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Dolutegravir/Abacavir/Lamivudine in Acute HIV-1 Results in Rapid Suppression and Restoration of CD4 T-cell Subsets Without Accelerated Decay of Latent HIV-1

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Background. We evaluated rapid start of integrase-based antiretroviral therapy (ART) during acute HIV-1.

Methods. Adult participants initiated co-formulated dolutegravir/abacavir/lamivudine within 30 days of acute HIV-1 diagnosis. HLA-B*57-positive participants were excluded by rapid, flow cytometry screening. We evaluated HIV-1 RNA levels, CD4+ T-cell subsets, and change in replication competent HIV-1.

Results. Forty adults screened with 3 excluded due to positive HLA-B*57:01 or hepatitis B surface antigen results. All 37 participants starting study treatment suppressed to <200 copies/mL by week 24 (median of 4 weeks, interquartile range 3.4–5.1); 86% and 95% were <50 copies/mL at weeks 48 and 96, respectively. We observed a median 2.4-fold decline in frequency of resting CD4+ T-cell infection in a subset of participants providing 96 week samples. ART in acute HIV-1 resulted in CD4+ T-cell memory subpopulations similar to people without HIV-1 and preserved CD4+ and CD8+ T-cell frequencies compared to people starting ART in chronic HIV. Thirty-four participants required rapid HLA-B*57 testing at screening; 97% resulted ≤24 hours, and 71% started ART ≤24 hours.

Conclusions. Integrase-based ART during acute HIV-1 resulted in brisk viral suppression, preservation of CD4+ T-cell subsets, and decline in resting CD4+ T-cell infection.

Keywords. Abacavir; acute HIV-1 infection; CD4 t cell subsets; integrase-based ART; rapid ART.

BACKGROUND

Rapid initiation of antiretroviral therapy (ART) improves rates of HIV-1 viral suppression and retention in care [1–3]. Rapid ART during acute HIV-1 infection carries additional potential clinical benefits of preserving immune function [4–6], limiting viral diversification [7, 8], decreasing immune activation [9–11], normalizing the $CD4^+/CD8^+$ ratio [6], and limiting the size of the latent HIV-1 reservoir [12–16]. Accordingly, more rapid viral suppression with integrase strand transfer inhibitor (INSTI)-based ART in acute HIV-1 might further limit the size of the latent reservoir.

INSTI-based ART leads to rapid suppression in chronic HIV-1 infection (CHI) [17]. Early initiation of INSTI-based ART also minimizes transmitted integrase resistance [18–20] and is associated with fewer metabolic toxicities [21]. The primary objective of this trial (PHI05) was to evaluate efficacy of fixed-dose combination (FDC) dolutegravir/abacavir/lamivudine (DTG/ABC/3TC) in acute HIV-1, which was first-line ART per guidelines during enrollment [22]. We compared time to suppression in the PHI05 study to 2 prior acute HIV-1 treatment studies, 1 using non-nucleoside reverse transcriptase inhibitor (NNRTI)-based ART (PHI02) and another using INSTI-based ART (PHI04). Prompt administration of abacavir-containing regimens was limited by the need to screen for HLA-B*57:01, associated with increased risk of abacavir hypersensitivity reactions [23]. To facilitate rapid ART start containing abacavir, we used an initial, rapid 2-digit flow cytometry-based screen for HLA-B*57.

Durable HIV-1 suppression of more than 2 years has been associated with restoration of T-cell functions including cellular activation [24]. We hypothesized that more rapid HIV-1

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suppression in acute HIV-1 with INSTI-based ART would limit HIV-associated immune dysregulation. We compared T-cell subtypes among acutely treated PHI05 participants to individuals treated in CHI- and HIV-seronegative individuals. Given reported weight increase among people with HIV-1 (PWH) on INSTI-based therapy [25–27], we retrospectively evaluated participant weight over 96 weeks after starting DTG/ABC/3TC in acute HIV-1.

METHODS

The PHI05 study was a single-arm, open-label trial initiating FDC dolutegravir 50 mg/abacavir 600 mg/lamivudine 300 mg (DTG/ABC/3TC; Triumeq) from September 2015 through September 2019 at The University of North Carolina at Chapel Hill, Chapel Hill, NC (UNC) and Duke University, Durham, NC (NCT02384395). Individuals ≥18 years of age diagnosed with acute HIV-1 within the previous 30 days were eligible, defined as date of first positive standard HIV-1 antibody, rapid HIV-1 antibody, or qualitative or quantitative HIV-1 RNA assay. Participants screened for hepatitis B surface antigen (HBsAg), HLA-B*57 and/or HLA-B*57:01, and had an HIV genotype. Exclusion criteria included pregnancy/breastfeeding, coronary artery disease, moderate to severe hepatic impairment, and active hepatitis B or C infection. Participants were evaluated at weeks 0, 2, 4, 8, 12, 16, 24, 36, 48, 60, 72, 84, and 96.

Patient Consent Statement

All participants provided written informed consent per local institutional review board requirements.

The primary endpoint was efficacy of DTG/ABC/3TC, defined as HIV-1 RNA <200 copies/mL (c/mL) at week 24. Secondary endpoints included efficacy of HIV-1 RNA <50 c/mL at week 48 and time to viral suppression. Efficacy estimates were calculated using the last viral load carried forward to a given visit. Statistics for the efficacy analysis are primarily descriptive, providing longitudinal presentation and 95% confidence intervals (CI) for participants with HIV-1 RNA <200 c/mL at week 24 and <50 c/mL at weeks 48 and 96. Virologic failure was defined as inability to achieve HIV-1 RNA ≤200 c/mL by week 24, or 2 or more consecutive HIV-1 RNA levels >200 c/mL at least 1 week apart from week 24 through 96.

Time to viral suppression <200 or <50 c/mL was assessed both unadjusted and adjusted for median baseline HIV-1 RNA level and $CD4^+$ T-cell count. We compared time to suppression and efficacy at weeks 24, 48, and 96 with 2 prior acute cohort treatment studies, PHI02 [28] and PHI04 [29], conducted at UNC and Duke (described later), using Kaplan–Meier curves and log-rank *P* values, corrected for multiple pairwise comparisons. Participants were censored at their last study visit if lost to follow-up before demonstrating viral suppression before week 24 or if they discontinued treatment.

HLA-B*57:01 expression was determined using a 2-step algorithm with a flow cytometric assay as an initial rule-out test, with positive results reflexed to a genotyping assay (see Supplementary Material). One site employed rapid HLA-B*57 screening, and participants enrolled but were instructed not to start a 7-day ART supply until notification of negative HLA-B*57 (or HLA-B*57:01) and HBsAg results. Participants testing positive for either were discontinued from study. At the second site, participants did not undergo rapid HLA-B*57 screening, instead DTG/ABC/3TC was started at a subsequent study visit after confirming negative HLA-B*57:01 and HBsAg results. HBsAg testing was performed on the automated Abbott Architect system using a chemiluminescent microparticle immunoassay, with results expected within 8 hours. Feasibility of rapid HLA-B*57 screening was assessed by calculating time (days) from sample collection to treatment start.

Acute HIV-1 Treatment Cohorts

Efficacy, time to viral suppression and weight outcomes in PHI05 were compared to 2 previous cohorts of participants starting ART during acute HIV-1. All 3 acute treatment studies were conducted at UNC and Duke University with a harmonized primary endpoint of HIV-1 RNA-1 < 200 c/mL at week 24 after ART initiation. The PHI02 study (n = 90) was a single-arm, open-label, 96-week study of FDC efavirenz/emtricitabine/tenofovir disphosphate (EFV/FTC/TDF) in acute HIV-1 between January 2005 and 2011 (NCT00924898) [28]. The PHI04 study (n = 31) was a single-arm, open-label, 96-week study of FDC elvitegravir/cobicistat/FTC/TDF (EVG/COBI/FTC/TDF) in acute HIV-1 between September 2012 and April 2015 (NCT01694420) [29]. The same acute HIV-1 definition was used across all 3 studies, defined as: (1) negative/indeterminant HIV-1 antibody, antigen, or HIV-1 RNA test within 30 days of study entry, plus 1 of the following: detectable HIV-1 RNA, positive p24 antigen, positive HIV-1 antibody test; (2) positive fourth-generation HIV-1 Ag/Ab combination assay with a negative HIV-1 rapid test or negative/indeterminate Western Blot and a detectable HIV-1 RNA test within 30 days of entry; or (3) positive HIV-1 antibody test within 30 days after an initial negative/indeterminate HIV-1 antibody, antigen, or HIV-1 RNA test.

Seronegative and Chronic HIV-1 Cohorts

Samples from 10 healthy donors without HIV (HD) all ≥18 years of age, were collected in 2018 and 2019 on institutional review board–approved research conducted by the UNC Center for AIDS Research whereby participants provided written informed consent for use of biological samples for other research. Samples were also obtained from 10 participants treated during CHI and enrolled in research studies at the UNC HIV

Cure Center and the Women's Interagency HIV-1 Study (NCT00000797) who provided written informed consent for use of biological samples for other research. Characteristics for participants with CHI included ≥18 years of age, stable ART, HIV-1 RNA <50 c/mL for ≥24 months, and self-reported not missing more than 2 consecutive days or >4 cumulative days of ART in the prior 24 weeks. Plasma suppression was documented by a minimum of three tests below the detection limit of the assay within 24 months before sample collection date. Participants with CHI had a median age of 51 years (range 27–61), were primarily male (80%), 60% White, 40% Black, all non-Hispanic, with ART duration for a median of 6.1 years (range 1.1–31.1), including 5 (50%) on (INSTI)-based and 5 (50%) on NNRTI-based ART at sample collection.

Mass Cytometry Staining

The mass cytometry panel included 31 markers largely focusing on T-cell markers (Supplementary Table 1). Optimization and standardization of the mass cytometry panel was detailed previously [30]. Briefly, peripheral blood mononuclear cells (PBMCs) from participants with acute HIV-1 (week 120), CHI (1.1–31.1 years post-ART) and people without HIV (10 per group) were thawed and rested overnight at 37°C. Cell-ID Cisplatin 195 (Fluidigm Cat# 201195) was added to samples and staining quenched with Maxpar Cell Staining Buffer (CSB) (Fluidigm Cat# 201068) and then incubated with Fc block (Biolegend Cat# 422301). Surface antibodies were added to sample and washed after 30 minutes. FoxP3 Fixation/Permeabilization (Thermofisher Cat# 00-5523-00) was used according to manufacturer's instructions. Intracellular antibodies were added to samples. Samples were washed and then incubated in 1 mL 2% paraformaldehyde for 10 minutes at room temperature. Cell intercalation solution (Fluidigm Cat# 201192A) was added to each sample and left overnight at 4°C. Samples were washed with cell staining buffer, then cell acquisition solution (Fluidigm Cat# 201240) and acquired on the Helios (Fluidigm). A total of 700,000 events were acquired for each sample with an average of 60 000 $CD4^+$ T cells and 68 000 $CD8^+$ T cells analyzed. T-cell populations and frequencies were analyzed 2 ways, using the machine learning algorithm, CITRUS (Version 1.2) and by manual gating (Cytobank v9.1). Settings for the CITRUS algorithm were clusters characterized by abundance (%) of major lymphocyte lineages, 5000 events were sampled per file, minimum cluster size of 5%, and cross-validation fold of 5. Workflow is shown in Figure 1*A*. Statistical differences for cell clusters was determined by Significance Analysis of Microarrays analysis with a false discovery rate of 1% [31]. For manual analyses, cell frequencies were compared between groups using a Kruskal-Wallis with Dunn's multiple comparison test. $P \leq .05$ was considered significant.

Resting $CD4^+$ T-cell Reservoir

Resting $CD4^+$ T cells were purified from PBMCs by negative selection as previously described [32]. PBMCs were isolated from leukapheresis product by Ficoll-gradient purification. A quantitative viral outgrowth assay was performed as previously described to recover replication competent HIV-1 [33]. The frequency of resting cell infection was estimated using a maximum likelihood method and reported as infectious units per million (IUPM) resting $CD4^+$ T cells [33]. Differences in the frequency of resting cell infection between week 48 and 96 after ART initiation was determined using the Wilcoxon matched-pairs signed-rank statistical test. $P < .05$ was considered significant.

Weight Analysis

In post hoc analysis, we evaluated percent change in weight from baseline through week 96 after starting DTG/ABC/3TC in acute HIV-1 and compared to weight change among acutely treated participants on PHI02 (NNRTI-based ART) and PHI04 (integrase-based ART) acute HIV-1 treatment studies. In addition to participants excluded for efficacy analysis, for the weight analysis we also censored participants at study treatment discontinuation or ART switch. If weight was missing at week 0, weight at week 1 or −1 was used as baseline weight (Supplementary Table 2). Weight measurements >2 standard deviations from a participant's mean weight were excluded to avoid measurement error. To explore the effect of different ART regimens on weight, linear mixed models were estimated, where week on study drug was treated as a random effect (slope), both crude and adjusted for a priori selected confounders including baseline age (≥26 vs <26 years), weight (≥79.8 vs <79.8 kg), $CD4^+$ cell count (≥487 vs <487 cells/μL), HIV-1 RNA level (≥463 347 vs <463 347 c/mL), and race/ethnicity (White non-Hispanic vs all other).

RESULTS

Forty participants diagnosed in acute HIV-1 infection enrolled from September 2015 to September 2019 and were followed through week 96. Three participants (8%) discontinued before starting study treatment; 2 (5%) tested HLA-B*57:01-positive and 1 (3%) tested HBsAg-positive, resulting in 37 participants who started DTG/ABC/3TC. Participants were primarily men (97%), Black (65%), non-Hispanic (89%), with a median age 26 years (range 18–52, 44% < 26 years) (Table 1). Most identified as men who have sex with men (86%) of which 63% were Black men who have sex with men. Eight (22%) participants were diagnosed with a sexually transmitted infection within 8 weeks of acute HIV-1 diagnosis including chlamydia (n = 2), gonorrhea (n = 3), and syphilis (n = 3). No participants had baseline drug resistance to DTG/ABC/3TC.

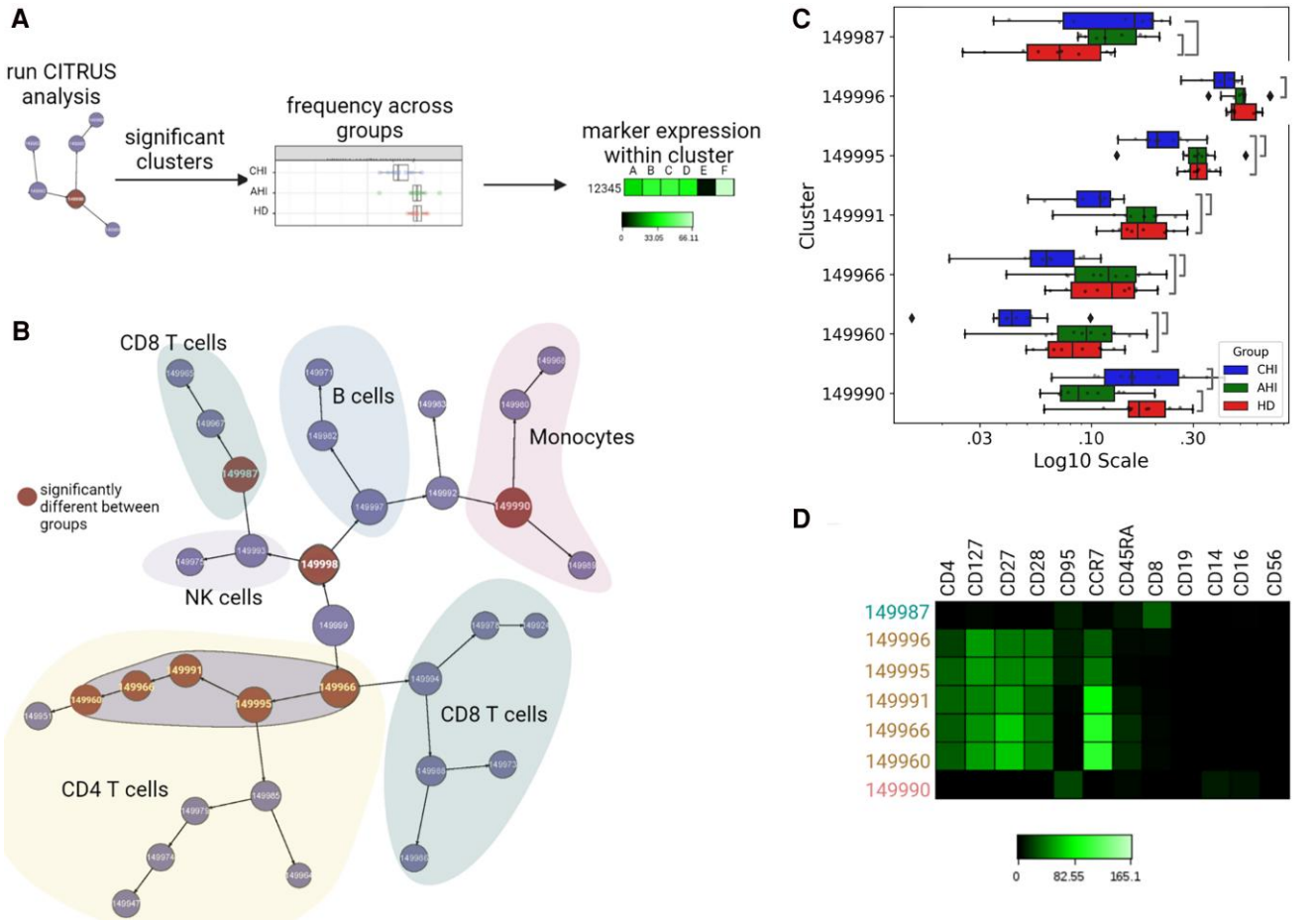

Figure 1. CITRUS analysis of HIV-negative and persons with acute HIV-1 and chronic HIV-1 infection. *A*, CITRUS analysis of cell abundance (% of parent) workflow run on peripheral blood mononuclear cells from people without HIV (HD), people with HIV initiating antiretroviral therapy (ART) in acute (AHI) or chronic (CHI), n = 10/group (*B*) Dendrogram identifying clusters (minimum cluster size 5%) that were significantly different between groups (red) in groups by Significance of Microarrays (SAM, 1% false discovery rate). Major lymphocyte lineages have been annotated and shaded. A megacluster within CD4 T cells is grouped and shaded (purple). Nesting of clusters indicated by arrows. *C*, Frequency across each group clusters of clusters in annotated lineages. Brackets identify significantly different groups (SAM). *D*, Heatmap showing median signal intensity of protein markers in clusters listed in *C*.

Among 40 participants screened, 6 presented with prior HLA-B*57:01 results, resulting in 34 individuals who underwent rapid HLA-B*57 screening. Of these 34 participants, HLA results were available for 82% (n = 28) same day as screening, 97% (n = 33) within 24 hours, and 1 within 48 hours due to holiday closures. Nine (26%) participants tested HLA-B*57 antibody-positive, with 2 (6%) confirmed HLA-B*57:01-positive on reflex genotype testing. Of 9 samples reflexed for confirmatory testing, 26% (n = 2) resulted the same day as screening and 67% (n = 6) resulted within 24 hours; results were delayed for 72 hours for 1 hospitalized participant.

Of 37 eligible participants, 10 (27%) started ART the day of screening, 24 (65%) within 24 hours of screening, and 29 (78%) within 48 hours. Delays in ART start >48 hours were due to pending HLA reflex testing, HBsAg results (n = 4), or personal reasons (n = 3) (ie, pending repeat HIV test results). One additional participant started ART >96 hours after screening because of elevated liver enzymes per eligibility but started provider-initiated ART within 24 hours pending qualifying aspartate aminotransferase/alanine transaminase results.

Overall, 92% (34/37), 89% (33/37), and 81% (30/37) of participants were retained on study through week 24, 48, or 96, respectively. Treatment-related adverse reactions (AEs) were primarily grade 1 (62%) or grade 2 (36%) with 1 grade 3 AE of elevated aspartate aminotransferase, which self-resolved on continued study treatment. Grade 1 AEs were primarily gastrointestinal-related (13/26; 50%). There were no treatment-related serious AEs. One participant with preexisting irritable bowel syndrome reported abdominal cramping, stopped treatment, and withdrew from the study at week 12. Overall, 5 (14%) participants stopped study treatment due to gastrointestinal-related side effects.

Efficacy was similar to that observed in prior acute HIV-1 treatment studies. Of 37 participants starting study treatment,

Table 1. Baseline Characteristics by Acute HIV-1 Infection Treatment Study Cohort

Characteristic	*PHI05* (N = 37)	*PHI04* (N = 32)	*PHI02* (N = 90)
Variable			
Age (y), median (IQR)	26 (23–32)	26 (22.5–39.5)	27.5 (22–38)
Race/ethnicity, n (%)	…	…	…
Black/African American	24 (64.9%)	20 (62.5%)	52 (57.8%)
White/non-Hispanic	9 (24.3%)	10 (31.3%)	36 (40.0%)
White Hispanic	4 (10.8%)	2 (6.3%)	2 (2.2%)
Sexual risk group, n (%)	…	…	…
MSM	32 (86.5%)	23 (74.2%)	70 (77.8%)
Heterosexual male	2 (5.4%)	1 (3.2%)	9 (10.0%)
Unknown male	2 (5.4%)	0 (0.0%)	0 (0.0%)
Female	1 (2.7%)	7 (22.6%)	11 (12.2%)
Weight (kg), median (IQR)	76.7 (69.1–91.4)	84.3 (74.8–92.5)	80.6 (69.5–92.2)
BMI (kg/m^2), median (IQR)	29.2 (20.9–36.8)	27.5 (22.6–34.9)	27.3 (23.5–36.9)
Time from diagnosis to ART start (d), median (IQR)	14 (11–20)	13 (10–21.5)	19 (14–25)
HIV-1 RNA level (c/mL), median (IQR)	382 000 (74 126–1 750 000)	81 717 (16 727–2 095 300)	594 670 (94 000–2 585 000)
CD4$^+$ cell count (cells/μL), median (IQR)	477 (311.5–691)	500 (408–712)	487 (319–651)

Abbreviations: ART, antiretroviral therapy; BMI, body mass index; IQR, interquartile range; MSM, men who have sex with men.

Table 2. Comparison of Efficacy of ART Regimens Started During Acute HIV-1 Infection

	Unadjusted			Adjusted		
Comparison	HR	(95% CI)	*P*	HR	(95% CI)	*P*
PHI05 versus	ref	-	-	ref	-	-
PHI04	…	…		…	…	…
<200 c/mL	0.95	(0.59–1.5)	.84	1.1	(0.66–1.9)	.67
<50 c/mL	0.85	(0.53–1.4)	.51	1.1	(0.68–1.9)	.61
PHI02	…	…		…	…	…
<200 c/mL	3.1	(2.0–4.7)	<.01	3.2	(2.1–4.9)	<.01
<50 c/mL	2.1	(1.4–3.1)	<.01	2.6	(1.8–4.0)	<.01

Unadjusted and adjusted hazard ratios comparing time to <50 or <200 c/mL across acute HIV treatment cohorts. Estimates were adjusted for median baseline HIV RNA level (≤463 347 vs >463 347 c/mL) and median baseline CD4$^+$ cell count (≤487 vs >487 cells/μL).

Abbreviations: CI, confidence interval; c/m, copies/mL; HR, hazard ratio.

97% (n = 36; 95% CI, 86–100) suppressed to <200 c/mL at or before week 24, and 86% (n = 32; 95% CI, 71–95) and 95% (n = 35; 95% CI, 81–99) were suppressed <50 c/mL at week 48 and 96, respectively. Only 1 participant (3%) met criteria for virologic failure as lost to follow-up after week 8 when HIV-1 RNA was >200 c/mL. Similarly, in the PHI02 study of EFV/FTC/TDF, 95% and 91% of participants suppressed by week 24 and week 48, respectively [28], and in the PHI04 study of EVG/COBI/FTC/TDF, 97% suppressed by week 24 and at week 48 (Table 2) [29].

In this PHI05 study, participants achieved suppression <200 c/mL at a median of 4.0 weeks (interquartile range [IQR]: 3.4–5.1) and <50 c/mL at a median 7.8 weeks (IQR: 3.9–11.7). Time to suppressions was similar with alternative INSTI-based ART (EVG/COBI/FTC/TDF) among PHI04 participants with median time to <200 c/mL at 3.7 weeks (IQR: 2.0–5.0) and to <50 c/mL at 7.7 weeks (IQR: 3.9–11.7) (Bonferroni-corrected log-rank *P* value: 1.0) (Figure 2). In contrast, PHI02 participants on NNRTI-based ART (EFV/FTC/TDF) took longer to reach <200 c/mL at a median of 9.2 weeks (IQR: 6.0–14.9) and to reach <50 c/mL at a median of 15.0 weeks (IQR: 9.0–23.6) (corrected $P < .01$ for both thresholds). Overall, PHI02 participants had a longer period (5–6 days longer) from acute HIV-1 diagnosis to ART start compared to the other studies with integrase-based ART; however, baseline median/range CD4$^+$ T-cell count was similar across all three studies; baseline HIV-1 RNA levels were higher in PHI02 participants (see Table 1), with unclear impact on time to suppression.

We performed a comparative analysis of lymphocytes between PWH treated in acute-HIV-1, CHI (CHI) and people without HIV (HD). Data were analyzed by both manual gating of T-cell phenotypes summarized in Table 3 and machine

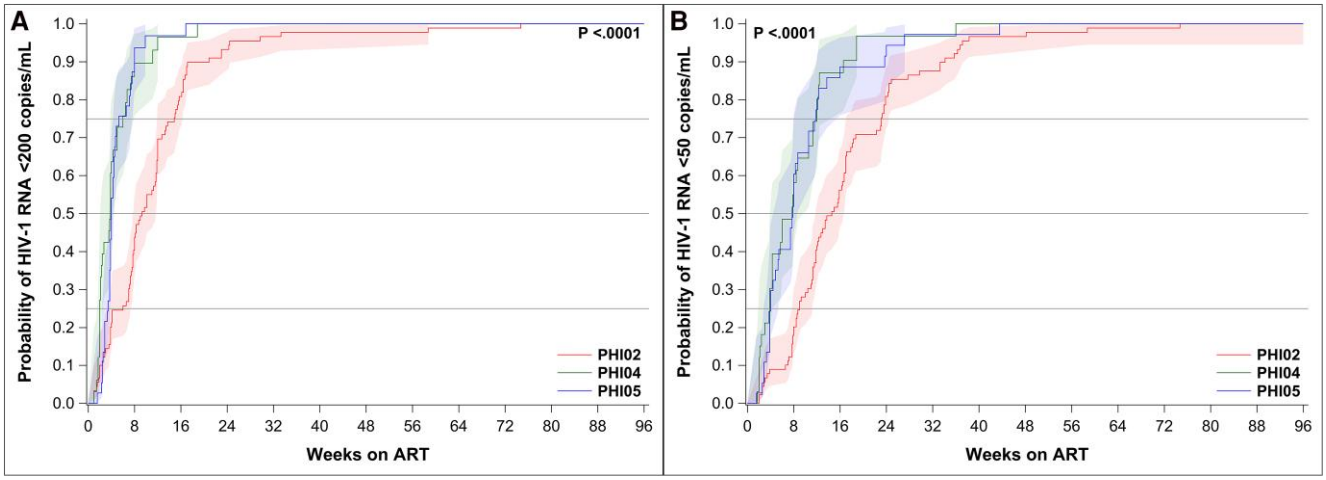

Figure 2. Time to viral suppression following treatment start in acute HIV-1 infection. Time to HIV-1 RNA <200 c/mL (*A*) and <50 c/mL (*B*) by AHI cohort. Log-rank *P* values test the equality of curves across AHI cohort studies.

learning analysis of PBMC lymphocyte lineages using the CITRUS algorithm shown in Figure 1 [31, 34]. Significant differences were detected between groups by both analysis approaches. Consistent with previous reports [35, 36], significantly higher frequencies of total $CD8^+$ T cells were detected in the CHI group relative to HD by manual gating (Table 3). CITRUS clustering identified a subset of $CD8^+$ T cells that was higher in both PWH groups than the HD group (Figure 1*B-D*). This $CD8^+$ cluster expressed low-level CD95 and was negative for CCR7, CD28, and CD27, suggestive of more differentiated effector-like $CD8^+$ T cells (Figure 1*D*). No other differences were detected in $CD8^+$ T-cell subsets between groups by either gating method (Figure 1, Table 3).

More differences were observed between $CD4^+$ T-cell subsets between groups. Manual gating found that terminal effector cells were significantly higher in CHI than HD whereas $CD127^+CD4^+$ T-cell frequencies were significantly lower in acute HIV-1 and trended lower in CHI (Table 3). CD127 is the α chain of the interleukin-7 receptor. In both people with and without HIV, CD127 is expressed by the majority of $CD4^+$ T cells but is most highly expressed on naïve T cells [37]. CITRUS detected multiple nested $CD4^+$ T-cell clusters (Figure 1*B*, red and purple shading) that were significantly lower in the CHI group relative to both the acute HIV-1 and HD groups (Figure 1*C*). These clusters expressed different levels of CD127, the lymph node homing receptor CCR7 and co-receptors CD27 and CD28, and low expression of CD45RA and the death receptor, CD95 (Figure 1*D*). The profiles of these nested clusters are all indicative of subsets of naïve $CD4^+$ T cells. CITRUS also identified a monocyte ($CD14^+$) cluster 149990, that also expressed CD16 and CD95 that was lower in the acute HIV-1 group (Figure 1*B-D*), consistent with a previous study reporting lower frequencies of monocytes in pre-ART acute HIV-1 infection [38].

Manual gating identified one other significant difference, specifically that acute HIV-1 participants harbored higher average frequencies of T-regulatory cells than either HD or CHI groups. While the manually gated data are consistent with a previous study reporting higher frequencies of regulatory $CD4^+$ T cells of pre-ART acute HIV-1 infection [38], we did not detect differences in T regulatory-like $CD4^+$ T cells in CITRUS. Additional studies are needed to confirm this observation.

Using quantitative viral outgrowth assay, we measured frequency of replication competent HIV-1 in resting $CD4^+$ T cells obtained from a subset of 14 participants who initiated DTG/ABC/3TC. Six participants donated samples at only 48 weeks after ART initiation and 8 participants donated samples at both 48 and 96 weeks after ART start, allowing for evaluation of reservoir dynamics with prolonged ART. At 48 weeks after ART, reservoir size ranged from 0.200 to 6 IUPM resting $CD4^+$ T cells (median IUPM 1.187, Supplementary Table 3). With prolonged ART, we observed a median of 2.4 (range 1.2–8.3)-fold decline in frequency of resting $CD4^+$ T-cell infection in participants who provided samples at 96 weeks, consistent with prior observations [39] (Figure 3, Supplementary Table 3).

PHI05 participants experienced a 3.9% increase in weight from baseline through week 96 (95% CI, 1.2–6.7). We evaluated weight from baseline through 96 weeks across the 3 acute treatment cohorts; none showed an increase >10% (Figure 4). Mixed-model estimated percent change in mean weight for participants on PHI05 was 3.8% over 96 weeks (95% CI, 0.67–7.0) in comparison to a 3.5% increase in PHI02 (95% CI, 1.3–5.6) and a 4.1% increase in PHI04 (95% CI, 0.58–7.6) (Supplementary Table 2). Upon adjustment for confounding

Table 3. Frequency of CD4+ and CD8+ T-cell Subsets Applying Manual Gating

		CD4+ T Cells				CD8+ T Cells			
		HD (%)	PWH AHI (%) Week120	PWH CHI (%)	Significance[a]	HD (%)	PWH AHI (%) Week120	PWH CHI (%)	Significance[a]
Total	…	54.2 (31.7–67.7)	49.6 (21.6–72.3)	41.4 (24.8–59.9)	ns	34.4 (21.7–57)	40.4 (21.2–67.9)	48.6 (23–69.1)	$P = .025$ (CHI, HD)
Naïve	CD45RA+CCR7+ CD28 + CD95–	30.5 (15.3–43)	26.6 (16.7–51.1)	27.3 (12.6–49.8)	ns	26.2 (4.4–55.2)	25.9 (12.6–51.4)	15.3 (6.1–34.1)	ns
Stem cell memory	CD45RA+CCR7+ CD28 + CD95+	1.2 (0.5–1.9)	0.97 (0.5–1.3)	5.1 (0.5–32.1)	ns	3.4 (0.9–5.7)	3.2 (1.1–7.6)	5.1 (1–13.3)	ns
Central memory	CD45RA– CCR7+ CD28 + CD95+	37.9 (24.3–51.4)	40.1 (24.4–52)	33.3 (11.1–47.6)	ns	14.7 (5.0–23.4)	12.2 (4.9–26.5)	9.2 (1.2–20.9)	ns
Transitional memory	CD45RA– CCR7– CD28 + CD95–	9.9 (6.9–16.1)	9.3 (5.3–22.2)	15.7 (4–26.9)	ns	10.6 (3.0–17.4)	7.5 (3.7–13.6)	11.1 (1.5–24.5)	ns
Effector memory	CD45RA– CCR7– CD28– CD95–	2.8 (0.3–10.8)	5.3 (0.6–12.2)	3.4 (0.5–8.9)	ns	9.7 (2.7–20.5)	16.6 (5.7–38.0)	11.4 (0.6–33.2)	ns
Terminal effector memory	CD45RA+CCR7– CD28 + CD95–	0.58 (.02–3.5)	1.3 (.03–6.7)	1.97 (.52–7.5)	$P = .008$ (CHI, HD)	19.6 (6.6–41.2)	19.3 (9.9–29.7)	31 (10.7–57.8)	ns
CD127+	…	93.7 (91.7–95.4)	89.1 (76.4–93.2)	90.4 (79.1–94.7)	$P = .014$ (AHI, HD)	69.8 (53.6–83.9)	63.9 (36.9–78.3)	59.6 (44.8–81.9)	ns
CD25+	…	8.2 (3.7–12.7)	10.7 (5.4–15.1)	9.5 (4–15.8)	ns	1.0 (0.3–2.9)	1.2 (0.3–3.9)	0.64 (0.2–1.2)	ns
PD-1+	…	25 (17.3–46)	28.1 (15.9–41.8)	28.3 (14.4–45.6)	ns	29.7 (11.8–44.2)	21.9 (8.8–35.2)	29.9 (15.5–40.5)	ns
Bcl-2+	…	92.1 (84.2–97.4)	92.9 (86.6–96.4)	90.6 (79.1–95.1)	ns	97.3 (95.7–98.3)	96.2 (93.7–98.8)	97.6 (95.4–99.2)	ns
T_{H1}	CXCR3+CCR4– CCR6– CCR10–	17.4 (9.3–27)	12.2 (4.5–16.2)	17.2 (10.4–21.2)	**ns**[b]	ND[g]	ND	ND	ND
T_{H2}	CXCR3– CCR4+ CCR6– CCR10-	7.1 (3.1–10.4)	8.1 (4.4–14.9)	8.6 (4.9–14.2)	ns	ND	ND	ND	ND
$T_{H17.1}$	CXCR3+ CCR4– CCR6- CCR10-	6.7 (3.9–12.6)	4.7 (1–11.6)	5.6 (1.9–10.1)	ns	ND	ND	ND	ND
T_{H17}	CXCR3– CCR4+CCR6 +CCR10–	4.3 (2.1–11.4)	5.5 (3.4–10.1)	5.9 (2.5–14)	ns	ND	ND	ND	ND
T_{H9}	CCR4–CCR6+	10.4 (7.1–19.2)	8.9 (3.4–15.7)	7.7 (2.9–13.1)	ns	ND	ND	ND	ND
T_{H22}	CCR4+CCR6+CCR10+	1.1 (0.4–2.8)	0.93 (0.4–2)	1.6 (0.7–3.4)	ns	ND	ND	ND	ND
T_{reg}	CD25+ CD127–FoxP3+	2.1 (0.8–2.3)	3.4 (2.3–4.9)	1.8 (0.8–3.4)	$P = .003$ (AHI, HD) $P < .001$ (CHI, HD)	ND	ND	ND	ND

Abbreviations: AHI, initiated ART in acute HIV-1 infection; CHI, initiated ART in chronic HIV-1 infection; HD, healthy donors without HIV-1; ND, no data; ns, not significant following Dunn's test ($P > .05$).

[a]Kruskal-Wallis and post hoc Dunn's test. Significantly different groups are indicated in parentheses.

[b]Bolded ns = $P < .05$ in Kruskal-Wallis comparison of median ranks, but $P > .05$ in post hoc Dunn's test.

factors, weight increase at 96 weeks among PHI04 participants exceeded that in PHI05 participants (PHI05 vs PHI04 RD: −1.9%) but was not statistically significant (95% CI, −6.8 to 2.9; $P = .44$). Relative to PHI02 participants, PHI05 participants' weight increase was slightly elevated, but the difference was not statistically significant (PHI05 vs PHI02 RD: 0.48%; 95% CI, −3.3–4.3; $P = .80$). Data not publicly available.

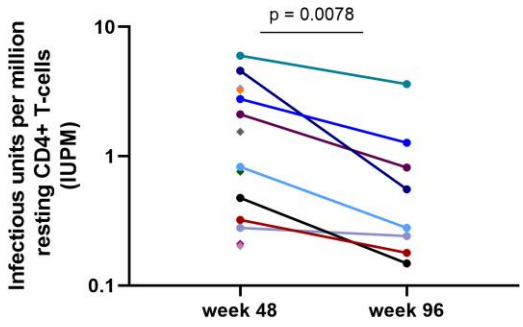

Figure 3. Significant decline of the replication-competent resting $CD4^+$ T-cell reservoir with increased duration on antiretroviral therapy. Each color represents a distinct participant. Diamond symbol indicates participants for whom week 96 samples were not available. $P = .0078$, Wilcoxon matched-pairs signed-rank test.

CONCLUSIONS

INSTI-based ART in our study led to rapid viral suppression within weeks of starting ART during acute HIV-1. Treatment was well-tolerated, effective, and durable over 96 weeks. Efficacy of DTG/ABC/3TC was consistent with a NNRTI-based and another INSTI-based ART regimen, both initiated during acute HIV-1. INSTI-based treatment resulted in more rapid virologic suppression compared to NNRTI-based ART, supporting selection of INSTI-based regimens for rapid ART in acute and chronic HIV-1. We observed a decline in frequency of resting $CD4^+$ T-cell infection in 8 participants at 96 weeks, consistent with prior studies of resting cell infection following treatment in acute HIV-1 [12–16, 40].

Abacavir-containing regimens are no longer recommended as first-line therapy, which limits generalizability of our findings. DTG/ABC/3TC was selected as recommended as initial treatment at the time of study accrual, in addition to data suggesting INSTI-based treatment resulted in rapid viral suppression, and its safety profile with clinically significant renal disease given rapid ART start on the study. Although newer INSTI-based regimens eliminate the need for HLA-B57 testing, we demonstrated feasibility of using a rapid screening HLA-B*57 test to exclude presence of HLA-B*57:01, allowing 82% of participants to start ART the day of screening. Our results support ART regimens for rapid start that also treat hepatitis B infection if hepatitis B test results are not available in

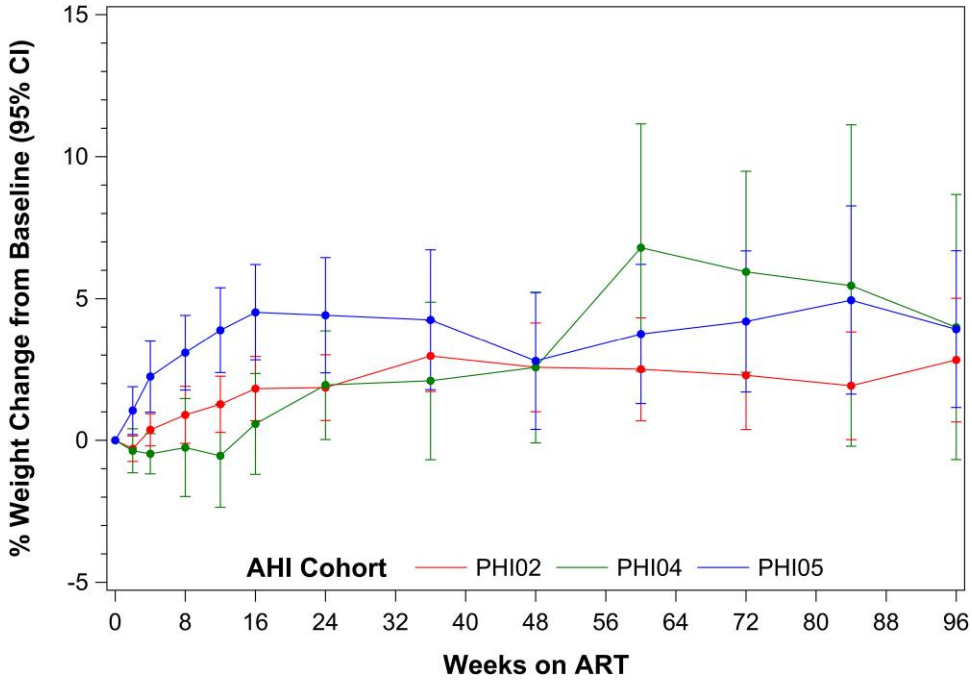

Figure 4. Weight change following integrase-based ART initiation during acute HIV-1 infection. Percent change in mean weight (and 95% confidence intervals) from baseline to 96 weeks in 3 acute HIV-1 treatment studies with different antiretroviral therapy regimens.

both acute and chronic HIV-1, given 1 participant was newly diagnosed with hepatitis B infection at screening.

Relative to individuals without HIV, acutely treated participants exhibited lower frequencies of $CD127^{+}CD4^{+}$ T cells and higher frequencies of T-regulatory cells by manual gating and higher $CD8^{+}$ effector T-cell frequencies identified using machine learning. We lack long-term follow-up of these participants, so we are unable to determine if these T-cell subsets normalized with longer time on ART. Our observations among acutely treated participants contrast with observations in CHI participants who, despite a much longer average time on ART (average, 6.1 years vs 2.3 years), exhibited sustained differences in total $CD8^{+}$ T-cell frequencies and multiple subsets of naïve $CD4^{+}$ T cells. Data in the CHI group are consistent with other studies describing elevated $CD8^{+}$ T cells and dysregulation of $CD4^{+}$ T-cell subsets [41], including our recent longitudinal analysis finding that ART-mediated restoration of multiple $CD4^{+}$ T-cell subsets in CHI is slow, typically occurring over years [37]. While our study is limited by the small group sizes (10/group), altogether our data are consistent with other reports that suggest prompt suppression of HIV-1 replication after acquisition mostly limits immune dysregulation [42, 43], providing additional evidence for the clinical benefit of rapid viral suppression during acute HIV-1.

Our weight analysis, including 2 INSTI-based and 1 NNRTI-based ART regimen started in acute HIV-1, showed no statistically significant differences in weight gain through week 96. Notably, acutely infected individuals can present with recent weight loss resulting from symptoms of acute retroviral syndrome, which could potentially overestimate weight increase in the first weeks of starting ART in acute HIV-1, but this was not observed across 3 acute HIV-1 treatment studies (Figure 4). The strongest data in support of INSTI-associated weight gain derives from 2 randomized controlled trials in ART-naïve PWH [44]: the NAMSAL study randomized 613 participants to DTG/FTC/TDF or EFZ/FTCTDF [45] and the ADVANCE study randomized 1053 PWH to EFV/FTC/TDF, DTG + FTC/TDF, or DTG + FTC/TAF [46]. Both studies showed more weight gain in those randomized to DTG than EFZ, with DTG + FTC/TAF independently associated with at least 10% weight increase. The lack of a similar weight increase among acutely versus ART-naïve chronically infected individuals starting INSTI-based ART is intriguing and may be partially explained by the predominance of men in our acute HIV-1 treatment studies, given weight gain with INSTI-based ART in CHI-1 has been more commonly observed in women [44] and by the lack of TAF within the regimen, also associated with weight gain [44]. The small sample size of our acute cohorts and the use of 2 different INSTI-based regimens limit interpretation of our weight analysis; however, findings add to data on weight gain with INSTI-based ART.

In summary, integrase-based ART initiated during acute HIV-1 in our study resulted in brisk viral suppression, preservation of $CD4^{+}$ T-cell subsets, and decline in resting $CD4^{+}$ T-cell infection. Our results provide additional evidence for the clinical benefit of ART during acute HIV-1 and support wider implementation of programs facilitating rapid ART for individuals with acute HIV-1.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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