Effect of Human Immunodeficiency Virus Type 1 (HIV-1) Subtype on Disease Progression in Persons from Rakai, Uganda, with Incident HIV-1 Infection

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(See the editorial commentary by Kuritzkes on pages 638–9.)

Background. Human immunodeficiency virus type 1 (HIV-1) subtypes differ in biological characteristics that may affect pathogenicity.

Methods. We determined the HIV-1 subtype–specific rates of disease progression among 350 HIV-1 seroconverters. Subtype, viral load, and CD4+ cell count were determined. Cox proportional hazards regression modeling was used to estimate adjusted hazard ratios (HRs) of progression to acquired immunodeficiency syndrome (AIDS) (defined as a CD4+ cell count of ≤250 cells/mm³) and to AIDS-associated death.

Results. A total of 59.1% of study subjects had subtype D strains, 15.1% had subtype A, 21.1% had intersubtype recombinant subtypes, 4.3% had multiple subtypes, and 0.3% had subtype C. Of the 350 subjects, 129 (37%) progressed to AIDS, and 68 (19.5%) died of AIDS. The median time to AIDS onset was shorter for persons with subtype D (6.5 years), recombinant subtypes (5.6 years), or multiple subtypes (5.8 years), compared with persons with subtype A (8.0 years; P = .022). Relative to subtype A, adjusted HRs of progression to AIDS were 2.13 [95% confidence interval (CI), 1.10–4.11] for subtype D, 2.16 [95% CI, 1.05–4.45] for recombinant subtypes, and 4.40 [95% CI, 1.71–11.3] for multiple subtypes. The risk of progression to death was significantly higher for subtype D (adjusted HR, 5.65; 95% CI, 1.37–23.4), recombinant subtypes (adjusted HR, 6.70; 95% CI, 1.37–23.4), and multiple subtypes (adjusted HR, 7.67; 95% CI, 1.27–46.3), compared with subtype A.

Conclusions. HIV disease progression is affected by HIV-1 subtype. This finding may impact decisions on when to initiate antiretroviral therapy and may have implications for future trials of HIV-1 vaccines aimed at slowing disease progression.
counting for >95% of global infections [1, 2, 8]. Differences in the genetic characteristics of HIV may play a role in the dynamics of HIV infection. HIV-1 is more virulent than HIV type 2 (HIV-2) [3, 4], and group M viruses appear to have a higher replication and transmission fitness than group O or HIV-2 strains [9]. HIV-1 subtypes also differ in biological characteristics that may affect pathogenicity, such as chemokine coreceptor use, syncytium-forming properties, viral fitness, and plasma viral loads [10–13]. These differences may theoretically influence infectivity and transmissibility, the rate of disease progression, and the response to antiretroviral therapy (ART).

Studies in sub-Saharan Africa have found higher rates of disease progression among individuals infected with subtype D virus, compared with persons infected with subtype A virus [10, 14–16]. However, the populations in these studies consisted primarily of persons with prevalent HIV-1 infection of unknown duration, and viral load was not controlled for in most analyses. Additionally, HIV-1 subtype data were generated by either heteroduplex mobility assay or serologic analysis of the response to subtype-specific V3 peptides, both of which have a limited ability to identify recombinant forms of the virus. Thus, the interpretation of results from these studies is hampered by a lack of information on the interval between seroconversion and AIDS onset and by the inability to adjust for viral load, which is a strong predictor of HIV-1 disease progression [17–19]. Also, the role of intersubtype-recombinant strains (hereafter, “recombinant subtypes”) and multiple HIV strains on disease progression was not assessed. To address these issues, we assessed the time between infection onset and progression to a CD4+ cell count of ≤250 cells/mm³ and to AIDS-associated death among persons with seroincident infection due to subtype A or D strains, recombinant subtypes, or multiple subtypes in a general population cohort in the Rakai district of Uganda.

SUBJECTS, MATERIALS, AND METHODS

Study population. Since 1994, the Rakai Health Sciences Program (RHSP) has conducted annual surveillance in a community-based cohort of adults aged 15–49 years. Participants who provided written informed consent were enrolled in the study. At each survey visit, a standardized questionnaire on sociodemographic characteristics, sexual behaviors, and health status was administered in private by same-sex interviewers, and venous blood was collected for HIV-1 testing [20]. All HIV-1 seroconverters identified during the annual cohort surveys between 1997 and 2002 were enrolled into a supplementary investigation known as the Molecular Epidemiological Research (MER) study. The MER study was conducted during 1999–2004, before ART became available in Rakai. MER study participants were seen 1, 3, 6, and 12 months after seroconversion was detected and annually thereafter. At each visit, a standardized questionnaire was administered, and a clinical examination was performed. Venous blood was collected for HIV-1 subtyping, viral load quantification, and determination of the CD4+ cell count. Participants were provided with free voluntary HIV counseling and testing, condoms, and treatment for sexually transmitted infections and opportunistic infections.

Enrollment and follow-up examinations were conducted at mobile clinics (referred to as “hubs”) in the communities and at the RHSP main clinic. Participants who did not return for follow-up examination were actively followed up in their homes. In case of death, a structured verbal autopsy questionnaire was administered to the person closest to the deceased individual, to obtain information on date and cause of death. Verbal autopsy forms were reviewed by a physician, who determined whether death was due to AIDS or to an AIDS-related illness. At the end of the MER study (in 2002), participant follow-up continued via the annual community cohort surveys, and beginning in June 2004, eligible participants received free treatment with trimethoprim-sulfamethoxazole and ART, funded by the President’s Emergency Plan for AIDS Relief. Institutional review board approvals were obtained from the Uganda Virus Research Institute’s Science and Ethics Committee, the Uganda National Council for Science and Technology, and collaborating US institutions (Walter Reed Army Institute of Research [Silver Spring, MD], Columbia University [New York, NY], and Johns Hopkins University [Baltimore, MD]).

Laboratory analysis. All participants had 2 serum specimens tested simultaneously for HIV-1 by an enzyme immunoassay [EIA] (Vironostika HIV-1 [Organon Teknika and Cambridge Biotech]). Western blot analysis (HIV-1 Western Blot [bioMerieux-Vitek]) was used to determine the serostatus of specimens with discordant results and to confirm the positive serostatus of specimens with concordant positive results. The plasma HIV-1 load was determined using a reverse-transcriptase polymerase chain reaction (PCR) assay (Amplicor HIV-1 Monitor, version 1.5 [Roche Molecular Systems]) that has been validated for all group M subtypes of HIV-1, including subtypes A and D, which predominate in Uganda. The standard reverse-transcriptase PCR, which has a lower detection limit of 400 copies/mL, was used. CD4+ cell counts were determined using the BD FacsCalibur system through 2003, after which the BD FacsCount system was used. Testing was done in accordance with the manufacturers’ protocols.

HIV-1 subtypes were assigned on the basis of findings of the MHA-assay assay, as described elsewhere [21, 22]. In brief, viral RNA was extracted from plasma, using the Magna pure total nucleic acid robotic extraction procedure (Roche Diagnostics). RNA at 5 regions of the HIV-1 genome (gag, pol, vpu, env, and gp41) was amplified by real-time PCR. A second real-time PCR that used a Taqman probe specific for subtypes A, C, or D was performed on each of the first-round products. An HIV-1 subtype was assigned for each region on the basis of the reactivity of the probes. Samples with identical reactivity for each region of
the viral genome were considered to consist of a pure subtype, those with reactivity to different probes in different regions were considered to consist of a recombinant subtype, and those that had a region of the virus where multiple subtype–specific probes reacted were considered to consist of multiple subtypes.

**Statistical analysis.** Enrollment characteristics were compared for persons infected with different HIV-1 subtypes. Analysis of variance was used for continuous variables, and chi-square analysis and the Fisher exact test were used for categorical variables.

Time-to-event analyses were used to assess the effect of HIV-1 subtype on disease progression following infection. The time of HIV infection was estimated as the midpoint between the last seronegative and the first seropositive survey visits. HIV-1 subtype was the main exposure variable, and progression to AIDS (defined as a CD4+ cell count of ≤250 cells/mm³) and death due to AIDS were the study end points. A CD4+ cell count of ≤250 cells/mm³ was used to define AIDS onset, because this is the level at which persons become eligible for ART in the Rakai ART program. Persons who initiated ART were censored at their last pre-ART visit. The time of AIDS onset was estimated as the midpoint between the last visit with a CD4+ cell count of ≥250 cells/mm³ and the first visit with a CD4+ cell count of ≤250 cells/mm³. The time to achieving a CD4+ cell count of ≤250 cells/mm³ was calculated as the interval between the estimated date of infection and the estimated date when the CD4+ cell count decreased to ≤250 cells/mm³. For 22 participants who did not have CD4+ cell count data recorded before death, the date of death was used as the estimated date of AIDS onset. The time to AIDS-associated death was calculated as the interval between the estimated date of infection and the date of death. Deaths from non-AIDS-related causes (e.g., traffic accidents) were censored as nonevents at the time of death. Viral loads were log₁₀ transformed for analysis.

Multivariable Cox proportional hazards regression analysis was used to estimate adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) of progression to AIDS and to death due to HIV-1 subtype D, recombinant HIV-1 subtypes, and multiple HIV-1 subtypes relative to HIV-1 subtype A. To account for multiple comparisons between subtypes, the type I error (α) was adjusted using Holm’s procedure [23]. This is a step-up procedure whereby individual P values are ranked in increasing order and the adjusted α for a given hypothesis [H_{00}] is estimated as P(i) < α/(G-i + 1), where G is the number of related hypotheses being tested. For the 3 comparisons of non–subtype A strains (i.e., subtype D, recombinant subtypes, and multiple subtypes) with subtype A, the adjusted α were 0.017 (0.05/3), 0.025 (0.05/2), and 0.05 (0.05/1), respectively. Differences in rates of progression between non–subtype A strains were assessed by estimating HRs for the following comparisons, using the same adjusted α described above: recombinant subtypes versus subtype D strains, multiple subtypes versus subtype D strains, and multiple subtypes versus recombinant subtypes.

The proportional hazards assumption was tested by graphical methods and by goodness-of-fit analysis, using Schoenfeld residuals. In univariate analyses, a P value of <.10 and biological plausibility were used to select covariates for multivariable models. Analyses were done using Stata, version 8.0 (Stata).

**RESULTS**

Population characteristics. Of the 491 HIV-1 seroconverters from the cohort, 488 (99.4%) were enrolled in MER, and 3 (0.6%) refused enrollment. HIV subtype data were available for 350 enrolled seroconverters (71.7%); 207 (59.1%) had subtype D, 53 (15.1%) had subtype A, 74 (21.1%) had a recombinant subtype, 15 (4.3%) had multiple subtypes, and 1 person (0.3%) had subtype C. The single subtype C case was eliminated from further analyses. All recombinant subtypes involved subtypes A and D. Persons with subtype data were older than those for whom subtype data were not available (mean age, 29.3 vs. 26.7 years; P = .002) but did not differ with respect to other sociodemographic characteristics. Among the 349 persons with incident HIV-1 infection included in analyses of disease progression, 60% were females, and 76% were aged <35 years. Twenty-two participants (6.3%) did not have CD4+ cell data recorded before death; 14 were infected with subtype D, and 8 were infected with recombinant subtypes.

Table 1 shows demographic and clinical characteristics of participants, according to HIV-1 subtype. Baseline plasma viral load, sex, and age at enrollment did not differ with respect to HIV-1 subtype. However, the median age at enrollment was 29 years (interquartile range [IQR], 25–35 years) among men, compared with 27 years (IQR, 22–33 years) among women (P < .02), and the mean viral load among men was 4.74 log₁₀ copies/mL, compared with 4.53 log₁₀ copies/mL among women (P = .007). Overall, 129 individuals (37.0%) achieved CD4+ cell counts of ≤250 cells/mm³, 74 (21.2%) died of any cause, 68 (19.5%) died of AIDS-related causes, and 14 (4.0%) were lost to follow-up. A significantly lower percentage of persons with subtype A (18.9%) progressed to a CD4+ cell count of ≤250 cells/mm³, compared with persons with subtype D (39.6%), recombinant subtypes (39.2%), or multiple subtypes (53.3%) (P = .03). Subtype A was also associated with a significantly lower proportion of AIDS-associated deaths, compared with other non-A subtypes combined (P = .004). Mortality due to AIDS was higher among men (24.1%) than among women (16.3%); this difference was not statistically significant (P = .07) but is epidemiologically important. Persons lost to follow-up did not differ from those who remained under observation with regard to sex (P = .42), age (P = .08), HIV-1 subtype (P = .77), and plasma viral load (P = .85). Seventy-five persons (21.5%) progressed to World Health Organization (WHO) clinical stage 3 or 4 disease, of whom 22 (29.3%) progressed to WHO clinical stage 3 or 4 disease before their CD4+...
cell count decreased to <250 cells/mm³. However, for the remaining 53 subjects whose CD4⁺ cell count decreased to ≤250 cells/mm³ before the onset of clinical AIDS, the median time between reaching a CD4⁺ cell count of ≤250 cells/mm³ to onset of clinical AIDS was 3.6 years.

**Time to onset of AIDS.** The median times between the estimated onset of infection and the onset of AIDS was 6.48 years (IQR, 4.50–8.05) overall, 6.49 years (IQR, 4.15–7.85) years for subtype D, 5.57 years (IQR, 4.51–7.46) years for recombinant subtypes, 5.80 years (IQR, 3.94–6.46) years for multiple subtypes, and 8.05 years for subtype A. Over the observed range of the data, the probability of progressing to AIDS did not reach 75% for infection with subtype A; hence, the upper quartile for this group could not be estimated. In sensitivity analyses excluding the 22 participants with no CD4⁺ cell data recorded before death, the median times between onset of infection and the onset of AIDS were 6.68 years (IQR, 4.60–8.20) years overall, 6.54 years (IQR, 4.57–9.02) years for subtype D, 6.98 years (IQR, 4.53–7.46) years for recombinant subtypes, 5.80 years (IQR, 3.94–6.45) years for multiple subtypes, and 8.05 years for subtype A. Exclusion of persons who were lost to follow-up and the 22 persons with no CD4⁺ cell count recorded before death only changed the median time to onset of AIDS for persons with multiple subtypes to 4.36 years (IQR, 2.85–7.18 years). Figure 1 shows the Kaplan-Meier survival curves from the estimated time of infection to AIDS onset, according to HIV-1 subtype. Infection with subtype A was associated with a longer time to progression to a CD4⁺ cell count of ≤250 cells/mm³, compared with infection with the other subtypes (P = .022, by the log-rank test).

Table 2 shows HRs for the association between HIV-1 subtypes and progression to a CD4⁺ cell count of ≤250 cells/mm³. Covariates included in the multivariable model were age, sex, educational status, baseline body mass index, genital ulcer disease, plasma viral load, and HIV-1 subtype. Covariates that did not improve model prediction were dropped, but sex and age were retained in the final model because viral load was higher in men than in women, men were older than women, and age of infection is known to be inversely associated with survival. Each covariate in the multivariable model met the proportional hazards assumption (P = .45 for the global test, using Schoenfeld residuals). After controlling for viral load, age, and sex and adjusting for multiple comparisons, we found that infection with multiple subtypes (adjusted HR, 4.40; 95% CI, 1.71–11.3; P < .002), subtype D (adjusted HR, 2.13; 95% CI, 1.10–4.11; P < .024), and recombinant subtypes (adjusted HR, 2.16; 95% CI, 1.05–4.45; P < .036) resulted in significantly faster progression to AIDS than did infection with subtype A. Infection with multiple subtypes was associated with faster progression to AIDS, compared with recombinant subtypes (adjusted HR, 3.23; 95% CI, 1.32–7.95; P = .01). The hazard of progression to AIDS

**Figure 1.** Kaplan-Meier estimates of the time from onset of HIV-1 infection to onset of AIDS (defined as a CD4⁺ cell count of ≤250 cells/mm³), by HIV-1 subtype, in a population from Rakai, Uganda. M, multiple subtypes; R, intersubtype-recombinant strains.
was higher for multiple-subtype infection than for subtype D infection, but this was of borderline significance (adjusted HR, 2.06; 95% CI, 0.97–4.38; P = .06). There was no difference in progression between infection with recombinant subtypes and infection with subtype D (adjusted HR, 1.01; 95% CI, 0.66–1.55; P = .92). A 1-log_{10} increase in plasma viral load was associated with a significantly increased adjusted HR of progression to AIDS (adjusted HR, 2.28; 95% CI, 1.72–3.01; P < .001).

**Time to death.** Over the observed range of the data, the probability of death did not reach 50%, so the median time from infection onset to death could not be estimated. Overall, there was a 25% probability of death within 5.80 years after HIV infection was acquired. A mortality rate of 25% occurred within 5.54 years after infection with subtype D, 5.30 years for recombinant subtypes, and 4.34 years for multiple subtypes. The probability of death did not reach 25% for infection with subtype A, indicating a longer duration of survival, compared with infection due to non-A subtypes. Figure 2 shows the Kaplan-Meier survival curves of time from infection to death due to AIDS. Infection with subtype A was associated with a significantly longer survival duration, compared with infection due to non-A subtypes (P = .022, by the log-rank test).

Table 3 shows HRs for the effect of HIV-1 subtype on progression to death. In univariate analyses, viral load, HIV-1 subtype, and age were statistically significant predictors of progression to death, but in multivariable analyses, only viral load and HIV-1 subtype remained significant. Relative to subtype A, progression to death was significantly higher for infection with subtype D (adjusted HR, 5.65; 95% CI, 1.37–23.4; P = .017), recombinant subtypes (adjusted HR, 6.70; 95% CI, 1.56–28.8; P = .011), and multiple subtypes (adjusted HR, 7.67; 95% CI, 1.27–46.3; P = .026). A 1-log_{10} increase in viral load was associated with an adjusted hazard of death of 1.98 (95% CI, 1.35–2.90; P < .001).

The proportional hazards assumption was met by all covariates in the multivariate model (P = .99, by the Schoenfeld residuals test). No differences in progression to death were observed between recombinant subtypes and subtype D (adjusted HR, 1.19; 95% CI, 0.69–2.04; P = .54), between multiple subtypes and subtype D (adjusted HR, 1.34; 95% CI, 0.41–4.39; P = .63), and between multiple subtypes and recombinant subtypes (adjusted HR, 1.32; 95% CI, 0.37–4.66; P = .67).

**DISCUSSION**

We found that persons infected with subtype D, recombinant subtypes, and multiple subtypes had faster progression from infection onset to AIDS (defined as a CD4 \(^+\) cell count of \(\leq 250\) cells/mm\(^3\)) and to death, compared with persons infected with subtype A. We also found that infection with multiple subtypes was associated with faster progression to AIDS, compared with
infection with recombinant subtypes, but no differences in progression to AIDS were observed between multiple subtypes and subtype D and between recombinant subtypes and subtype D. The observed differences in rates of disease progression may partly be explained by subtype differences in coreceptor tropism. In the course of HIV-1 infection, the emergence of CXCR4 (X4) tropic viruses is associated with a more rapid decrease in the CD4 cell count. Subtype D has been shown to have a higher frequency of syncytium formation and X4 use, compared with other subtypes [11, 13, 24].

The finding of faster progression for subtype D relative to A in this study supports findings from previous studies that included predominantly HIV-1–seroprevalent individuals with unknown durations of infection. Three previous Ugandan studies and 1 study involving pregnant women in Tanzania found faster progression for subtype D, compared with subtype A [10, 14, 15, 25]. In a study of female sex workers with known durations of infection in Dakar, Senegal, progression to AIDS was also faster among women infected with non-A subtypes, relative to those infected with subtype A [26]. The finding of rapid progression in persons infected with recombinant subtypes or with multiple subtypes is novel, and in this study we found that infection with multiple subtypes was associated with faster disease progression, compared with infection with a single subtype. These findings suggest that infection with subtype A is less aggressive than infection with non-A subtypes. This has implications for future trials of HIV-1 vaccines aimed at slowing disease progression [27], in which it will be necessary to assess subtype-specific responses.

We found an overall median time from infection to AIDS of 6.5 years in Rakai, which is shorter than the 9.4-year duration estimated in the neighboring Masaka district [28] and in studies from industrialized countries. The difference between estimates from Rakai and Masaka may be attributable to differences in the relative prevalence of subtype A, which is associated with slower disease progression. In Masaka, the frequency of subtype A was 36%–40% [14, 15], compared with 15% in Rakai [29]. Furthermore, the onset of AIDS in the Masaka study was defined clinically as WHO clinical stage 3 and 4 disease. However, a decrease in the CD4 cell count precedes the onset of symptoms or signs of AIDS, so use of clinical staging is likely to overestimate the time from infection onset to AIDS onset. In this study, the median time from achievement of a CD4 cell count of $\leq 250$ cells/mm$^3$ to clinical AIDS was 3.6 years, implying that estimation of AIDS-free survival by use of clinical AIDS as an end point in Rakai would yield results similar to those from Masaka and industrialized countries. We believe that CD4 cell counts are more appropriate for estimating the time from infection to onset of immunodeficiency requiring ART.

Over the observed range of data in our study, the probability of death did not reach 50%, so the median time from HIV infection to death could not be estimated. Similar findings were observed in another study from Masaka, where median survival times could not be estimated over 6 years of follow up [14]. We observed a large sample of HIV-1 seroconvertors with a known time of HIV infection in a community-based population cohort, so we believe that these results are representative of rural Uganda. A study of subtype E infections in Thailand estimated a median time from infection to death of 7.7 years (unpublished data), which is compatible with survival times for subtype D and recombinant subtypes in the present study (figure 1). In this study, baseline viral load was a strong predictor of progression to AIDS and to death, but age and sex did not significantly predict disease progression.

This study is not without limitations. First, information about dates and causes of death was obtained by use of verbal autopsy, since medical certification of death does not occur in these rural communities. However, any biases caused by inaccurate dates

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<th>Table 3. Hazard ratios (HRs) for progression from HIV-1 seroconversion to AIDS-associated death, Rakai, Uganda.</th>
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**NOTE.** M, multiple subtypes; R, intersubtype-recombinant strains.

* Results were significant after adjusting for multiple comparisons.
and assignment of causes of death would be expected to be non-
differential across HIV subtypes, and misclassification, if it oc-
curred, is likely to have biased the observed results towards the
null. Second, use of the date of death as the date of AIDS onset
for the 22 persons for whom CD4+ cell counts were not mea-
sured before death could potentially result in overestimation of
their AIDS-free survival. We believe this did not affect our over-
all findings, since 14 of these participants had subtype D and 8
had recombinant subtypes, both of which led to faster disease
progression to AIDS, compared with subtype A. Furthermore, a
sensitivity analysis excluding these 22 persons showed an in-
crease in the median time to AIDS overall and for subtype D and
recombinant subtypes. Finally, we did not study the role of host
genetics on HIV disease progression, yet certain genes (HLA-B
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In conclusion, disease progression is faster with subtype D
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rating subtype D than with subtype A. Determination of HIV-1
subtype may be important in trials of HIV vaccines aimed at
slowing disease progression and in the management of HIV-
infected individuals, particularly with regard to deciding the
CD4+ cell count at which to initiate ART.

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