Early Markers of HIV-1 Disease Progression in a Prospective Cohort of Seroconverters in Bangkok, Thailand

Implications for Vaccine Trials

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Background: Some candidate HIV-1 vaccines may not prevent HIV-1 infection but may alter the course of disease. Surrogate endpoints based on early laboratory makers in HIV-1–infected persons who are antiretroviral therapy (ART)–naive will be useful for evaluating vaccine efficacy in slowing disease progression (VE_p). We examined pretreatment HIV-1 viral loads and CD4 cell counts in recent HIV-1 seroconverters to inform selection of these endpoints.

Methods: We studied 130 newly HIV-1–infected injection drug users identified from a prospective cohort of initially uninfected persons in Bangkok during 1995 through 1998. We analyzed trends in HIV-1 viral loads and CD4 cell counts as well as progression to the surrogate endpoint, defined as 2 consecutive CD4 cell counts of fewer than 350 cells/mm³, during 24 months after the first HIV-1 seropositive (FP) visit.

Results: Median HIV-1 RNA copies/mL with interquartile ranges were 43,693 (14,320–94,767) at the FP visit, 46,924 (16,273–104,314) at 6 months, 28,446 (11,292–54,325) at 12 months, and 18,080 (8713–54,059) at 18 months. HIV-1 viral loads at the FP visit and at 18 months were positively correlated ($r = 0.53$, $P < 0.0001$). Of 130 participants, 12% reached the surrogate endpoint by 6 months,

16% by 12 months, and 27% by 18 months. In Cox regression analyses, HIV-1 viral loads of more than 50,000 copies/mL at the FP visit (hazard ratio [HR] = 2.3, 95% confidence interval [CI]: 1.1–4.8) and first CD4 cell count of 500 or fewer cells/mm³ (HR = 7.6, 95% CI: 3.2–17.6) were independently associated with faster progression to the surrogate endpoint.

Conclusions: Participants with high HIV-1 RNA levels and low CD4 cell counts close to the time of seroconversion were more likely to experience early immunologic progression. Approximately one quarter of seroconverters reached the surrogate immunologic endpoint within 18 months of their FP visit and before starting ART, suggesting the utility of this endpoint for analyses of VE_p in some ongoing and planned HIV-1 vaccine efficacy trials.

Key Words: HIV-1 vaccine endpoints, vaccine efficacy; early HIV disease progression

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Because of numerous challenges in the development of a vaccine against HIV-1,[1] the first-generation vaccines available for public health use may not prevent HIV-1 infection.[2,3] Some current HIV-1 vaccine candidates, however, may reduce disease progression in vaccinated individuals who subsequently become infected by lowering HIV-1 viral load during and after primary infection, as illustrated by studies of nonhuman primates.[4,5] Consequently, the current and future phase 3 trials of HIV-1 vaccines must assess both vaccine efficacy in reducing susceptibility to HIV-1 infection and vaccine efficacy in slowing HIV-1 disease progression (VE_p) by comparing markers such as CD4 cell counts and HIV-1 RNA levels of vaccinees and controls who become HIV infected during the trial.[6,7]

HIV-1 RNA levels and CD4 cell counts in early and established infection are strong and independent predictors of clinical HIV-1 disease progression and mortality.[8–10] Surro-

gate endpoints for clinical outcomes based on threshold levels or changes in HIV-1 RNA and CD4 cell counts have been used to support the licensure of antiretroviral medications.[11] These surrogate end points will also be valuable for evaluating the efficacy of HIV-1 vaccines in slowing disease progression.[12,13] In the era of effective antiretroviral therapy (ART), it is neither ethical nor feasible to study the effects of a vaccine on the long-term progression of HIV-1 disease in the absence of treatment; the analyses of VE_p thus must focus on early immunologic and virologic events before ART is initiated. The use of early progression endpoints allows a preliminary assessment of vaccine efficacy on disease progression during a relatively short follow-up of HIV-infected trial participants. Longer term follow-up, however, remains important to elucidate the extent to which the potential effects on surrogate endpoints parallel the effects on clinical endpoints.

The HIV-1 epidemic among injection drug users (IDUs) in Bangkok has been well characterized for more than a decade.[14] After extensive vaccine preparatory work in the Bangkok Metropolitan Administration (BMA) cohort of IDUs during 1995 through 1998,[15] a phase 3 HIV-1 vaccine trial was launched in 1999.[16,17] The continued follow-up of seroconverters from the BMA vaccine preparatory cohort provides an opportunity to examine the levels and variability in early CD4 T-cell counts and HIV-1 viral loads[18] before the use of ART, which can guide sample size requirements for analyses of continuous VE_p endpoints. It also allows us to investigate early HIV-1 disease progression and to explore the frequencies of some categorical immunologic endpoints for evaluating VE_p. Finally, studying risk factors for early disease progression in this cohort can help us to identify potential confounders to adjust for when assessing VE_p. The key objectives of our analyses were to (1) describe the immunologic and virologic profiles during the first 24 months after HIV-1 seroconversion, (2) evaluate the relationship between the initial HIV-1 RNA viral load and CD4 cell counts and later immunologic deterioration, and (3) examine the role of HIV-1 subtype in HIV-1 disease progression.

METHODS

Study Population

The BMA manages a large municipal drug treatment program in Bangkok, Thailand, where clients receive methadone, medical care, and information about HIV-1 prevention. As described previously,[15,18] by screening participants for HIV-1 antibodies every 4 months, 130 seroconverters were identified from a vaccine preparatory cohort of IDUs during 1995 through 1998. Following a positive HIV-1 antibody test result, these persons were offered, with voluntary informed consent, enrollment in a prospective study of HIV-infected persons. Blood specimens were collected as soon as possible after the first HIV-1–seropositive visit (FP), 1 month later, and

every 4 months thereafter. This study protocol was approved by the Research and Human Subjects Review Committee, Ministry of Public Health, Nonthaburi, Thailand, and by the Institutional Review Board, Centers for Disease Control and Prevention, Atlanta, Georgia.

Data Collection

At each study visit, participants were evaluated clinically and referred for treatment according to BMA guidelines for the treatment of HIV infection.[15] In 1999, 2 antiretroviral drugs were offered after a person had 2 CD4 cell counts of fewer than 500 cells/mm^3; starting in October 2001, 3 antiretroviral drugs and prophylaxis for opportunistic infections were offered after a person had 1 CD4 cell count of fewer than 200 cells/mm^3.

Blood specimens from the last seronegative visit, the FP visit, and all later visits were tested to determine HIV-1 RNA levels by the Amplicor HIV-1 Monitor Test, version 1.5 (Roche Diagnostics, Branchburg, NJ). The lower limit of quantitation was 400 RNA copies/mL. CD4 cell counts were determined by FACScan cytometry.

Genetic sequencing and phylogenetic analyses had revealed that 103 (79%) study participants were infected with subtype CRF01_AE (a circulating recombinant form AE, referred to here as subtype E) and 27 (21%) were infected with subtype B.[19] IDUs infected with subtypes B and E were similar in terms of sociodemographic and behavioral characteristics.[18] Although IDUs infected with subtype E had significantly higher RNA HIV-1 levels during the first 6 months after seroconversion than did IDUs infected with subtype B, these differences diminished over time.[18]

Analyses

The seroconversion interval was defined as the time between the dates of the last HIV-1–seronegative visit and the FP visit. The date of seroconversion was estimated as the midpoint of the seroconversion interval. The analysis data set included all available observations up to 24 months after the FP visit, except for observations on 6 persons who received ART during this time; data on these persons were right-censored at the last pre-ART visit.

HIV-1 RNA levels were summarized at the FP visit and at visits closest to 6, 12, and 18 months (±3 months) after the FP visit. Nine HIV-1 RNA measurements below the limit of detection (<400 copies/mL) were set at 200 copies/mL for purposes of analysis. CD4 cell counts were first assessed at the second study visit, which was scheduled as soon as possible after the FP visit. CD4 cell counts were thus summarized as first available within 3 months of the FP visit and at visits closest to 6, 12, and 18 months (±3 months) after the FP visit.

Trajectories of HIV-1 RNA and CD4 cell counts were described using the lowess procedure, which draws a representative smooth curve through data using robust local regres-

sions.[20] Trends in CD4 cell counts and $\log_{10}$ HIV-1 RNA levels 6 to 24 months after the FP visit were analyzed using mixed-effects regression models that adjusted for within-person correlations of measurements.[21] These models provide estimates of average linear marker trajectories over time. We also estimated the mean loss in CD4 cell count during the first 6, 12, and 18 months from the FP visit to account for the decreasing rate of CD4 cell loss over time.

We defined the endpoint for early immunologic disease progression as 2 consecutive CD4 cell counts of fewer than 350 cells/mm^3 (to discount early transient drops in CD4 cell counts in primary infection). We chose this endpoint for our analyses of pretreatment HIV-1 disease progression because of supporting epidemiologic data and current recommendations for initiating ART when HIV-infected persons have CD4 cell counts of 200 to 350 cells/mm^3.[22–25] We also chose this endpoint because few HIV-1–infected persons may be expected to reach CD4 cell counts of fewer than 200 cells/mm^3 in the time frame of a standard phase 3 vaccine trial. We used Cox proportional hazard models and Kaplan-Meier estimates with log-rank tests[26] to examine progression to the endpoint by the HIV-1 viral load at the FP visit and the first available CD4 cell count (referred to here as "baseline" predictors). In defining baseline predictor variables, we chose CD4 cell count strata of ≤500 and >500 cells/mm^3 and HIV-1 RNA strata of ≤50,000 and >50,000 copies/mL because these cutoff levels are clinically meaningful for prognosis of HIV disease progression,[10,25] and each divided our relatively small population of 130 seroconverters into 2 well-balanced subgroups. We did not assess the predictive value of HIV-1 viral load at 6 months or later, because a substantial number of participants had already reached the immunologic endpoint by 6 months after the FP visit. We assessed whether risk factors were similar for progression to other immunologic endpoints. We used graphics methods to verify that proportional hazards assumptions were not violated. All analyses were performed using Statistical Analysis Software (SAS), version 8.02 (SAS Institute, Cary, NC).

RESULTS

Of the 130 IDUs who seroconverted, 116 (89%) were men, and 14 (11%) were women; 103 were infected with HIV-1 subtype E, and 27 were infected with subtype B. The mean age at enrollment was 29.8 years. The median seroconversion interval was 4.1 months (interquartile range [IQR]: 3.9–4.4). Six IDUs died within 24 months of the FP visit with cause of death recorded as AIDS (n =1), pneumonia (n =1), lung and kidney failure (n = 1), overdose (n =2), and murder (n = 1). By 6, 12, and 18 months after the FP visit, 118, 113, and 107 participants, respectively, remained in follow-up and continued to contribute CD4 cell count and HIV-1 viral load data. A total of 847 HIV-1 RNA values and 709 CD4 cell counts were available for analysis.

Median HIV-1 RNA was 43,694 (mean = 129,648) copies/mL at the FP visit (Table 1). After 1 outlying viral load of more than 6 million copies/mL was excluded, mean HIV-1 RNA at the FP visit was 81,009 copies/mL (SD = 122,477). In cross-sectional analyses of all viral loads available at landmark time points (see Table 1), 46% of participants had HIV-1 RNA of more than 50,000 copies/mL at their FP visit; that proportion diminished to 27% at 18 months. HIV-1 RNA levels at the FP visit were positively correlated with RNA levels at 18 months after the FP visit (Spearman $r = 0.53$, $P < 0.0001$). The median (mean) peak HIV-1 RNA levels within 3 months of the FP visit were 79,997 (mean = 236,604) copies/mL; in 63% of participants HIV-1 RNA peaked after the FP visit. Only 4 participants had HIV-1 RNA levels below the limit of detection during the 24 months. After initial increases, the population-averaged HIV-1 viral loads fell to stable levels, but interindividual variability in viral loads was high throughout the 24 months after seroconversion (Fig. 1). Using longitudinal regression analyses, we estimated a mean change in HIV-1 viral load of −0.015 $\log_{10}$ RNA copies/mL between 6 and 24 months after the FP visit ($P = 0.0004$).

The 115 participants whose first measurement was within 3 months of the FP visit had a median CD4 cell count of 540 cells/mm^3 (see Table 1). Of these persons, 19 (17%) had a first CD4 cell count of fewer than 350 cells/mm^3 and 12 (10%) maintained a CD4 cell count of fewer than 350 cells/mm^3 up to 24 months. On average, CD4 cell counts decreased most rapidly during the first 6 months after seroconversion and at a slower rate thereafter (Fig. 2). In the longitudinal regression analyses, CD4 cell counts were estimated to decline at a mean rate of −3.0 cells/mm^3 per month between 6 and 24 months after the FP visit. The mean decline in CD4 cell count was estimated at −77 cells/mm^3 from the FP visit to 6 months and at −112 cells/mm^3 from the FP visit to 18 months (Table 2). Although participants whose HIV-1 RNA was more than 50,000 copies/mL at the FP visit had lower initial (intercept) CD4 cell counts than did those with HIV-1 RNA of 50,000 or fewer copies/mL (520 vs. 611 cells/mm^3; $P = 0.04$), we found no differences in the rates of CD4 cell loss according to HIV-1 RNA level at the FP visit (see Table 2). Participants with lower baseline CD4 cell counts experienced slower loss or transient increases in CD4 cell counts (see Table 2).

Kaplan-Meier estimates of the proportion of participants reaching the immunologic endpoint (2 consecutive CD4 cell counts of fewer than 350 cells/mm^3) were 12% by 6 months, 16% by 12 months, and 27% by 18 months. First RNA of more than 50,000 copies/mL was associated with faster progression to the endpoint ($P = 0.002$; Fig. 3), as was first CD4 cell count of 500 or fewer cells/mm^3 ($P = 0.0001$; Fig. 4). Progression rates did not differ by HIV-1 subtype ($P = 0.65$). In the univariate Cox regression models, the hazard of progression to the immunologic endpoint was higher for participants whose baseline CD4 cell count was 500 or fewer cells/mm^3 or for

TABLE 1. CD4 Cell Counts and HIV-1 RNA Values at Landmark Time Points After the FP Visit in the BMA Cohort (n = 130)

Time Period	First <3 Months*	6 (±3) Months	12 (±3) Months	18 (±3) Months†
HIV-1 RNA level				
No. persons	130	114	102	91
Mean	129,648	109,761	64,314	44,781
Median	43,694	46,925	28,446	18,080
IQR	14,320–94,767	16,273–104,314	11,292–54,325	8713–54,059
Range	943–6,403,956	200–708,006	200–732,558	200–353,178
SD	567,821	163,058	110,535	64,721
n (%) >50,000	60 (46)	56 (49)	27 (26)	25 (27)
Mean ($\log_{10}$)	4.6	4.6	4.4	4.3
SD ($\log_{10}$)	0.6	0.7	0.7	0.6
CD4 cell count				
No. persons	115	114	102	90
Mean	549	504	474	447
Median	540	489	438	423
IQR	384–703	390–620	338–564	332–551
Range	160–1046	73–1066	134–1102	37–1670
SD	202	178	203	211
n (%) <350	19 (17)	21 (18)	30 (29)	26 (29)

*First RNA was measured at the FP visit. See text for the description of the effect of 1 outlying HIV-1 RNA observation. First CD4 cell count was obtained as soon as possible after the FP visit (median of 1 month after the FP visit). All CD4 cell counts are reported as cells/mm³, and RNA values are reported as copies/mL, except where $\log_{10}$ scale is indicated.

†Of 107 participants who were in follow-up at 18 months after the FP visit, only 91 had HIV-1 RNA and/or CD4 cell count measurements available in the interval period of 18 (±3) months.

those whose HIV-1 RNA level was more than 50,000 copies/mL (Table 3). The risk of disease progression, however, was not associated with HIV-1 viral subtype, participant's age or gender, calendar year of the FP visit (see Table 3),

or frequency of injection or needle sharing (data not shown). In the multivariate analyses, higher baseline HIV-1 RNA level and lower CD4 cell count remained independently associated with progression to the immunologic endpoint (see Table 3).
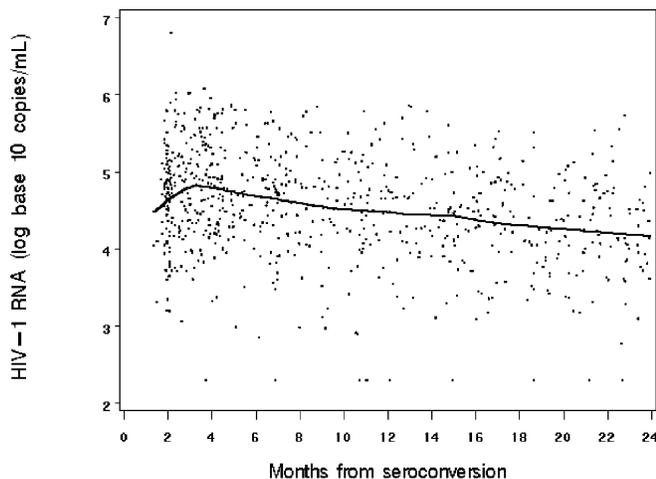
FIGURE 1. HIV-1 RNA levels from the estimated date of seroconversion with lowess smooth regression line (n = 847 measurements from 130 individuals).
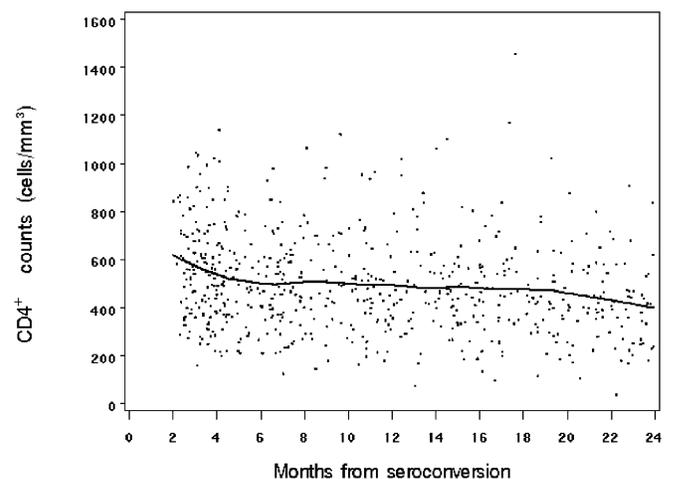
FIGURE 2. CD4 cell counts from the estimated date of seroconversion with lowess smooth regression line (n = 709 measurements from 130 individuals).

TABLE 2. Mean Changes in CD4 Lymphocyte Counts at 6, 12, and 18 Months After FP Visit in the BMA Cohort (n = 130)*

Variable	At 6 Months ΔCD4	P	At 12 Months ΔCD4	P	At 18 Months ΔCD4	P
Overall	−77	0.0035	−95	0.0003	−112	0.0001
HIV-1 RNA at FP visit						
>50,000	−97	0.68	−103	0.96	−116	0.89
≤50,000	−75		−100		−110	
CD4 <3 months of FP visit						
>500	−156	0.001	−158	0.0016	−165	0.002
≤500	56		−1		−30	

*Changes in CD4 cell count from the FP visit were estimated using mixed-effects regression models with separate intercepts and slopes for each level of variable. Probability values are reported for the difference in slopes, except for the category "overall."

None of the results changed appreciably after we excluded 7 persons with seroconversion intervals of more than 12 months or after we excluded 5 persons whose first CD4 count was measured 4 months or more after the FP visit. We also explored the consistency of risk factor associations for progression to 1 CD4 cell count of fewer than 250 cells/mm^3. We chose this alternate endpoint because 27 participants reached a CD4 cell count of fewer than 250 cells/mm^3 during the 24 months after the FP visit, whereas only 12 participants reached 1 CD4 cell count of fewer than 200 cells/mm^3. Analyses of baseline markers for progression to 1 CD4 cell count of fewer than 250 cells/mm^3 revealed similar associations: adjusted hazard ratio (HR) of 8.7 (95% confidence interval [CI]: 3.0–25.5) for CD4 counts of fewer than 500 cells/mm^3 and adjusted HR of 2.1 (CI: 0.9–4.8) for HIV-1 RNA of more than 50,000 copies/mL.

DISCUSSION

In this well-characterized cohort of HIV-1 seroconverters, high HIV-1 viral load and low CD4 cell counts close to the time of seroconversion were predictive of progression to the early immunologic endpoint, defined as 2 consecutive CD4 cell counts of fewer than 350 cells/mm^3. A substantial proportion (27%) of participants reached the immunologic endpoint by 18 months after the FP visit. These results and the data on pretreatment levels and variability of HIV-1 viral load and CD4 cell counts in Table 1 provide a useful reference for determining sample sizes and for modeling both categorical and continuous outcomes in the analyses of HIV-1 vaccine efficacy on disease progression in the ongoing and future phase 3 vaccine trials.

Although HIV-1 disease progression has been previously examined in cohorts of recently HIV-1–infected IDUs,[27–29] the particular strengths of our study are that CD4 cell counts and HIV-1 RNA levels were measured frequently and that the first measurements were performed soon after seroconversion. The median viral load of 43,694 copies/mL at the FP visit (a median of 2 months after the estimated date of seroconversion) in Thai IDUs was similar to that reported for male IDUs in the United States (50,766 copies/mL at a median
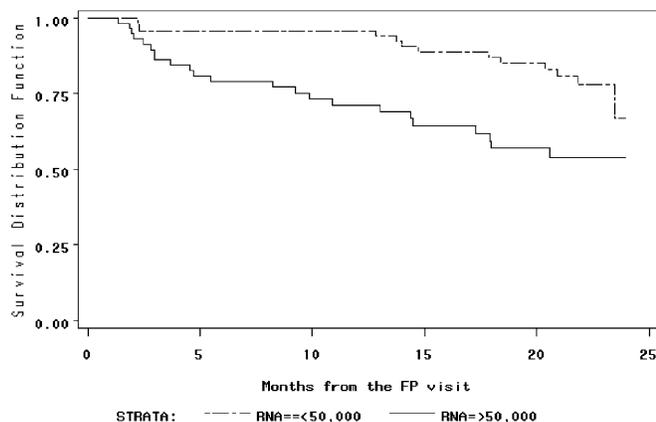
FIGURE 3. Probability of progression to the endpoint (2 consecutive CD4 counts of fewer than 350 cells/mm^3) by first HIV-1 RNA level (n = 130).
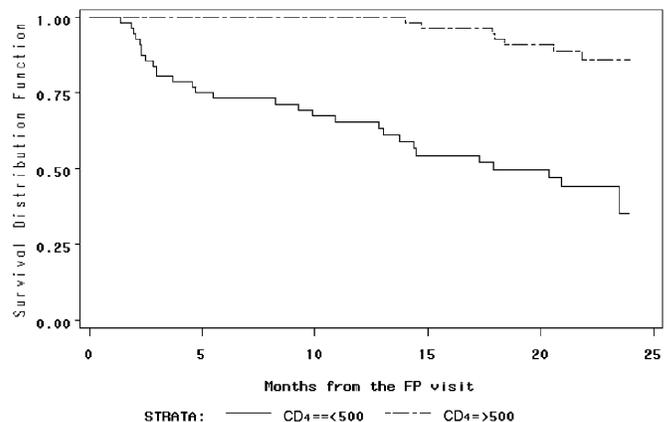
FIGURE 4. Probability of progression to the endpoint (2 consecutive CD4 counts of fewer than 350 cells/mm^3) by first CD4 cell count (n = 130).

TABLE 3. Association Between Risk Factors at FP Visit and Hazard of Progression to Early Endpoint* in the BMA Cohort (n = 130)

Variables	No.	Univariate HR (95% CI)	Multivariate HR (95% CI)†
CD4 count			
≤500	57	7.6 (3.3–17.4)	7.6 (3.2–17.6)
>500	73	Referent	Referent
HIV-1 RNA level			
≤50,000	71	Referent	Referent
>50,000	59	2.8 (1.4–5.6)	2.3 (1.1–4.8)
Subtype			
E (CRF01_AE)	103	1.3 (0.5–3.2)	1.4 (0.6–3.6)
B	27	Referent	Referent
Age (y)			
>30	70	1.2 (0.6–2.4)	1.2 (0.6–2.3)
≤30	60	Referent	Referent
Year of FP visit			
1995–1996	55	Referent	Referent
1997	44	1.6 (0.7–3.4)	1.4 (0.6–3.1)
1998	31	1.5 (0.6–3.6)	1.7 (0.7–4.2)

*Endpoint was defined as 2 consecutive CD4 counts of fewer than 350 cells/mm^3.

†Multivariate analyses included all factors included in the table.

of 4.3 months after the estimated date of seroconversion).[29] The median HIV-1 RNA levels and CD4 cell counts during the first year after seroconversion in our study population were also similar to those in other studies of recently HIV-infected persons, predominantly homosexual men, with short seroconversion intervals.[30,31] Compared with participants with well-defined times of HIV-1 seroconversion enrolled in the Multicenter AIDS Cohort Study in the United States,[32] the French SEROCO cohort,[33] and the HIV Network for Prevention Trials,[34] however, the participants in our study had somewhat higher RNA levels and lower CD4 cell counts during the first year after the FP visit, but they had similar rates of CD4 cell count decline. Some differences in early laboratory marker values between studies may be caused by differences in the length of seroconversion intervals or by variability in laboratory assays. Furthermore, HIV-1 RNA levels, CD4 cell counts, and the rate of HIV-1 disease progression may be affected by other factors, including age, gender, race/ethnicity, comorbidities and coinfections (including those related to injection drug use), host immune factors, and viral characteristics, as previously described.[27,28,35–43]

Higher HIV-1 viral loads around the time of seroconversion and in the first several months of infection are prognostic of clinical HIV-1 disease progression[9,32,33,44] and, based on our study, appear to have prognostic value for early HIV disease progression as well. Although we detected no differences in the rate of CD4 cell decline by HIV-1 RNA level at the FP visit, we found a moderate association between higher RNA level at the FP visit and progression to the immunologic endpoint stringently defined as 2 consecutive CD4 cell counts of fewer than 350 cells/mm^3. As in other studies,[28,31] IDUs in our study who had low CD4 cell counts shortly after seroconversion were at an increased risk for disease progression. Of note, there were no substantial statistically significant differences in participants' seroconversion intervals according to the RNA level at the FP visit (≤50,000 vs. >50,000 copies/mL) or CD4 cell count closest to the FP visit (≤500 vs. >500 cells/mm^3), suggesting that differences in the risk of early disease progression for participants in these subgroups did not result from confounding by duration of HIV infection.

Although some new candidate HIV-1 vaccines may reduce HIV-1 viral loads during early infection[4] and may alter the trajectory of CD4 cell counts, it remains unclear whether changes in laboratory marker values close to the time of seroconversion will reliably predict longer term vaccine efficacy on clinical HIV-1 disease progression. Studies evaluating the utility of laboratory markers as surrogate endpoints in ART trials have found that treatment-mediated changes in early CD4 cell counts and HIV-1 RNA levels are imperfect surrogates for clinical disease progression because they do not fully reflect the changes in the risk for AIDS or death associated with use of different ART regimens.[45–47] In addition, the vaccine-induced suppression of early HIV-1 viral load and the preservation of CD4 cell counts may not have the same long-term clinical benefit as natural control of early HIV-1 infection by some persons. Finally, findings of vaccine efficacy on disease progression based on the differences in the immunologic or virologic profiles of the HIV-1–infected vaccine and placebo recipients must be interpreted cautiously because of the potential for selection bias resulting from the fact that these analyses only include a subset of the original randomized population. For example, VE$_p$ may be underestimated if a candidate vaccine disproportionately protects persons with stronger immune function such that vaccine recipients who do become HIV-1 infected are also the ones more likely to experience rapid immunologic decline.[48]

Several considerations should guide the choice of surrogate endpoints based on either HIV-1 viral load or CD4 cell counts for analyses of VE$_p$. First, whereas HIV-1 RNA levels near time of seroconversion reflect the ability of the immune system to control the infection, declining CD4 cell counts are indicative of cumulative immunologic deterioration and therefore may be more appropriate than HIV-1 RNA levels as a measure of disease progression. Second, it is important to choose secondary endpoints that occur relatively soon after the infection and before patients begin taking ART. One of our key findings is that 27% of participants reached 2 consecutive CD4 cell counts of fewer than 350 cells/mm^3 by 18 months after the

FP visit. This endpoint seems to be relevant and evaluable for analyses of VE$_p$ in future HIV-1 vaccine trials, particularly in Thailand and other developing countries, where HIV-infected persons are likely to remain ART naive until their CD4 cell counts decline to 350 or fewer cells/mm^3. Our study also suggests that virologic "failure" endpoints are common in the first few months after seroconversion. For example, at 6 months after the FP visit, close to half of our participants had an HIV-1 viral load of more than 50 000 copies/mL and approximately one quarter had a viral load of more than 100 000 copies/mL (see Table 1). Third, data on variability in HIV-1 viral load and CD4 cell counts at various points in time (see Table 1) can be useful for estimating the sample sizes necessary for well-powered analyses of VE$_p$ based on continuous outcomes. For a vaccine trial of a given size, selecting an endpoint with a smaller variance will make it more likely to detect a difference (if it exists) in mean or median laboratory marker levels of HIV-infected vaccinees and placebo recipients.

We limited our analyses to the first 24 months after the FP visit, because the initial evaluations of VE$_p$ in an HIV-1 vaccine trial will likely be based on similar or shorter follow-up of HIV-infected trial participants (before they begin ART). As was the case in our cohort, few persons who become infected in an HIV-1 vaccine trial may be expected to progress to AIDS or death during this time period. Therefore, our analyses focused on progression to the immunologic endpoint of 2 consecutive CD4 cell counts of fewer than 350 cells/mm^3, which was reached by a larger number of participants (n = 36) during the first 24 months after the FP visit than was the endpoint of 1 CD4 cell count of fewer than 250 cells/mm^3 (n = 27) or 1 CD4 cell count of fewer than 200 cells/mm^3 (n = 12). We could not well assess the risk for progression to this immunologic endpoint by HIV-1 viral load levels at 6 or 12 months after the FP visit, because a substantial number of participants had already reached the immunologic endpoint by that time (12% by 6 months and 16% by 12 months), and excluding these "fast progressors" from analysis could have introduced bias.

Evaluation of VE$_p$ in future HIV-1 vaccine trials will be challenging, because some participants will likely begin ART soon after infection, which can dramatically alter the course of HIV-1 disease,[11] whereas those who delay or are not eligible to receive ART may be a select subset of healthier persons. Gilbert et al[12] proposed to use aggregate endpoints combining virologic or immunologic failure and time to initiation of ART. This method can be particularly useful in settings where standardized guidelines for ART initiation are followed. Because only 6 of our participants received ART during the 24 months after the FP visit and the BMA treatment guidelines have continued to evolve since the inception of this cohort, we did not incorporate time to ART use in our analyses.

It is important that future HIV-1 vaccine trials evaluate VE$_p$, because an HIV-1 vaccine that mitigates HIV-1 disease

and controls HIV-1 viral load may have important public benefits worldwide in terms of improving and prolonging the lives of those who become HIV-1 infected and potentially reducing the risk of HIV transmission by these vaccinated HIV-1–infected individuals.[49–53] The BMA seroconverter cohort provides useful reference data, including the magnitude and variability in early CD4 cell counts and HIV-1 RNA levels, for treatment-naive recently HIV-1–infected IDUs. These data can guide the analyses of vaccine efficacy in slowing disease progression in planned HIV-1 vaccine efficacy trials in Thailand and elsewhere.[54]

ACKNOWLEDGMENTS

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