CD4+ T-cell count may not be a useful strategy to monitor antiretroviral therapy response in HTLV-1/HIV co-infected patients

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Abstract:

Background: HTLV-1/HIV co-infection is known to elevate the CD4+ T-cell counts of treatment-naïve persons. We investigated whether HTLV-1/HIV co-infected patients continued to have elevated CD4+ T-cell counts after developing virologic failure on antiretroviral therapy (ART).

Methods: The data comes from a drug resistance study located in the KwaZulu-Natal province of South Africa. All participants (N=383) presented for repeated CD4+ T-cell count and HIV viral load level testing between January 2006 and March 2014. We used a random-coefficient model to estimate the change in CD4+ T-cell count and HIV viral load level by HTLV-1/HIV co-infection status over time, adjusting for age, sex, and duration of virologic failure.

Results: HTLV-1/HIV co-infected participants (n=8) had higher CD4+ T-cell counts, with a positive difference of 117.2 cells/μL at the ART initiation date (p-value=0.001), 114.7 cells/μL (p-value<0.001) 12 months after this date, and 112.3 cells/μL (p-value=0.005) 24 months after this date, holding all else constant. In contrast, there was no difference in the HIV viral load level by HTLV-1/HIV co-infected status throughout the observation period.

Conclusions: We show that HTLV-1/HIV co-infected participants continued to have elevated CD4+ T-cell counts after developing virologic failure on ART, despite no difference in their HIV viral load levels when compared with HIV mono-infected participants. Our results indicate that CD4+ T-cell count testing may not be a useful strategy to monitor ART response in the presence of HTLV-1/HIV co-infection.

1. INTRODUCTION

Human T-lymphotropic virus type 1 (HTLV-1) is the etiologic agent of adult T-cell leukemia/lymphoma,[1] tropical spastic paraparesis,[2, 3] and other inflammatory diseases including HTLV-1-associated infective dermatitis[4] and uveitis.[5] HTLV-1 is transmitted via sexual contact, breastfeeding, blood transfusion, and intravenous drug use, similar to the transmission of HIV. Both HTLV-1 and HIV infect CD4+ T-cells. HTLV-1 stimulates the proliferation of infected CD4+ T-cells through a mechanism mediated by one of HTLV's proteins (trans activator x–*tax* protein).[6, 7] HIV has the opposite effect by depleting infected CD4+ T-cells over time, causing AIDS. The differing impact of HTLV-1 and HIV infection on CD4+ T-cells is due to the viral replication process. HIV proliferation is determined by active replication while HTLV-1 is characterized by clonal replication and cell-to-cell transmission.[8]

The HTLV-1 stimulation of infected CD4+ T-cells has implications for the treatment and management of HIV. In resource-limited settings, CD4+ T-cell count testing is often used in combination with HIV clinical staging to determine the timing of antiretroviral therapy (ART).[9] It is possible that higher CD4+ T-cell counts in the presence of HTLV-1 infection could unnecessarily delay the ART initiation date.[10-15] Furthermore, it has been suggested that HTLV-1/HIV co-infected patients will continue to have elevated CD4+ T-cells counts after initiating ART, with no immunologic benefits.[16] This result is problematic and may compromise the accuracy of CD4+ T-cell cut-offs to identify patients who are responding unsuccessfully to their treatment regimens. To the best of our knowledge, it is unclear if HTLV-1 infection will stimulate the proliferation of CD4+ T-cell counts once patients start to develop virologic failure on ART.

In this paper, we used data from a drug resistance study to quantify the difference in the CD4+ T-cell count by HTLV-1/HIV co-infection status. All participants in the study underwent repeated CD4+ T-cell count and HIV RNA viral load level testing at 17 public health-care facilities in the KwaZulu-Natal province of South Africa. The HTLV-1 prevalence in this region is estimated to be as high as 6%.[17] We were also interested in quantifying the difference in the HIV viral load level by HTLV-1/HIV co-infection status. HIV viral load testing is currently recommended by the World Health Organization (WHO) as a more accurate treatment monitoring strategy.[9] Our study has implications for the resource-limited setting, where some HIV treatment programs still exclusively implement CD4+ T-cell count testing on the basis of its perceived affordability.[18]

2. METHODS

The data comes from a drug resistance study nested within the Hlabisa HIV Treatment and Care Programme.[19] The programme is based in the northern KwaZulu-Natal province of South Africa, and is described in detail elsewhere.[20] A total of 384 participants were enrolled into the drug resistance study between January 2006 and March 2014. All but one participant had >2 CD4+ T-cell count measurements and received ART for >12 months, which was the inclusion criteria for this analysis. Our final analytic sample therefore consisted of 383 participants.

HIV viral load testing was scheduled at 6 and 12 months, and then every 12 months thereafter if HIV viral loads were <400 copies/mL. Participants with detectable HIV viral loads >1000 copies/mL were tested every 3 months.[21] Two successive HIV viral loads >1000 copies/mL resulted in a drug resistance test to determine virologic failure. The duration of virologic failure on ART was calculated from the date of the first HIV viral load >1000 copies/mL to either: the

first drug resistance test or follow-up HIV viral load <50 copies/mL. If there were no follow-up HIV viral loads ≤1000 copies/mL, then the duration of virologic failure was calculated from the ART initiation date. CD4+ T-cell count measurements were taken every 6 months as per national guidelines.[21]

At the time of this analysis, the Western Blot test for confirming HTLV-1 infection was not available in South Africa. We therefore submitted 5ml blood samples for HTLV Antibody ELISA (Diagnostic Automation, Inc) testing. To determine HTLV-1 sequences, we extracted nuclear DNA from antibody positive plasma samples using a QIAGEN QIAamp® DNA Blood Kit. Following the procedure of Takemura et al. [22], we then submitted the positive samples from the ELISA test to a nested-PCR using the HTLV-1 long terminal repeat (LTR) 5' region. The data were stored in the RegaDB database of the SATuRN Treatment Network.[23] The Biomedical Research Ethics Committee of the University of KwaZulu-Natal (BF052/010) approved the study.

3. STATISTICAL ANALYSIS

We performed a descriptive analysis of the key variables, including the participant's age, sex, and duration of virologic failure over the observation period. The observation period was defined from the ART initiation date (or closest CD4+ T-cell count measurement within 3 months of this date) to the date of the first drug resistance test.

We used a random coefficient model for our statistical analysis. The model is represented by the following equation:

$$y_{ij} = (\beta_0 + b_{0j}) + (\beta_1 + b_{1j})x_{ij} + (\beta_2 z_j x_{ij}) + \epsilon_{ij}, \quad i = 1, \dots, n_j;\ j = 1, \dots, N \qquad (1)$$

where b_{0j} represents the random deviation of participant *j*'s mean CD4+ T-cell count from the overall mean CD4+ T-cell count (β_0) at ART initiation ($i = 1$); b_{1j} represents the random deviation of participant *j*'s CD4+ T-cell count slope from the overall slope (β_1); x_{ij} is the time in months since ART initiation; β_2 represents the difference in the linear effect of time between the HTLV-1/HIV co-infected and HIV mono-infected participants, where z_j is a variable indicating the co-infection status of participant *j*; and ϵ_{ij} is the within-participant error which represents the deviation of the observed CD4+ T-cell count from the fitted CD4+ T-cell count value at time-point *i*. Here, b_i represents the between-participant variability, distributed as $b_i \sim \mathcal{N}(0,\ \sigma_b^2)$, and the within-participant variability, distributed as $e_{ij} \sim \mathcal{N}(0, \sigma^2)$. We used the same equation to estimate the change in $\log_{10}$ HIV viral load levels by HTLV-1/HIV co-infection status over the observation period.

We considered three models for the CD4+ T-cell count outcome in our analysis. For Model 1, we included variables indicating: i) the participant's HTLV-1/HIV co-infection status, ii) time in 6-month intervals from the date of ART initiation, and iii) an interaction term of these two variables. For Model 2, iv) age and v) sex were added to the Model 1 variables. For Model 3, we added vi) the duration of virologic failure to the Model 1 and 2 variables. We also considered the same three models for the HIV $\log_{10}$ viral load outcome. However, some patients did not have an HIV viral load measurement at the date of ART initiation. In this case, we amended our definition slightly so that the duration of observation was measured from the first available HIV viral load test date to the first drug resistance test date.

We interpreted the results at five clinically relevant time-points: the date of ART initiation, and 6, 12, 18, and 24 months thereafter. At each time-point, we computed the mean difference in CD4+ T-cell count (and HIV viral load level) by HTLV-1/HIV co-infection status, and obtained standard errors, 95% confidence intervals, and p-values from the linear combination

of coefficients estimated by the three models. We performed all analyses with Stata version 13.1.

4. RESULTS

We screened 383 HIV-1 positive participants for HTLV-1 infection. The ELISA test identified the HTLV antibodies of eight (2.1%) participants, and the PCR analysis confirmed the HTLV-1 status of seven of these eight participants. We classified the eight participants as HTLV-1 positive for the following three reasons: 1) there was a strong reaction of the ELISA test to the HTLV antibodies of the eight participants; 2) the PCR technique has a high false-negative rate[24]; and 3) HTLV-1 is the circulating HTLV virus in the KwaZulu-Natal region.[17]

The median age of the eight HTLV-1/HIV co-infected participants was 39 years (IQR: 36–44), and 36 years (IQR: 31–43) for the 375 HIV mono-infected participants. Six (75%) HTLV-1/HIV co-infected and 272 (73%) HIV mono-infected participants were woman. The median time on ART (duration of observation) was slightly higher for the HTLV-1/HIV co-infected participants, 52 (IQR: 41–61) months, than the HIV mono-infected participants, 46 (IQR: 32–58) months. However, the duration of treatment failure on ART was equivalent, with a median of 26 (IQR: 12–40) and 26 (IQR: 16–36) months for the HTLV-1/HIV co-infected and HIV mono-infected participants, respectively (see Table 1). Student t-tests revealed that HTLV-1/HIV co-infected participants did not have significantly different Age, duration on ART, and duration of virologic failure distributions when compared with HIV mono-infected participants ($p > 0.05$).

We quantified the difference in the CD4+ T-cell count by HTLV-1/HIV co-infection status using a random coefficient model. Results show that HIV mono-infected participants had a significantly lower mean CD4+ T-cell count than their HTLV-1/HIV co-infected counterparts

at the date of ART initiation (204.8 vs. 322 cells/μL, p=0.002; see Table 2). The CD4+ T-cell counts of HIV mono-infected participants increased at a mean rate of 11.08 cells/μL every 6 months on ART (p<0.001) and was not significantly different than the HTLV-1/HIV co-infected participants over this period (a difference of −1.235 cells/μL, p=0.89). This result means that HTLV-1/HIV co-infected participants continued to have higher CD4+ T-cell counts for a period of 24 months after initiating ART.

We further quantified the difference in the mean CD4+ T-cell count by HTLV-1/HIV co-infection status at multiple time-points using estimates from the random coefficient models. Our results show that HTLV-1/HIV co-infected participants had significantly higher CD4+ T-cell counts at 6, 12, 18, and 24 months after starting ART. This result did not change when adjusting for age, sex, and duration of virologic failure. For example, Table 3 shows that the mean CD4+ T-cell count of HTLV-1/HIV co-infected participants was 114.7 cells/μL (p=0.009) higher 12 months after ART, and 112.3 cells/μL (p=0.005) higher 24 months after ART, holding all else constant.

In contrast, we could not find any statistical difference in the HIV viral load levels by HTLV-1/HIV co-infection status at the first HIV viral load measurement (after ART initiation; see Table 2). Further, HIV viral load levels did not significantly differ by HTLV-1/HIV co-infection status at 6, 12, 18, and 24 months, as shown in Figure 2 and Table 3.

5. DISCUSSION

Our results show that HTLV-1/HIV co-infected participants had higher CD4+ T-cell counts at the date of ART initiation (when compared with HIV mono-infected participants). This result is well known within the literature. Previous studies have shown that HTLV-1/HIV co-infection increases the CD4+ T-cell counts of treatment-naïve patients.[10-16] In resource-limited

settings, immunologic monitoring is often used in combination with HIV clinical staging to determine the timing of ART. It is possible that elevated CD4+ T-cell counts could unnecessarily delay the start of treatment and care services for HTLV-1/HIV co-infected patients.

The HTLV-1 stimulation of CD4+ T-cells during virologic failure has yet to be definitively established in the literature. Pomier et al.,[16] recently showed that while ART decreased HIV replication, it progressively increased the CD4+ T-cell counts of HTLV-1/HIV co-infected patients with no immunologic benefits. Our work shows for the first time that HTLV-1/HIV co-infected participants continued to have higher CD4+ T-cell counts after developing virologic failure on ART. However, we did not find a statistically significant difference in the HIV viral load levels of HTLV-1/HIV co-infected and HIV mono-infected participants. We suggest that HIV viral load testing may be a more appropriate strategy to monitor patient response to ART in the presence of HTLV-1 infection.

Our study benefits from the use of longitudinal data, in which an average of six CD4+ T-cell measurements were obtained per participant over a mean observation period of four years. We leveraged the flexibility of a multivariate, random coefficient model to account for the heterogeneity in CD4+ T-cell counts (and HIV viral load levels) between participants, and to capture the change in CD4+ T-cell count (and HIV viral load level) within each participant over time. This approach enabled us to evaluate the difference in CD4+ T-cell counts by HTLV-1/HIV co-infection status at multiple time-points over the observation period. To the best of our knowledge, few (if any) studies have used a longitudinal approach to examine the difference in CD4+ T-cell count and HIV viral load level by HTLV-1/HIV co-infection status in a cohort of patients failing ART. We do, however, acknowledge that only 8 participants in our resistance cohort tested positive for HTLV-1/HIV co-infection. Nevertheless, we were still able to detect

a statistically significant difference in the CD4+ T-cell counts by HTLV-1/HIV co-infection status for a period of up to two years on ART.

Treatment monitoring has become an increasingly relevant topic in recent years given the rapid roll-out of ART and the emerging problems associated with drug adherence and resistance. Immunologic monitoring is often used in resource-limited settings to identify treatment failure, primarily because it is perceived to be more affordable than virologic monitoring.[18] Our study shows that HTLV-1/HIV co-infected participants continued to have higher CD4+ T-cell counts after initiating ART, despite no significant difference in their HIV viral load levels when compared with HIV mono-infected participants. In this case, higher than average CD4+ T-cell counts could further compromise the accuracy of immunologic monitoring to identify HTLV-1 infected patients who are failing ART.

6. CONCLUSION

Our results support the argument that immunologic criteria may not be an accurate classifier of treatment failure in HIV-infected patients more generally.[18, 25-27] This work aligns with WHO recommendations that virologic monitoring be used to evaluate patient response to ART.[9] We highlight the importance of identifying HTLV-1 infection once HIV-positive patients present for treatment and care services. Clinical management practices can then be tailored to improve the health and survival outcomes of HTLV-1/HIV co-infected patients before and after ART initiation.

TABLES

Table 1. Demographic and clinical characteristics of HTLV-1/HIV-1 co-infected and HIV-1 mono-infected participants on antiretroviral therapy (ART).

Participant Characteristics (N=383)	**HTLV-1/HIV-1 positive**	**HIV-1 positive**
Co-infection status, N (%)	8 (2.1)	375 (97.9)
Females, N (%)	6 (75)	272 (73)
Age, Median (IQR)	39 (36-44)	36 (31-43)
Time points per participant, Median (IQR)	6.5 (5.5-9.5)	6 (4-7)
Time on ART (months),[a] Median (IQR)	52 (41-61)	46 (32-58)
Duration of virologic failure (months),[b] Median (IQR)	26 (12-40)	26 (16-36)

The table shows the demographic and clinical characteristics of a cohort of 383 HIV-1 participants with virologic failure on ART. The participant characteristics are stratified by HTLV-1/HIV co-infection status. Student t-tests did not reveal any statistically significant differences (at the 0.05 level) in the age, time-points, time on ART, and duration of virologic failure dsitributions by HTLV-1/HIV co-infection status. IQR, interquartile range. [a]Duration of observation was computed in months from the ART initiation date until the first drug resistance test. [b] Duration of virologic failure was calculated from the date of the first HIV viral load >1000 copies/mL to either: the first drug resistance test or follow-up HIV viral load <50 copies/mL. If there

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Table 2: Shows the change in CD4+ T-cell count and HIV log_{10} viral load level by HTLV-1/HIV co-infection status, adjusting for age, sex, and duration of virologic failure.

	Full Model	
Variables	CD4+ T-cell count	HIV log_{10} viral load level
HTLV-1/HIV co-infected	117.2**	-0.530
	(38.45)	(0.328)
Time on ART (6-months)	11.08***	0.0598***
	(1.245)	(0.00993)
HTLV-1/HIV * Time on ART (6-months)	-1.235	0.0849*
	(9.024)	(0.0412)
Female	31.80	-0.0999
	(16.88)	(0.0876)
Age (12-months)	-0.399	-0.00751*
	(0.907)	(0.00345)
Duration of virologic failure (one-month)	-0.841*	0.0170***
	(0.408)	(0.00213)
HIV infected (Intercept)	204.8***	3.392***
	(49.21)	(0.172)
Observations	2,248	2,248
Participants	383	383

Standard errors in parenthesis. ** $p<0.01$, * $p<0.05$. The table shows the difference in the CD4+ T-cell count by HTLV-1/HIV co-infection status for participants with virologic failure on ART. The CD4+ model shows that the mean CD4+ T-cell count for HTLV-1/HIV co-infected participants was 117.2 cells/μL ($p<0.05$) higher than the HIV mono-infected participants (204.8 cells/μL). Importantly, the difference in the rate of change in CD4+ T-cell counts for HTLV-1/HIV co-infected participants was not statistically significant at the 0.05 level (−1.235 cells/μL, $p=0.89$). In contrast, there was no statistically significant difference in the mean HIV log_{10} viral load levels by HTLV-1/HIV co-infection status throughout the observation period.

Table 3: Shows the difference in the mean CD4+ T-cell count and mean HIV log_{10} viral load level by HTLV-1/HIV co-infection status at different time-points after ART initiation.

	HTLV-1/HIV co-infected		HIV mono-infected			
	Mean	**SE**	**Mean**	**SE**	**Difference**	**P-value**
Mean CD4 + T-cell counts (cells/μL) at:						
ART initiation	322.0	62.8	204.8	49.2	117.2	0.0012
6 months	331.8	61.7	215.9	49.0	116.0	0.0007
12 months	341.7	61.9	226.9	48.9	114.7	0.0009
18 months	351.5	63.4	238.0	48.8	113.5	0.0018
24 months	361.4	66.0	249.1	48.8	112.3	0.0046
Mean log_{10} viral load level (copies/mL) at:						
ART initiation	2.77	0.36	3.30	0.153	-0.53	0.95
6 months	2.86	0.33	3.36	0.151	-0.51	0.96
12 months	2.94	0.29	3.42	0.148	-0.48	0.97
18 months	3.03	0.26	3.48	0.147	-0.46	0.98
24 months	3.11	0.24	3.54	0.146	-0.43	0.99
Total	8		375			

The table shows the difference in the mean CD4+ T-cell count and HIV log10 viral load level by HTLV-1/HIV co-infection status at the date of ART initiation and 6, 12, 18, and 24 months thereafter. The CD4+ T-cell results show that the average difference between the HTLV-1/HIV co-infected and HIV mono-infected patients was 117.2 cells/μL at ART initiation. At 12 and 24 months this difference was 114.7 cells/μL and 112.3 cells/μL respectively. In contrast, there was no statistically significant difference in the HIV log_{10} viral load levels by HTLV-1/HIV co-infection status throughout the observation period.

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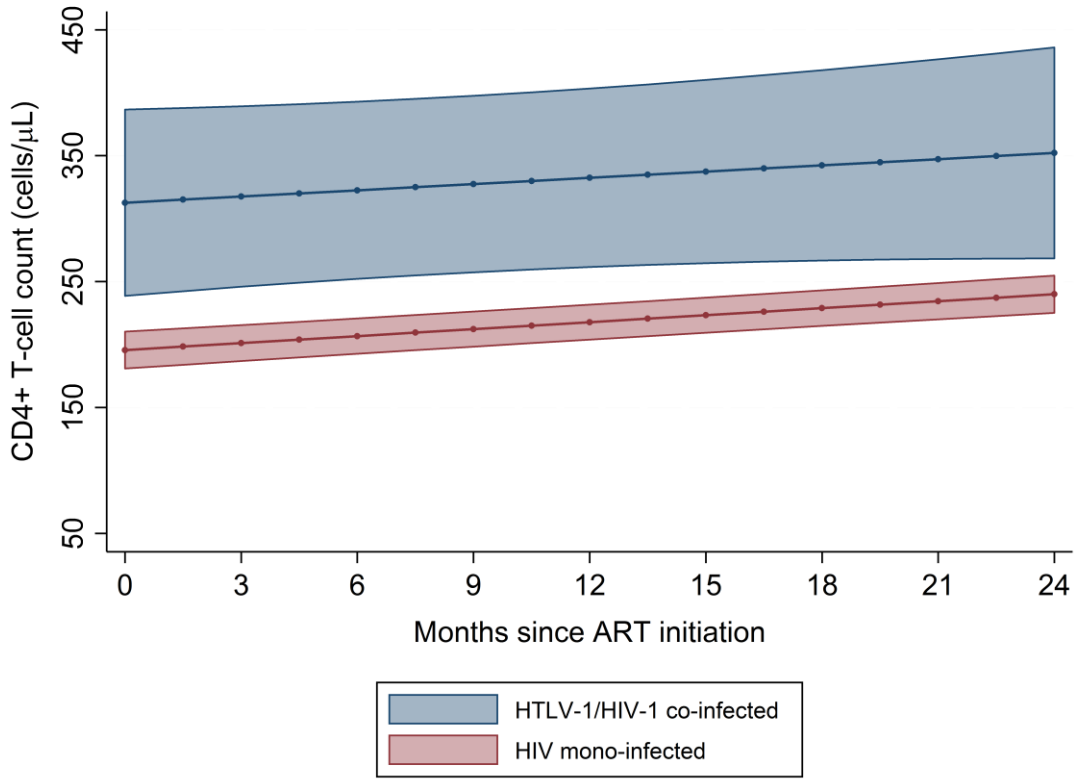
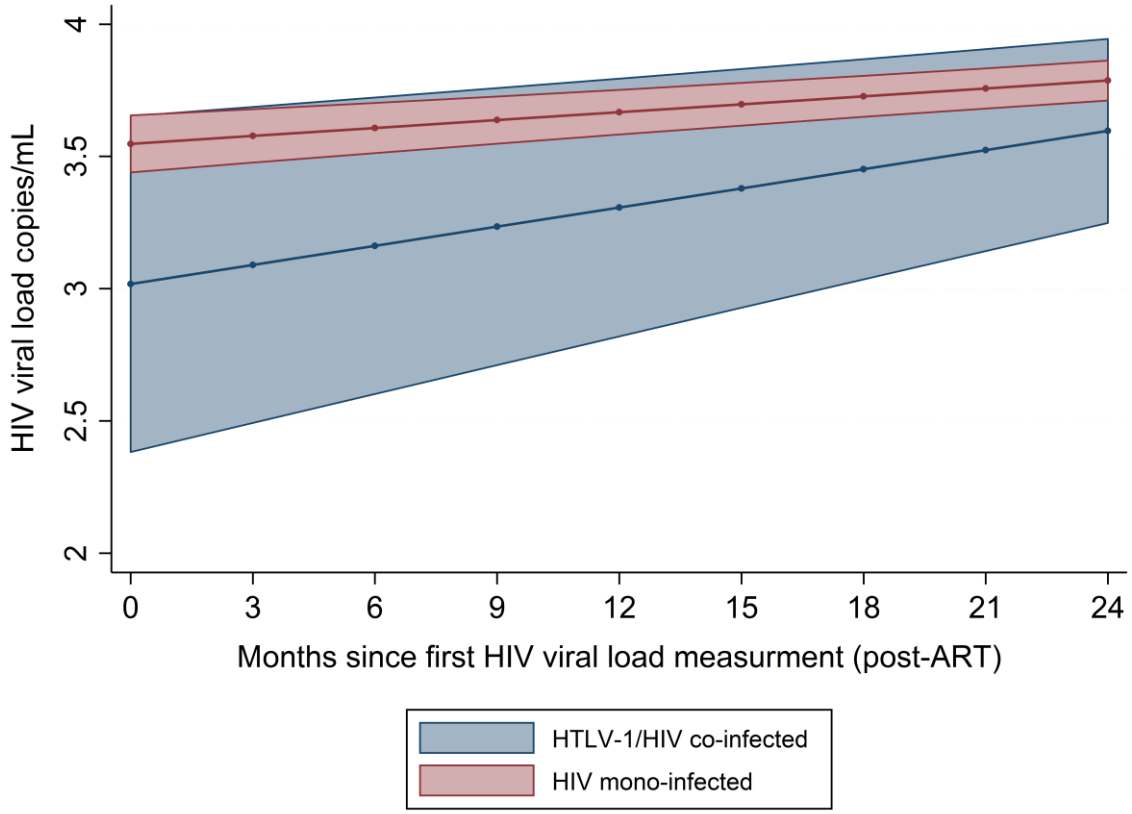
Figures

Figure 1: Shows that HTLV-1/HIV co-infected participants continued to have higher mean CD4+ T-cell counts after developing virologic failure on ART.



Results were adjusted for age, sex, and duration of virologic failure. The estimates are presented with 95% confidence bands for a two year period following the ART initiation date.

Figure 2: Shows that there was no difference in the mean HIV $\log_{10}$ viral load levels by HTLV-1/HIV co-infection status after the first HIV viral load test measurement (post ART).



Results were adjusted for age, sex, and duration of virologic failure. The estimates are presented with 95% confidence bands for a two year period following the ART initiation date.

LIST OF ABBREVIATIONS

Human T-cell Lymphotropic Virus type 1 (HTLV-1)

Antiretroviral therapy (ART)

Interquartile Range (IQR)

CONFLICT OF INTEREST

All authors have declared no conflict of interests.

SOURCES OF SUPPORT

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AUTHOR'S CONTRIBUTIONS

AV, FFAR, and TO wrote the paper. FFAR did the genotyping and HTLV-1 detection. AV did the statistical analysis. AV, FFAR, and TO designed the study. All authors helped with the discussion.

AVAILABILITY OF DATA AND MATERIALS

The data for this study is available from a data repository managed and maintained by the Wellcome Trust Africa Centre for Population Health. The GenBank accession numbers for the new HTLV-1 LTR5' fragments are KF042345 to KF042351.

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