

# Rapid Clearance of Virus after Acute HIV-1 Infection: Correlates of Risk of AIDS

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**Objective.** Our objective was to define early virologic and immunologic determinants of human immunodeficiency virus (HIV) type 1 disease progression among 22 case subjects with acute infection from the Trinidad Seroconverter Cohort.

**Methods.** A linear segmented regression model was fitted to sequential quantitative virus load measurements. Parameters of virus kinetics during different phases of primary infection were correlated with clinical and immunologic end points, by use of Kaplan-Meier estimates and Cox regression.

**Results.** Ten individuals developed acquired immunodeficiency syndrome (AIDS)-defining events. In univariate analysis, progression to AIDS was associated with rate of initial HIV clearance ( $P = .002$ ), virus load during set point ( $P = .008$ ), and CD4<sup>+</sup> cell count during steady state ( $P = .04$ ). In the multivariate analysis, a rapid rate of initial clearance was the sole independent predictor of subsequent progression to AIDS and was associated with a 92% reduction in the risk of AIDS. The rate of initial clearance is inversely correlated with the number of early symptoms ( $r = -0.66$ ;  $P = .0008$ ). However, symptoms did not predict subsequent risk of AIDS.

**Conclusion.** Among a subset of patients, rapid clearance of plasma HIV-1 after peak viremia is associated with lower viral set point, prolonged virus suppression before loss of virologic control, and decreased risk of AIDS. These findings are consistent with the hypothesis that effective immune responses during the earliest phase of infection are important determinants of the subsequent natural history.

During primary HIV-1 infection, the complex interaction between the virus and the infected host determines the subsequent natural history and pattern of disease progression [1–4]. Although it is well established that virus load has significant prognostic implications [5], studies of the initial pattern of HIV-1 suppression point to events early during infection affecting subsequent natural history [2, 3]. The period from exposure to detectable acute infection is a critical window in this process, in which virologic and/or host factors that modulate initial seeding of the host appear to pre-

dict subsequent virologic patterns [4]. This seeding appears to be widespread at the earliest stages of infection [6], with a rapid doubling time during initial expansion [7]. The period of acute infection is characterized by a rapid increase in uncontrolled viremia; symptomatic infection is frequently observed, and the characteristics (duration and severity) of these symptoms appear to affect clearance of virus [4, 8] and disease progression [9]. Within a short period, virus load peaks and then rapidly declines to a so-called viral set point.

Clearance of virus is a dynamic process that involves adaptive and innate immune responses, including chemokine receptor–chemokine signal ligand interactions and modulation of receptor expression and polymorphism [10–12], as well as innate immune responses mediated by levels of CC- $\beta$  chemokine expression [13–15]. Robust HIV-1-specific CD8<sup>+</sup> cytotoxic T cell counts and persistence of CD4<sup>+</sup> helper responses are also central to clearance and virologic control, with host major histocompatibility recognition of class 1 epitopes affecting the quality and breadth of host immune responses. The present study investigates virologic and

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**Table 1. Descriptive statistics of individuals included and those excluded from the analysis.**

Variable	Included individuals (n = 22)	Excluded individuals (n = 8)	P <sup>a</sup>
No. of HIV-1 RNA level measurements, median (IQR)	26 (12)	13 (14)	.035
Length of follow-up, median (IQR), months	46.1 (33.3)	48.6 (34.1)	.56
Developed AIDS during follow-up	10 (45)	3 (37)	1.00
Had CD4 <sup>+</sup> cell count <200 cells/mm <sup>3</sup> during follow-up	6 (27)	1 (12)	.63
Died during follow-up	5 (23)	3 (37)	.64
Age at enrollment, median (IQR), years	30.7 (7.9)	23.2 (10.2)	.47
Crack cocaine use	6 (27)	1 (12)	.64
STD history <sup>b</sup>	16 (73)	3 (43)	.10
Syphilis	5 (23)	1 (12)	1.00
Gonorrhea	10 (45)	1 (12)	.19
Genital herpes	4 (18)	1 (12)	1.00
Genital ulcer	9 (41)	2 (25)	.67
Genital discharge	4 (18)	1 (12)	1.00
Male	16 (73)	7 (87)	.63

**NOTE.** Data are no. (%) of subjects, unless otherwise noted. IQR, interquartile range.

<sup>a</sup> Wilcoxon test comparing medians or Fisher's exact test comparing proportions.

<sup>b</sup> Any syphilis, gonorrhea, genital herpes, ulcer, or discharge.

immunologic correlates of the subsequent risk of clinical immunodeficiency in relation to early virus markers identified by use of a linear segmented regression model.

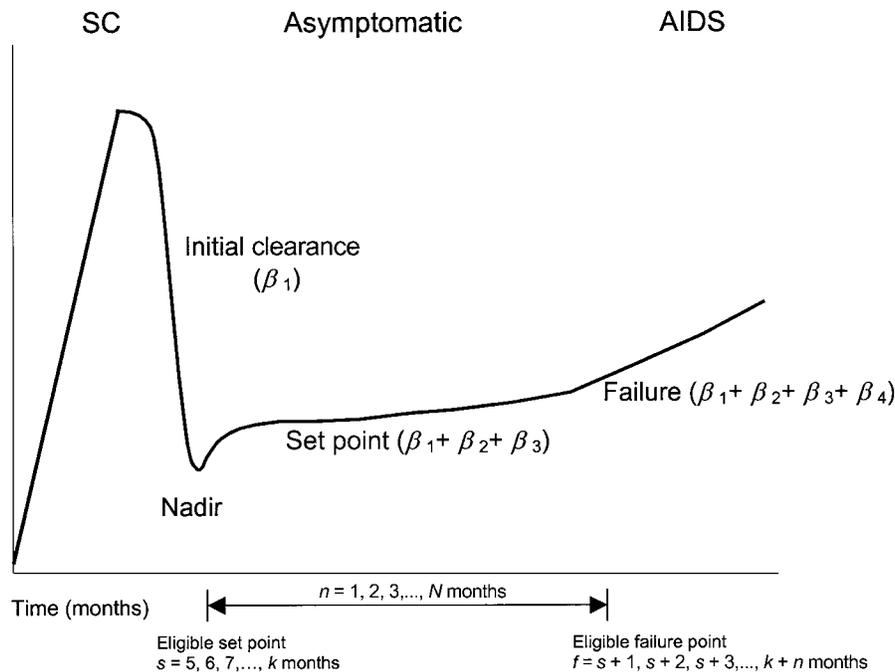
## SUBJECTS AND METHODS

**Description of populations and sampling.** A total of 30 case subjects with acute HIV infection were ascertained and enrolled, by screening attendees of the Queens Park Counseling Center, the centralized sexually transmitted disease (STD) service located in Port of Spain, Trinidad. Two approaches were used to identify cases of acute infection. Method 1 involved consecutive p24 antigen screening of all clinic attendees, and those positive for p24 (confirmed by competitive binding) and negative for HIV antibodies were enrolled. Method 2 enrolled patients with genital ulcer disease who were prospectively followed monthly for 4 months, and those with interval seroconversion were enrolled. The initial cohort ( $n = 23$  patients) was enrolled between 1993 and 1996, and the second cohort ( $n = 7$  patients) was enrolled between 1997 and 2001. After development of clinical AIDS or CD4<sup>+</sup> cell counts <200 cells/mm<sup>3</sup>, according to the local standard, antiviral therapy was provided—such medications had recently become available in the country. Since these are the main end points for the study, treatment did not confound the definition of this end point, and none of the CD4<sup>+</sup> cell count or virus load data reported were for patients who had received therapy before these end points. This project was reviewed and approved by the institutional review boards of the National Cancer Institute (1993–

1997) or the University of Maryland (1997–present) and by the Caribbean Epidemiology Center, Port of Spain, Trinidad (1993–present).

Clinical follow-up and obtaining of serial blood samples were scheduled at weekly intervals during the first month, at monthly intervals for 6 months, and, subsequently, quarterly after seroconversion. The occurrence and date of symptoms were recorded through structured questionnaires at enrollment and at each follow-up visit. Each patient was prompted to identify specific symptoms that occurred during the 4 weeks before each study visit. Symptoms occurring outside the 4-week interval were also recorded. To ensure robust estimates of the linear segmented regression, 8 study participants were excluded from the analysis because they lacked the minimal requirement of 3 virus load measurements/segment of the regression. With the exception of the total number of virus load measurements, no difference in demographics or clinical history was observed between the included and the excluded participants (table 1). The final study population included 22 individuals, with a median of 26 serial virus load measurements and a median length of follow-up of 46.1 months.

**Laboratory methods.** HIV-1 antibody was measured by use of standard ELISA (Vironostika) and was confirmed by use of Western blot (Viral Diagnostics). p24 antigen (DuPont de Nemours) screening of all volunteers was performed by use of an acid dissociation and neutralization confirmation. Plasma HIV-1 RNA copies were measured by reverse-transcriptase polymerase chain reaction, by use of the Amplicor HIV-1 Monitor Test (Roche Diagnostic Systems), in accordance with the



**Figure 1.** Idealized model for defining virus kinetics parameters in relation to clinical and immunologic phases. SC, seroconversion.

manufacturer's specifications. Samples below the limit of detection (400 copies/mL) were assigned a value of 200 copies/mL, for statistical purposes. CD4<sup>+</sup> and CD8<sup>+</sup> lymphocyte counts were measured prospectively at each study visit by use of flow cytometry (Duke University, Durham, NC) and were certified by the National Institute of Allergy and Infectious Diseases quality-assurance program.

**Statistical methods.** We performed a 2-stage analysis. During the first stage, a linear segmented regression of virus load on time since infection was fitted for each individual, to obtain estimates of rates of virus load change ( $\log_{10}$  copies per milliliter per month), virus load ( $\log_{10}$  copies per milliliter), and duration of a parameter interval (months). During the second stage, these estimates were combined for all individuals, to obtain a group estimate and to evaluate the effect of these virologic measures on progression to AIDS. We used the virologic measures as continuous variables and as categories based on the value greater than or equal to the median. Fisher's exact test and Wilcoxon 2-sample test were used to test for differences in the proportion and median values, respectively. All analyses were performed by use of SAS software (version 8.0; SAS Institute). Stated *P* values were for 2-sided tests of comparison.

The statistical methods used to estimate the rate of change and absolute level of virus load, for a given individual, have been described (M.C. and K.A.O., unpublished data) (figure 1). In brief, a segmented regression model of the form  $Y_{ij} = \beta_{i0} + \beta_{i1}(t_{ij}) + \beta_{i2}(t_{ij} - T_{\text{nadir}i}) + \beta_{i3}(t_{ij} - T_{\text{si}}) + \beta_{i4}(t_{ij} - T_{\text{fi}}) + \varepsilon_i$  was fitted for all sequential virus load measurements, where  $Y_{ij}$  rep-

resented  $\log_{10}$  plasma HIV-1 RNA for the measurement of the *i*th individual at the time  $t_{ij}$ .  $T_{\text{nadir}i}$  was a priori defined as the time of the lowest virus load measured within 120 days of p24 antigenemia.  $T_{\text{si}}$  was the estimated time of steady state for the *i*th individual.  $T_{\text{fi}}$  was the estimated time of failing to sustain steady state. The parameter  $\beta_{i1}$  represented the slope of initial viral decline. The parameters  $\beta_{i2}$  and  $\beta_{i3}$  represented the rate of change during the adjustment and steady-state periods, respectively.  $\beta_{i4}$  represented the rate of change for the last segment. To determine the  $\beta_{i4}$  (slope) value that best discriminated the group of individuals who failed to maintain steady state ( $\beta_{i4} > 0$ ) and the group whose HIV-1 RNA levels continued to remain steady throughout the segments ( $\beta_{i4} \leq 0$ ), we calculated the value that maximized the sensitivity and specificity for the development of AIDS, using receiver-operator characteristic curves [16]. Individuals with  $\beta_{i4}$  values higher than the cutoff ( $\geq 0.01 \log_{10}$  copies/mL/month) were defined as having experienced virologic failure, whereas those with values less than the cutoff were defined as having experienced maintenance of steady state.

The Kaplan-Meier product limit method was used to estimate the cumulative probability of AIDS-free survival. The main outcome measure was time to AIDS, according to the 1993 Centers for Disease Control and Prevention definition [17]. For each of the 22 HIV-infected individuals, we determined survival times through 1 January 2001. Those individuals alive at the end of follow-up contributed censored observations to the survival analysis of time to AIDS. Differences in survival were tested by

use of the log-rank test. A Cox proportional hazards model was constructed to estimate the relative hazards of AIDS at the univariate and multivariate levels. The assumption of proportionality was assessed by Kaplan-Meier profile for each predictor. Covariates that were significantly associated with the risk of AIDS were combined in the multivariate regression analysis, to evaluate the independent effect of each virus load measurement.

## RESULTS

**Study population.** As detailed in table 1, 10 (45%) of the subjects in the study population developed AIDS, with a median time to development of 55.1 months. Reflecting the demographics of an STD clinic, 16 (73%) of the 22 individuals were men, and 16 had a history of either syphilis, gonorrhea, genital herpes, genital ulcerations, or genital discharge. The median age at the time of infection was 31 years (interquartile range [IQR], 23.1–38.9 years). Individuals who developed AIDS were, on average, 6 years older than those who remained AIDS free (34 vs. 28 years;  $P = .13$ ). History of crack cocaine use was identified in 27% of the participants.

**Relationship between rate of initial HIV clearance and T cell subsets.** Efficient early clearance of HIV (defined as  $\geq 0.63$  log copies/mL/month) was associated with a significantly lower virus load during steady state. There was a difference of 0.71 log copies/mL ( $P = .03$ ) in steady-state virus load between individuals with rapid clearance (median, 3.96 log copies/mL; IQR, 3.76–4.23 log copies/mL) and those with less-rapid clearance (median, 4.67 log copies/mL; IQR, 4.09–4.79 log copies/mL). Rapid clearance was also associated with prolonged duration of steady-state set point (median, 48.2 vs. 12.0 months, a 4-fold difference;  $P = .001$ ). The rate of increase in virus load after failure to maintain steady state was not associated with the rate of initial clearance (0.03 log<sub>10</sub> copies/mL/month for the group with a rapid rate of initial clearance vs. 0.05 log<sub>10</sub> copies/mL/month for the group with a less-rapid rate of initial clearance [ $P = .92$ ]). Among 11 individuals with a slower rate of initial clearance ( $< 0.63$  log<sub>10</sub> copies/mL/month), 8 failed to maintain steady state, whereas 3 of the 11 with a more efficient rate of clearance ( $\geq 0.63$  log<sub>10</sub> copies/mL/month) failed to maintain steady state.

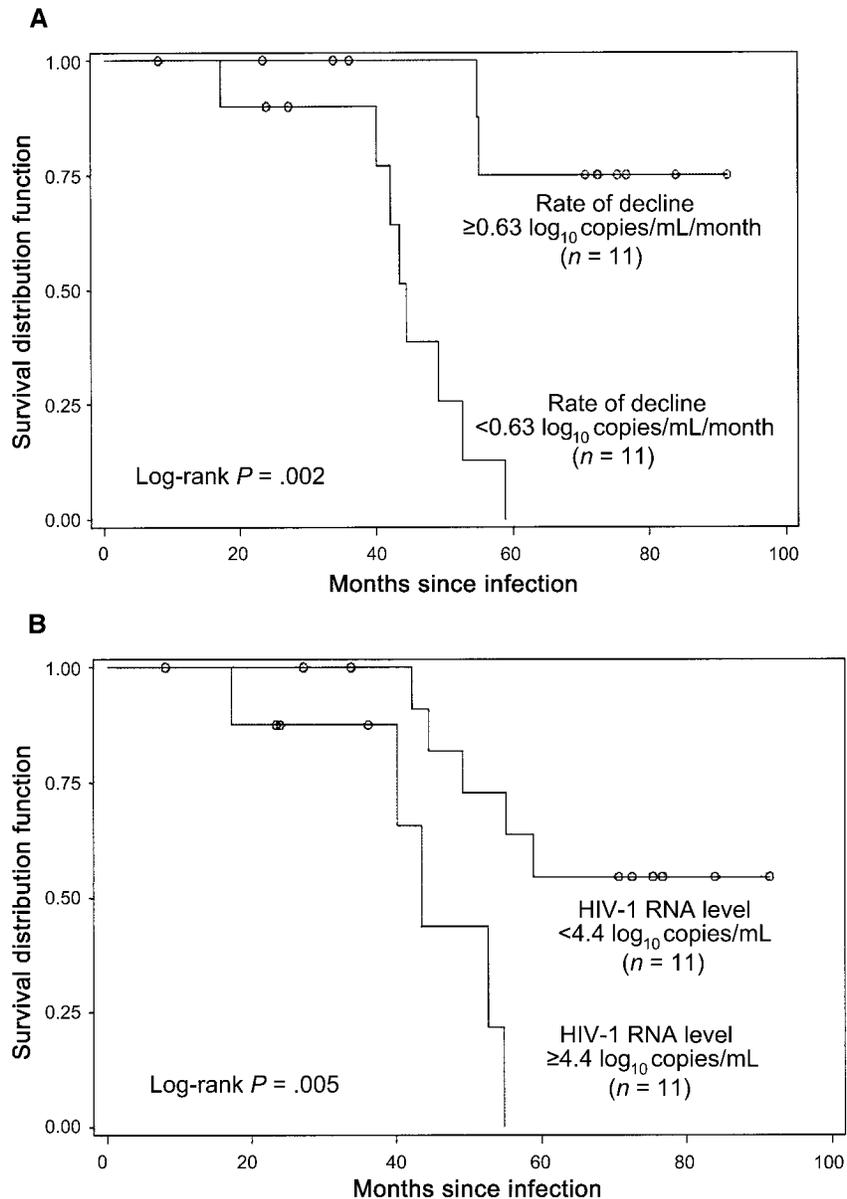
T cell subsets during the phase of initial clearance were not associated with a more rapid rate of clearance (data not shown). Although the difference was not significant, we observed a 20% lower level in CD8<sup>+</sup> HLA-DR dual-positive cells among individuals who effectively cleared virus. Initial clearance also affected T cell markers during the steady-state set-point phase. Total steady-state CD4<sup>+</sup> cell counts were significantly higher: 31% among individuals with rapid clearance, compared with 24% ( $P = .035$ ) among those with slower clearance. In addition, total CD4<sup>+</sup> cell counts were significantly higher among

individuals with virus loads  $< 4.40$  log<sub>10</sub> copies/mL during steady state (median, 30% vs. 20%, respectively;  $P = .03$ ). Median CD8<sup>+</sup> HLA-DR cell counts were lower among individuals with lower steady-state virus loads ( $< 4.40$  log<sub>10</sub> copies/mL), with a median of 37% among individuals with lower steady-state virus loads, compared with 50.5% among those with higher steady-state virus loads ( $P = .017$ ). Similarly, CD8<sup>+</sup>CD38<sup>+</sup> cell counts were also lower among individuals with lower steady-state virus loads (median, 31% vs. 61%;  $P = .023$ ). Other subsets, including naive and memory subsets, were not significantly different between individuals with low and those with high steady-state virus loads.

**Early markers of progression to AIDS.** Figures 2A and 2B show the Kaplan-Meier estimates of the cumulative probability of AIDS-free survival and demonstrate that the rate of initial clearance (figure 2A;  $P = .002$ ) and steady-state virus load (figure 2B;  $P = .005$ ) are correlated with favorable survival patterns. Cox proportional hazards models, summarized in table 2, demonstrate that the relative hazard (RH) of progressing to AIDS is significantly reduced among individuals with a rapid rate of initial clearance (RH, 0.10;  $P = .003$ ) and a long duration of steady state (RH, 0.08;  $P = .002$ ), whereas higher steady-state virus load is associated with the risk of disease progression (RH, 6.40;  $P = .013$ ). As a continuous variable, per 1-log increment in virus load after steady state, the risk of AIDS is increased (RH, 3.45;  $P = .012$ ), whereas, per 6 months at steady state, the risk is reduced (RH, 0.59;  $P = .018$ ). The risk of AIDS is reduced per 10% increment in CD4<sup>+</sup> percentage during steady state (RH, 0.71;  $P = .058$ ). There was no association between risk of AIDS and activated CD8<sup>+</sup>DR<sup>+</sup> cell counts, acute HIV symptoms, or history of STDs.

As shown in table 3, by sequential Cox proportional hazards models, efficient initial clearance has a significant protective effect on the risk of AIDS ( $P = .002$ ). When steady-state virus load and rate of initial clearance are considered together in model 2, steady-state virus load is no longer significant ( $P = .07$ ), but the rate of initial clearance remains independently associated with disease progression (RH, 0.10;  $P = .006$ ), indicating the importance of early control of viremia for subsequent progression to AIDS. This association remained after further adjustment for CD4<sup>+</sup> cell count (model 3).

**Relationship between symptoms at the time of acute infection and the risk of AIDS.** Since patients in the Trinidad Seroconverter Cohort were identified by p24 antigen screening of high-risk STD clinic patients, independent of symptoms, the study was able to investigate the relationship between the presence or absence of symptoms and subsequent natural history. At each follow-up visit during the first 120 days of infection, a structured questionnaire recorded that symptoms were frequently reported during interval follow-up. Fever, pharyngitis, fatigue, headache, swollen glands, facial and body rashes, my-



**Figure 2.** A, Kaplan-Meier estimates of time to AIDS, according to the rate of initial clearance of virus and virus load trajectory. Median rate of decline for individuals developing AIDS is  $-0.62 \log_{10}$  copies/mL/month, compared with  $-1.04 \log_{10}$  copies/mL/month for those who remained AIDS free. B, Kaplan-Meier estimates of time to AIDS, according to virus load during steady state. Median steady-state virus load for individuals developing AIDS is  $4.54 \log_{10}$  copies/mL, compared with  $4.09 \log_{10}$  copies/mL for those who remained AIDS free.

algia, and night sweats were reported by at least 50% of subjects during this acute-infection period. Neither the multiple constellation of symptoms nor the presence of any single symptom was associated with heightened risk of subsequent development of AIDS (table 2). There was, however, an inverse correlation between the number of acute symptoms and the rate of initial clearance during primary infection ( $r = -0.66$ ;  $P = .0008$ ; figure 3). The median rate of initial clearance was  $-1.3 \log_{10}$  copies/mL/month (IQR,  $-1.84$  to  $-0.81 \log_{10}$  copies/mL/month) for individuals who reported  $\geq 7$  symptoms, compared with  $-0.6 \log_{10}$  copies/mL/month (IQR,  $-0.69$  to  $-0.31 \log_{10}$  copies/mL/

month) for those whose values were below this threshold ( $P = .03$ ). Thus, a greater number of initial symptoms appeared to be associated with a more robust clearance pattern. The virus load during steady state was  $0.60 \log_{10}$  lower among individuals with more symptoms during the primary infection period than among individuals with fewer symptoms (median,  $4.05$  vs.  $4.64$  symptoms, respectively;  $P = .07$ ). No immune marker was associated with symptoms during steady state. However,  $CD8^+DR^+$  cell counts were significantly lower among individuals with  $\geq 7$  symptoms than among those with fewer symptoms (median, 26% vs. 47%, respectively;  $P = .04$ ).

**Table 2. Univariate analysis of relative hazards (RHs) of AIDS.**

Variable	RH of AIDS (95% CI)	P
Rate of initial clearance of HIV-1 >0.63 copies/mL/month	0.10 (0.03–0.40) <sup>a</sup>	.002
Steady-state virus load ≥4.4 copies/mL	6.40 (1.49–27.6) <sup>b</sup>	.013
Duration of steady state before failure ≥19.6 months	0.08 (0.02–0.40) <sup>c</sup>	.002
Total CD4 <sup>+</sup> lymphocyte count during initial clearance of HIV-1 ≥30%	0.80 (0.18–3.58)	.77
Total CD4 <sup>+</sup> lymphocyte count during steady state ≥30%	0.35 (0.10–1.10) <sup>d</sup>	.042
Diagnosed with ≥7 symptoms during the first 120 days of p24 antigenemia	0.77 (0.20–2.98)	.70
CD8 <sup>+</sup> HLA-DR cell percentage during initial clearance of HIV-1 ≥40%	2.23 (0.40–12.4)	.36
CD8 <sup>+</sup> HLA-DR cell percentage during steady state ≥40%	1.50 (0.42–5.40)	.53
Had any sexually transmitted disease	1.88 (0.40–8.93)	.43

**NOTE.** RH estimates are based on Cox proportional hazard models, in which the categories are based on the median values. CI, confidence interval.

<sup>a</sup> RH, 0.20 (95% CI, 0.03–1.10) per 1-log increment in clearance of virus; *P* = .065.

<sup>b</sup> RH, 3.45 (95% CI, 1.32–9.06) per 1-log increment in virus load during steady state; *P* = .012.

<sup>c</sup> RH, 0.59 (95% CI, 0.47–0.74) per 6 months of steady state; *P* = .018.

<sup>d</sup> RH, 0.71 (95% CI, 0.41–0.97) per 10% increment in CD4<sup>+</sup> cell percentage during steady state; *P* = .058.

## DISCUSSION

Among individuals with primary HIV infection, initial exposure to HIV is followed by a well-characterized sequence of widespread seeding of the lymphoid compartment that culminates in massive production of virions and, shortly thereafter, a robust but not completely effective immune response that diminishes but does not eliminate persistent viral replication [18–21]. In the present analysis, a segmented statistical model was developed to describe the dynamics of this kinetic process, to characterize the relationship between the parameters defined by this model and disease progression. Such a segmented model was previously used to demonstrate the loss of T-cell homeostasis that signals immunologic collapse during the later stages of progression to AIDS [22, 23]. In the virus kinetics model presented here, rate of initial clearance, initial steady-state virus load (set point), duration of sustained virus suppression, and

subsequent rate of loss of virologic control each describe an aspect of the host-virus interaction.

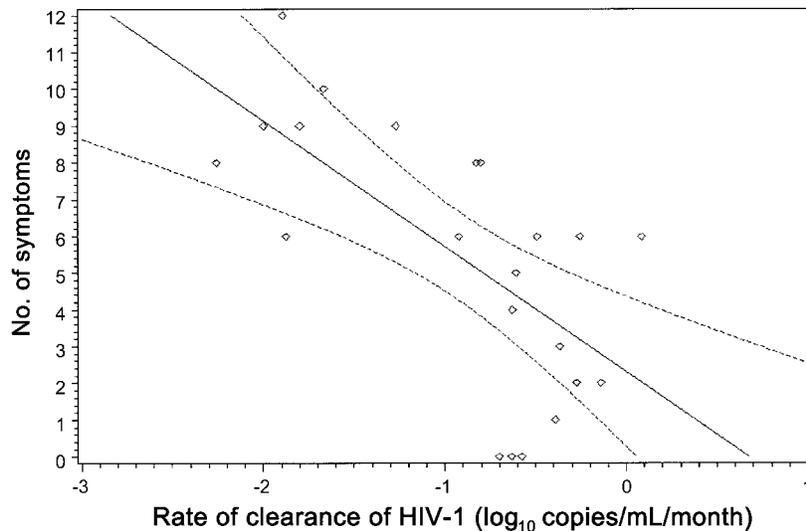
In the cohort in the present study, the key determinant of HIV natural history is the efficiency with which the host clears initial viremia. Individuals with a more rapid rate of clearance achieve a significantly lower steady-state virus load, sustain higher CD4<sup>+</sup> cell counts, and are less likely to experience subsequent virologic failure. After controlling for steady-state virus load and CD4<sup>+</sup> cell counts, the rate of initial clearance remained independently associated with AIDS. A study of Australian patients with primary infection documented that peak, nadir, and median HIV-1 RNA levels during the first 30 days after the onset of acute infection syndrome predicted the HIV-1 load at 6–12 months, whereas nadir virus load was the only parameter to predict CD4<sup>+</sup> cell counts during the first year of infection [2]. In a subsequent analysis that investigated the relationship

**Table 3. Sequential Cox proportional hazards models relating progression to AIDS to initial clearance of HIV.**

Variable	Multivariate	
	RH of AIDS (95% CI) <sup>a</sup>	P
Model 1		
Rate of initial clearance of HIV-1 >0.63 copies/mL/month	0.10 (0.03–0.40)	.002
Model 2		
Rate of initial clearance of HIV-1 >0.63 copies/mL/month	0.11 (0.02–0.50)	.006
Steady-state virus load ≥4.40 copies/mL	4.18 (0.89–19.6)	.07
Model 3		
Rate if initial clearance of HIV-1 >0.63 copies/mL/month	0.08 (0.01–0.47)	.005
Steady-state virus load ≥4.40 copies/mL	2.71 (0.49–15.0)	.26
Steady-state CD4 <sup>+</sup> cell count ≥30%	0.43 (0.08–2.32)	.32

**NOTE.** CI, confidence interval; RH, relative hazard.

<sup>a</sup> Each value was adjusted for the other variable in the model.



**Figure 3.** Correlation between no. of symptoms during the first 120 days of infection and the rate of clearance of HIV-1

between events from initial exposure and symptomatic infection, the combined Swiss and Australian Seroconverter Cohorts demonstrated that a short period from the time of initial infection to the appearance of symptoms is associated with rapid progression to AIDS [4]. Once symptoms develop, a prolonged persistence of the symptoms of acute infection syndrome is linked to more-rapid progression to AIDS. A Swedish group found that peak virus loads (copies per milliliter) correlated with subsequent virus loads during the first 2 years of follow-up [24]. Since the present study did not identify most cases at the peak of viremia, we were not able to address the relationship between initial peak virus load and progression to AIDS. The present study supports the hypothesis that initial immune response during the earliest window of infection has critical implications for subsequent natural history.

Retrospectively determining virus loads from samples obtained during the first year of infection from longitudinal US and European cohorts documents that virus loads early in HIV infection predict subsequent risk of AIDS, an observation that contributed to the concept of a long-lived viral set point in HIV natural history [1–3, 25–28]. In the present analysis, steady-state virus load is defined by the average of multiple determinations of virus load during the period after peak viremia and before the loss of virologic control. Progression to AIDS was less likely among Trinidad study subjects with a median steady-state virus load  $\leq 25,100$  copies/mL ( $4.4 \log_{10}$  copies/mL) than among those with a virus load above this level. Individuals with lower steady-state virus loads were also more likely to have a prolonged steady state before virologic failure and to sustain a higher CD4<sup>+</sup> cell count. Although, in our cohort, the incubation time from infection to AIDS-defining condition is shorter than that reported in European and US

cohorts [29–32], the median virus load for our cohort, which demarcated progressors from nonprogressors, is quite similar to that reported for other clade-B cohorts ( $4.09$ – $4.34 \log_{10}$  copies/mL) [33], suggesting that other, yet to be defined factors account for the observed accelerated progression.

After the initial peak and the subsequent first-phase clearance, patients with HIV achieve steady states of varying duration. The parameter in our segmental model that, independent of the rate of initial clearance and set point, most strongly predicts risk of AIDS is the duration of the steady state. Among individuals who maintained a steady state for at least 19.6 months, only 2 (20%) of the 10 developed AIDS. Among individuals who had a shorter duration of steady state, most developed AIDS between 40 and 50 months. In individuals who experienced virologic failure in which virus load increased from the level at steady state, progression to AIDS occurred within 2–3 years. Although they did not map the steady-state interval with the level of detail in the present study, other investigators have documented that upward trends in HIV-1 load during the first years after infection are predictive of more-rapid progression to AIDS [26, 34, 35].

On the basis of an evolving understanding of the host-virus interaction, derived from human and animal studies, virologic control involves HLA class I CD8<sup>+</sup> cytotoxic T lymphocytes [36–45] and CD8<sup>+</sup>-mediated noncytolytic suppression of viral replication [46]. In the present study, rapid initial clearance resulted in lower virus load and prolonged steady state, suggesting that early effective host responses are able to effect favorable natural history. Detailed studies focusing on characterizing these cell-mediated immune responses are ongoing in this population.

Unlike other studies of cohorts of patients with acute infec-

tion, in which subjects are identified primarily via symptomatic acute HIV infection (i.e., cohorts in which patients with more severe and prolonged symptomatic infection tend to progress faster to clinical disease) [2, 4, 8, 24], the present study ascertained subjects without regard to symptoms and found that frequent symptoms during the first 3 months of infection are associated with rapid clearance but not with subsequent progression to AIDS. The lack of association between the presence of symptoms and subsequent risk of AIDS may be attributable to small sample size. Although the finding of prolonged and severe symptoms in previous cohorts is thought to reflect ineffectual immune responses, the multiple mild symptoms observed during the first 3 months of infection in the cohort in the present study may represent cytokine-mediated immune responses, such as  $\beta$ -chemokines [14, 15], that affect clearance, a hypothesis that needs to be investigated in future studies.

In the Trinidad cohort, a lower set point during steady state is associated with decreased numbers of CD8<sup>+</sup> cells coexpressing the activation markers HLA-DR or CD38 during that phase of infection. Since viral activation of the immune system is an important tool used by the virus to augment viral spread and to escape from immune surveillance, it is possible that the component of immune response that down-regulates immune activation plays an important role in subsequent capacity of the host immune response to sustain virus suppression. For example, the sooty mangabey simian immunodeficiency virus model is characterized by detectable, ongoing virus production, but with down-modulation of immune activation [47–50]. Immune activation has also been linked in human cohorts to progression of HIV [51–54]. Thus, the observation in the Trinidad cohort that low steady-state virus loads follow rapid clearance suggests that maintenance of effective immune down-modulation plays a role in the host capacity to control virus load, a hypothesis that requires further study in this cohort.

In summary, the present prospective study of 22 case subjects from Trinidad—who had acute infection, seroconverted, and were ascertained by use of p24 antigen screening, without regard to initial symptoms—demonstrates that efficient early clearance of HIV-1 strongly predicts subsequent hazard of progression to AIDS. This finding is consistent with a growing body of data suggesting that effective immune responses during the earliest phase of infection are important determinants of disease progression. The finding that multiple symptoms are associated with rapid initial clearance is consistent with a cytokine-mediated augmentation of adaptive, presumably cytotoxic CD8<sup>+</sup>-mediated viral cell killing, as has been suggested in some model systems [55]. A down-modulation of CD8<sup>+</sup> activation observed during steady state, among patients with lower virus load set point, may involve different immune effector mechanisms, such as the Th2 response reported as a predictor of prolonged virus-host homeostasis in some nonhuman primate

models [47]. The segmented model developed for this analysis provides a robust model for isolating different stages of HIV natural history and affords an important opportunity to map the nature of host immune responses that affect this complex host-virus interaction.

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