by HIV, with a global HIV prevalence of 19·9% among this population, which is 66-fold higher than the HIV prevalence among the general population of individuals aged 15 years and older.[4] Within the context of overall HIV prevalence across geographic regions, HIV infections among transgender women are highest in Latin America, followed by Asia, and North America.[4] Transgender and gender diverse people experience health disparities, including a high prevalence of HIV and sexually transmitted infections, substance use disorders, and mental health conditions that are driven by a complex array of individual, interpersonal, and structural factors.[5,6] These factors impede progress at each stage of the HIV care continuum. Detailed knowledge of HIV care in these populations is further compromised by non-standardised or inaccurate data capture of gender identity and lack of representation in public health surveillance initiatives.[7,8] These barriers to positive health outcomes could be minimised by the provision of HIV treatment and prevention services in a gender-affirmative environment.[9]

PrEP represents an important opportunity for improving health for transgender women, but marginalisation within the public health system, medical and research mistrust, knowing one's HIV status, and stigma are all barriers to PrEP initiation.[10,11] Challenges in the uptake and persistence of oral tenofovir disoproxil

fumarate plus emtricitabine have been observed among transgender women in PrEP efficacy and demonstration trials.[12,13] In the iPrEx (Pre-Exposure Prophylaxis Initiative) trial, none of the transgender women participants who acquired HIV had quantifiable concentrations of tenofovir in plasma or tenofovir-diphosphate in peripheral blood mononuclear cells.[14] In the iPrEx open-label extension, transgender women who reported use of feminising hormones were less likely to have protective intraerythrocytic tenofovir-diphosphate concentrations collected as dried blood spots compared with cisgender men or transgender women not using hormones.[14] Recent data from a baseline survey of a multisite cohort of transgender women in eastern and southern USA reported high participant awareness of PrEP, but low uptake.[15] In light of the adherence challenges with daily oral PrEP, alternative agents, including long-acting injectables, have been pursued to increase the range of biomedical HIV prevention options available to individuals most at risk. Furthermore, pharmacological assessments of novel biomedical products in the intended populations, inclusive of transgender and gender diverse populations, are needed.

Gender affirming hormone therapy is a key component of the standard of care for transgender people, and is administered to achieve changes consistent with an individual's embodiment goals, gender identity, or both.[16] Data from a US survey reported that 71% of transgender respondents had ever used gender affirming hormone therapy.[17] Gender affirming hormone therapy consisting of oestrogen and anti-androgenic agents is commonly used to induce feminisation and mitigate gender dysphoria; however, gonadotropin-releasing hormone agonists and other progestogens have also been used.[18] There is heterogeneity in doses and formulations in gender affirming hormone therapy, and the use of these therapies can result in changes in fat deposition, renal changes, and alterations in protein activity in pharmacological pathways.[2] Although medically provided gender affirming hormone therapy is safe, individuals should be monitored to minimise adverse events.[18]

We aimed to describe selected participant characteristics, safety, prevention efficacy, bodyweight changes, and pharmacokinetics of injectable cabotegravir in transgender women during the blinded phase of HPTN 083.

Methods

Study design

HPTN 083 is an ongoing, phase 2b/3, randomised, multicentre, double-blind, double-dummy clinical trial done at 43 sites in seven countries (Argentina, Brazil, Peru, the USA, South Africa, Thailand, and Viet Nam). The study design and primary outcomes of the blinded phase of HPTN 083 have been described previously.[1] Participants aged 18 years and older who were in general good health as determined by clinical and laboratory assessments, without HIV, were randomly assigned (1:1) to either injectable cabotegravir or tenofovir disoproxil fumarate plus emtricitabine study groups.

There was a 5-week oral lead-in (step 1), up to 148 weeks of intramuscular injections (step 2), and a 48-week tail, in which all participants were offered open-label tenofovir disoproxil fumarate plus emtricitabine (step 3). Participants randomly assigned to the injectable cabotegravir group received oral daily cabotegravir (30 mg tablets daily) in step 1, followed by cabotegravir intramuscular injections (600 mg) in step 2, with placebo tablets in both phases. The first two cabotegravir injections were administered 4 weeks apart starting at week 5, followed by injections every 8 weeks thereafter. Participants randomly assigned to the tenofovir disoproxil fumarate plus emtricitabine group received once daily fixed-dose combination of 300 mg tenofovir disoproxil fumarate plus 200 mg emtricitabine tablets in steps 1 and 2 of the study, as well as placebo pills during the oral lead-in and placebo intramuscular injections during step 2. Participants in both groups received open-label daily tenofovir disoproxil fumarate plus emtricitabine in step 3. An enrolment minimum of transgender women of 10% was prespecified. Transgender women were randomly assigned to study groups. Full details of the trial design can be found in the trial protocol (appendix pp 24–498). The current analyses were not prespecified in the protocol and include data on transgender women participants enrolled in HPTN 083 collected from Dec 6, 2016, to May 14, 2020, when the study was unblinded by an independent data safety monitoring board.[1]

The HPTN 083 protocol was approved by institutional review boards, ethics committees, ministries of health, or a combination of these entities, at each participating site. The Division of AIDS (Rockville, MD, USA) was responsible for clinical monitoring of the trial. All participants provided written informed consent.

Procedures

Participant sociodemographic data were collected at enrolment and throughout the study by a health-care professional. Feminising hormones were defined as oestrogens (any route of administration), progestogens, or anti-androgens; gender affirming hormone therapy use was captured at each study visit. Computer assisted self-interview methods were used to capture data on sexual behaviours, alcohol use, and recreational drug use. Structured behavioural assessments, done with an interviewer, collected data on demographics (gender identification [with options of male, female, transgender male, transgender female, gender queer, gender variant or gender non-conforming, other self-identification, and prefer not to answer], age, education level, marital status, employment status, and income), intimate partner violence (emotional and physical), childhood sexual abuse, HIV risk perceptions, and depression. Assessments were

done at baseline for demographics, and approximately every second injection cycle for variables that can change over time. Counselling for adherence and risk reduction, and assessment of adverse events, were done at every visit; injection-site reactions were assessed at post-injection visits. Bodyweight measurements occurred at enrolment, and every other study visit. An Alcohol Use Disorders Identification (AUDIT-C) score of 4 or more was used as a cutoff to identify potential hazardous drinking or active alcohol use disorders.[19] A short form Center for Epidemiologic Studies Depression Scale (CES-D) score of 10 or more was considered a positive depression screening.[20] Participants answered questions about HIV risk perceptions at select visits throughout the study.

	Tenofovir disoproxil fumarate plus emtricitabine group (n=304)	Injectable cabotegravir group (n=266)
Gender self-identification		
Female	43 (14%)	47 (18%)
Transgender male	0	0
Transgender female	213 (70%)	187 (70%)
Gender queer	18 (6%)	14 (5%)
Gender variant or gender non-confirming	27 (9%)	16 (6%)
Other self-identification	3 (1%)	2 (1%)
Prefer not to answer	0	0
Age, years		
18–29	244 (80%)	227 (85%)
30–39	42 (14%)	29 (11%)
≥40	18 (6%)	10 (4%)
Median	23 (21–28)	23 (21–27)
Geographic region		
USA	71 (23%)	54 (20%)
Latin America	113 (37%)	92 (35%)
Asia	110 (36%)	115 (43%)
Africa	10 (3%)	5 (2%)
Education		
Secondary or lower	143 (47%)	125 (47%)
Technical training	22 (7%)	24 (9%)
College or university or higher	139 (46%)	117 (44%)
Marital status		
Married, civil union, or legal partnership	7 (2%)	3 (1%)
Living with primary or main partner	14 (5%)	16 (6%)
Have primary or main partner, not living together	19 (6%)	26 (10%)
Single, divorced, or widowed	264 (87%)	219 (82%)
Other	0	2 (1%)
Employment status		
Full or part time	188 (62%)	166 (62%)
Not employed	116 (38%)	100 (38%)
Household monthly income, US dollars*		
Median	482 (279–955)	366 (195–698)

Data are n (%) or median (IQR). *Income of countries other than the USA was converted from local currency to US dollars using the exchange rate on Jan 1, 2017.

Table 1: **Baseline demographic characteristics of transgender women participants**

Additional details on the scoring of behavioural assessments are in the appendix (pp 2–4). Additional details on study procedures have been published previously.[1]

Routine laboratory testing for safety was performed at all study visits, except the week 5 visit. Testing for HIV and sexually transmitted infections was done as previously described.[1,21] An independent adjudication committee reviewed HIV testing results from study sites and the HPTN Laboratory Center (Baltimore, MD, USA) determined HIV infection status, and identified the date of the first visit at which the participant tested HIV positive. Cabotegravir and tenofovir measurements in plasma and intraerythrocytic tenofovir-diphosphate measurements from dried blood spots were done with validated liquid chromatographic-tandem mass spectrometric assays.[21–23] The in-vitro protein-adjusted 90% cabotegravir inhibitory concentration (PA-IC_{90}) is 0·166 µg/mL.[24]

Drug concentrations were evaluated in a cohort of 389 randomly selected participants who were in the tenofovir disoproxil fumarate plus emtricitabine study group (340 cisgender men; 49 transgender women) to assess adherence to oral PrEP during the blinded phase of the study. Tenofovir-diphosphate concentrations of 700–1249 fmol/punch were associated with four tenofovir disoproxil fumarate plus emtricitabine doses per week and a concentration of 1250 fmol/punch or greater was associated with daily tenofovir disoproxil fumarate plus emtricitabine dosing in the preceding 4–8 weeks.[25] Adherence to injectable cabotegravir was defined as administration of injections within 2 weeks of a scheduled visit.

Select visits were evaluated from a select subset of transgender women in the injectable cabotegravir study group to understand the effect of gender affirming hormone therapy on cabotegravir pharmacokinetics. Participants included in this analysis received all injectable cabotegravir injections within 1 week before or after a scheduled visit, had no missed injections through to study week 57, and reported (n=30) or denied (n=23) gender affirming hormone therapy use. Cabotegravir concentrations were measured from these participants and mean cabotegravir concentrations were compared at evaluated study visits.

All visits included an assessment of adverse events. The severity of all adverse events was graded according to the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, corrected version 2.1.[26] The primary safety population comprised participants who received at least one dose of any of the oral tablets or injections.

Statistical analysis

We described sociodemographic, behavioural, clinical, and laboratory characteristics according to study group among all randomly assigned transgender women. We estimated prevalence and incidence of syphilis and

rectal chlamydia and gonorrhoea, and used the exact Poisson method to calculate incidence rates and their 95% CIs. The HIV incidence was compared using a Cox proportional hazards model, accounting for geographic region. We compared bodyweight changes by study group, according to gender affirming hormone therapy use and time of initiation, using linear mixed effects regression analysis, Mood's median test, and Wilcoxon p value (threshold for significance p<0·05). We used SAS (version 9.4) for statistical analyses. The HPTN 083 study is registered with ClinicalTrials.gov, NCT02720094, and is ongoing.

Role of the funding source

The funders of the study commented on the report but had no role in study design, data collection, data analysis, or data interpretation.

Results

Of 4566 participants enrolled in the study, 570 (12%) were transgender women, 304 of whom were randomly assigned to receive tenofovir disoproxil fumarate plus emtricitabine and 266 to receive injectable cabotegravir. 400 participants (70%) identified as transgender female, 90 (16%) as female, 43 (8%) as gender variant or gender non-conforming, 32 (6%) gender queer, and five (1%) did not identify as any of these categories. Transgender women were primarily enrolled from Asia and Latin America. Gender identity was not captured at post-enrolment study visits. At enrolment, the median age of transgender participants was 23 years (IQR 21–28; table 1). Enrolment characteristics for men who have sex with men are included in the appendix (p 5).

At enrolment, recreational drug use and problematic alcohol were common (table 2). Almost half of participants reported emotional intimate partner violence and almost a third reported physical intimate partner violence. A quarter had history of child sexual abuse. Enrolment behavioural characteristics did not differ between the study groups. As a comparison, enrolment behavioural data for men who have sex with men, categorised by study groups, are included in the appendix (p 6).

Among transgender women participants, at enrolment, the median number of sex partners in the previous month was three (IQR 2–8), with 20 (4%) of 570 reporting having at least one sex partner living with HIV. For the assessment of self-perceived HIV risk, 159 (28%) participants had an average item response that would correspond to generally disagreeing that they are at risk for HIV; this did not differ between study groups (p=0·42; table 2).

During the blinded phase of the study, adverse events grade 2 or higher among transgender women were similar between the tenofovir disoproxil fumarate plus emtricitabine group and the injectable cabotegravir group (table 3). The frequency of grade 2 or worse adverse events among transgender women was consistent with the frequency among men who have sex with men (table 3). Among transgender women, serious adverse events rates were similar between the tenofovir disoproxil fumarate plus emtricitabine group and the injectable cabotegravir group, and were consistent with the observed frequency among men who have sex with men (table 3; appendix p 7). Two deaths were recorded among transgender women during the study period, one in each study group; the deaths were not considered to be study-product related.

Among transgender women participants, 516 received at least one injection (266 in the tenofovir disoproxil fumarate plus emtricitabine group; 250 in the injectable cabotegravir group). Injection-site reactions were more commonly reported in the injectable cabotegravir group compared with the tenofovir disoproxil fumarate plus emtricitabine group (table 3). Permanent discontinuation of injections occurred in 51 (10%) of 516 transgender women (26 [10%] of 266 in the tenofovir disoproxil fumarate plus emtricitabine group; 24 [10%] of 250 in the injectable cabotegravir group); one (<1%) participant in the injectable cabotegravir group permanently discontinued study product due to injection-site reactions.

In a random subset of participants in the tenofovir disoproxil fumarate plus emtricitabine group,

	Tenofovir disoproxil fumarate plus emtricitabine group (n=304)	Injectable cabotegravir group (n=266)
Any recreational drug use in the previous 6 months	116/295 (39%)	104/262 (40%)
Positive alcohol screening*	137/295 (46%)	111/262 (42%)
Sex partners in the previous month	4 (2–8)	3 (2–7)
Sex partners living with HIV		
One	9/295 (3%)	4/262 (2%)
Two or more	6/295 (2%)	1/262 (<1%)
Receptive anal sex acts	5 (3–10)	4 (2–10)
Intimate partner violence		
Emotional abuse†	143/304 (47%)	127/266 (48%)
Physical abuse‡	92/304 (30%)	80/266 (30%)
Childhood sexual abuse before 18 years old	176/304 (58%)	147/266 (55%)
HIV risk perception categorisation§		
Disagrees that they are at risk	80/304 (26%)	79/266 (30%)
Neutral	113/304 (37%)	95/266 (36%)
Agrees that they are at risk	82/304 (27%)	67/266 (25%)
Positive depression screening¶	72/304 (24%)	70/266 (26%)

Data are n/N (%) or median (IQR). *Alcohol Use Disorders Identification score of 4 or greater. †Emotional abuse defined as being belittled or called stupid, or having an upset or suspicious partner. ‡Physical abuse defined as being punched, beaten, forced to perform sex acts, or abused when partner drinks alcohol. §Based on the sentences: (1) I am worried about getting infected with HIV, (2) my sexual experiences put me at risk for HIV, (3) I think that I really could get HIV, (4) I am unlikely to get infected with HIV, and (5) it is likely that I will be infected with HIV within the next year. Response options ranged from strongly disagree (1), disagree (2), neither agree nor disagree (3), agree (4), strongly agree (5), and don't know. Average scores of <2·5 suggest lower agreement with statements around being at risk for HIV, while scores >3·5 suggest higher agreement with statements around being at risk for HIV; and scores ranging from 2·51 to 3·49 were categorised as neutral. ¶Based on short-form (ten-item) Center for Epidemiologic Studies Depression Scale score ≥10.

Table 2: **Baseline behavioural characteristics among transgender women participants**

	Transgender women		Men who have sex with men	
	Tenofovir disoproxil fumarate plus emtricitabine group (n=304)	Injectable cabotegravir group (n=266)	Tenofovir disoproxil fumarate plus emtricitabine group (n=1978)	Injectable cabotegravir group (n= 2014)
Number of participants with grade 2 or worse adverse events*	270 (89%)	246 (92%)	1846 (93%)	1860 (92%)
Number of participants with grade 3 or worse adverse events*	76 (25%)	66 (25%)	691 (35%)	661 (33%)
Serious adverse events*	12 (4%)	17 (6%)	109 (6%)	103 (5%)
Participants who received at least one injection	266 (88%)	250 (94%)	1815 (92%)	1867 (93%)
Number of participants who have reported any injection site reaction	77 (29%)	217 (87%)	575 (32%)	1507 (81%)

MedDRA=Medical Dictionary for Regulatory Activities. *Included are only adverse events that were assigned MedDRA, version 23.1 terms by clinical staff. Injection-site reactions and sexually transmitted infections are not included. Inappropriately enrolled participants, including enrolled participants who were later found to have failed to meet a key inclusion or exclusion criterium, and participants who did not receive any oral trial drug are excluded. In cases in which a participant had multiple events with the same MedDRA term, only one event is counted.

Table 3: **Grade 2 or worse and grade 3 or worse adverse events, serious adverse events, and injection-site reaction summary by cohort and study group**

intraerythrocytic tenofovir-diphosphate concentrations consistent with four to six doses of tenofovir disoproxil fumarate plus emtricitabine per week (700–1249 fmol/punch) were observed in 82 (34%) of 243 evaluated samples from transgender women; concentrations consistent with daily adherence (tenofovir-diphosphate ≥1250 fmol/punch) were observed in 59 (24%) of 243 evaluated samples (appendix p 9). Among transgender women, tenofovir disoproxil fumarate plus emtricitabine persistence waned over time: based on tenofovir-diphosphate concentrations of 700 fmol/punch or greater, adherence decreased from 32 (67%) of 48 at study week 4 to four (40%) of ten at week 105. Among participants included in the adherence cohort, the proportion of specimens from transgender women with tenofovir-diphosphate concentrations of 700 fmol/punch or greater was significantly lower than for men who have sex with men: 141 (58%) of 243 versus 1331 (74%) of 1791 (p<0·0001). Coverage of injectable cabotegravir injections among transgender women in the injectable cabotegravir group was 315 (92%) of 343, as defined by person-years of injections covered divided by person-years of injections observed and injections having been received with a delay of less than 2 weeks; injection coverage among men who have sex with men in the injectable cabotegravir group was 2418 (92%) of 2639.

At enrolment, the prevalence of active syphilis (39 [7%] of 569), rectal gonorrhoea (41 [7%] of 570), and chlamydia (96 [17%] of 570) among transgender women was similar between the study groups (appendix p 11). During study follow-up, incidence of syphilis was 16·25% (95% CI 13·28–19·69), rectal gonorrhoea was 11·66% (9·14–14·66), and chlamydia was 20·61% (17·20–24·49). Sexually transmitted infection rates were similar to those observed among men who have sex with men (appendix p 10).

HIV incidence during the blinded phase of HPTN 083 has been previously reported.[1] Nine transgender women acquired HIV during the blinded phase of the study (seven tenofovir disoproxil fumarate plus emtricitabine; two injectable cabotegravir), with an overall incidence of 1·19 per 100 person-years (95% CI 0·54–2·25). HIV incidence among transgender women was 1·80 per 100 person-years (95% CI 0·73–3·72) in the tenofovir disoproxil fumarate plus emtricitabine group and 0·54 per 100 person-years (0·07–1·95) in the injectable cabotegravir group (hazard ratio [HR] 0·34, 95% CI 0·08–1·56). The HR is consistent with the overall HPTN 083 trial (figure A). None of the incident HIV cases in transgender women in the tenofovir disoproxil fumarate plus emtricitabine group had plasma tenofovir or intraerythrocytic tenofovir-diphosphate concentrations consistent with prevention-effective PrEP adherence, and five of seven did not have quantifiable drug concentrations at the first HIV-positive visit. Of the two transgender women participants who acquired HIV in the injectable cabotegravir group, one acquired HIV during the cabotegravir oral lead-in phase: cabotegravir concentrations were $8\times PA\text{-}IC_{90}$ (1·33 µg/mL) or more at the first HIV-positive visit. The other participant acquired HIV 849 days after their last injection and had unquantifiable cabotegravir concentrations at the first HIV-positive visit.

At enrolment, 249 (44%) transgender women participants reported accessing gender affirming hormone therapy; an additional 81 (14%) transgender women reported gender affirming hormone therapy use after enrolment. 310 (94%) of 330 transgender women who used gender affirming hormone therapy reported oestrogen use, 252 (76%) reported anti-androgenic use, and 117 (35%) reported progestogen use. The most commonly reported gender affirming hormone therapies were estradiol valerate (147 [45%]), spironolactone (107 [32%]), estradiol (94 [28%]), and cyproterone acetate (92 [28%]). There were no differences in types of gender affirming hormone therapy accessed between study groups (table 4; appendix pp 11–12). Gender affirming hormone therapy was used not only by transgender women in the study: 32 (1%) of 3996 cisgender men also reported the use of gender affirming hormone therapy (seven at enrolment and

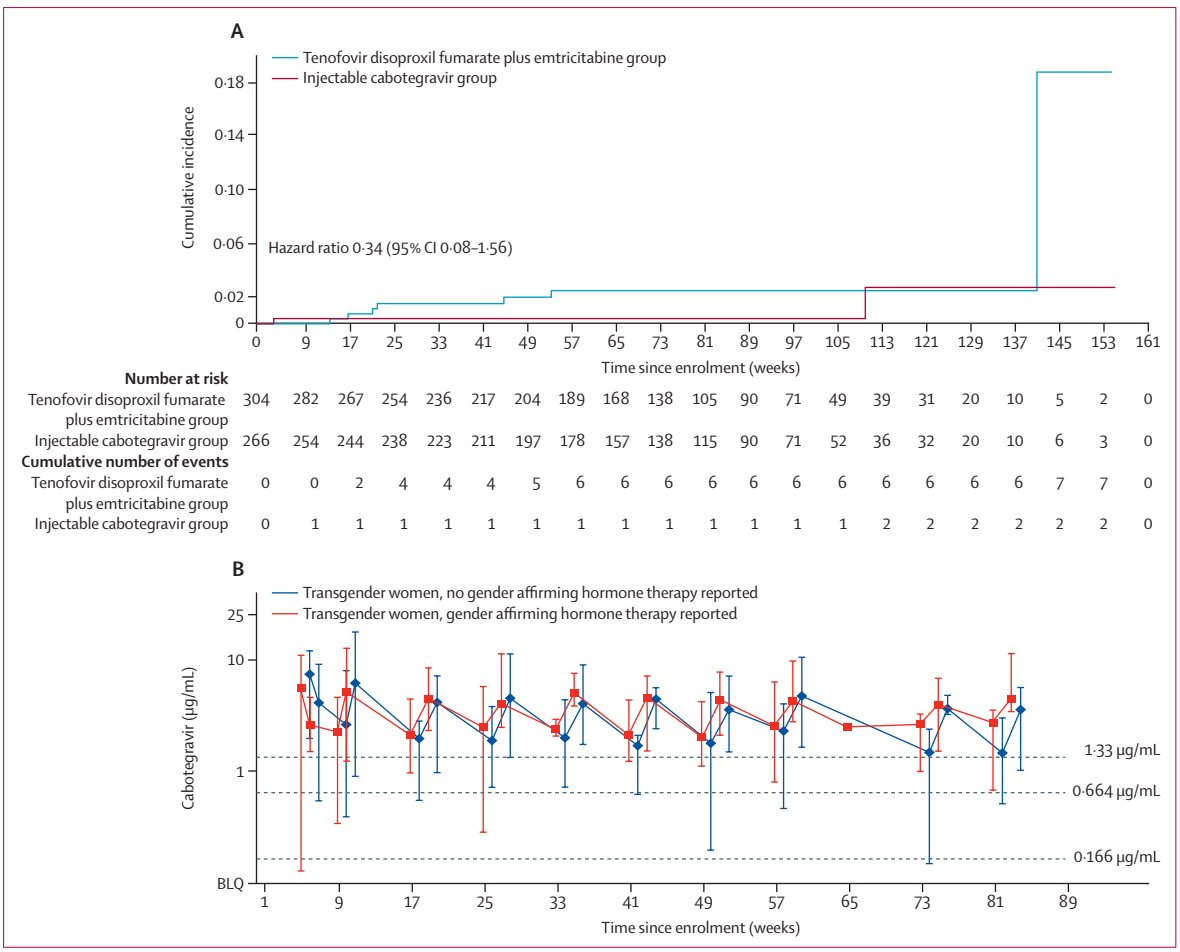

Figure: **HIV incidence among transgender women in HPTN 083 and cabotegravir pharmacokinetics in transgender women in the presence or absence of gender affirming hormone use**

(A) Kaplan-Meier estimates of cumulative incidence of HIV infection among transgender women in the intention-to-treat cohort. (B) Median cabotegravir concentrations in transgender women in the absence or presence of gender affirming hormone therapy. Error bars show the lower 5% and upper 95% of cabotegravir concentrations observed at each timepoint. 0·166 µg/mL=1 × PA-IC_{90}. 0·664 µg/mL=4 × PA-IC_{90}. 1·33 µg/mL=8 × PA-IC_{90}. BLQ for cabotegravir is 0·025 µg/mL. BLQ=below the limit of quantitation. PA-IC_{90}=in vitro protein-adjusted 90% cabotegravir inhibitory concentration.

25 post-enrolment). Oestrogens were most commonly used among these participants (table 4).

Bodyweight changes from baseline were compared by study group, gender affirming hormone therapy use, and time of initiation. A median increase in bodyweight of 1·17 kg/year (95% CI 0·65–1·68) was noted in transgender women in the injectable cabotegravir group, compared with an increase of 0·69 kg/year (0·18–1·19) in the tenofovir disoproxil fumarate plus emtricitabine group. These differences were not statistically significant (mean difference 0·48, 95% CI –0·24 to 1·22; p=0·19; appendix p 14). Use of gender affirming hormone therapy did not result in significant differences in rates of bodyweight gain among transgender women (appendix p 13).

Cabotegravir concentrations were compared in the presence (n=30) or absence (n=23) of gender affirming hormone therapy in a select subset of transgender women participants who had high adherence to injectable cabotegravir injections. Although cabotegravir concentrations were nominally higher in transgender women accessing gender affirming hormone therapy than in those who were not, there were no statistically significant differences in cabotegravir concentrations at evaluated timepoints (p=0·78; figure B). Hormone dosing times were not captured and oestrogen measurements were not done; thus, an impact of cabotegravir on gender affirming hormone therapy was not assessed.

Discussion

This is the first report to describe transgender-women-specific participant characteristics, safety, behavioural, efficacy, bodyweight changes, and pharmacological data from the HPTN 083 clinical trial. Our findings suggest that injectable cabotegravir is a safe and effective HIV prevention strategy for transgender women, providing high levels of protection among these participants;

	Transgender women			Men who have sex with men		
	GAHT use reported at baseline	GAHT initiated during follow-up	Total GAHT use reported	GAHT use reported at baseline	GAHT initiated during follow-up	Total GAHT use reported
Participants who self-reported any type of GAHT	249/570 (44%)	81/570 (14%)	330/570 (58%)	7/3996 (<1%)	25/3996 (1%)	32/3996 (1%)
GAHT type*						
Anti-androgens	202/249 (81%)	50/81 (62%)	252/330 (76%)	5/7 (71%)	16/25 (64%)	21/32 (66%)
Oestrogens	239/249 (96%)	71/81 (88%)	310/330 (94%)	6/7 (86%)	20/25 (80%)	26/32 (81%)
Progestogens	91/249 (37%)	26/81 (32%)	117/330 (35%)	2/7 (29%)	9/25 (36%)	11/32 (34%)

GAHT=gender affirming hormone therapy. *Numerator refers to the number of participants who reported each hormone therapy regimen; denominators refer to the number of participants who reported GAHT use at baseline or during follow-up.

Table 4: **Reported GAHT use by cohort, study group, and starting period**

these findings are consistent with overall study results.[1] Furthermore, these data highlight important considerations for the recruitment and inclusion of transgender participants in HIV prevention research.

Traditionally, transgender and gender diverse people have not been prioritised in HIV efficacy trials.[18] However, transgender women were successfully enrolled and retained in HPTN 083, representing the largest cohort of transgender women included in a registrational trial to date. By adopting a prespecified recruitment target, HPTN 083 provided a unique opportunity to evaluate the efficacy of injectable cabotegravir in transgender women, as well as further expand insights into the use of tenofovir disoproxil fumarate plus emtricitabine in this population. Although inclusion of self-identifying transgender women was a recruitment goal, we also observed a spectrum of genders within the study. Of participants included in our analysis under the umbrella of transgender women, 14% of participants self-identified as queer, gender variant, gender non-conforming, or other gender identities. Across the entire cohort, 58% of transgender and gender-diverse participants accessed gender affirming hormone therapy before or after enrolment. Furthermore, 32 self-identified cisgender men who have sex with men reported gender affirming hormone therapy use, raising important considerations for how to adequately capture the range of gender identities in HIV research, consider the profile of gender affirming hormone therapy users, and be responsive to the evolution of gender identity and preferred pronouns and labels over time.[16] In HPTN 083, self-reported gender identity was not longitudinally assessed during study follow-up, but should be added to the list of demographic variables assessed throughout study participation.

Various co-occurring contextual variables might be important to consider in implementing PrEP for transgender women globally based on these data. Recreational drug and alcohol use were commonly reported, and nearly 25% of participants enrolled had clinically significant depressive symptoms. Transgender women experienced a high frequency of intimate partner violence and more than half of transgender women reported a history of childhood sexual abuse. Income levels were low and rates of unemployment were high. These syndemic problems have been reported previously among transgender and gender diverse people;[27,28] these data confirm that this is observed across geographies.

At enrolment, more than one quarter of transgender participants in our cohort had an average response across items assessing HIV risk perceptions indicating disagreement regarding their risk for HIV acquisition. These data were lower than perceived HIV risk captured in other studies, including those from Latin America and Asia; this might be attributed to methodological differences in how perceived HIV risk was evaluated.[29,30] Risk perception is an important variable in HIV-related health behaviour changes, as it is a direct[31] or indirect[32] component of various social cognitive models of HIV risk. HIV prevention among transgender women cannot be addressed in isolation from the sociobehavioural context within which HIV risk occurs, and low risk perception highlights the structural gaps in PrEP acceptance and uptake.

The enrolment prevalence of sexually transmitted infections was high across the entire study cohort, and rates among transgender women ranged from 7% to 17% for syphilis, rectal gonorrhoea, and chlamydia. Throughout the conduct of the trial, participants continued to be sexually active and had high rates of sexually transmitted infections. These data underscore not only the ongoing incidence of rectal sexually transmitted infections, but also risk for HIV acquisition and the benefits of PrEP uptake and use. The implications of rectal sexually transmitted infections include low rates of condom use, and re-emphasise the need for a broad choice of options for HIV prevention and sexually transmitted infection management acceptable to populations at risk.

Within HPTN 083, both tenofovir disoproxil fumarate plus emtricitabine and injectable cabotegravir were highly effective in the prevention of HIV among transgender women. Although the HR for transgender women was not statistically significant, the magnitude and direction of the effect favouring cabotegravir was consistent with overall trial results. Of the transgender women

participants in the tenofovir disoproxil fumarate plus emtricitabine group who acquired HIV, none had drug concentrations at the first HIV-positive visit consistent with protection-effective oral tenofovir disoproxil fumarate plus emtricitabine adherence; these findings are largely consistent with results from the entire cohort.[21] During the blinded phase of the trial, no transgender women participants who received on-time cabotegravir injections acquired HIV. However, one transgender woman in the injectable cabotegravir group acquired HIV during the oral phase of the study. The participant acquired HIV 27 days after enrolment (cabotegravir concentration at first HIV-positive visit: 6·30 μg/mL), and had a cabotegravir concentration 8×PA-IC_{90} or greater at the preceding visit. Although pill counts were used to assess adherence during the trial, direct observation was not performed; thus, it is unclear if the participant used oral cabotegravir consistently. It is also possible that the participant acquired HIV shortly after enrolment and that this was not detected until the week 4 visit.

Although data were unavailable to do a bidirectional evaluation of interactions between drugs and hormones, we compared drug concentrations among transgender women in the presence or absence of gender affirming hormone therapy use in a small subset (n=53) of transgender participants in the injectable cabotegravir group. Cabotegravir concentrations were nominally higher in transgender women who reported using gender affirming hormone therapy; however, differences were not statistically significant. Of note, pharmacological parameters, including steady state cabotegravir concentrations with repeated dosing, were higher in cisgender women than cisgender men.[22,33] These differences might be influenced by BMI or body size. Although we were able to compare cabotegravir concentrations in the background of gender affirming hormone therapy, we were unable to characterise the impact of cabotegravir on this therapy. This remains an important research gap.

Given the challenges faced by transgender women to adhere to oral tenofovir disoproxil fumarate plus emtricitabine PrEP, an injection every 2 months is convenient and discreet, and might address the barriers to daily oral pill-taking, such as competing life priorities, HIV stigma, discrimination, and violence. Of note, 83% of transgender women participants were younger than 30 years, making the preserved advantage of injectable cabotegravir among a young and at-risk population of transgender women a remarkable advance in global HIV prevention.[12,34]

There are limitations to the presented work. Although there was a target enrolment of 10% or more transgender women in HPTN 083, the enrolled sample size was not large enough for a fully powered statistical comparison. Furthermore, gender identity was only captured at enrolment, and additional data on participant feelings surrounding gender were not captured throughout the study. Last, hormone concentrations were not evaluated, and the study design did not lend itself to a formal analysis of interactions between drugs and hormones.

Results from this study specific to transgender women are consistent with the overall HPTN 083 study result, which found that injectable cabotegravir administered intramuscularly every 8 weeks was well tolerated, safe, and highly effective in preventing HIV infection in men who have sex with men and transgender women at substantial risk for acquiring HIV.[13] Cabotegravir concentrations were not statistically different between transgender women who reported using gender affirming hormone therapy compared with transgender women who reported not using this therapy. However, additional studies, which capture detailed gender affirming hormone therapy dosing information and hormone concentrations, are needed to more fully characterise the relationship between cabotegravir and these therapies.

Contributors

BG, RJL, MM, and MSC designed the HPTN 083 trial with input from AA, ARR, BH, CP, DD, JL, JFR, MAM, SAS, and SHE. BG, JF, and RJL were site principal investigators; BM, EJ, TK, YS, JV, and KM were subinvestigators. MAM, PAR, PS, and SHE oversaw the quality assurance, assay performance, and pharmacokinetic analysis. BH, DD, and ZW performed the statistical analysis. AJ, KGF, and MM provided protocol support. SAS and CP performed behavioural analyses. JL, NC, and NS provided community support. CC provided support in the preparation, editing, and review of the manuscript with intellectual content. ARR, JFR, and SF provided pharmaceutical support. BG and MAM wrote the first draft of the report and subsequent versions. BG, BH, and MAM accessed and verified the data. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication. All authors commented on the report and approved the final version.

Declaration of interests

MAM has received grant funding from ViiV/GSK and Gilead Sciences for industry-sponsored research. RJL reports receiving study products and additional support for study conduct to sites from ViiV Healthcare and was given study products from Gilead Sciences during the conduct of the study. RJL received advisory scientific board fees, and travel support from Merck Inc outside the submitted work. JFR is a paid employee and stockholder of Gilead Sciences. ARR is a paid employee and stockholder of ViiV Healthcare. CP reports grants from the National Institutes of Health (NIH), advisory board fees from University of North Carolina at Chapel Hill, The Fenway Institute, and University of California, Los Angeles, outside the submitted work, and participated in data safety monitoring boards at University of North Carolina at Chapel Hill and Massachusetts General Hospital. JF reports grants from ViiV Healthcare UK and the National Institute of Allergy and Infectious Diseases, during the conduct of the study. SF was a paid employee and stockholder of GSK during the conduct of the study. MSC reports grants from NIH, scientific and medical advisory board fees, respectively, from Aerium and Atea, honoraria for lectures from MJH Life Sciences, Clinical Care Solutions, Virology Education, Amgen, Medscape, and UpToDate, and for an educational panel from Astra Zeneca. MSC reports travel support from GSK and was co-chair in the HIV Prevention Trials Network and COVID-19 Prevention Network. All other authors declare no competing interests.

Data sharing

Data collected for this study may be made available upon request. The data archive will be held at the Fred Hutchinson Cancer Center (Seattle, WA, USA). Requests can be sent to HPTN-Data-Access@scharp.org.

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