

Plasma Viral Loads During Early HIV-1 Infection Are Similar in Subtype C- and Non-Subtype C-Infected African Seroconverters

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Recent data suggest that infection with human immunodeficiency virus type 1 (HIV-1) subtype C results in prolonged high-level viremia (>5 log₁₀ copies/mL) during early infection. We examined the relationship between HIV-1 subtype and plasma viremia among 153 African seroconverters. Mean setpoint viral loads were similar for C and non-C subtypes: 4.36 vs 4.42 log₁₀ copies/mL (*P* = .61). The proportion of subtype C-infected participants with viral loads >5 log₁₀ copies/mL was not greater than the proportion for those with non-C infection. Our data do not support the hypothesis that higher early viral load accounts for the rapid spread of HIV-1 subtype C in southern Africa.

Keywords. HIV-1; group M subtype; plasma viral load; early infection; Africa.

Human immunodeficiency virus type 1 (HIV-1) group M, which was introduced into the human population by a zoonotic transmission event, has diversified over time and

currently clusters into 9 subtypes whose envelope sequences differ by 15%–20%. HIV-1 subtypes differ substantially in their geographic distributions, with subtype B predominant in the Americas, likely reflecting a founder event, and subtype C predominant in southern Africa, where HIV-1 prevalence is highest [1]. Data support a relationship between some HIV-1 subtypes and the rate of CD4 T-cell decline and clinical outcome, suggesting that subtype may be related to virulence [2].

The level of viremia in infected individuals is strongly associated with HIV-1 transmission [3] and disease progression [4]. Shortly after an individual acquires HIV-1, the number of viral copies in the bloodstream increases exponentially and then typically falls to a lower, relatively constant level where it remains or increases slowly until late in infection. The stable, lower concentration of virus in blood that follows peak viremia during acute infection is known as the viral setpoint. The impact of subtype on setpoint is unclear, with some studies showing equivalent viral loads across subtypes [5] and others showing intersubtype differences [6].

A recent analysis found that nearly one-fifth of subtype C-infected individuals had extended high viremia, with plasma viral loads >5 log₁₀ copies/mL during the first 1.5 years after HIV-1 acquisition [7]. The authors interpreted those findings as potentially explaining the dominant and rapid spread of subtype C in southern Africa. We sought to understand the relationship between HIV-1 subtype and virulence using similar measures of plasma viremia. The goal of our study was to compare viremia during early infection in a multinational study of African HIV-1 seroconverters with different subtypes and to assess for the proportion with extended high viremia across subtypes. Participants were studied using identical methods in 2 regions with generalized HIV-1 epidemics, East and southern Africa, enabling comparisons of viremia in subtype C and other subtypes.

METHODS

Study Population

Participants included HIV-1 seroconverters from 2 prospective studies among African HIV-1 serodiscordant heterosexual couples. The Partners in Prevention HSV/HIV Transmission Study enrolled 3408 couples in a phase 3 trial of genital herpes suppression for HIV-1 prevention at sites in Botswana, Kenya, Rwanda, South Africa, Tanzania, Uganda, and Zambia [8]. An additional 485 HIV-1 serodiscordant couples were

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enrolled in a parallel observational study in Kampala, Uganda, and Soweto, South Africa [9].

Procedures

Participants were followed quarterly for up to 24 months. HIV-1 seroconversion was determined by on-site dual rapid antibody testing and confirmed by enzyme-linked immunosorbent assay and Western blot at the University of Washington. HIV-1 RNA was measured in plasma, including from visits before seroconversion, to improve precision of the estimated date of infection. Viral load was quantified using the Roche COBAS Ampli-Prep/COBAS TaqMan 1.0 platform.

Timing of HIV-1 Infection

Fiebig staging, taking into account HIV-1 antibody and viral load measurements, was used to estimate the date of HIV-1 infection [10]. We defined participants with detectable viral load in blood plasma at preseroconversion visits as acutely infected, and the HIV-1 infection date was calculated as 17 days before the first positive plasma viral load measurement. In participants without detectable viremia before seroconversion, the HIV-1 infection date was calculated as either the midpoint between the date with undetectable antibodies and the seroconversion visit or 45 days before seroconversion, whichever was most recent.

HIV-1 Subtyping

We sequenced partial HIV-1 *env* and *gag* to determine whether seroconverters' viruses were genetically linked to those of their enrolled partners [8]. Viral subtypes were determined with the REGA subtyping tool version 2.0 (<http://dbpartners.stanford.edu/RegaSubtyping/>).

Data Analysis

We assessed the relationship between viral subtype and several measures of early viremia to evaluate for consistency across measures and to compare our findings to other published analyses. First, we assessed viral setpoint, defined as viral load measured ≥ 4 months after the estimated date of HIV-1 infection because that definition has been used in previous publications [4, 11] and has been associated with the risk of subsequent HIV-1 disease progression. Second, to directly compare our results with those of Novitsky et al [7], we assessed for extended high viremia by evaluating viral loads 100–300 days postseroconversion. We calculated mean viral loads by dividing the sum of viral load measurements by the number of study visits, and we also determined the proportion of extended high viremia, including mean, first, and highest viral load $>5 \log_{10}$ copies/mL. We used logistic regression models adjusted for age and sex to compare viremia by subtype, performing each analysis separately for viral subtypes determined by *env* and *gag* sequencing. Finally, we did a sensitivity analysis to examine the impact of acute infection on the level of viremia at setpoint and at 100–300 days postseroconversion by *env* subtype. We included all available plasma viral

load measurements in the analyses, except for those at visits with reported antiretroviral therapy use. Analyses were performed using SAS version 9.2 (SAS Institute, Cary, NC).

RESULTS

Subtypes in *env* and/or *gag* were available from 153 seroconverters. Sixty-three percent were from East Africa (Kenya, Tanzania, and Uganda), and 37% were from southern Africa (Botswana, South Africa, and Zambia). The median age was 30 years (interquartile range [IQR], 25–38), and 57% were male. Seroconverters were followed for a median of 404 days (IQR, 312–454) after the estimated HIV-1 infection date. Most seroconverters had either subtype A (*env/gag*, 46%/45%) or C (*env/gag*, 36%/31%) viruses, with a minority having subtype D or other inter-subtype recombinant forms (D *env/gag*, 16%/10%; other *env/gag*, 3%/14%). Subtype C viruses were found in *env* in 5.6% and 78.8% of seroconverters in East and southern Africa, respectively. Eighty-one percent had agreement in subtype classification between genes.

Mean viral loads at setpoint and 100–300 days postseroconversion were 4.39 (IQR, 3.82–5.08) and 4.36 (IQR, 3.75–5.09) \log_{10} copies/mL (Table 1). Based on *env* subtyping, seroconverters with mean, first, and highest setpoint viral load $>5 \log_{10}$ copies/mL comprised 25%, 29%, and 40% of the overall cohort, respectively. Approximately one-third had mean and highest viral load $>5 \log_{10}$ copies/mL 100–300 days postseroconversion.

Viral loads were similar for participants infected with subtype C vs non-C viruses. Mean setpoint viral load for subtype C- and non-C-infected participants classified by *env* subtype were 4.36 (IQR, 3.85–4.94) and 4.42 (IQR, 3.82–5.13) \log_{10} copies/mL, respectively (Student's *t*-test, 2-tailed, $P = .61$). Mean viral loads 100–300 days postseroconversion were 4.28 (IQR, 3.63–4.97) and 4.44 (IQR, 3.84–5.12) \log_{10} copies/mL (Student's *t*-test, 2-tailed, $P = .26$) in subtype C and non-subtype C infected participants.

Subtype C-infected participants were not statistically more likely to have mean, first, and highest setpoint viral load $>5 \log_{10}$ copies/mL compared with non-subtype C- infected participants (Table 2). The proportion with highest setpoint viral load $>5 \log_{10}$ copies/mL was higher for those with non-C infection than for those with subtype C infection (*env*: 46% vs 28%, $P = .04$; *gag*: 46% vs 23%, $P = .01$). Subtype C-infected participants were not more likely than those infected with non-C viruses to have mean and highest viral load $>5 \log_{10}$ copies/mL 100–300 days postseroconversion.

We performed a sensitivity analysis, limited to *env* subtype, for those seroconverters identified during acute infection (ie, viremic and antibody negative). Fifty (32.7%) seroconverters were identified during acute infection, 46 of whom had *env* subtyping and setpoint viral load. Mean viral setpoints were equal (4.66 \log_{10} copies/mL) in subtype C- and non-subtype

Table 1. Measurements of Plasma Viremia According to Subtype

Measurement of Plasma Viremia	Subtype				Total
	A	C	D	Other	
<i>env</i> Subtype					
Female, No. (%)	31 (46%)	16 (30%)	14 (61%)	2 (50%)	63 (43%)
Median age in years (IQR)	30 (26–38)	32 (26–39)	27 (22–30)	26 (19–40)	30 (25–38)
Setpoint viral load, No. ^a	68	53	23	4	148
Mean, log ₁₀ copies/mL (IQR)	4.43 (3.86–5.19)	4.36 (3.85–4.94)	4.45 (3.83–5.06)	4.20 (3.62–4.97)	4.39 (3.82–5.08)
Setpoint viral load >5 log ₁₀ copies/mL, No. (%)	20 (29%)	10 (19%)	6 (26%)	1 (25%)	37 (25%)
Viral load >5 log ₁₀ copies/mL					
First measurement, No. (%)	21 (31%)	11 (21%)	10 (43%)	1 (25%)	43 (29%)
Highest measurement, No. (%)	31 (46%)	15 (28%)	11 (48%)	2 (50%)	59 (40%)
Viral load 100–300 days postseroconversion, No. ^a	60	46	20	4	130
Mean, log ₁₀ copies/mL (IQR)	4.43 (3.86–5.12)	4.28 (3.63–4.97)	4.52 (3.97–5.38)	4.21 (3.68–5.04)	4.36 (3.75–5.09)
Viral load >5 log ₁₀ copies/mL					
First measurement, No. (%)	19 (32%)	11 (24%)	6 (30%)	2 (50%)	38 (29%)
Highest measurement, No. (%)	23 (38%)	12 (26%)	7 (35%)	2 (50%)	44 (34%)
<i>gag</i> Subtype					
Female, No. (%)	30 (48%)	11 (25%)	6 (43%)	12 (60%)	59 (42%)
Median age in years (IQR)	30 (26–38)	32 (26–39)	26 (22–30)	30 (26–35)	30 (26–38)
Setpoint viral load, No. ^a	63	44	14	20	141
Mean, log ₁₀ copies/mL (IQR)	4.50 (3.85–5.27)	4.15 (3.54–4.81)	4.52 (4.05–5.03)	4.40 (3.95–4.98)	4.39 (3.82–5.08)
Setpoint viral load >5 log ₁₀ copies/mL, No. (%)	22 (35%)	7 (16%)	2 (14%)	5 (25%)	36 (26%)
Viral load >5 log ₁₀ copies/mL					
First measurement, No. (%)	22 (35%)	6 (14%)	3 (21%)	7 (35%)	38 (27%)
Highest measurement, No. (%)	30 (48%)	10 (23%)	4 (29%)	11 (55%)	55 (39%)
Viral load 100–300 days post-seroconversion, No. ^a	57	37	13	18	125
Mean, log ₁₀ copies/mL (IQR)	4.53 (3.86–5.28)	4.07 (3.17–4.76)	4.58 (4.08–4.99)	4.37 (3.74–4.98)	4.36 (3.75–5.09)
Viral load >5 log ₁₀ copies/mL					
First measurement, No. (%)	23 (40%)	7 (19%)	2 (15%)	5 (28%)	37 (22%)
Highest measurement No. (%)	25 (44%)	8 (22%)	2 (15%)	7 (39%)	42 (34%)

^a Sample sizes in *env* and *gag* comparisons differ because of differences in availability of subtype data by gene.

C-infected participants identified during acute infection (Supplementary Table 1). At 100–300 days postseroconversion, mean viral loads were similar: 4.59 (IQR, 4.17–5.29) and 4.41 (IQR, 3.86–5.04) log₁₀ copies/mL in those with C and non-C infection respectively.

Finally, we evaluated confounding and effect modification by viral genetic linkage to the enrolled partner to determine whether setpoint was influenced by HIV-1 acquisition from an enrolled partner versus an outside partner. We found no evidence that the level of plasma viremia was modified by transmission linkage status.

DISCUSSION

We evaluated plasma HIV-1 load in seroconverters from East and southern African countries. Among 153 seroconverters

followed for a median of 1 year postseroconversion, we assessed the level of plasma viremia according to 2 criteria: (1) setpoint viral load, defined as any measurement ≥ 4 months after infection, and (2) viral load 100–300 days postseroconversion. In multiple analyses, we found no evidence that subtype C was associated with higher early plasma viral load, and thus our results do not support the hypothesis that higher or prolonged viremia in early infection in subtype C explains its dominance in southern Africa.

The levels of viremia in our cohort paralleled those in other African cohorts. Thirty-four percent of the subtype C-infected individuals in Botswana and South Africa described by Novitsky et al had plasma viral load >5 log₁₀ copies/mL at 100–300 days postseroconversion [7]. Among subtype C-infected participants in the Center for HIV Vaccine Immunology acute infection cohort, 31% had setpoint plasma viral load >5 log₁₀

Table 2. Associations Between HIV-1 Subtype C vs Non-Subtype C Infection and Plasma Viral Load Measurements

Plasma Viral Load Measurement	Subtype C, No. (%)	Non-Subtype C, No. (%)	Adjusted Odds Ratio ^a	95% CI	P Value
No. with setpoint viral load measurements	53	95			
Mean setpoint viral load >5 log ₁₀ copies/mL					
<i>env</i>	10 (19%)	27 (28%)	0.60	.26–1.39	.20
<i>gag</i>	7 (16%)	29 (30%)	1.02	.98–1.06	.10
First setpoint viral load >5 log ₁₀ copies/mL					
<i>env</i>	11 (21%)	32 (34%)	0.58	.26–1.30	.20
<i>gag</i>	6 (14%)	32 (33%)	0.33	.13–0.88	.03
Highest setpoint viral load >5 log ₁₀ copies/mL					
<i>env</i>	15 (28%)	44 (46%)	0.47	.23–.98	.04
<i>gag</i>	10 (23%)	45 (46%)	0.35	.15–.79	.01
No. with viral load 100–300 days postseroconversion measurements	46	84			
Mean >5 log ₁₀ copies/mL					
<i>env</i>	11 (24%)	27 (32%)	0.69	.30–1.59	.40
<i>gag</i>	7 (19%)	30 (34%)	0.48	.19–1.25	.10
Highest >5 log ₁₀ copies/mL					
<i>env</i>	12 (26%)	32 (38%)	0.58	.26–1.31	.20
<i>gag</i>	8 (22%)	34 (39%)	0.44	.18–1.11	.08

^a Odds ratio adjusted for age and gender. Data were not corrected for multiple comparisons.

copies/mL (unpublished data described in [12]). We found that the mean setpoint viral load was 4.39 log₁₀ copies/mL (IQR, 3.82–5.08) and that 25% of seroconverters had viral loads >5 log₁₀ copies/mL. Thus, our data confirm the pattern of setpoint viral load in the 4–5 log₁₀ copies/mL range, as observed in other African cohorts.

Our analysis had several strengths. Our study protocol was implemented consistently in 2 high HIV-1 prevalence regions with diverse strains of HIV-1, allowing comparisons of viral load between subtypes. Few prior studies have been able to directly compare the relationship between subtype and HIV-1 viremia because many subtypes are geographically isolated. Quarterly HIV-1 serologic testing to identify seroconverters increased precision in estimated dates of HIV-1 infection and permitted viral dynamics to be monitored from soon after infection through >1 year after infection. Finally, seroconverters' viral subtypes were determined by sequencing *env* and *gag*, with analyses of each gene showing similar results.

Some limitations should be considered. First, the majority of seroconverters had subtype A and C infections, with few cases of subtype D, G, or recombinant forms. Although the study was not powered to assess differences in viral setpoint in each subtype, the mean and IQR for viral load overlapped in all subtypes, suggesting that substantial differences are unlikely. Because host genetics affects viral setpoint [13], it would have been ideal to compare viral load by HIV-1 subtype in the same host genetic background, but this was not feasible because of the geographic distribution of subtypes in Africa. Thus, host genetic effects on viral load may confound our results. Furthermore,

several studies have found correlations in setpoint viral load among transmission pairs [14]. Accordingly, our study may be biased toward lower levels of viremia because HIV-1-infected partners in serodiscordant couples who have not transmitted over several years may have lower viral loads and may not fully reflect transmissions in other seroconverter populations. However, the similar plasma viral load distribution and viral setpoints in our cohort compared with other studies suggest that our study design did not substantially confound our results.

In conclusion, we compared levels of plasma viremia during early HIV-1 infection in East and southern Africa and found that seroconverters infected with subtypes A, C, D, and other subtypes had similar viral loads at setpoint and 100–300 days postseroconversion. Our analyses indicate that high viral loads (>5 log₁₀ copies/mL) are not more common in subtype C than in non-subtype C HIV-1 infection. Thus, our data do not support the hypothesis that higher early viremia explains the rapid and substantial spread of subtype C in southern Africa.

Supplementary Data

Supplementary materials are available at *The Journal of Infectious Diseases* online (<http://jid.oxfordjournals.org/>). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

Notes

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