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HIV-1 Viral Subtype Differences in the Rate of CD4+ T-Cell Decline Among HIV Seroincident Antiretroviral Naive Persons in Rakai District, Uganda

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Abstract

Background—Data on the effect of HIV-1 viral subtype on CD4$^+$ T-cell decline are limited.

Methods—We assessed the rate of CD4$^+$ T-cell decline per year among 312 HIV seroincident persons infected with different HIV-1 subtypes. Rates of CD4$^+$ decline by HIV-1 subtype were determined by linear mixed effects models, using an unstructured convariance structure.

Results—A total of 59.6% had D, 15.7% A, 18.9% recombinant viruses (R), and 5.8% multiple subtypes (M). For all subtypes combined, the overall rate of CD4$^+$ T-cell decline was −34.5 [95% confidence interval (CI), −47.1, −22.0] cells/μL per yr, adjusted for age, sex, baseline CD4$^+$ counts, and viral load. Compared with subtype A, the adjusted rate of CD4 cell loss was −73.7/μL/yr (95% CI, −113.5, −33.8, $P < 0.001$) for subtype D, −43.2/μL/yr (95% CI, −90.2, 3.8, $P = 0.072$) for recombinants, and −63.9/μL/yr (95% CI, −132.3, 4.4, $P = 0.067$) for infection with multiple HIV subtypes. Square-root transformation of CD4$^+$ cell counts did not change the results.

Conclusions—Infection with subtype D is associated with significantly faster rates of CD4$^+$ T-cell loss than subtype A. This may explain the more rapid disease progression for subtype D compared with subtype A.

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Keywords

HIV-1 subtypes; rate of $CD4^+$; cell decline; HIV disease progression

Introduction

Progressive untreated HIV infection is characterized by declines in the number and functionality of $CD4^+$ T cells, leading to immunodeficiency. The $CD4^+$ T-cell count is a marker of HIV disease progression and a criterion for initiation of antiretroviral therapy (ART) and changes in $CD4^+$ T-cell counts, together with viral load, are also used assess the response to ART.[1] Despite the evidence for a differential rate of HIV disease progression between HIV-1 subtypes,[2–6] the effect of HIV-1 subtypes on the rate of $CD4^+$ T-cell decline has not been well documented. Rates of $CD4^+$ T-cell decline between −33 and −77 cells/μL per year have been reported in North America and Europe where subtype B predominates[6,7] and studies in sub–Saharan Africa have estimated rates of decline ranging from −21.5 to −47.1 cells/μL per year, based primarily on data in HIV prevalent populations (in whom the date of HIV acquisition is unknown) or small and highly selected populations of seroincident individuals infected with subtype C.[8–10] Prior studies of the rates of $CD4^+$ T-cell loss by HIV-1 viral subtype have been hindered by the fact that there are few populations with multiple circulating subtypes and uniform modes of HIV transmission with known dates of infection, which would permit a direct assessment of the contribution of subtype per se to the rates of $CD4^+$ T-cell loss.

The population of Rakai district, Uganda, represents a unique opportunity to compare effects of different HIV-1 subtypes, because HIV subtypes A and D, and multiple recombinant strains cocirculate and are transmitted almost exclusively through heterosexual vaginal intercourse. We previously reported more rapid HIV disease progression for non-A subtypes compared with subtype A in the Rakai population.[4] In this paper, we describe rates of $CD4^+$ T-cell decline in seroincident ART-naive adults heterosexually infected with HIV subtypes A, D, circulating recombinant viruses (R), or multiple HIV subtypes (M) in rural Rakai, where 74% of the population belongs to 1 tribal group, the Baganda.

Subjects, Materials, and Methods

Study Population

Since 1994, the Rakai Health Sciences Program (RHSP) has conducted community-based cohort surveillance of adults aged 15–49 years. Consenting HIV-1 seroconverters identified between 1997 and 2002 were enrolled into a supplementary investigation—the Molecular Epidemiological Research (MER) study. The study procedures have been previously described.[4] Briefly, participants were seen at 1, 3, 6, and 12 months after seroconversion was detected, and annually thereafter. At each visit, a standardized questionnaire was administered, clinical examination was done, and blood was collected for HIV-1 subtyping, viral load quantification, and $CD4^+$ T-cell counts. Participants were provided with free voluntary HIV counseling and testing, condoms, and treatment for sexually transmitted infections and opportunistic infections. Study activities were conducted at mobile clinics (“hubs”) located in the communities and at the RHSP main clinic. Participants who did not return for scheduled visits were actively followed up in their homes.

The MER study was conducted from 1999 to early 2004, before routine Cotrimoxazole prophylaxis and ART became available in Rakai district. At the end of the MER study (2004), participant follow-up continued via the annual community cohort surveys. Starting in June 2004, with support from the President's Emergency Plan for AIDS Relief, HIV-infected participants were provided with free Cotrimoxazole and ART was initiated in persons with

CD4 counts ≤250 or World Health Organization stage 3 or 4 disease. All participants who were not yet ART eligible received CD4 screening and clinical examination to determine whether ART was indicated. Institutional Review Board approvals were obtained from Uganda Virus Research Institute's Science and Ethics Committee, Uganda National Council for Science and Technology, and Institution Review Boards of collaborating US institutions (Walter Reed Army Institute of Research, Columbia University, and Johns Hopkins University).

Laboratory Analysis

HIV serology was conducted using 2 enzyme immunoassays (EIAs) (Vironostika HIV-1, Organon Teknika, Charlotte, NC and Cambridge Biotech, Worcester, MA). EIA discordant and all concordant-positive seroconversion samples were confirmed by Western blot (HIV-1 Western blot, Bio-Merieux-Vitek, St. Louis, MO). HIV-1 plasma viral load was determined by a reverse-transcriptase polymerase chain reaction assay (AMPLICOR HIV-1 MONITOR version 1.5 Roche Molecular Systems, Branchburg, NJ) which has been validated in all group M subtypes of HIV-1, including subtypes A and D, which predominate in Uganda. The standard assay with a lower limit of detection of 400 copies/mL was used. $CD4^+$ T-cell counts were performed using a BD FACScount system until 2004 and BD Facscalibur flow cytometer thereafter. Syphilis was tested by use of rapid plasma reagin and positive rapid plasma reagins were confirmed by the *Treponema pallidum* particle aggluniation test. Testing was done following manufacturers protocols. HIV-1 subtypes were determined by the multiregion hybridization assay (MHA_{acd}) which can distinguish between pure, recombinants, and multiple subtypes for subtypes A, C, and D as previously described.[11,12] Briefly, viral RNA was extracted from plasma using the MagNA pure total nucleic acid robotic extraction procedure (Roche Diagnostics Corp., Indianapolis, IN). RNA was amplified for 5 regions (*gag*, *pol*, *vpu*, *env*, and *gp41*) of the HIV-1 genome by real-time PCR. A second round real-time PCR using a TaqMan probe specific for subtypes A, C, or D was performed on each of the first round products. HIV-1 subtype was assigned for each region based on the reactivity of the probes. Samples with the identical reactivity for each region of the viral genome were considered pure subtypes, those with reactivity to different probes in different regions were considered recombinants, and those that had a region of the virus where multiple subtype specific probes reacted were considered multiple virus strains.

Statistical Analysis

The study population comprised 312 HIV-1 incident persons with 2 or more $CD4^+$ T-cell measurements. Baseline characteristics were compared according to infecting HIV-1 subtype and differences were assessed using ANOVA for continuous variables and chi-square and Fisher Exact tests for categorical variables. The intervals between $CD4^+$ T-cell measurements were adjusted to an annual scale to facilitate the interpretation of rates of $CD4^+$ T cells decline per year. Rates of $CD4^+$ T cells decline per year were estimated using raw and square-root transformed $CD4^+$ T-cell values; square-root transformation provides variance stabilization for repeated measures analysis and has been previously used for $CD4^+$ T-cell trajectory analysis.[7,13,14] Multilevel linear mixed effects models with robust standard error estimation to account for correlation between repeated measurements within each individual were used to estimate the annual rate of CD4 cell decline, assuming an unstructured covariance structure.[15,16] The final model adjusted for age, sex, baseline CD4 cell counts, and HIV viral load ($\log_{10}$). Incident syphilis, which in previous studies was found to be associated with an increase in HIV viral load and a decrease in CD4 cell counts,[17,18] and body mass index were dropped from the model because they did not improve model fit. To estimate the natural rate of CD4 cell decline, follow-up was restricted to the period before the introduction of Cotrimoxazole prophylaxis and ART in the study population. Analyses were done using Stata Release 10 (Stata Corporation, 4905 Lakeway Drive, College Station, TX).

Results

Among the 312 persons, 59.6% infections were subtype D, 15.7% subtype A, 18.9% intersubtype recombinants (R), and 5.8% with multiple strains (M). The median interval between the estimated date of seroconversion and date of the baseline $CD4^+$ T-cell measurement was 10.3 (IQR; 8.2–30.7) months which did not differ by subtype ($P = 0.57$). The median total follow-up time was 35.3 months (IQR; 22.1–50.0). About a half (56.1%) were aged below 30 years, 59.3% were women, 11% had no formal education, and 76% had a body mass index of ≥20 at baseline (Table 1). The median baseline $CD4^+$ T-cell count was 524 (IQR; 384–717) and 54% of the participants had a baseline $CD4^+$ T-cell count of >500 cells/μL.

There were no statistically significant differences in the characteristics of persons infected with the 4 subtype groups with respect to age ($P = 0.16$), sex ($P = 0.46$), and mean $\log_{10}$ HIV viral load ($P = 0.75$) (Table 2). However, there were borderline statistical differences in baseline $CD4^+$ T-cell counts across subtypes; the mean baseline $CD4^+$ T-cell counts were 537 cells/μL for persons infected with subtype D, 568 cells/μL for recombinants, 632 cells/μL for subtype A, and 632 cells/μL for multiple HIV subtypes ($P = 0.05$). The baseline $CD4^+$ T-cell counts were significantly higher for subtype A relative to D ($P = 0.01$), but no statistically significant differences in baseline $CD4^+$ cell counts were observed between recombinant viruses and subtype A ($P = 0.19$). Men were older than women (31.4 versus 28.8 years, respectively, $P = 0.003$) and had higher HIV viral loads (4.93 versus 4.53, respectively, $P < 0.001$) (data not shown). Of the 28 pre-ART AIDS-associated deaths that occurred, 2% (1/48) were among subtype A–infected persons, 6.8% (4/55) among R, 11.1% (2/16) for M, and 11.3% (21/165) for subtype D Although across all subtypes differences in mortality were not statistically significant ($P = 0.21$), significant differences were observed between subtypes A and D ($P = 0.048$).

Regardless of infecting HIV-1 subtype, the overall adjusted rate of CD4 decline was −34.5 cells/yr [95% confidence interval (CI), −47.1, −22.0] cells/μL per year, adjusted for age, sex, baseline CD4 counts, and HIV viral load. Relative to subtype A, the adjusted rate of CD4 cell loss was −73.7/μL per year (95% CI, −113.5, −33.8, $P < 0.001$) for subtype D, 243.2/μL per year (95% CI, −90.2, 3.8, $P = 0.072$) for recombinants, and −63.9/μL per year (95% CI, −132.3, 4.4, $P = 0.067$) for infection with multiple HIV subtypes (Table 3). Square-root transformation of $CD4^+$ cell counts did not change the results; the adjusted slope of $CD4^+$ T-cell decline was significantly higher for subtype D relative to subtype A [−1.49/yr (95% CI,−2.36, −0.61, $P = 0.001$)]. Intersubtype recombinant viruses [−0.89/yr (95% CI, −1.92, 0.14, $P = 0.09$)] and multiple subtypes [−1.06/yr (95% CI; −2.56, 0.43, $P = 0.16$)] were also associated with higher adjusted slopes of $CD4^+$ T-cell loss than subtype A but the differences did not attain statistical significance.

Discussion

In ART and Cotrimoxazole-na-ve HIV-1 seroconverters in chronic stage of HIV disease, the adjusted annual rate of $CD4^+$ cell decline was significantly greater among persons infected with subtype D compared with those with subtype A. Higher rates of $CD4^+$ decline were also observed for recombinant viruses and multiple HIV-1 subtypes compared with subtype A, but the differences were of borderline statistical significance. We believe this is the first study to directly assess subtype differences in $CD4^+$ cell loss among HIV seroincident persons in a population with multiple circulating subtypes acquired through one predominant mode of transmission, heterosexual vaginal intercourse. Intravenous drug use is not practiced by this rural population, and anal intercourse is rare, as has been determined both by interview and through physical examination in Rakai Program sexually transmitted infection clinics. We also

previously published on a lack of association between HIV acquisition and receipt of injections in Rakai.[19] The relative homogeneity of the population (three quarters are members of the Baganda ethnic group), and of the mode of transmission, minimize confounding which may occur in settings where diverse modes of HIV transmission could potentially affect long-term health outcomes.

Our findings are consistent with previous reports of rapid HIV disease progression for non-A viruses.[2–6] Differences in rates of $CD4^+$ decline by HIV-1 subtype might partly be explained by differential chemokine coreceptor usage and virulence.[19–22] The emergence of CXCR4 (X4) tropic viruses is associated with a more rapid decline in $CD4^+$ T cells. Studies from this population and the population in the neighboring Masaka district have found higher frequencies of X4 tropism for subtype D compared with subtype A and recombinant viruses.[20–23]

For all subtypes, the overall adjusted annual rate of CD4 cell loss in Rakai was −34.5 (95% CI, −47.1, −22.0) cells/μL which is similar to rates reported in previous sub–Saharan African studies[9–11] and in North America and Europe.[6,7] We also found that subtype A was associated with higher baseline $CD4^+$ cell counts than subtype D (537 versus 632, cells/μL, $P = 0.01$). Because the median duration between seroconversion and baseline $CD4^+$ T-cell measurements was 10.3 months, lower baseline $CD4^+$ counts among subtype D–infected persons compared with those with subtype A could reflect early disease progression. Overall, the median $CD4^+$ cell count at baseline was 524 (IQR; 384–717) which is not statistically different from $CD4^+$ counts among HIV-uninfected adults in Uganda,[24] Kenya,[25] and Tanzania.[26]

This study has limitations. First, we did not control for host genetics yet certain genes (HLA-B and C) are associated with HIV disease progression[27] but it is unlikely that genetic heterogeneity would vary by subtype of infecting virus. Secondly, because of small numbers, $CD4^+$ cell decline could not be assessed by levels of HIV viral load. Third, $CD4^+$ decline in advanced stages of HIV disease could not be determined because the period of observation before the availability of Cotrimoxazole prophylaxis and or ART in late 2004 was not sufficiently long. Lastly, CD4 decline rates were modeled linearly yet the rate of CD4 decline immediately after seroconversion differs from that in chronic or late stage disease. Because most participants were first assessed 10 months after infection and the duration of observation was relatively short, we believe they were largely in latent stage of disease during which time CD4 decline is likely to be more linear.

In conclusion, among persons in latent stage of HIV disease, non-A subtypes (ie, subtype D, recombinants, or multiple strains incorporating subtype D) have a higher rates of $CD4^+$ cell loss compared with subtype A. In areas such as sub–Saharan Africa where the prevalence of subtype D is high, it may be beneficial to initiate ART at CD4 cell counts greater than 200 cells/μL[28] and to monitor $CD4^+$ counts more frequently before ART initiation.

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TABLE 1

Descriptive Characteristics of the Study Population (N = 312)

Age at enrolment (yrs)	
16–29, n (%)	175 (56.1%)
30–39, n (%)	92 (29.5%)
40+, n (%)	45 (14.4%)
Sex	
Male, n (%)	127 (40.7%)
Female, n (%)	185 (59.3%)
Highest education level	
No education, n (%)	34 (10.9%)
Primary, n (%)	198 (63.5%)
Secondary or more, n (%)	80 (25.6%)
$CD4^+$ cell counts data	
Mean initial count (SD)	563 (240)
Median initial count (IQR)	524 (384–717)
Median no. of $CD4^+$ measurements (IQR)	3 (2–4)
Median time interval between consecutive measurements [months(IQR)]	10.3 (3.15–12)
Median interval between seroconversion and initial $CD4^+$ measurements [months(IQR)]	10.3 (8.2–30.7)
Analyses follow up time (mo)	
Mean (range)	37.9 (2.0–83.5)
Median (IQR)	35.6 (22.4–51.0)
Initial $CD4^+$ cell count	
>500, n (%)	169 (54.2%)
351–500, n (%)	85 (27.2%)
≤350, n (%)	58 (18.6%)
Body mass index	
≤20, n (%)	75 (24.0%)
20–24.9, n (%)	196 (62.8%)
25–29.9, n (%)	41 (13.1%)
HIV load (log_{10})	
Mean (SD)	4.69 (0.72)
Median (IQR)	4.76 (4.23–5.27)
HIV-1 subtype	
D, n (%)	186 (59.6%)
R, n (%)	59 (18.9%)
A, n (%)	49 (15.7%)
M, n (%)	18 (5.8%)

TABLE 2

Comparison Study Population Characteristics by Infecting HIV-1 Viral Subtype

	HIV-1 viral subtype					
Characteristic	**All (N = 312)**	**A (n = 49)**	**D (n = 186)**	**R (n = 59)**	**M (n = 18)**	***P***
Age (yrs)						
16–29	175 (56.1%)	34 (19.4%)	94 (53.7%)	36 (20.6%)	11 (6.3%)	
30–39	92(29.5%)	9 (9.8%)	66 (71.4%)	13 (14.1%)	4 (4.3%)	
40+	45(14.4%)	6 (13.3%)	26 (57.8%)	10 (22.2%)	3 (6.7%)	0.16
Sex						
Male	127 (40.7%)	20 (15.7%)	70 (55.1%)	29 (22.8%)	8 (6.3%)	
Female	185 (59.3%)	29 (15.7%)	116 (62.7%)	30 (16.2%)	10 (5.4%)	0.46
Baseline $CD4^+$ (cells/μL)						
Mean (SD)	563 (240.5)	632 (275.0)	537 (230.1)	568 (236.5)	632 (228.5)	0.05
No. of CD4 measurements						
Mean (SD)	4.4 (1.6)	5.1 (1.6)	4.8 (1.6)	5.1 (1.7)	3.9 (0.8)	0.11
Median (IQR)	4(3–5)	5 (4–6)	5 (4–6)	5 (4–6)	4 (3–5)	0.12
Plasma HIV RNA (log_{10})						
Mean (SD)	4.69 (0.72)	4.69 (0.69)	4.75 (0.73)	4.62 (0.66)	4.84 (0.57)	0.75
Median (IQR)	4.76 (4.23–5.27)	4.59 (4.35–5.16)	4.84 (4.22–5.37)	4.73 (4.15–5.15)	4.85 (4.43–5.12)	0.20

TABLE 3

Rates of $CD4^+$ T-Cell Decline Per Year by HIV-1 Viral Subtype, Adjusted for Age, Sex, Baseline $CD4^+$ T-Cell Counts, and Plasma HIV RNA Load (Viral Load)

	Rates on raw $CD4^+$ counts			Rates on square-root scale		
HIV-1 subtype	**Rate**	**95% CI**	***P***	**Rate**	**95% CI**	***P***
D	−73.7	(−113.5, −33.8)	<0.001	−1.49	(−2.36, −0.61)	0.001
Recombinants	−43.2	(−90.2, 3.8)	0.072	−0.89	(−1.92, 0.14)	0.09
Multiple strains	−63.9	(−132.3, 4.4)	0.067	−1.06	(−2.56, 0.43)	0.16
A (referent)						