

https://dspace.org/

HIV DNA Levels in Persons Who Acquired HIV in the Setting of LongActing Cabotegravir for HIV Prevention Analysis of Cases from HPTN 083 and 084

J Fogel; D Persaud; E Piwowar-Manning; P Richardson; Carrie-Anne Mathew ...

https://hdl.handle.net/10539/48924
WOS

Downloaded from a DSpace repository. https://dspace.org/

AIDS RESEARCH AND HUMAN RETROVIRUSES
Volume 41, Number 1, 2025
© Mary Ann Liebert, Inc.
DOI: 10.1089/aid.2024.0049

Open camera or QR reader and scan code to access this article and other resources online.

HIV DNA Levels in Persons Who Acquired HIV in the Setting of Long-Acting Cabotegravir for HIV Prevention: Analysis of Cases from HPTN 083 and 084

Jessica M. Fogel,[1] Deborah Persaud,[2] Estelle Piwowar-Manning,[1] Paul Richardson,[1] Joseph Szewczyk,[2] Mark A. Marzinke,[1,3] Zhe Wang,[4] Xu Guo,[4] Marybeth McCauley,[5] Jennifer Farrior,[5] Ha Viet Tran,[6] Chaiwat Ungsedhapand,[7,8] Carrie-Anne Mathew,[9] Juliet Mpendo,[10] Alex R. Rinehart,[11] James F. Rooney,[12] Myron S. Cohen,[13] Brett Hanscom,[4] Beatriz Grinsztejn,[14] Mina C. Hosseinipour,[13] Sinead Delany-Moretlwe,[9] Raphael J. Landovitz,[15] and Susan H. Eshleman[1];
for the HPTN 083 and HPTN 084 Study Teams

Abstract

We evaluated HIV DNA levels in individuals who received long-acting cabotegravir (CAB-LA) or tenofovir disoproxil fumarate/emtricitabine (TDF/FTC) pre-exposure prophylaxis in the HPTN 083 and 084 trials and had HIV DNA testing performed to help determine HIV status. HIV DNA testing was performed using peripheral blood mononuclear cell (PBMC) samples collected after a reactive HIV test was obtained at a study site. DNA was quantified using droplet digital PCR (lower limit of detection [LLOD]: 4.09 copies/million PBMCs). Final HIV status and the timing of the first HIV-positive visit were determined by an independent adjudication committee based on HIV test results from real-time site testing and retrospective testing at a centralized laboratory. HIV DNA testing was performed for 133 participants [21 HIV-positive (7 CAB-LA arm, 14 TDF/FTC arm) and 112 HIV-negative; 1–6 tests/person]. For persons with HIV, the time between the first HIV-positive visit and collection of the first sample for DNA testing was a median of 81 days for those receiving CAB-LA (range 41–246) and 11 days for those receiving TDF/FTC (range 3–127). Four (57.1%) of the seven CAB-LA cases with infection had a low initial DNA result [three detected <LLOD; one near the LLOD (4.2 copies/10^6 PBMCs); in 2/4 cases, the DNA level was still <10 copies/10^6 PBMCs ≥40 weeks after the first HIV-positive visit. In contrast, only 3/14 (21.4%) of the TDF/FTC cases had a low or negative initial DNA test result (one not detected; two <10 copies/10^6 PBMCs). In this study, the time between the first HIV-positive visit and the first DNA test was longer in the CAB-LA cases than the TDF/FTC cases. Despite this difference, low or undetectable DNA levels were more

[1]Department of Pathology, [2]Department of Pediatrics, [3]Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA.
[4]Fred Hutchinson Cancer Center, Seattle, Washington, USA.
[5]FHI 360, Durham, North Carolina, USA.
[6]The University of North Carolina—Vietnam, Hanoi City, Vietnam.
[7]Division of HIV Prevention, U.S. Centers for Disease Control and Prevention, Atlanta, Georgia, USA.
[8]Division of HIV Prevention, Thailand Ministry of Public Health-U.S. Centers for Disease Control and Prevention Collaboration, Nonthaburi, Thailand.
[9]Wits RHI, University of the Witwatersrand, Johannesburg, South Africa.
[10]Uganda Virus Research Institute-International AIDS Vaccine Initiative HIV Vaccine Program, Entebbe, Uganda.
[11]ViiV Healthcare, Research Triangle Park, North Carolina, USA.
[12]Gilead Sciences, Foster City, California, USA.
[13]Department of Medicine, University of North Carolina, Chapel Hill, North Carolina, USA.
[14]Instituto de Pesquisa Clinica Evandro Chagas-Fiocruz, Rio de Janeiro, Brazil.
[15]Center for Clinical AIDS Research & Education, University of California, Los Angeles, Los Angeles, California, USA.

frequently observed in the CAB-LA cases. This suggests that CAB-LA exposure may limit seeding of the HIV reservoir in early infection.

Keywords: HIV, pre-exposure prophylaxis, prevention, cabotegravir, DNA, HIV Prevention Trials Network

Introduction

The HIV Prevention Trials Network (HPTN) 083 and 084 trials found that long-acting injectable cabotegravir was superior to daily oral tenofovir disoproxil fumarate/emtricitabine (TDF/FTC) when used as pre-exposure prophylaxis (PrEP) to prevent sexual transmission of HIV.[1–4] Both trials are ongoing as open-label studies. Characterization of HIV infections in these trials revealed that the features of HIV infection in the setting of long-acting cabotegravir (CAB-LA) are distinct from those observed in persons who acquire HIV infection who are not on PrEP or are using tenofovir-based oral PrEP agents.[5–7] In the setting of CAB-LA PrEP, detection of HIV infection may be delayed for long periods due to a lack of clinical symptoms, drug-induced viral suppression, and delayed/diminished antibody responses. We previously reported that HIV RNA levels can remain low or undetectable for months, even after injections are stopped and drug concentrations decline. We refer to this new paradigm as long-acting early viral inhibition.[8] In the setting of CAB-LA PrEP, HIV RNA assays often detect HIV infections earlier than antibody-based HIV rapid tests or laboratory-based antigen/antibody (Ag/Ab) tests.[9,10] A total nucleic acid assay that detects both HIV RNA and DNA was less sensitive than HIV RNA assays for detecting infections in this setting.[10]

In this study, we evaluated HIV DNA levels in HPTN 083 and 084 participants who had a reactive rapid HIV test and/or Ag/Ab test and had HIV DNA testing performed to help determine HIV status for clinical management. We also compared HIV DNA levels in participants receiving CAB-LA versus TDF/FTC PrEP to determine the impact of CAB-LA on HIV DNA levels in early infection.

Methods

Study cohort

HPTN 083 (NCT02720094) and HPTN 084 (NCT03164564) are ongoing phase 3 clinical trials evaluating CAB-LA for HIV PrEP. Both trials included a double-placebo, double-blind, and an active-controlled period with participants randomized to either the CAB arm or the TDF/FTC arm. Participants in the CAB arm received daily oral CAB for 5 weeks, followed by CAB injections (600 mg) for up to 3 years (two injections 1 month apart and then every 2 months). Participants in the TDF/FTC arm received daily oral TDF/FTC. The primary outcomes of the trials were reported previously.[1,2] After study unblinding, both trials continued with participants remaining on their originally-randomized study arm while awaiting the open-label phase of the trials.[3,4] This report includes data for visits that occurred during the blinded phase and the first unblinded year of both trials (through May 15, 2021, for HPTN 083; through November 5, 2021, for HPTN 084). Data were only included for visits prior to initiation of antiretroviral therapy (ART).

HIV testing at study sites

All participants were required to have a negative HIV RNA test within 14 days of study enrollment. Participants were screened for HIV infection at enrollment and at follow-up visits using one or two HIV rapid antibody tests and a laboratory-based Ag/Ab test. If a reactive test result was obtained, results were sent to a centralized committee that provided recommendations for additional testing to determine HIV status for real-time clinical management. The committee for each trial included expert consultants (two–three clinicians and a laboratory scientist). In most cases, HIV status was resolved using locally available HIV antibody testing and/or HIV RNA testing; use of these two tests to resolve HIV status varied among study sites and cases. In selected cases, the centralized committee recommended collection of peripheral blood mononuclear cells (PBMCs) for real-time HIV DNA testing at a specialized laboratory in the United States.

HIV DNA testing

HIV DNA testing was performed using nonviable PBMCs isolated at study sites from whole blood. Dried cell pellets were shipped to the CLIA-certified CURE Laboratory at Johns Hopkins University (Baltimore, MD) for testing. HIV DNA was quantified using a laboratory-developed, pan-subtype, droplet digital PCR (ddPCR) HIV-1 DNA assay with a previously established lower limit of detection (LLOD) of 4.09 copies/million PBMCs.[11] Given that the performance characteristics of the assay were not previously determined in high-risk adult populations, results for samples with HIV DNA detected below the previously established LLOD were reported as "detected <LLOD."

Retrospective testing

Additional HIV testing was performed retrospectively at the HPTN Laboratory Center (Baltimore, MD) for all cases in HPTN 083 and 084 that had one or more reactive HIV screening test.[5,6] The panel of assays used for this testing included the Architect HIV Ag/Ab Combo assay [Abbott Diagnostics, Wiesbaden, Germany, the Geenius HIV 1/2 Supplemental Assay (Bio-Rad Laboratories, Redmond, WA), the APTIMA HIV-1 RNA Qualitative Assay (Hologic Marlborough, MA), and the RealTime HIV-1 Viral Load Assay (lower limit of quantification [LLOQ]: 40 copies/mL; Abbott Molecular, Des Plaines, IL)]. A single copy HIV RNA assay was performed in selected cases at the University of Pittsburgh.[12] To identify the first HIV-positive visit, testing was also performed on samples collected before the site first obtained a reactive screening test result. Plasma CAB concentrations were measured using liquid chromatography–tandem mass spectrometry (LC-MS/MS, LLOQ: 0.025 μg/mL); LC-MS/MS was also used to quantify tenofovir (TFV) in plasma and tenofovir-diphosphate (TFV-DP) in dried blood spots (DBS).[5,6]

HIV status determination

An independent Endpoint Adjudication Committee performed periodic, formal, and retrospective reviews of all HIV test results from the study sites and HPTN Laboratory Center for cases that had at least one reactive/positive site test. This committee determined the final HIV status and identified the first HIV-positive visit in each case[5–7]; in some cases, the date of the first HIV-positive visit was before the first site-positive visit (i.e., before the site first obtained a reactive HIV screening test result). Cases were adjudicated HIV positive if the participant had a positive antibody discriminatory/confirmatory test, a positive RNA test, or a DNA result detected above the LLOD (>4.09 copies/million PBMCs). A single DNA result of detected <LLOD was not considered to be sufficient to classify a case as HIV positive.

Statistical methods

Fisher's exact test and chi-square test were used to compare proportions.

Ethical considerations

The HPTN 083 and HPTN 084 protocols were approved by the institutional review boards and/or ethics committees and ministries of health for all participating sites. All participants provided written informed consent.

Results

Participants with HIV DNA test results

During the study periods evaluated, 319 participants in HPTN 083 and 084 had at least one reactive HIV screening test with an adjudicated final HIV status (176 HIV positive and 143 HIV negative). DNA testing was performed for 21 (11.9%) of the 176 persons with HIV (PWH; seven in the CAB arm, 14 in the TDF/FTC arm; Table 1) and 112 (78.3%) of the 143 persons without HIV (63 in the CAB arm, 49 in the TDF/FTC arm; Supplementary Table S1). The median time between the first site-positive visit and collection of the sample for DNA testing was 9 days for persons with a final status of HIV positive [interquartile range (IQR) 4–13] and 8 days for persons with a final status of HIV negative (IQR 4–18). The proportion of participants with HIV who had DNA testing performed was higher for those randomized to receive CAB-LA compared with those randomized to receive TDF/FTC; however, this difference was not statistically significant (17.1% vs. 10.4%, $p = .25$). There was no significant difference in the proportion of participants who had DNA testing performed in HPTN 083 compared to HPTN 084 (HIV positive: 10.9% vs. 13.6%, $p = .59$, HIV negative: 83.7% vs. 75.5%, $p = .26$).

DNA levels among participants in the CAB and TDF/FTC study arms

Characteristics of the 21 PWH evaluated in this study are shown in Figure 1 and Table 2. A total of 29 DNA tests were performed for these cases (median: 1 test/participant, range: 1–4 tests). Twenty-two (75.9%) of the samples had DNA detected above the LLOD, five (17.2%) had DNA detected below the LLOD, and two (6.9%) had no DNA detected (Table 1).

In the CAB arm, four participants had HIV infection at study enrollment that was not detected at the study site until a subsequent study visit; the remaining three participants acquired HIV infection during study follow-up. In all seven cases, there was a delay between the first HIV positive visit and the visit where the site first detected the possibility of infection. In the TDF/FTC arm, all 14 participants acquired HIV infection during study follow-up; detection of HIV infection at the study site was delayed in only two of these cases (Table 2). The median number of days between the first HIV-positive visit (based on real-time and retrospective testing) and the first DNA test was longer in the CAB arm than the TDF/FTC arm due to the delayed detection of infection in the CAB arm [81 (41–246) days in the CAB arm vs. 11 (3–127) days in the TDF/FTC arm].

Among the seven participants in the CAB arm, four (57.1%) had a low initial DNA result (one had 4.2 copies/million PBMCs, three had DNA detected <LLOD); the other three participants had a high DNA level at that visit (one had 682 DNA copies/million PBMCs, one had 97.8 DNA copies/million PBMCs, and one had 81.5 DNA copies/million PBMCs). The median (IQR) DNA level was 4.2 (<LLOD—89.7) copies/10^6 PBMCs for these seven samples. The plasma CAB concentration was ≥8× the *in vitro* protein-adjusted (PA) 90% CAB inhibitory concentration (IC) (PA-IC_{90}) for six of the seven participants at the time of the initial DNA test and was 4–8× PA-IC_{90} for one case at that visit (Table 2). In two of the seven cases, the DNA levels were still low ≥40 weeks after the first HIV-positive visit (one had 5.8 DNA copies/million PBMCs, one had 4.4 DNA copies/million PBMCs; Fig. 1).

Table 1. DNA Test Results for Participants with a Final Adjudicated Status of HIV Positive[a]

Study arm	*Study*	*# PWH*	*# PWH with one or more DNA test result*	*# DNA tests performed*	*# (%) Detected >LLOD*	*# (%) Detected <LLOD*	*# (%) Not detected*
CAB	HPTN 083	34	6 (17.6%)	11	7 (63.6%)	3 (27.3%)	1 (9.1%)
	HPTN 084	7	1 (14.3%)	3	2 (66.7%)	1 (33.3%)	0 (0%)
	Total	41	7 (17.1%)	14	9 (64.3%)	4 (28.6%)	1 (7.1%)
TDF/FTC	HPTN 083	76	6 (7.9%)	6	6 (100%)	0 (0%)	0 (0%)
	HPTN 084	59	8 (13.6%)	9	7 (77.8%)	1 (11.1%)	1 (11.1%)
	Total	135	14 (10.4%)	15	13 (86.7%)	1 (6.7%)	1 (6.7%)
Overall		**176**	**21 (11.9%)**	**29**	**22 (75.9%)**	**5 (17.2%)**	**2 (6.9%)**

[a]The table shows the number of participants in HPTN 083 and HPTN 084 who acquired HIV infection by the end of the first unblinded year (final adjudicated HIV status: HIV positive, $n = 176$) and the number of those participants who had at least one DNA test result ($n = 21$).

CAB, cabotegravir; HPTN, HIV Prevention Trials Network; LLOD, lower limit of detection; PWH, persons with HIV; TDF/FTC, tenofovir disoproxil fumarate/emtricitabine.

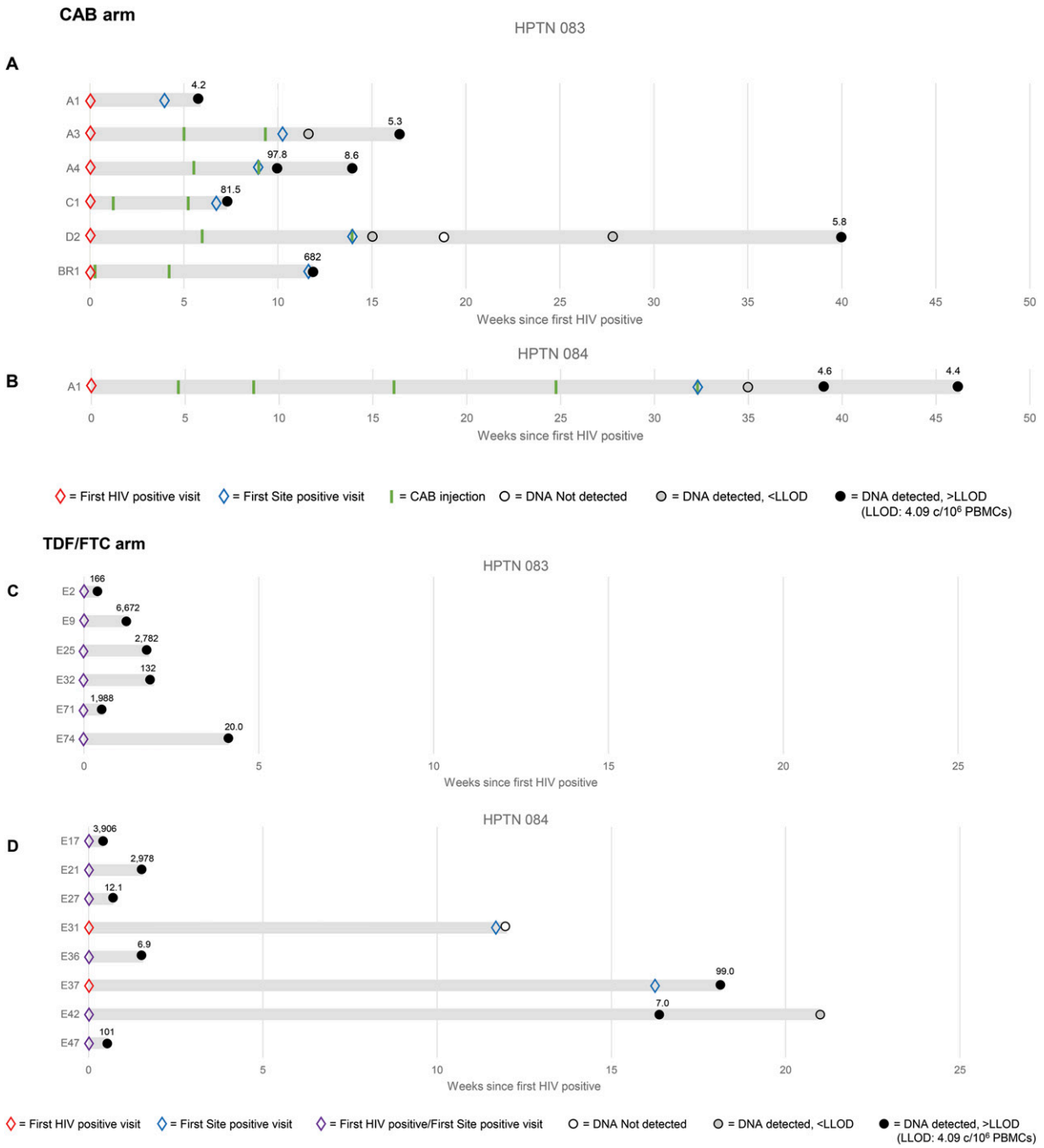


FIG. 1. DNA levels for persons with HIV (PWH) who had one or more DNA test result. The figure shows DNA test results from PWH in the CAB arm **(A** and **B)** and the TDF/FTC arm **(C** and **D)** of HPTN 083 and HPTN 084. In (**A**), participant A1 received oral CAB only. Participants A1–A4 had HIV infection at the time of study enrollment that was not detected by site testing. Participant C1 acquired HIV infection while receiving oral cabotegravir prior to CAB injections. Participant D2 acquired HIV infection despite on-time CAB injections. DNA test results are shown as DNA copies/million PBMCs. The standard LLOD for this assay is 4.09 DNA copies/million PMBCs. CAB, cabotegravir; $c/10^6$, copies/million; LLOD, lower limit of detection; PBMCs, peripheral blood mononuclear cells; TDF/FTC, tenofovir disoproxil fumarate/emtricitabine.

We also assessed DNA levels for the 14 participants in the TDF/FTC arm who had a DNA test performed. Ten of the 14 participants had intraerythrocytic TFV-DP concentrations below the limit of quantification at the first visit, where HIV DNA testing was performed. Furthermore, TFV and TFV-DP testing performed using samples collected near the time of the first HIV-positive visit found that 13/14 participants had poor adherence to the daily oral TDF/FTC and the remaining participant had only partial adherence at that time. Three (21.4%) of the 14 participants had a low initial DNA result (two had ~7 DNA copies/million PBMCs and one no DNA detected). The other 11 participants (78.6%) had a high initial DNA result (Fig. 1, Table 2). The median (IQR) DNA level was 117 (14–2,584)

Table 2. Characteristics of Persons with HIV with One or More DNA Test Result[a]

Study arm	Study	Case[b]	Detection delay[c]	VL at 1st HIV pos visit (c/mL)	TDF/FTC adherent at 1st HIV pos visit[d]	First visit with DNA results[e]			
						Days since 1st HIV pos visit	HIV RNA[f]	DNA (c/10^6 PBMC)	ARV drug concentration[g]
CAB (7 cases)	083	A1	Yes	4,010	—	41	Detected <40	4.2	3.68
		A3	Yes	1,360	—	81	NR	Detected <LLOD	3.37
		A4	Yes	44,180	—	70	NR	97.8	4.90
		C1	Yes	120	—	51	2,549	81.5	3.65
		D2	Yes	6.1	—	105	NR	Detected <LLOD	2.67
		BR1	Yes	450	—	83	100,260	682	1.29
	084	A1	Yes	21.4	—	246	SCA negative	Detected <LLOD	2.16
TDF/FTC (14 cases)	083	E2	No	34,180	No	3	50,050	166	BLQ (3 days prior)
		E9	No	505,690	No	9	82,397,780	6672	BLQ (9 days prior)
		E25	No	36,976,550	No	13	13,150,570	2,782	BLQ
		E32	No	11,310	No	14	14,360	132	BLQ
		E71	No	711,390	No	4	674,200	1,988	BLQ (4 days prior)
		E74	No	358	No	29	Not detected	20.0	BLQ (29 days prior)
	084	E17	No	2,706,990	No	3	2,144,273	3,906	BLQ
		E21	No	15,800	No	11	7,400	2,978	36.6
		E27	No	1,005,760	No	5	11,600	12.1	BLQ
		E31	Yes	71	Inconsistent	84	SCA 0.8	Not detected	432
		E36	No	Not detected	Partial	11	SCA negative	6.9	541
		E37	Yes	9,160	No	127	NR	99.0	1,051
		E42	No	Not detected	No	115	SCA negative	7.0	BLQ
		E47	No	113,080	No	4	33,165	101	BLQ

[a]The table shows test results for participants with a final adjudicated status of HIV positive who had at least one DNA test result.

[b]Alphanumeric case designations and additional information for each case are described in prior publications.[5–7] Case letter designations are as follows: A: baseline case, HIV infection acquired prior to study enrollment; C: HIV infection acquired during the oral cabotegravir (CAB) lead-in phase; D: HIV infection acquired despite on-time injections; BR: HIV infection acquired more than 6 months after the last injection and detected at the time the participant restarted injectable cabotegravir; E: HIV infection acquired in participants in the tenofovir disoproxil fumarate/emtricitabine (TDF/FTC) study arm.

[c]Detection delay indicates that detection of HIV infection was delayed at the study site.

[d]TDF/FTC adherence at the first HIV positive visit was assessed based on drug concentrations of tenofovir (TFV) in plasma and tenofovir-diphosphate (TFV-DP) in dried blood spot samples. None of the 14 TDF/FTC cases had drug concentrations that indicated good adherence (7 TDF/FTC doses/week). Case E31 had inconsistent adherence (2–4 doses/week) and Case E36 had partial adherence (4–6 doses/week) at the first HIV positive visit.

[e]Laboratory results are shown for the first visit with a DNA test result. The standard lower limit of detection (LLOD) for this assay is 4.09 DNA copies/million peripheral blood mononuclear cells (PMBCs).

[f]For HIV RNA, results are shown as either quantitative (copies/mL) or qualitative (NR: nonreactive) depending on the assay used for testing. Viral load results include results from a single copy HIV RNA assay (SCA).

[g]Plasma CAB concentrations are shown as μg/mL. Dried blood spot concentrations of TFV-DP are shown as fmol/punch. The plasma CAB levels were ≥8× the *in vitro* protein-adjusted 90% CAB inhibitory concentration (PA-IC_{90}) for all but one case in the CAB arm at the first visit with a DNA test result. The CAB concentration for 083 Case BR1 at the first visit with a DNA test result was 4–8× PA-IC_{90}.

ARV, antiretroviral; BLQ, below limit of quantification; c, copies; mL, milliliter; NR, nonreactive; PBMC, peripheral mononuclear cells; pos, positive; SCA, single-copy RNA assay.

copies/10^6 PBMCs for the 14 TDF/FTC cases with DNA results.

One or more DNA test result detected <LLOD was also observed for 16 (14.3%) of the 112 persons without HIV who had at least one test performed (1 participant in HPTN 083, 15 participants in HPTN 084; 1–6 tests/person; Supplementary Table S1); the false positive rate for the DNA test in this participant group was 8.3% (18/216 tests positive). The proportion of participants who had one or more false positive DNA test result was higher in HPTN 084 [2.4% (1/41) for HPTN 083; 21.1% (15/71) for HPTN 084; $p = .005$].

A higher portion of false positive DNA test results was obtained for samples from HPTN 084 compared to HPTN 083 [1.3% (1/75 tests positive) for HPTN 083; 12.1% tests (17/141 tests positive) for HPTN 084; $p = .008$]. Among persons without HIV, there was no difference in the proportion of DNA test results detected <LLOD by study arm (CAB: 11/119 = 9.2%; TDF/FTC: 7/97 = 7.2%; $p = .59$, Supplementary Table S1).

Discussion

This study compared HIV DNA levels in PMBCs in persons randomized to receive CAB-LA or TDF/FTC PrEP in the HPTN 083 and 084 trials. In these trials, HIV DNA testing was performed for a subset or participants to help determine HIV status for clinical management. This cohort included 21 PWH (seven in the CAB arm and 14 in the TDF/FTC arm). Pharmacologic analysis revealed that 13 of the 14 participants in the TDF/FTC group had poor or inconsistent adherence to the daily oral regimen and the remaining participant had only partial adherence to the oral PrEP regimen. Therefore, DNA levels in this group cannot be considered to reflect the levels that would be observed in persons with consistent, daily TDF/FTC dosing.

In these two trials, collection of the PBMC samples used for HIV DNA testing occurred at various times after the first HIV-positive visit. This was mostly because detection of HIV infection was delayed at the study sites. These delays occurred in all seven CAB cases and 2/14 TDF/FTC cases. These delays could potentially bias the results to higher DNA levels in CAB cases since those infections would have been of longer duration when the PBMC samples were collected. In contrast, a higher proportion of participants in the CAB group had low or undetectable DNA levels (57.1% vs. 21.4% in the TDF/FTC group, $p = .16$). In addition, some participants in the CAB group had sustained low DNA levels for 8 months or longer. Taken together, these findings suggest that DNA levels may tend to be lower in persons receiving CAB-LA PrEP compared with those randomized to receive TDF/FTC PrEP.

In this study, total HIV DNA levels were measured using a single-plex assay. This assay does not distinguish intact and defective proviruses and therefore cannot provide estimates of reservoir seeding; the total HIV DNA result obtained with this assay provides the near maximal estimate of infected cells.[13] More than half of the participants with HIV in the CAB-LA arm of the studies who had DNA testing performed had HIV DNA levels below and near the LLOD of the assay. This suggests that long-acting formulations of integrase strand transfer inhibitors can profoundly suppress cell-associated infection in a subset of individuals.[14] This would be consistent with our findings from prior studies that show prolonged/profound suppression of viral load in persons who acquire HIV infection in the setting of CAB-LA PrEP.[8]

The HIV DNA assay used in this analysis is more sensitive than commercially available HIV DNA assays; less sensitive assays may fail to detect DNA in this setting. We recently compared the performance of different nucleic acid assays for detecting HIV in low viral load "challenge" samples from HPTN 083.[10] That study included evaluation of the Xpert HIV-1 Qual XC test, which detects HIV RNA and DNA in DBS samples. That assay detected HIV in only 1/10 DBS samples with viral loads <200 copies/mL, which was lower than the rate of detection of HIV RNA in plasma samples using qualitative and quantitative HIV RNA assays. We also found that false positive HIV DNA results were obtained in some cases, which could complicate clinical management. Taken together, these findings suggest that HIV DNA testing may have limitations for HIV diagnosis in the setting of CAB-LA PrEP.

One limitation of this study is the small sample size; only 133 participants (21 HIV positive and 112 HIV negative) had HIV DNA testing performed in the two trials. Furthermore, the criteria that the centralized committee used to recommend DNA testing in each case may have impacted which participant had DNA testing performed and how many samples from each case were tested. The variable number of tests performed in each case (median: 1 test/person; range: 1–6 tests/person) may have confounded some of the analyses. Despite these limitations, we feel that the data in this report helps inform our understanding of HIV infections in the setting of CAB-LA PrEP. It would be helpful to obtain a larger, unbiased, systematically collected set of HIV DNA data in this setting. However, the very low frequency of infections in persons using CAB-LA PrEP and the challenges detecting infections and determining the timing of HIV infection in this setting may complicate collection of those data, even in a clinical trial setting. The AIDS Clinical Trials Group A5321 study will provide more information on HIV reservoirs in adults, who acquired HIV infection while receiving CAB-LA PrEP. This study, and other studies using long-acting biologics such as broadly neutralizing antibodies for HIV prevention, may inform HIV reservoir formation and the potential for ART-free remission and HIV cure.

Acknowledgments

The authors thank the HPTN 083 and HPTN 084 study teams (Supplementary Data S1) and participants; the HPTN 083 and HPTN 084 site Principal Investigators; the laboratory staff at the study sites and the HPTN Laboratory Center; and the members of the HPTN 083 and HPTN 084 Endpoint Adjudication Committees and centralized committees that provided guidance to sites on HIV testing (Drs. William Meyer, Jeanne Marrazzo, Adrian Puren, Nittaya Phanuphak, Carole Wallis, Aida Asmelash, Eric Daar, Francesca Conradie, Halima Dawood, and Michelle Moorhouse).

Authors' Contributions

All authors participated in the study, contributed to article preparation, and reviewed the article. Additional roles are shown below. J.M.F.: Analyzed data and drafted the article. D.P.: Responsible for HIV DNA testing. E.P.-M.: HPTN LC Coordinator for HPTN 084. P.R.: HPTN LC Coordinator for HPTN 083. J.S.: Performed HIV DNA testing. M.A.M.:

Responsible for pharmacology testing. Z.W.: Data analyst for HPTN 083. X.G.: Data analyst for HPTN 084. M.M.: Project Manager for HPTN 083. J.F.: Project Manager for HPTN 084. H.V.T.: Site PI for HPTN 083. C.U.: Site PI for HPTN 083. C.-A.M.: Site PI for HPTN 084. J.M.: Site PI for HPTN 084. A.R.R.: Provided pharmaceutical support. J.F.R.: Provided pharmaceutical support. M.S.C.: HPTN Leadership and Operations Center PI. B.H.: Protocol statistician for HPTN 084. B.G.: HPTN 083 Protocol Co-Chair. M.C.H.: HPTN 084 Protocol Co-Chair. S.D.-M.: HPTN 084 Protocol Chair. R.J.L.: HPTN 083 Protocol Chair. S.H.E.: Protocol Virologist for HPTN 083 and HPTN 084; designed the study, analyzed data, and drafted the article.

Author Disclosure Statement

None of the authors has a commercial or other association that might pose a conflict of interest, with the following exceptions: R.J.L. has served on scientific advisory boards for Merck, on a data safety monitoring board for RedQueen Therapeutics and as a consultant to Merck, ViiV Healthcare, and Gilead Sciences. A.R.R. is an employee of ViiV Healthcare. J.F.R. is an employee and stockholder of Gilead Sciences.

Funding Information

This work was supported by the National Institute of Allergy and Infectious Diseases, Office of the Director, National Institutes of Health, the National Institute of Mental Health, the National Institute on Drug Abuse, and the Eunice Kennedy Shriver Institute for Child Health and Human Development, under award numbers UM1AI068619 (HIV Prevention Trials Network [HPTN] Leadership and Operations Center), UM1AI 068617 (HPTN Statistical and Data Management Center), and UM1AI068613 (HPTN Laboratory Center). ViiV Healthcare and Gilead Sciences donated trial medications and matching placebos, and ViiV Healthcare provided additional funding.

Supplementary Material

Supplementary Data S1
Supplementary Table S1

References

1. Landovitz RJ, Donnell D, Clement ME, et al. HPTN 083 Study Team. Cabotegravir for HIV prevention in cisgender men and transgender women. N Engl J Med 2021;385(7): 595–608; doi: 10.1056/NEJMoa2101016
2. Delany-Moretlwe S, Hughes JP, Bock P, et al. HPTN 084 study group. Cabotegravir for the prevention of HIV-1 in women: Results from HPTN 084, a phase 3, randomised clinical trial. Lancet 2022;399(10337):1779–1789; doi: 10 .1016/S0140-6736(22)00538-4
3. Landovitz RJ, Hanscom BS, Clement ME, et al. Efficacy and safety of long-acting cabotegravir compared with daily oral tenofovir disoproxil fumarate plus emtricitabine to prevent HIV infection in cisgender men and transgender women who have sex with men 1 year after study unblinding: A secondary analysis of the phase 2b and 3 HPTN 083 randomised controlled trial. Lancet HIV 2023;10(12):e767–e778; doi: 10.1016/ S2352-3018(23)00261-8
4. Delany-Moretlwe S, Hughes JP, Bock P, et al. Long acting injectable cabotegravir: Updated efficacy and safety results from HPTN 084. AIDS 2022 Montreal, Canada Abstract #OA LBX0108.
5. Marzinke MA, Grinsztejn B, Fogel JM, et al. Characterization of Human Immunodeficiency Virus (HIV) infection in cisgender men and transgender women who have sex with men receiving injectable cabotegravir for HIV prevention: HPTN 083. J Infect Dis 2021;224(9):1581–1592; doi: 10.1093/infdis/jiab152
6. Eshleman SH, Fogel JM, Piwowar-Manning E, et al. Characterization of Human Immunodeficiency Virus (HIV) infections in women who received injectable cabotegravir or tenofovir disoproxil fumarate/emtricitabine for HIV prevention: HPTN 084. J Infect Dis 2022;225(10):1741–1749; doi: 10.1093/infdis/jiab576
7. Marzinke MA, Fogel JM, Wang Z, et al. Extended analysis of HIV infection in cisgender men and transgender women who have sex with men receiving injectable cabotegravir for HIV prevention: HPTN 083. Antimicrob Agents Chemother 2023;67(4):e0005323; doi: 10.1128/aac.00053-23
8. Landovitz RJ, Delany-Moretlwe S, Fogel JM, et al. HPTN 083 and 084 Study Teams. Features of HIV infection in the context of long-acting cabotegravir preexposure prophylaxis. N Engl J Med 2024; doi: 10.1056/NEJMc2402088
9. Eshleman SH, Fogel JM, Halvas EK, et al. HPTN 083 Study Team. HIV RNA screening reduces integrase strand transfer inhibitor resistance risk in persons receiving long-acting cabotegravir for HIV prevention. J Infect Dis 2022;226(12): 2170–2180; doi: 10.1093/infdis/jiac415
10. Fogel JM, Piwowar-Manning E, Moser A, et al. HPTN 083 Study Team. Evaluation of Xpert point-of-care assays for detection of HIV infection in persons using long-acting cabotegravir for pre-exposure prophylaxis. Microbiol Spectr 2024;12(8):e0030724; doi: 10.1128/spectrum.00307-24
11. Powell L, Dhummakupt A, Siems L, et al. Clinical validation of a quantitative HIV-1 DNA droplet digital PCR assay: Applications for detecting occult HIV-1 infection and monitoring cell-associated HIV-1 dynamics across different subtypes in HIV-1 prevention and cure trials. J Clin Virol 2021;139:104822; doi: 10.1016/j.jcv.2021.104822
12. Tosiano MA, Jacobs JL, Shutt KA, et al. A simpler and more sensitive single-copy HIV-1 RNA assay for quantification of persistent HIV-1 viremia in individuals on suppressive antiretroviral therapy. J Clin Microbiol 2019;57(3): e01714–e01718; doi: 10.1128/JCM.01714-18
13. Bruner KM, Hosmane NN, Siliciano RF. Towards an HIV-1 cure: Measuring the latent reservoir. Trends Microbiol 2015;23(4):192–203; doi: 10.1016/j.tim.2015.01.013
14. Deeks SG, Archin N, Cannon P, et al. International AIDS Society (IAS) Global Scientific Strategy working group. Research priorities for an HIV cure: International AIDS Society Global Scientific Strategy 2021. Nat Med 2021;27(12):2085–2098; doi: 10.1038/s41591-021-01590-5

Address correspondence to:
Susan H. Eshleman
Department of Pathology
Johns Hopkins University School of Medicine
Ross Building, Room 646
720 Rutland Ave.
Baltimore, MD 21205
USA

E-mail: seshlem@jhmi.edu