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Fixed dose combination emtricitabine/tenofovir/efavirenz initiated during Acute HIV Infection; 96-week efficacy and durability

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Abstract

Objective—Demonstrate rapid initiation of co-formulated treatment during acute HIV infection (AHI) is feasible and efficacious.

Design—Prospective, single-arm open label study of once daily emtricitabine/tenofovir/efavirenz initiated during AHI.

Methods—We provide final data through week 96-week of emtricitabine/tenofovir/efavirenz initiated during AHI. The primary endpoint was the proportion of responders with HIV RNA <200 copies/mL by week 24. We examined time-to-viral-suppression, retention and CD8 cell activation through week 96 in relation to baseline characteristics.

Results—Between January 2005 and December 2011, 92 AHI participants enrolled. Most participants (78%) were MSM, and 42% were young MSM (18–25 years of age). Two participants withdrew leaving 90 patients for analysis. Eighty-one (90%) remained on therapy and achieved viral suppression to <200 copies/mL by week 24, and 71 (79%) to <50 copies/mL at week 48. The median time from ART initiation to suppression <200 copies/mL was 65 days (range 7–523) and to <50 copies/mL was 105 days (range 14–523). The frequency of CD8 activation declined from a median of 67% to 16% through week 96. Retention on study was maintained in 92% of participants at week 48 and in 83% through week 96. Among 75 participants retained through

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week 96, 92% were suppressed to <50 copies/mL. Among 39 young MSM, 79% completed a week 96 visit and 67% were suppressed at week 96.

Conclusions—ART during AHI resulted in rapid and sustained viral suppression with high rates of retention in care and on ART in this cohort including a large proportion of young MSM.

Keywords

Acute HIV infection; NNRTIs; antiretroviral therapy; viral dynamics; young men who have sex with men; immune activation

Introduction

In 2013, HIV treatment guidelines were revised to recommend initiation of antiretroviral therapy (ART) during acute HIV infection (AHI) [1], including immediate treatment initiation modified, if indicated, by a HIV drug resistance genotype [2]. The shift toward treatment during early infection and AHI drew from accumulating data on the potential benefits of early ART including preservation of immune function [3, 4], decreased HIV RNA set point [5–7], reduced size of the latent HIV pool [8–11], and limited viral diversity due to the suppression of viral mutations [12, 13]. Reducing the risk of onward transmission of HIV to sex partners is a likely additional benefit of early ART based on evidence of the preventive efficacy of treatment in serodiscordant couples [14] and the strong association between transmission risk and HIV RNA levels in plasma and genital secretions, typically very high during the acute period [15, 16]. Finally, recent studies have demonstrated a clinical benefit of earlier versus delayed initiation of ART [17]. Accordingly, guidelines have shifted toward recommending ART for all patients, including those with AHI.

Despite the evolution in guidelines on when to start ART, data on what specific ART drugs should be initiated during AHI remain limited. Updated guidelines continue to recommend a protease inhibitor (PI)-based regimen if treatment is started prior to ARV drug resistance testing, based on low rates of transmitted resistance to PIs and a higher barrier to PI resistance. However, PI-based therapy requires multiple pills with adherence implications, the potential for decreased tolerability and drug-drug interactions.

We previously reported interim results from a study showing that co-formulated, once-daily emtricitabine/tenofovir/efavirenz (FTC/TDF/EFV) initiated during AHI achieved rapid and sustained HIV suppression despite initial high viremia [18]. In our interim results with 61 AHI participants, 92% were suppressed to <200 copies/mL by week 24, and 85% with the potential to reach week 48 remained suppressed. We demonstrated that immediate initiation of ART prior to baseline HIV genotype results did not prevent viral suppression in the small number of participants with baseline mutations conferring resistance to the study regimen, following the assessment of ART resistance by an HIV genotype to guide changes to the regimen. Finally, we observed a trend toward a shorter time to viral suppression among participants treated during AHI in comparison with a historical cohort of patients who started similar ART with established infection, despite higher pre-ART viral loads among the acutely infected participants [18].

We now provide additional data on responses to a co-formulated single tablet, once-daily, NNRTI-based ART regimen initiated in 92 individuals with AHI through 96 weeks of follow-up. As in the prior report, our primary goal was to demonstrate that rapid linkage of acutely-infected individuals to simple, effective ART would facilitate prompt and sustained HIV-1 suppression. Although fixed-dose combination FDC FTC/TDF/EFV is no longer a recommended first line regimen in the United States [2], our findings inform decisions on the provision of ART for acutely infected individuals related to pill burden, postponement of treatment for results of resistance testing, the risk of virologic failure and de novo resistance, as well as adherence and retention, particularly among young men who have sex with men (MSM), a group that comprises a majority of acutely infected individuals in the Southeastern United States [19, 20].

Methods

The study population included individuals ≥18 years of age referred from the North Carolina (NC) Screening and Tracing Active Transmission (STAT) Program, a statewide screening program for AHI in publicly funded testing sites [21]. Additional cases are identified through HIV testing performed at primary care testing sites and referred and/or reported to the NC Department of Health and Human Services (DHHS). Following identification of suspected or confirmed acute HIV cases through rapid notification from the STAT program to the NC DHHS or from primary care sites, specially trained NC DHHS Disease Intervention Specialists (DIS) ensure notification and make referrals to HIV care within 72 hours. All acutely infected individuals referred to UNC and Duke and meeting eligibility criteria were offered the opportunity to enroll on the study.

This study was a dual-center, single-arm open-label study of the safety and efficacy of once daily, FTC/TDF/EFZ administered to participants with AHI as previously described [18]. Prior to October 25, 2006, participants received study treatment as a two-tablet regimen of fixed dose combination FDC FTC/TDF (Truvada) and Efavirenz (Sustiva) both taken once daily, while those enrolled afterwards were administered FDC FTC/TDF/EFZ (Atripla). AHI was defined as a negative or indeterminate enzyme immunoassay (EIA) or a negative HIV RNA test within 30 days of enrollment plus a reproducibly detectable HIV by amplification methods. AHI diagnosis date was defined as the date of the first test detecting the presence of HIV. The estimated-date-of-infection was calculated as 14 days prior to onset of symptoms consistent with acute retroviral syndrome [22].

Exclusion criteria were minimal and included the following: pregnancy, breastfeeding, inability to commit to acceptable contraceptive methods to prevent pregnancy, recent history of acute hepatitis, severe acute illness, incarceration or recent/current administration of experimental therapy, immune-modulating agents or contraindicated medications. Baseline resistance testing was performed on all participants at enrollment, but ART initiation was not delayed for receipt of genotype results. Baseline resistance was assessed as the presence of any of the surveillance drug resistance mutations listed by the World Health Organization [23]. In most cases, participants were screened, enrolled and started study treatment on day of their initial evaluation for AHI. Participants were evaluated on study at weeks 1, 2, 4, 8, 12, 16, 24, 36, 48, 60, 72, 84 and 96 and received $25.00 per study visit as reimbursement.

HIV RNA was measured using the Roche Amplicor Monitor ultrasensitive assay, version 1.5 with a 50 copies/mL lower limit of detection prior to December 2008, and with the Abbott RealTi*m*e HIV-1 assay with a 40 copies/mL lower limit of detection thereafter. The level of circulating $CD8^+HLA\text{-}DR^+CD38^+$ T cells was measured in a subset of participants through June 2010 in fresh blood samples collected in EDTA tubes by flow-cytometry at enrollment, 24 weeks after starting ART, and every six months thereafter through week 96. Circulating activated $CD8^+$ cells were identified using the following panel of antibodies: aCD3-PerCP; aCD8-FITC; aHLA-DR-APC: and aCD38-PE. The samples were acquired using a 4-color Calibur flow cytometer instrument (Becton Dickinson, San Jose, CA). The study was approved by the University of North Carolina at Chapel Hill (UNC) and Duke University Institutional Review Boards. All participants provided written informed consent.

The distribution of demographic and clinical characteristics was examined for all participants. The demographics of interest included age, sexual risk group, and race/ethnicity. Clinical characteristics included STD diagnosis within 8 weeks of acute HIV diagnosis, serostatus at ART initiation, duration from estimated-date-of-infection until treatment, and viral loads (copies/mL) and CD4 cell counts (cells/mm^3) throughout the study. We defined virologic failure as failure to suppress to <200 copies/mL by week 24 [23] or HIV RNA >50 copies/mL at week 48.

We updated our analysis of time to viral suppression in relation to baseline characteristics with the 89 AHI participants who remained on treatment at designated time points. Time to viral suppression was defined as the time (days) to HIV RNA <50 copies/mL after ART initiation. As before, parameters included baseline $CD8^+$ cell activation, duration from estimated-date-of-infection until treatment, and baseline HIV RNA level. Each parameter was dichotomized into those less than or equal to the median value and those above the median value. Participants were censored if they stopped treatment, were lost to follow-up or had their last visit before week 24. Log-rank tests were used to test differences in suppression times between exposure groups. Multivariable proportional hazards regression was used to estimate hazard ratios for the association between baseline $CD8^+$ cell activation and time to viral suppression. Potential confounders included baseline HIV RNA, CD4 cell count and age. Confounders that resulted in a 10% or greater change in estimate were retained in the model. Our final model included log transformed baseline HIV RNA and CD4 cell count.

The frequency of $CD38^+HLA\text{-}DR^+$ $CD8^+$cells measured by flow cytometry was compared between AHI participants on treatment and a seronegative cohort using two sample T-test statistics. To determine the clinical characteristics associated with baseline frequency of activated CD8+ cells, we performed linear tests for trend. We used linear regression to assess for the association between baseline CD4 cell count and the binary indicator of CD8 activation at week 96 (above and below the median) by mean and median CD4 at baseline. We also performed bivariate analysis to assess for associations between demographic and clinical characteristics and retention on study at or after week 48. We used the Fisher's exact test for categorical variables and the Kruskal Wallis test for continuous variables. All statistical analyses were performed with SAS version 9.4 (SAS Institute; Cary, N.C.).

Results

Between January 2005 and December 2011, 92 acutely-infected participants enrolled in the study and began therapy. The median age of participants at enrollment was 27 years (range 18–66), with 42 participants (46%) aged ≤ 25 years (Table 1). Most participants (78%) were MSM, including 39 MSM (42%) between 18 and 25 years of age. Over half (59%) of AHI participants were African American. The median initial HIV RNA level for AHI participants was 614,898 copies/mL (range 615–29,807,640), and the median observed peak HIV RNA level was 746,103 copies/mL (range 5,470–160,000,000); this analysis included pre-enrollment HIV RNA levels performed on samples obtained on the initial HIV testing date. The median HIV RNA level at enrollment on study was 169,365 copies/mL. Using an estimated date of infection [22, 24], the median time from HIV acquisition to the date of ART initiation was 42 days (range 21–140). The median baseline CD4 cell count at enrollment was 487 cells/mm^3 (range 13–1316) and increased to 638 cells/mm^3 at week 24, 700 cells/mm^3 at week 48 and 765 cells/mm^3 at week 96 (Table 1). Two participants initiated study treatment but withdrew at 4 and 13 days following enrollment due to baseline resistance to efavirenz and to join an alternative treatment study. They were excluded from further analysis except for baseline resistance.

Eighty-one (90%) of the 90 participants suppressed to <200 copies/mL prior to or at week 24. Among the 9 (10%) participants who met criteria for treatment failure at week 24, 3 (3%) were lost to follow-up prior to week 24, 3 (3%) had ongoing viral decline with HIV RNA <200 copies/mL at week 36, and one had viremia >200 copies/mL through week 36 but suppressed to <50 copies/mL at week 60 (missed week 48) and thereafter. One participant had an isolated low viral load at week 24 preceded and followed by viral suppression, and the final participant stopped study treatment within 2 weeks due to rash attributed to study treatment and was followed off ART until after week 48 per participant preference. No participant had sustained plasma HIV RNA rebound on therapy.

At week 48, 71 (79%) participants had an HIV RNA <50 copies/mL. Of the 19 (21%) participants who did not have documented suppression at week 48, 7 (8%) had detectable plasma HIV RNA preceded and followed by durable viral suppression, 5 (6%) were lost to follow-up, 4 (4%) were off ART, 2 (2%) had HIV RNA <50 before and after week 48 but missed the week 48 visit, and 1 (1%) had persistent viremia on treatment at week 48. The participant with viremia at week 48 had baseline NNRTI resistance and missed weeks 16 through 36, but suppressed to <50 copies/mL on an integrase-based ART regimen initiated after week 48. Among the 4 participants who remained on study but off ART at week 48, three later suppressed to <50 copies/mL after re-initiation of ART. All participants who remained on study at week 48 and chose to continue or restart ART maintained or re-established virologic suppression.

The percentage of participants retained on the study and ART was high through week 96 (Figure 1). Overall at week 24, 87 (97%) participants were retained on the study; 77 (86%) remained on initial therapy with FDC FTC/TDF/EFZ, 9 (10%) were on an alternative therapy, and one (1%) participant was off therapy (Figure 2). Three participants were lost to follow-up. At week 48, 85 (94%) participants were retained in care and on the study with 74

(82%) still on FDC FTC/TDF/EFZ, 7 (8%) on alternative therapy, and 4 (4%) off therapy; 5 (6%) were lost to follow-up. Overall, 78 (85%) participants completed a study visit at week 72 or after (Figure 1). Retention in the study at week 48 or after was not associated with age, risk group, race, ethnicity, county at AHI diagnosis, history of substance use or time to viral suppression.

Seventy-five (83%) of 90 participants completed a week 96 study visit, with the remaining 15 (17%) lost to follow-up. At week 96, 65 (72%) participants remained on the initial study regimen and 60 (92%) were suppressed to <50 copies/mL (Figure 2). Among participants with viremia at week 96, two were <1000 copies/mL, two had viral loads of 4678 and 12,964 copies/mL and the one participant off ART was viremic to 329,855 copies/mL. All nine participants on an alternative regimen at week 96 were suppressed to <50 copies/mL. Only one participant acquired resistance while on study treatment with a new K103N mutation on repeat genotype testing not seen at baseline and in the setting of viremia and self-report of non-adherence.

Given low reported rates of ART administration, viral suppression and retention in care among young MSM [25–27] and their prevalence among AHI cases, we assessed viral suppression and retention among participants between 18 and 25 years of age who self-reported as MSM. Among 37 young MSM, 35 (95%), 33 (89%) and 31 (84%) completed a study visit at week 24, 48 and 96, respectively. In addition, 31 (84%), 25 (68%) and 26 (70%) of young MSM were suppressed to <50 copies/mL at weeks 24, 48 and 96, respectively. Overall, loss to follow-up at week 96 was similar among young MSM at 16% (n=6) compared to 17% (n=9) (Chi-square p=0.92) among all other AHI participants on the study.

The median time from ART initiation to viral suppression <200 copies/mL was 65 days (range 7–523) and to <50 copies/mL was 105 days (range 14–523) (Figure 3). The median time to suppression among just young MSM (ages 18 to 25) was 54 days (range 7 to 171). In our interim analysis, higher viremia was associated with a longer time to suppression. However, repeat analysis with a larger sample size indicated that higher HIV RNA levels at ART initiation (Log-rank p=0.20), time of estimated date of infection to the initiation of ART (Log rank p=0.36), and baseline CD8+ cell activation (Log-rank p=0.29) were not associated with a longer time to viral suppression.

Of the 92 patients enrolled in the study, two (2%) withdrew due to transmitted resistance (both were subsequently enrolled in a different acute HIV infection study), and 15 (16%) changed to an alternative treatment while remaining in the study. Reasons for changing initial study treatment included detection of transmitted resistance to one of more of the drugs contained in the regimen (n=10; 11%), side effects (n=5; 5%) attributed to efavirenz, and non-adherence (n=2; 2%). Seventeen (18%) of the initial 92 acutely-infected participants had baseline resistance testing showing at least one of the surveillance drug resistance mutations [23]. Among these, 10 (11%) participants had baseline resistance to the NNRTI component of the study treatment regimen (K103N/S, 181C), two of whom withdrew to start a different ART regimen on another study (as stated above). Among the eight participants with baseline NNRTI resistance who remained on study, four (86%)

suppressed to <200 copies/mL by week 24, and remained suppressed to <50 copies/mL at weeks 48 and 96, following rapid genotype guided change in the ART regimen. Three others interrupted therapy and eventually restarted alternative ART and had HIV RNA <50 c/mL at week 96. One participant with baseline resistance suppressed to <50 copies/mL by week 16 on an alternate ART regimen, but later had confirmed low level viremia with self-reported non-adherence and remained off ART after week 36.

The median frequency of $CD8^+CD38^+HLADR^+$ T-cells among AHI participants at baseline was 67% (range 23–95) (Figure 4), a level significantly higher than among the seronegative cohort (p=<0.0001). The frequency of immune activation continued to decline over time to a median of 16% (range 9–66%) at week 96, although the rate of decline slowed considerably after week 24 (Figure 4). Both participants with much higher levels of immune activation of 62% at week 48 and 66% at week 96, as shown by open circles in Figure 4, were off ART and viremic at 54,721 copies/mL and 329,855 copies/mL, respectively. Baseline CD4 counts were inversely associated with activated $CD8^+$ cells at baseline (p<0.01) and log-transformed initial HIV RNA levels were marginally associated with activated $CD8^+$ cells at baseline (p=0.07). However, frequency of activated $CD8^+$ cells above the median of 67% was not significantly associated with time to viral suppression (adjusted HR = 0.92; 95% CI 0.55,1.56).

Among 9 participants with viral suppression and immune activation data at week 96, baseline CD4 cell count was not associated with $CD8^+$ activation at week 96.

Discussion

In this 96-week, prospective, open-label study of FDC FTC/TDF/EFZ initiated during AHI, most participants who remained on treatment achieved viral suppression <200 copies/mL by week 24 and <50 copies/mL by week 48 (90% and 79% respectively). Viral suppression rates in our analysis are comparable with those from large studies of ART efficacy (including FDC FTC/TDF/EFZ) among patients with established HIV. Of the 90 participants who remained on study, 75 (83%) were retained through week 96, most of whom remained on FDC FTC/TDF/EFZ [n=65 (72%)]. Of these, 60/65 (92%) had HIV RNA <50 copies/mL at week 96. Further, most participants completing a week 96 visit, regardless of their ART regimen, were suppressed to <50 copies/mL. Only one participant was off therapy at the end of the study and only one participant had virologic failure with emergence of resistance (K103N).

Our findings indicate that immediate ART in the setting of AHI is feasible, effective and allows for retention in care and durable viral suppression. Essentially all acutely infected individuals referred to UNC and Duke University were offered the opportunity to enroll on the study, and none were excluded from study participation due to lack of stable transportation or active substance abuse. Despite the minimal exclusion criteria, viral suppression rates remained high during the two years of follow-up among our AHI participants, which included a large proportion of young MSM. Young MSM remain the most heavily affected population with newly diagnosed HIV infection in the United States, and both incidence and prevalence continue to increase in this population. Our findings

indicate that more widespread programs targeting rapid and facilitated linkage to care and treatment for acutely infected young MSM are needed, feasible and effective. Prior published rates of viral suppression among HIV-infected African American youth [25] and young MSM [26] have ranged much lower from 18 to 27%, compared with the 64–79% suppression rates among young MSM observed in our population.

Treatment success may have been facilitated by the reimbursement ($25.00) provided to our participants at each study visit, and assistance with transportation to study visits for some participants likely enhanced retention in care. Despite these incentives, we believe the minimal exclusion criteria among newly diagnosed individuals in our study (including young MSM) make our data relevant to the immediate initiation of ART in acutely infected individuals in all clinical settings, for the benefit of both individuals and the public health. Treatment failure on our study, defined as an HIV RNA level >50 copies/mL or missing data at 48 or 96 weeks, was predominantly driven by lost to follow-up and not by overt virologic failure suggesting poor adherence. However, given the potential impact of reimbursement on retention and thus suppression in our study, intensive efforts to keep patients in care will be needed to achieve the UNAIDS goal of suppression rates of 90% for patients started on therapy [28–30].

FDC FTC/TDF/EFZ was well-tolerated with the most common reason for ART change the presence of baseline resistance to the NNRTI component. A previous study found a high prevalence (19%) of transmitted NNRTI resistance among a cohort of acutely infected individuals diagnosed in the Southeastern US, a rate higher than that which has been reported among patients with established HIV infection [31]. The 10% prevalence of transmitted NNRTI resistance in our study was lower, a finding that may be due to decreased onward transmission of NNRTI-resistant variants. Our data support the approach of prompt initiation of an NNRTI-based regimen in patients with AHI with rapid transition of those found to have transmitted NNRTI resistance to alternative regimens. Given the accumulating evidence of the benefits of earlier treatment [17] and the impact of immune activation on morbidity among HIV patients, our data showing substantial declines in immune activation through week 96 further supports earlier treatment intervention.

Although FDC FTC/TDF/EFZ is no longer a recommended first line regimen by US and European guidelines, internationally it remains the first-line regimen per recommendations of the World Health Organization (WHO) [32]. Our data also support the strategy of initiating a simple one-pill, once-daily integrase inhibitor-based regimen as opposed to a multiple-tablet PI-based ART while awaiting HIV genotype results. Taken together, these data should encourage clinics and providers to expeditiously link acutely infected patients to care and rapidly initiate ART.

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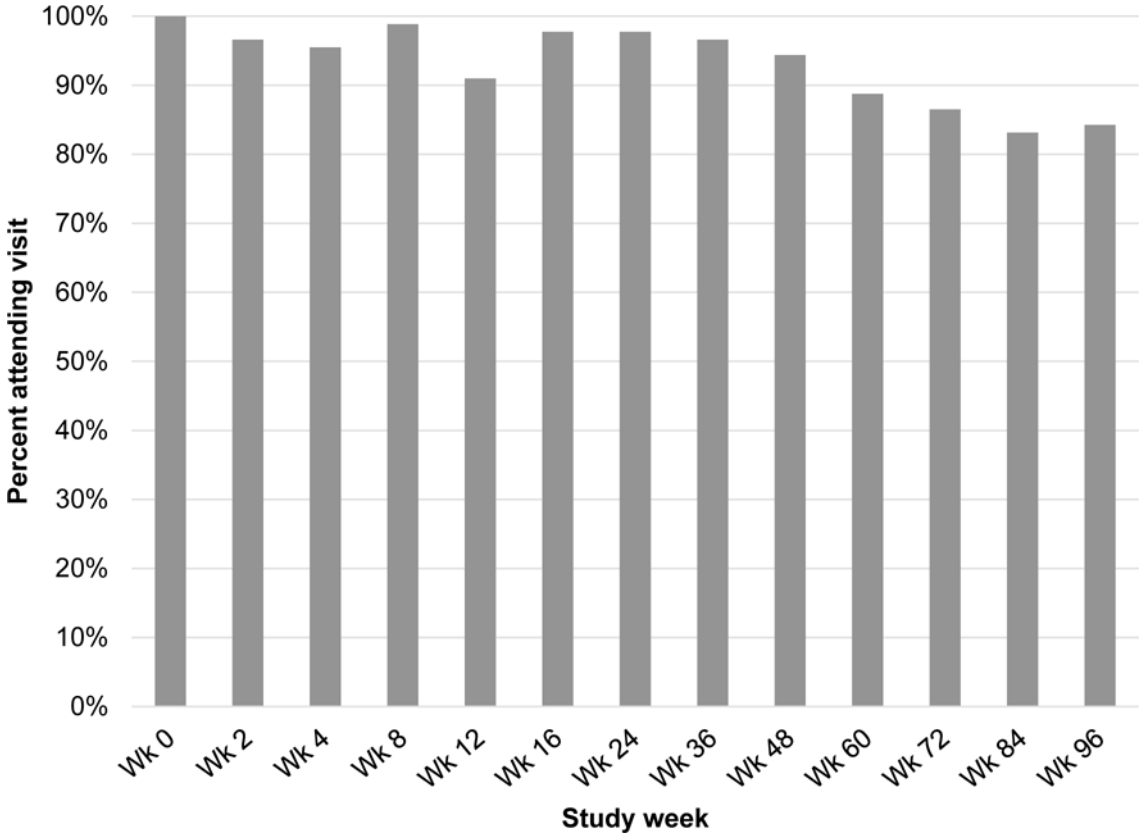

Figure 1.

Retention among AHI Participants. The figure shows the percentage of participants started on ART during AHI who attended study visits from baseline (week 0) through week 96.

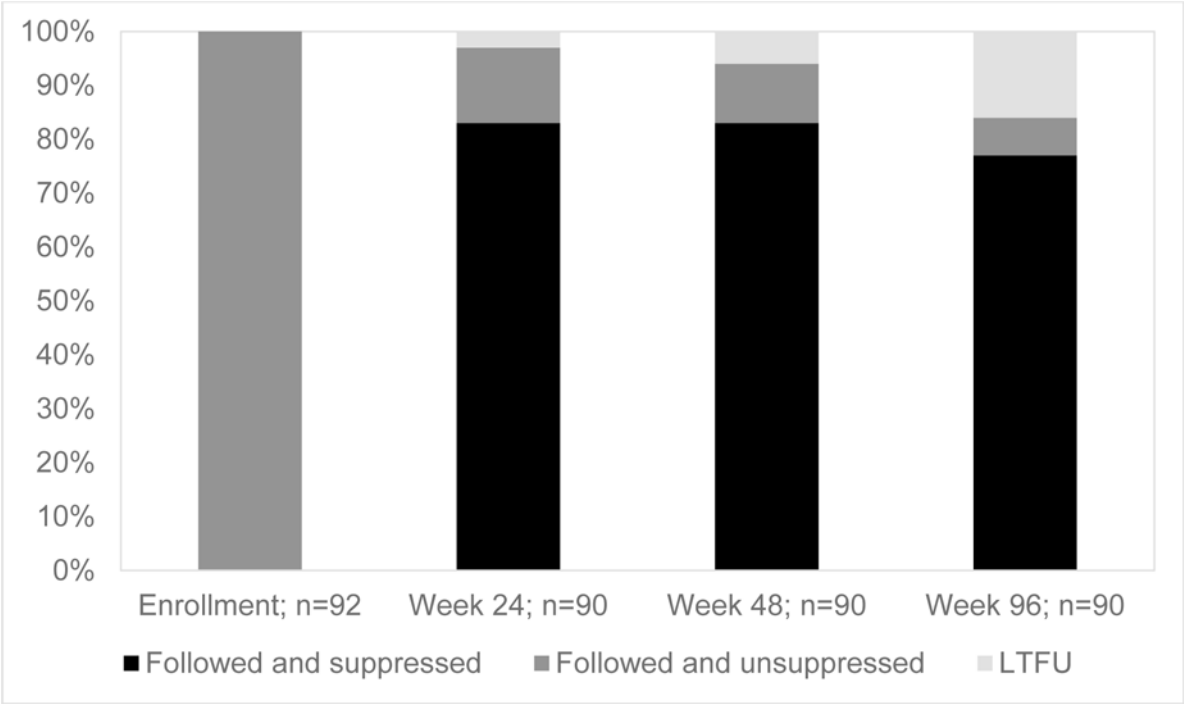

Figure 2. Proportion of participants suppressed, unsuppressed and lost to follow-up on study
LTFU = loss to follow-up

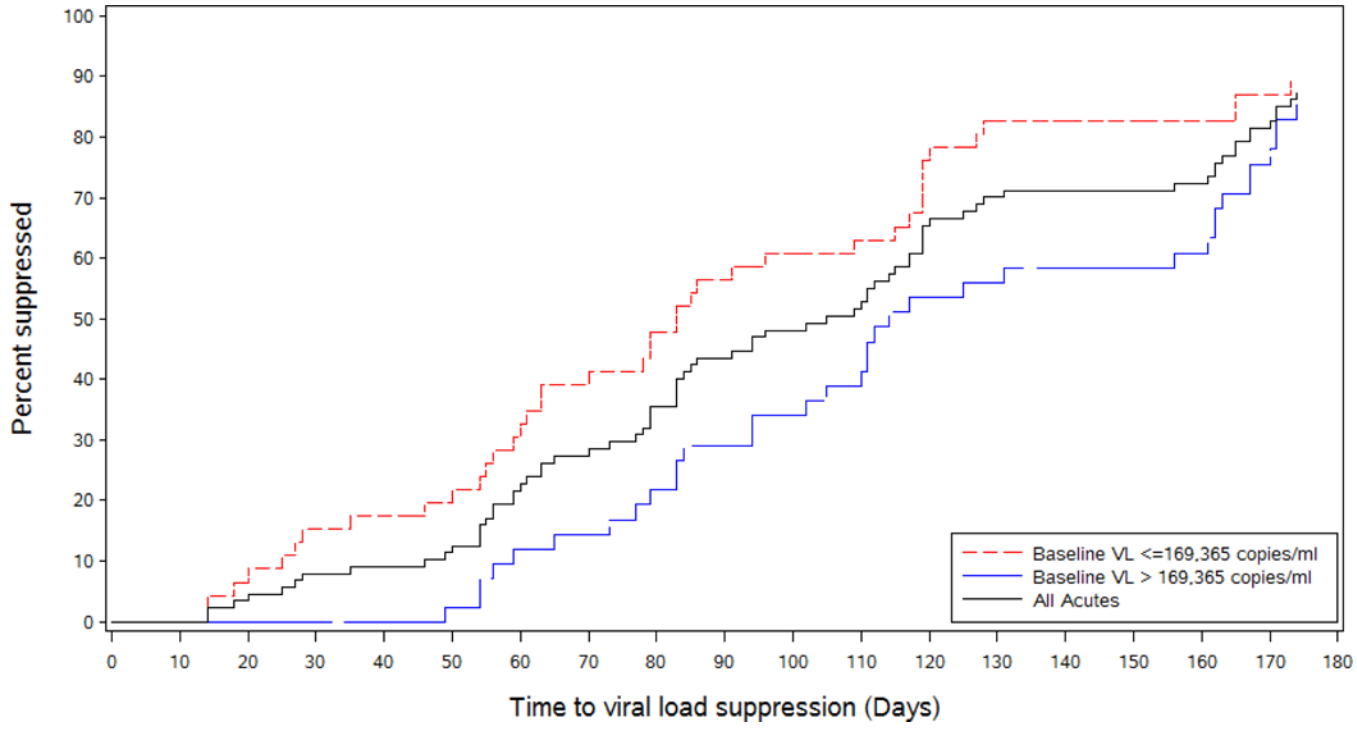

Figure 3.

Cumulative incidence of viral load supression <50 copies/mL among study participants initiating ART during AHI, by viral load measurement at ART initiation.

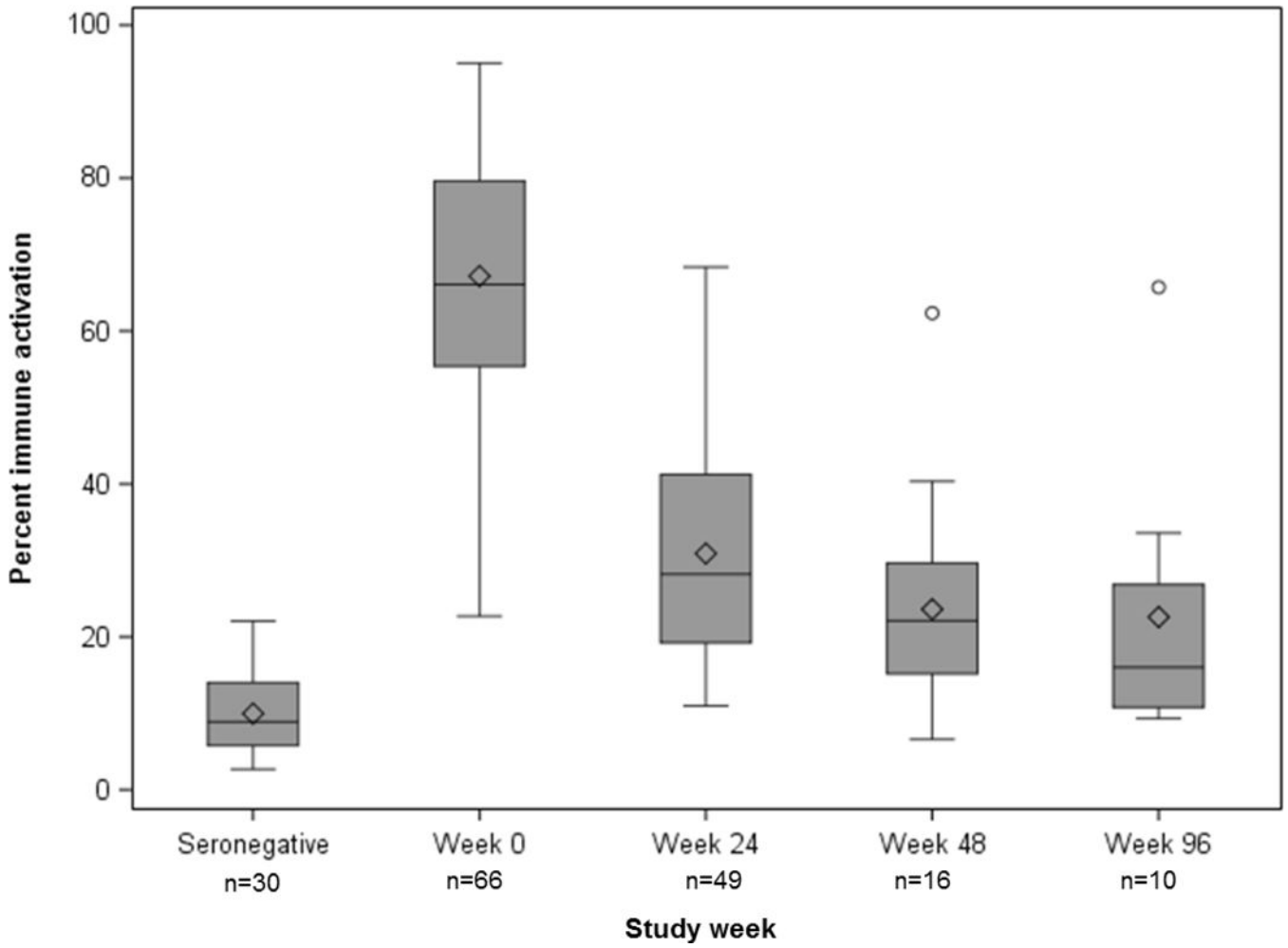

Figure 4.

Distribution of immune activation among study participants initiating ART during AHI through week 96 and a seronegative comparison group. The center lines of the boxplots represent the median and the left and right sides of the boxes denote the 25th and 75th percentiles, or interquartile ranges (IQR). The diamond shape represents the mean. The horizontal bars extend to the most extreme data points within 1.5 times the IQR. The circles beyond the lines represent outlying values.

Table 1

Demographic and clinical characteristics of acutely infected participants starting ART

	PHI02 N=92	
	N or Median	**% or Range**
Age (years)	27	18 – 66
Sexual risk groups		
Female	11	12%
Heterosexual Male	9	10%
MSM	72	78%
Race/ethnicity		
White, Non-Hispanic	36	39%
White, Hispanic	2	2%
African American	54	59%
Asian	0	0%
Symptoms		
STD <8 weeks prior to diagnosis	14	15%
Seronegative at ART start	63	68 %
Viral load (copies/mL)		
Initial	614,898	615 – 29,807,640
Peak observed[a]	746,103	5,470 – 160,000,000
CD4 cell count (cells/mm3)		
Nadir	400	13 – 1235
Baseline	487	13 – 1316
Week 24[b]	638	143 – 1429
Week 48[b]	700	167 – 1726
Week 96[b]	765	198 – 1449
Time, days		
Infection to ART	42	21– 140
Diagnosis to ART start	19	4 – 41
ART start to viral load <50 copies/mL[c]	105	14 – 523
ART start to viral load <200 copies/mL[c]	65	7 – 523

[a] HIV RNA levels prior to study enrollment were included when available.

[b] Includes CD4 cell counts for study participants who attended study visits for the designated week.

[c] 91 participants who achieved viral load <50 and <200 copies/mL included.