Rapid Disease Progression in HIV-1 Subtype C–Infected South African Women

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Background. Whereas human immunodeficiency virus (HIV) subtype B–infected individuals generally progress to AIDS within 8–10 years, limited data exist for other clades, especially from Africa. We investigated rates of HIV disease progression of clade C–infected South African women.

Methods. Prospective seroincidence cohorts in KwaZulu-Natal were assessed for acute HIV infection monthly (n = 245) or every 3 months (n = 594) for up to 4 years. Rapid disease progression was defined as CD4 decline to <350 cells/μL by 2 years postinfection. Serial clinical and laboratory assessments were compared using survival analysis and logistic regression models.

Results. Sixty-two women were identified at a median of 42 days postinfection (interquartile range, 34–59), contributing 282 person-years of follow-up. Mean CD4 count dropped by 39.6% at 3 months and 46.7% at 6 months postinfection in women with preinfection measurements. CD4 decline to <350 cells/μL occurred in 31%, 44%, and 55% of women at 1, 2, and 3 years postinfection, respectively, and to <500 cells/μL in 69%, 79%, and 81% at equivalent timepoints. Predictors of rapid progression were CD4 count at 3 months postinfection (hazard ratio [HR], 2.07; 95% confidence interval [CI], 1.31–3.28; $P = .002$), setpoint viral load (HR, 3.82; 95% CI, 1.51–9.67; $P = .005$), and hepatitis B coinfection (HR, 4.54; 95% CI, 1.31–15.69; $P = .017$). Conversely, presence of any of HLAB*1302, B*27, B*57, B*5801, or B*8101 alleles predicted non–rapid progression (HR, 0.19; 95% CI, .05–.74; $P = .016$).

Conclusions. Nearly half of subtype C–infected women progressed to a CD4 count <350 cells/μL within 2 years of infection. Implementing 2013 World Health Organization treatment guidelines (CD4 count <500 cells/μL) would require most individuals to start antiretroviral therapy within 1 year of HIV infection.

Keywords. HIV disease progression; acute HIV infection; subtype C; viral load; women.

Human immunodeficiency virus (HIV) disease progression is highly variable between individuals and populations and is determined by genetic, immunologic, virologic, and environmental factors [1–3]. $CD4^+$ T-cell decline has been recognized as one of the major markers of the rate of HIV disease progression. Once CD4 counts drop below 200 cells/μL, the risk of opportunistic infections and death increases dramatically. In addition to CD4 decline, disease progression can be defined by time to antiretroviral therapy (ART) initiation, diagnosis of AIDS-defining illnesses, or death. Whereas the majority of HIV-infected individuals (70%–80%) fall into an intermediate category, rapid progression and long-term nonprogression represent extreme phenotypes with respect to CD4 decline [4]. In addition, the infecting subtype can have a significant impact on the rate of CD4 decline [5, 6]. This has been best defined for clades A and D in East Africa,

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where studies demonstrated a shorter median time to AIDS in subtype D–infected individuals than in subtype A–infected individuals [7–9]. Studies from sub-Saharan Africa suggest faster disease progression in subtype C–infected individuals [10, 11], despite observations that subtype C may replicate less efficiently than subtype B [12].

A major immunologic predictor of progression is the level of host immune activation, which predicts rates of CD4 decline more accurately than plasma viral load (VL) [13]. African populations have reportedly higher levels of immune activation than US populations, possibly linked to a higher burden of comorbidities and micronutrient deficiencies [14, 15]. Indirect immune activation caused by microbial translocation and loss of gut-associated CD4 cells has also been demonstrated in HIV rapid progressors [16]. Another major host predictor of disease progression is the human leukocyte antigen (HLA) background. HLA-B35, B8, B45, and B53 have been associated with rapid progression, whereas HLA-B57 and B27 are more common in slow progressors [11, 17–19].

Results from mostly subtype B–infected cohorts suggest that rapid progression is uncommon, with only about 5% of individuals progressing from acute HIV infection to AIDS within 3 years [20, 21]. However, there are limited data on disease progression in other subtypes, especially from prospective African cohorts infected with subtype C. This study describes HIV type 1 (HIV-1) disease progression in South African women and identifies host and viral factors associated with progression.

METHODS

Study Population

Between August 2004 and May 2005, a cohort of HIV-uninfected women at high risk of HIV acquisition was enrolled into the Centre for the AIDS Programme of Research in South Africa (CAPRISA) 002 Acute Infection Study, recruited at 2 sites within the province of KwaZulu-Natal in South Africa—an urban site in Durban and a rural site in Vulindlela. The aim of the study was to describe immunologic, virologic, and clinical characteristics of HIV-1 subtype C acute infection and investigate the natural history of HIV-1 subtype C infection [22]. Women aged ≥18 years who self-reported as sex workers or having >3 sexual partners within the last 3 months were screened. Those testing HIV negative were offered enrollment and followed for up to 4 years, with monthly testing to identify acute HIV infections [23]. In addition, women were also recruited from a rural family planning and sexually transmitted infection (STI) clinics in Durban [24] with quarterly HIV testing and follow-up. Written informed consent was obtained from all participants, and ethical approval for the study was granted by the University of KwaZulu-Natal (E013/04), University of Cape Town (025/2004), and University of the Witwatersrand (M040202).

HIV Testing and Time of Infection

HIV diagnosis was based on antibody and/or nucleic acid detection. Two point-of-care antibody tests were used, the third-generation Determine (Abbott Laboratories, Abbott Park, Illinois) and Capillus (Trinity Biotech, Jamestown, New York). An HIV enzyme-linked immunosorbent assay was performed to confirm HIV diagnosis using the HIV enzyme immunoassay BEP 2000 (Dade Behring, Marburg, Germany). HIV reverse transcription polymerase chain reaction (RT-PCR) testing was performed at every testing with antibody-negative results. COBAS Amplicor version 1.5 RT-PCR testing (Roche Diagnostics, Rotkreuz, Switzerland) was performed using a pooling strategy of 24 samples per pool [25, 26]. Time of infection was estimated as the midpoint between last antibody-negative and first antibody-positive test or 14 days before a positive RT-PCR result for those diagnosed preseroconversion.

Once HIV diagnosis was confirmed, women were enrolled into the acute HIV infection cohort. The visit structure was divided into 3 phases: weekly to fortnightly visits up to 3 months postinfection (acute infection), monthly visits from 3 to 12 months (early infection), and quarterly visits thereafter (established infection) until ART initiation. Samples for immunologic, virologic, and clinical parameters were collected, and VL and CD4 counts (FACSCalibur Flow Cytometer, BD Biosciences, San Jose, California) were measured at each visit. Screening for STIs with multiplex PCR testing and Gram stain for bacterial vaginosis were performed at enrollment and every 6 months thereafter [27]. Women with positive results were recalled for treatment or referred to the nearest clinic. Any other STIs were treated syndromically on presentation according to South African National Guidelines.

High-resolution HLA typing was performed on all participants. DNA was extracted from either peripheral blood mononuclear cells or granulocytes using the Pel-Freez DNA Isolation kit. HLA-A, -B, and -C typing was performed by sequencing of exons 2, 3, and 4 using Atria AlleleSeqr kits (Abbott), and data were analyzed using Assign-SBT 3.5 (Conexio Genomics). Any ambiguities resulting from either polymorphisms outside the sequenced exons or identical heterozygote combinations were resolved using sequence-specific primers.

Statistical Analysis

Basic descriptive statistics were used to summarize frequencies and timing of the first occurrences of clinical signs and symptoms. Linear mixed models were used to estimate the CD4 slope within 12 months of HIV infection. Kaplan–Meier analyses were carried out using estimated time of infection to endpoints of CD4 counts of <200, <350, and <500 cells/μL. Stratified analyses using 3- and 6-month postinfection VL (<5 and ≥5 log copies/mL) were also performed. Whereas rapid disease progression is currently defined as ≥2 CD4 measurements <350 cells/μL within 3 years of seroconversion [28], we

Table 1. Demographic and Behavioral Characteristics of the Acute HIV Infection Cohort

Characteristic	All (N = 62)	Rapid Progressors (n = 27)	Non–Rapid Progressors (n = 35)	*P* Value
Days postinfection at enrollment[a], median (IQR)	42 (34–59)	42 (30–59)	46 (34–60)	.804
Age, y, median (IQR)	25 (21–33)	27 (23–36)	24 (21–33)	.163
Urban	74.2% (46)	85.2% (23)	65.7% (23)	.142
Completed high school	29.0% (18)	29.6% (8)	28.6% (10)	1.000
Marital status				
Married or stable partner	71.0% (44)	59.3% (16)	80.0% (28)	.240
Many partners	16.1% (10)	22.2% (6)	11.4% (4)	
No partners	12.9% (8)	18.5% (5)	8.6% (3)	
No. of sexual partners in last 3 mo prior to HIV infection[a]				
0–1	68.3% (41)	55.6% (15)	78.8% (26)	.093
≥2	31.7% (19)	44.4% (12)	21.2% (7)	
Commercial sex workers	32.3% (20)	33.3% (9)	31.4% (11)	1.000
Condom used at last sex act	56.5% (35)	59.3% (16)	54.3% (19)	.798
Ever had anal sex	14.5% (9)	22.2% (6)	8.6% (3)	.160
History of tuberculosis	8.1% (5)	3.7% (1)	11.4% (4)	.376
BMI[a], median (IQR)	26.6 (23.5–31.8)	26.8 (23.9–32.1)	26.4 (22.7–31.3)	.287
CD4 count[a], mean (SD)	520 (193.61)	413 (128.95)	603 (195.88)	<.001
Log viral load[a], median (SD)	4.62 (0.92)	4.96 (0.84)	4.36 (0.90)	.009
Bacterial vaginosis[a]	73.3% (44/60)	66.7% (18/27)	78.8% (26/33)	.382
Any STI[a,b]	44.3% (27/61)	40.7% (11/27)	47.1% (16/34)	.796
HSV-2 Ab positive[a]	91.9% (57)	92.6% (25)	91.4% (32)	1.000
HBcAb positive[a]	50.0% (31)	59.3% (16)	42.9% (15)	.306

Data are presented as % (No.) unless otherwise specified.

Abbreviations: Ab, antibody; BMI, body mass index; HBcAb, hepatitis B core antibody; HIV, human immunodeficiency virus; HSV-2, herpes simplex virus type 2; IQR, interquartile range; SD, standard deviation; STI, sexually transmitted infection.

[a] Measured at enrollment into acute HIV infection cohort.

[b] Any sexually transmitted disease, defined as testing positive for *Treponema pallidum*, *Trichomonas vaginalis*, *Neisseria gonorrhoeae*, *Chlamydia trachomatis*, *Mycoplasma genitalium*, or HSV-2 polymerase chain reaction.

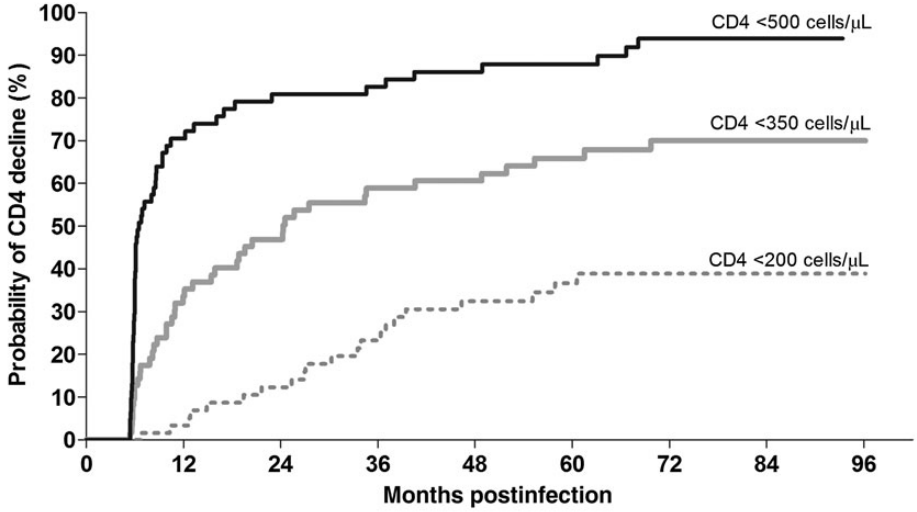
conservatively defined it as 2 consecutive CD4 counts <350 cells/μL between 6 months (to exclude seroconversion decline) and 24 months postinfection. Non–rapid progressors (NRPs) were those maintaining a CD4 count >350 cells/μL beyond 24 months. Baseline differences between rapid progressors (RPs) and NRPs were assessed by Wilcoxon rank-sum and Fisher exact tests. Cox proportional hazards regression modeling was used to assess predictors of rapid progression. Participants who did not progress rapidly were censored at their last follow-up visit or 24 months postinfection, whichever came first. Predictors in the unadjusted model with *P* values <.20, or deemed important, were included in the adjusted model. Statistical analysis was performed using SAS software, version 9.3 (SAS Institute Inc., Cary, North Carolina); graphs were prepared using Graph Pad Prism 5.

RESULTS

Baseline Characteristics of the Cohort

Of the 245 HIV-negative women followed up monthly for 4 years, 35 (14.3%) acquired HIV. The 594 HIV-negative women followed quarterly from seroincidence cohorts yielded 39 HIV seroconversions; 27 of these women consented to further follow-up. HIV incidence rates were similar between cohorts (6.5/100 person-years [95% confidence interval {CI}, 4.6–8.9] for the N = 594 women and 7.2/100 person-years [95% CI, 4.5–9.8] for the N = 245 women) [29], and the cohorts had minimal influence on progression rates (hazard ratio [HR], 0.61 [95% CI, .29–1.32]; *P* = .209). Of the 62 HIV infections, 17 (27%) were diagnosed before seroconversion. The median time from estimated date of infection to first HIV-positive sample was 42 days (interquartile range [IQR], 34–59 days).

Demographic, behavioral, and clinical characteristics of these women are summarized in Table 1. The median age at HIV infection was 25 years (IQR, 21–33 years), and most women (71.0%) were either married or had a stable partner. At enrollment into the acute HIV infection cohort, STIs were common (44.3%), and most women (91.9%) were seropositive for herpes simplex virus type 2 (HSV-2). The overall mean CD4 count at this first postseroconversion timepoint was 520 cells/μL. This was significantly lower than the preinfection CD4 counts



Months postinfection	12	24	36	48	60	72	84	96
Event: CD4 <200 cells/μL								
# reaching CD4 <200 (%)	2 (3.2%)	7 (11.3%)	13 (21.0%)	18 (29.0%)	20 (32.2%)	21 (33.8%)	21 (33.8%)	21 (33.8%)
Cumulative PY	59.9	110.6	155.4	193.6	226.1	250.1	263.8	268.4
Cumulative IR (95% CI)	3.3 (.4-12.1)	6.3 (2.6-13.0)	8.4 (4.5-14.3)	9.3 (5.5-14.7)	8.8 (5.4-13.7)	8.4 (5.2-12.8)	8.0 (4.9-12.2)	7.8 (4.8-12.0)
Event: CD4 <350 cells/μL								
# reaching CD4 <350 (%)	19 (30.6%)	27 (43.5%)	34 (54.8%)	35 (56.5%)	38 (61.3%)	40 (64.5%)	40 (64.5%)	40 (64.5%)
Cumulative PY	54.6	89.7	116	139.3	159	172.8	180.1	181.5
Cumulative IR (95% CI)	34.8 (21.0-54.4)	30.1 (19.9-43.8)	29.3 (20.3-41.0)	25.1 (17.5-34.9)	23.9 (16.9-32.8)	23.2 (16.5-31.5)	22.2 (15.9-30.3)	22.0 (15.8-30.0)
Event: CD4 <500 cells/μL								
# reaching CD4 <500 (%)	43 (69.4%)	49 (79.0%)	50 (80.6%)	52 (83.9%)	53 (85.5%)	56 (90.3%)	56 (90.3%)	56 (90.3%)
Cumulative PY	42	55.4	66.3	74.7	81.1	85.5	87.6	88.9
Cumulative IR (95% CI)	102.3 (74.1-137.8)	88.5 (65.5-117.0)	75.5 (56.0-99.5)	69.6 (52.0-91.2)	65.3 (48.9-85.5)	65.4 (49.4-85.0)	63.9 (48.3-83.0)	63.0 (47.6-81.8)

Figure 1. Superimposed Kaplan–Meier graphs of time to CD4 count <200, <350, and <500 cells/μL since estimated date of infection. Abbreviations: CI, confidence interval; IR, incidence rate; PY, person-years.

(mean CD4 count, 993 cells/μL available for 25 of 62 women; $P < .001$). The CD4 counts differed significantly between RPs and NRPs (413 vs 603 cells/μL; $P < .001$; Table 1) at first postseroconversion with a mean log VL of 4.62 log copies/mL (SD = 0.92) and higher levels in RPs than NRPs (4.96 vs 4.36 log copies/mL; $P = .009$).

Prospective Analysis

A total of 282 person-years of ART-naive follow-up amongst participants not yet initiated on ART were observed, including a median of 33 CD4 count or VL measurements (range, 3–45) per participant. In the first 2 years of HIV infection, the median number of CD4 count measures for RP and NRP participants was 19 (IQR, 16–20) and 19 (IQR, 18–20), respectively. At the time of analysis, 17 of 62 women remained ART-naive and were an estimated 6.4 years postinfection (IQR, 5.9–7.1 years) at their last follow-up visit. Of the remainder, 37 initiated ART, 5 died (2 HIV-related deaths), 2 were lost to follow-up (prior to ART initiation), and 1 declined study participation. Almost one-third (30.6%) reached a CD4 count of <350 cells/μL within 6–12 months of infection, 43.5% within 24 months, and 54.8% within 36 months postinfection (Figure 1). Increasing the treatment threshold to CD4 count <500 cells/μL, in keeping with the 2013 consolidated World Health Organization (WHO) guidelines [30], would have resulted in 69.4% of women qualifying for treatment within 6–12 months postinfection, 79.0% within 24 months, and 80.6% within 36 months.

Rapid progressors lost 11.5 $CD4^+$ cells/μL per month in the first year of infection, compared with NRPs who lost 6.1 $CD4^+$ cells/μL ($P = .019$). For the 25 women with available preinfection CD4 counts (mean, 993 cells/μL), this count dropped by 39.6% (SD, 20.25%) at 3 months and 46.7% (SD, 22.04%) at 6 months postinfection. Rapid progressors experienced a larger CD4 drop during acute infection (48.2% vs 30.2% from preinfection to seroconversion; $P = .023$). There were no significant differences in

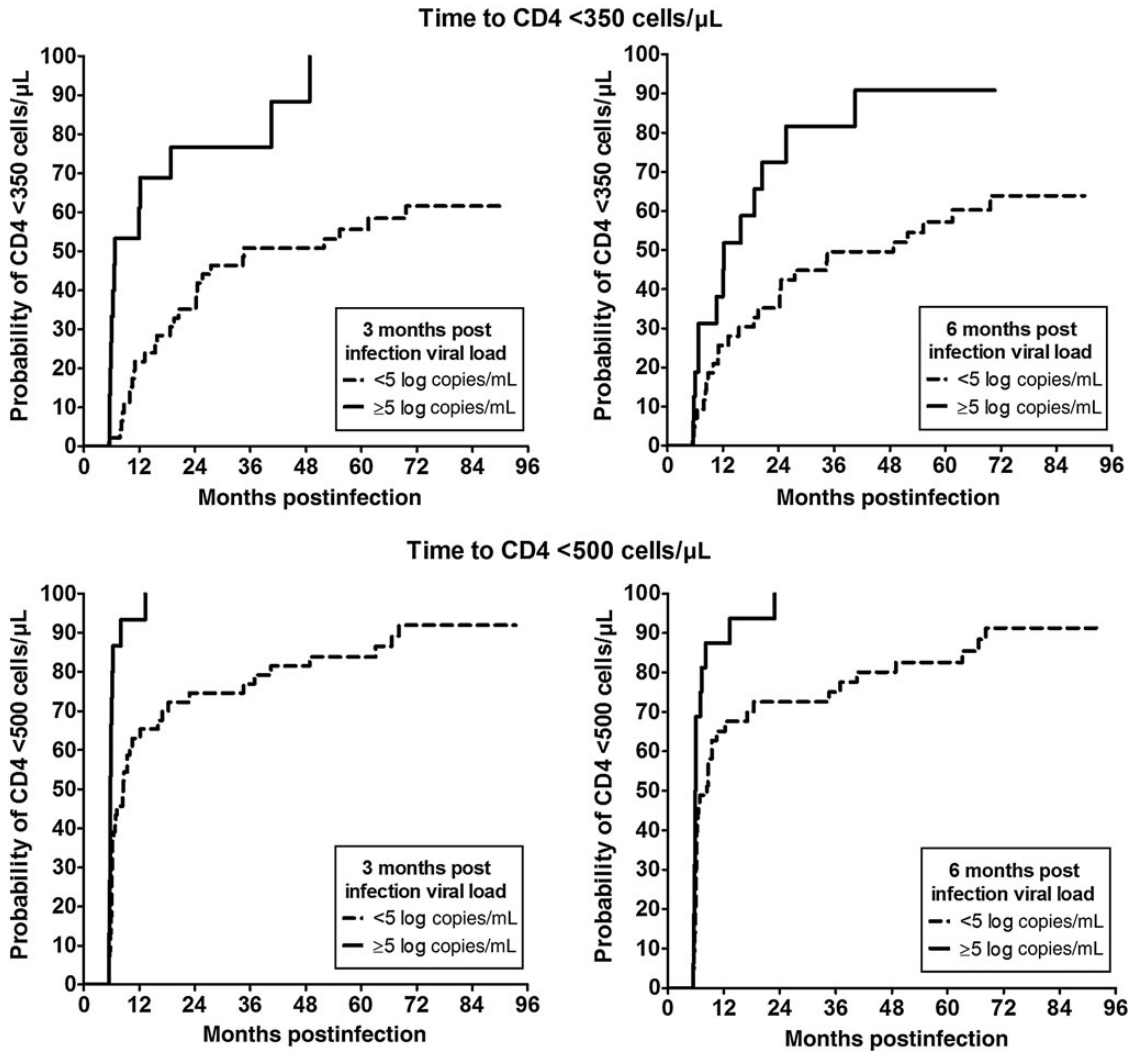


Figure 2. Kaplan–Meier graphs depicting time to CD4 <350 cells/μL and CD4 <500 cells/μL stratified by viral load at 3 and 6 months postinfection.

the preinfection CD4 counts between RPs and NRPs (mean CD4 count, 960 cells/μL and 1029 cells/μL, respectively; $P = .649$) (Supplementary Figure 1). These data suggest that severe depletion of CD4 T cells in early infection is highly predictive of subsequent disease progression.

Plasma Viral Loads as a Predictor of Rapid Disease Progression

The mean of the first available VL in this cohort (including the available preseroconversion RT-PCR results) was 4.83 log copies/mL (SD, 1.10), at a median of 31 days postinfection (IQR, 14–58 days), likely representing the decline following peak viremia. Mean VL dropped to 4.26 (SD, 0.91) and 4.20 (SD, 0.95) log copies/mL at 6 and 12 months, respectively, representing setpoint viremia. Viral loads were significantly higher in RPs than in NRPs, with a mean VL at 3 months postinfection of 4.86 log copies/mL (SD, 0.62) compared with 4.13 log copies/mL (SD, 0.86; $P < .001$).

To further determine the impact of VL on disease progression, we compared CD4 decline in participants with high VL, using a cutoff of 5 log copies/mL. Participants with higher VL at 3 months postinfection were more likely to reach a CD4 count <350 cells/μL sooner (log-rank $P < .001$), compared with women with lower VL. At 24 months postinfection, 77% of those who had high VL at 3 months reached the endpoint, compared with 35% of the lower VL group. The median time to endpoint for those with high VL was 6.7 months from infection compared with 34.6 months with a low VL (Figure 2). Similar results were obtained for VL at 6 months postinfection. The data for a CD4 count endpoint of <500 cells/μL were even more dramatic, with the probability of reaching the endpoint by 2

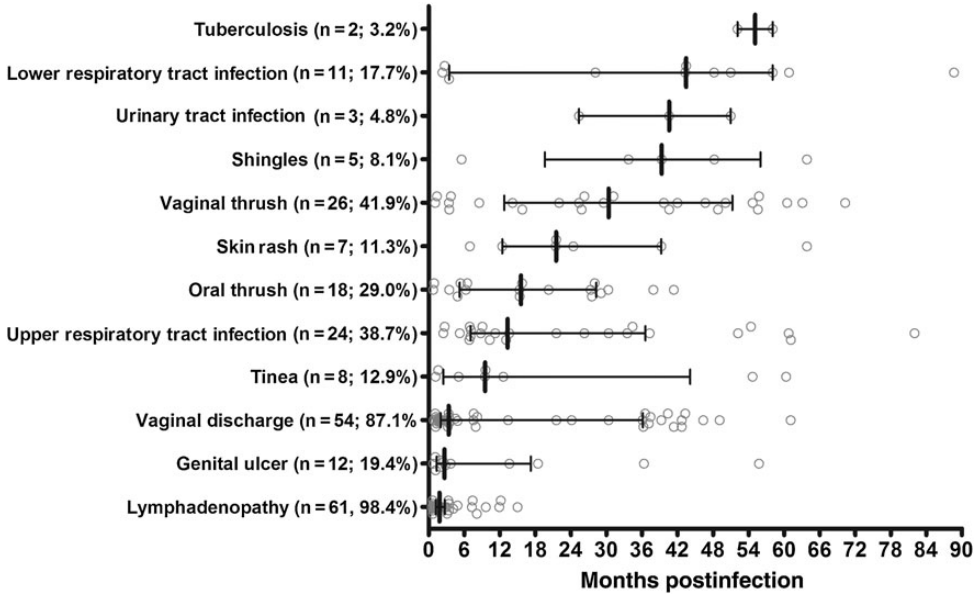


Figure 3. Time to first episode of clinical conditions from acute human immunodeficiency virus infection experienced by study participants. Circles represent participants and when they experienced the first episode of the corresponding clinical condition.

years postinfection for those with high and low VL, reaching 0.93 and 0.75, respectively.

Timing of Clinical Conditions From Acute Infection

The timing of the first presentation of clinical events during the acute phase and subsequent course of HIV infection is shown in Figure 3. Almost all participants experienced lymphadenopathy (98.4%), and many presented with upper respiratory tract infection (38.7%), vaginal discharge (87.1%), and genital ulcer disease (19.4%) during acute HIV infection. Whereas women presented with fungal infection and nonspecific skin rashes throughout the disease course, other infections such as shingles, lower respiratory tract infections, and tuberculosis were diagnosed later during HIV infection. Aside from 2 participants who died of HIV-related diseases (tuberculosis and cryptococcal meningitis), there were no other AIDS-defining diagnoses in the cohort. Of 41 participants, who became eligible and were referred for ART during the study, 37 have so far initiated ART.

Predictors of Rapid HIV Disease Progression

In the unadjusted analysis, associations were noted between rapid progression and not having a regular partner (HR, 3.03 [95% CI, 1.07–8.53]; $P = .036$), having ≥2 sexual partners in the 3 months prior to infection (HR, 2.06 [95% CI, .96–4.41]; $P = .063$), and being enrolled at the urban site (HR, 2.47 [95% CI, .85–7.14]; $P = .096$). CD4 count decline from pre–HIV infection (HR, 1.56 [95% CI, 1.12–2.17 per 10% decrease]; $P = .008$) and incident hepatitis B infection during the first 6 months (HR, 8.98 [95% CI, 2.21–36.47]; $P = .002$) were also predictive of rapid disease progression. Notably, in the 3 cases of incident hepatitis B infection identified between HIV acquisition and 6 months postinfection, all rapidly progressed to a CD4 count <350 cells/μL. No associations were observed for age, education, sex worker status, or clinical data including a history of tuberculosis, body mass index, an abnormal full blood count result, or STIs at enrollment into the acute HIV infection cohort (Table 2).

Overall, the best independent predictors of CD4 decline and rapid disease progression were CD4 count at 3 months (HR, 2.07 [95% CI, 1.31–3.28 per 100 cells/μL decrease]; $P = .002$), VL during early infection (HR, 3.82 [95% CI, 1.51–9.67 per 1-log increase]; $P = .005$), and hepatitis B infection at the time of HIV infection (HR, 4.54 [95% CI, 1.31–15.69]; $P = .017$). Conversely, the best predictors of non–rapid progression were any of the previously described protective HLA genotypes (B*1302, B*27, B*57, B*5801, B*8101), with an HR of 0.19 (95% CI, .05–.74; $P = .016$).

DISCUSSION

The rate of HIV disease progression is highly variable, with important implications for both clinical disease management and program planning. Previous studies have estimated that rapid HIV progression is relatively uncommon, using definitions of CD4 decline within 3 years [31]. Here, we show that nearly half of the clade C–infected women met our conservative definition of rapid disease progression (CD4 decline to <350 cells/

Table 2. Predictors of Rapid Disease Progression Defined as CD4 Count <350 Cells/μL Within 2 Years of Infection

Variable	Level	No. With Rapid Progression/ No. Total	Unadjusted Analysis		Adjusted Analysis[a]	
			HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Demographic and behavioral characteristics						
Age (per 5 y increase)			1.03 (.85–1.24)	.761	0.82 (.55–1.21)	.317
Completed high school	No	19/44	1.0 (Ref)			
	Yes	8/18	1.09 (.48–2.49)	.840		
Marital status	Married or stable partner	16/44	1.0 (Ref)		1.0 (Ref)	
	Many partners	6/10	2.05 (.80–5.25)	.135	0.19 (.03–1.42)	.105
	No partner	5/8	3.03 (1.07–8.53)	.036	0.22 (.03–1.64)	.139
Site	Rural	4/16	1.0 (Ref)		1.0 (Ref)	
	Urban	23/46	2.47 (.85–7.14)	.096	2.09 (.41–10.63)	.374
No. of sexual partners in last 3 m	0–1	15/41	1.0 (Ref)		1.0 (Ref)	
	≥2	12/19	2.06 (.96–4.41)	.063	4.21 (.70–25.35)	.117
Condom at last sex act	Yes	16/35	1.0 (Ref)			
	No	11/27	0.84 (.39–1.82)	.666		
Sex worker	No	18/42	1.0 (Ref)			
	Yes	9/20	1.07 (.48–2.39)	.864		
Ever had anal sex	No	21/53	1.0 (Ref)		1.0 (Ref)	
	Yes	6/9	1.93 (.78–4.79)	.157	0.91 (.23–3.57)	.894
Routine clinical and laboratory assessment						
Personal or family history of hypertension or diabetes	No	15/34	1.0 (Ref)			
	Yes	12/28	0.93 (.44–1.99)	.858		
Creatinine count at 3 mo postinfection			0.96 (.91–1.01)	.087	0.97 (.91–1.04)	.369
History of tuberculosis	No	26/57	1.0 (Ref)			
	Yes	1/5	0.40 (.05–2.97)	.373		
BMI at enrollment, kg/m^2			0.99 (.94–1.05)	.823		
Hemoglobin at 3 mo, g/dL	≥12	15/31	1.0 (Ref)			
	<12	12/31	0.72 (.33–1.53)	.387		
Neutrophil count at 3 mo, $\times 10^9$/L	≥2.5	13/29	1.0 (Ref)			
	<2.5	14/32	1.03 (.49–2.20)	.932		
Platelets at 3 mo, $\times 10^9$/L			1.00 (.99–1.00)	.692		
Elevated liver function tests at 3 mo[b]	No	22/51	1.0 (Ref)			
	Yes	5/11	1.00 (.38–2.65)	.993		
$CD4^+$ count decline from baseline (by 10% decrease)			1.56 (1.12–2.17)	.008		
$CD4^+$ count at 3 mo (by 100 cells/μL decrease)			1.98 (1.43–2.74)	<.001	2.07 (1.31–3.28)	.002
Log viral load at 3 mo (by 1 log increase)			2.77 (1.63–4.70)	<.001	3.82 (1.51–9.67)	.005
Any STI[c] at enrollment	No	16/34	1.0 (Ref)			
	Yes	11/27	0.58 (.38–1.78)	.621		
HBcAb status at enrollment	Negative	11/31	1.0 (Ref)		1.0 (Ref)	
	Positive	16/31	1.52 (.70–3.27)	.287	4.54 (1.31–15.69)	.017
HBcAb status at 6 mo	Remained negative	7/24	1.0 (Ref)			
	Baseline positive	14/27	2.10 (.85–5.22)	.109		
	New infection	3/3	8.98 (2.21–36.47)	.002		

Table 2 continued.

Variable	Level	No. With Rapid Progression/ No. Total	Unadjusted Analysis		Adjusted Analysis[a]	
			HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
HLA types						
Protective HLA-B types[d]	No	24/47	1.0 (Ref)		1.0 (Ref)	
	Yes	3/15	0.30 (.09–.99)	.048	0.19 (.05–.74)	.016
Harmful HLA-B types[d]	No	18/43	1.0 (Ref)			
	Yes	9/19	1.04 (.47–2.32)	.922		

Abbreviations: BMI, body mass index; CI, confidence interval; HBcAb, hepatitis B core antibody; HLA, human leukocyte antigen; HR, hazard ratio; Ref, reference; STI, sexually transmitted infection.

[a] Due to missing data, the adjusted analysis was performed on a total of 55 participants, with 26 events of rapid disease progression.

[b] Elevated liver function tests defined as having alanine aminotransferase level >35 IU/L and/or aspartate aminotransferase level >35 IU/L.

[c] Any sexually transmitted disease, defined as testing positive for *Treponema pallidum*, *Trichomonas vaginalis*, *Neisseria gonorrhoeae*, *Chlamydia trachomatis*, *Mycoplasma genitalium*, or herpes simplex virus type 2 polymerase chain reaction.

[d] Protective HLA-B types are B*1302, B*27, B*57, B*5801, B*8101. Harmful HLA-B types are B*1801, B*35, B*5802.

μL within 2 years of HIV-1 infection). Similar findings have been reported from Argentina where 26% of untreated acute HIV infections showed clinical or immunological progression within 12 months of infection [32]. The high proportion of women experiencing rapid disease progression suggests that this may be the dominant phenotype in the natural history of HIV-1 disease in our setting. This finding supports the argument of starting ART early, especially in settings where the risk of coinfections such as tuberculosis is high. The 2013 WHO guidelines suggest starting ART at a CD4 count of <500 cells/μL [30]. Here, we showed that nearly three-quarters of HIV-infected individuals will reach this threshold within 1 year of infection.

Preinfection CD4 counts in this population were similar to those in developed countries, with no association between preinfection CD4 counts and disease progression rate. A striking finding in this study is the magnitude of CD4 cell depletion during acute HIV infection, with nearly half of preinfection CD4 cells lost within the first 6 months of HIV infection. We observed very little CD4 cell rebound after acute infection, in contrast to the modest and transient loss described in most published studies. The rate of CD4 cell loss in the rapid progressors is higher than that observed in other HIV-1 subtype C–infected cohorts [5].

We have previously shown in this cohort that the magnitude or breadth of T-cell recognition across the expressed genome at 3 months had no association with viral setpoint at 12 months [33] and that recognition of more conserved epitopes in Gag tended to associate with slow disease progression in the first year of infection. This was in parallel with the accumulation of less differentiated Gag-specific $CD8^+$ T memory cells by 6–9 months postinfection in individuals with lower viral setpoints [34]. It appeared that the higher setpoint induced a greater level of immune activation, which resulted in high T-cell turnover being directly proportional to the level of viremia [13, 35]. This study confirms the direct association of high VL with rapid $CD4^+$ cell loss, which, in turn, is related to levels of T-cell activation [36]. Collectively, these data suggest that recognition of class I HLA–restricted variant epitopes and the late stage of $CD8^+$ memory differentiation are concentrated in women with rapid disease progression. We have previously shown that the frequency of conserved HLA-B restricted epitopes is more abundant in non–rapid progressors [37].

The long-term follow-up of this cohort enabled us to describe the trajectory of clinical signs and symptoms occurring in these women. STIs (genital ulcers and discharge) were common during early infection, whereas other infections such as varicella and tuberculosis occurred later. This is likely because the former are co-transmitted, or are the result of reduced mucosal barrier function as a result of CD4 loss, whereas the latter require more advanced immunodeficiency. Although this cohort showed rapid immunologic progression, there was little evidence of severe clinical disease or early AIDS-defining illnesses within the first 3 years of infection [32], compared with what has been observed in other cohorts. The most likely reason for this was the close follow-up of participants and prompt ART initiation prior to onset of AIDS.

A limitation of this acute HIV-infected cohort is the relatively small sample size, albeit comparable to similar cohorts, and our findings may therefore not be generalizable outside our setting. Because this was a female cohort, caution would need to be exercised when extrapolating these results on disease progression to the male population.

The rapid progression observed in this cohort provides additional motivation to implement earlier ART initiation.

Although this may present economic and operational challenges, the fact that half of individuals need ART in the first year of HIV infection provides compelling data for continued treatment roll-out. Long-term ART use will bring challenges of adherence and potential development of drug resistance, and require more health system strengthening to manage HIV as a chronic illness. Despite the challenges, this study suggests that earlier treatment initiation carries many benefits, including the potential for major impact on individual health by increasing survival and on public health by preventing transmission. The concept of "test and treat" might even be more pertinent in KwaZulu-Natal in South Africa, where we show that rapid disease progression in women is disturbingly common. Given the new WHO guidelines of ART initiation at a CD4 count of ≤500 cells/μL, more effort should be placed into diagnosing acute HIV infection to ensure that the large proportion of women requiring treatment within the first year of infection are not missed.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online (http://cid.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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