HLA-B*57 versus HLA-B*81 in HIV-1 Infection: Slow and Steady Wins the Race?

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Two human leukocyte antigen (HLA) variants, HLA-B*57 and -B*81, are consistently known as favorable host factors in human immunodeficiency virus type 1 (HIV-1)-infected Africans and African-Americans. In our analyses of prospective data from 538 recent HIV-1 seroconverters and cross-sectional data from 292 subjects with unknown duration of infection, HLA-B*57 (mostly B*57:03) and -B*81 (exclusively B*81:01) had mostly discordant associations with virologic and immunologic manifestations before antiretroviral therapy. Specifically, relatively low viral load (VL) in HLA-B*57-positive subjects ($P \leq 0.03$ in various models) did not translate to early advantage in CD4⁺ T-cell (CD4) counts ($P \geq 0.37$). In contrast, individuals with HLA-B*81 showed little deviation from the normal set point VL ($P > 0.18$) while maintaining high CD4 count during early and chronic infection ($P = 0.01$). These observations suggest that discordance between VL and CD4 count can occur in the presence of certain HLA alleles and that effective control of HIV-1 viremia is not always a prerequisite for favorable prognosis (delayed immunodeficiency). Of note, steady CD4 count associated with HLA-B*81 in HIV-1-infected Africans may depend on the country of origin, as observations differed slightly between subgroups enrolled in southern Africa (Zambia) and eastern Africa (Kenya, Rwanda, and Uganda).

In Africans infected with diverse human immunodeficiency virus type 1 (HIV-1) subtypes (clades), the virologic and immunologic outcomes can be highly variable, often depending on complex viral and host factors, especially human leukocyte antigen (HLA) variants that facilitate innate and adaptive immune responses (1–7). Population- and methodology-specific issues aside (8), strong and consistent evidence suggests that two relatively common *HLA-B* variants, HLA-B*57 and -B*81, may be universally favorable in the context of viral load (VL) control (4–6, 9). Confirmatory findings based on analyses of African-Americans are also convincing (10, 11), as are efforts to define the underlying functional mechanisms (12–16). Further translational research may require close attention to the timing of HLA class I (HLA-I)-mediated immune pathways (17–20).

The effects of favorable HLA class I alleles like HLA-B*57 are apparently more readily detected in primary (early) than chronic infection (4), presumably because viruses acquire immune escape and compensatory mutations over time to gain new phenotypes (14, 20–22). The long-term benefits of HLA-B*57 and -B*81 are still uncertain, as immunologic outcomes and disease progression are rarely examined for resource-poor African populations (3, 5). Relying on new prospective data from 538 African seroconverters with early chronic infection and cross-sectional data from 292 AIDS-free subjects with unknown duration of infection, our work here suggest that virologic and immunologic manifestations of HIV-1 infection are often discordant in subgroups of Africans defined by HLA-B*57 and -B*81.

MATERIALS AND METHODS

Study population and follow-up intervals. HIV-1-infected Africans, including 538 recent seroconverters (SCs) and 359 subjects already seropositive (seroprevalent subjects [SPs]) at first testing, were enrolled from Kenya, Rwanda, Uganda, and Zambia under a uniform study protocol developed and implemented by the International AIDS Vaccine Initiative (IAVI). The procedures for written informed consent and all other research protocols were approved by institutional review boards at all sponsoring organizations, with further compliance to human experimentation guidelines set forth by the U.S. Department of Health and Human Services. Clinical and laboratory tests during regular follow-up visits have been described in detail elsewhere (6, 23, 24). Access to health care and HIV-1 prevention is similar across all clinical sites in terms of HIV risk reduction, management of sexually transmitted infections, CD4⁺ T-cell (CD4) counts, general medical care, as well as family planning counseling (25). Initiation of antiretroviral therapy (ART) followed appropriate national guidelines (25), and all visits after ART were excluded. Analyses of the remaining longitudinal data targeted three time intervals in SCs, i.e., (i) acute phase within the first 3 months (91 days) after the estimated date

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TABLE 1 Overall characteristics of 538 HIV-1 seroconverters and 292 chronically infected subjects enrolled from four African countries^a

Characteristic ^b	Value for group ^c	
	SCs (n = 538)	SPs (n = 292)
No. of subjects (%) from the following country:		
Kenya	106 (19.7)	4 (1.4)
Rwanda	85 (15.8)	81 (27.7)
Uganda	128 (23.8)	69 (23.6)
Zambia	219 (40.7)	138 (47.3)
Sex ratio, M/F (no. of individuals)	1.7 (336/202)	0.8 (130/162)
Age at enrollment in study (mean ± SD) (yr)	31.1 ± 8.3	33.1 ± 7.7
Age ≥ 40 years, no. of subjects (%)	84 (15.6)	59 (20.2)
Estimated dates of infection		
Earliest	May 2005	Unknown
Latest	Aug 2011	Unknown
No. of subjects (%) with the following HIV-1 subtype:		
A1	179 (33.3)	7 (2.4)
C	211 (39.2)	4 (1.4)
D ^d	73 (13.6)	2 (0.7)
Other (B and recombinants) ^d	20 (3.7)	0 (0.0)
Unknown (no viral sequencing)	55 (10.2)	279 (95.5)
Viral load measure per patient, median (IQR)	8 (7–10)	1 (1–1)
Total person visits with viral load data	4,615	292
Viral load ^e (mean ± SD)	3.3 ± 1.3	4.2 ± 1.3
CD4 T-cell measure per patient, median (IQR)	9 (7–10)	1 (1–1)
Total person visits with CD4 count	4,676	292
CD4 count ^f (mean ± SD)	534 ± 239	475 ± 220

^a Chronically infected subjects (seroprevalent subjects) with <200 CD4⁺ T cells/μl were excluded from this study.
^b M, male; F, female; SD, standard deviation of the mean; IQR, interquartile range.
^c SCs, seroconverters; SPs, seroprevalent subjects.
^d The minor HIV-1 subtypes (D and other) are combined for analysis here. For SPs, viral subtypes are mostly unknown (lack of viral sequencing).
^e Nadir viral load (VL) in SCs after 3 months of infection or first available viral load in SPs.
^f At visits corresponding to VL measurements.

of infection (EDI) (6), (ii) set point in the 3- to 12-month period after the EDI (4), and (iii) early chronic phase corresponding to 12 to 24 months after the EDI. The EDI was established in three ways (whichever came first): (i) 10 days prior to the first detection of viral RNA in plasma accompanied by negative serology, (ii) 2 weeks prior to the first detection of HIV-1 p24 antigen in plasma with negative serology, and (iii) the midpoint between the last seronegative test and the first seropositive test. The chronically infected SPs were enrolled as the suspected transmission source partners of SCs. They made a single study visit to provide cross-sectional data for analysis here.

Virologic and immunologic phenotypes. Plasma viral load (VL = RNA copies/ml) was measured using the Amplicor Monitor v1.5 assay (Roche Applied Science, Indianapolis, IN) (24). For log₁₀ transformation, VL below the lower limit of detection (400 RNA copies/ml) was assigned a value of 1.300 (half of log₁₀400). CD4 counts were based on T-cell immunophenotyping, with assays done at individual clinics using the FACScount system (Beckman Coulter Ltd., London, United Kingdom).

TABLE 2 Sporadic relationships between timing of follow-up and several HIV-1-related outcomes in 538 HIV-1 seroconverters and 292 seroprevalent subjects

Interval tested	Median DOI or DOF (IQR) (wk) ^a	Correlation (Spearman rho [P]) ^b
DOI in SCs at three major intervals		
Peak viral load (VL)	17 (8–36)	−0.37 (<0.0001)
Set point VL	16 (13–24)	0.02 (0.625)
Nadir VL	60 (26–120)	−0.28 (<0.0001)
Peak CD4 ⁺ T-cell (CD4) count	16 (8–36)	0.00 (0.938)
Set point CD4 count	16 (13–24)	−0.15 (<0.001)
Nadir CD4 count	61 (38–84)	−0.11 (0.009)
DOF in SPs at the first test		
Chronic VL	0 (0–0)	0.03 (0.662)
Chronic CD4 count	0 (0–0)	−0.07 (0.213)

^a The duration of infection (DOI) for HIV-1 seroconverters (SCs) began at the estimated date of infection (see the text). The duration of follow-up (DOF) for seroprevalent subjects (SPs) began at the time of enrollment in the study. The interquartile range (IQR) is defined by the 25th to 75th percentile.
^b Correlation was measured by Spearman rho. For values shown in boldface type, *P* < 0.01.

The duration of infection (DOI) for each VL and CD4 measurement was calculated from the blood sample date and the EDI.

Viral sequencing and HLA genotyping. Methods for HIV-1 *pol* gene sequencing and HLA class I genotyping have been described elsewhere (4, 6, 24). Viruses were grouped into subtypes (mostly A1, C, and D) and recombinant forms (rare). Allelic variants at three HLA class I loci (*HLA-A*, *HLA-B*, and *HLA-C*) were fully resolved to their 4-digit specificities.

Statistical analysis. Using software packages in SAS, version 9.2 (SAS Institute, Cary, NC), SCs and SPs were evaluated primarily for virologic and immunologic outcomes. All SCs with adequate data in the first 24 months after EDI were analyzed, while 67 SPs with end-stage infection (CD4 count < 200 cells/μl) were excluded, leading to an effective sample size of 292 chronically infected SPs suitable for analysis of VL (Table 1). Comparative analyses followed strategies established in similar studies (4, 9), with an emphasis on (i) local regression (LOESS) and mixed models for repeated measures, (ii) analysis of variance (ANOVA), (iii) *t* test for quantitative variables with a normal distribution (CD4 count and log₁₀ VL), and (iv) Cochran-Armitage tests for trend across three ordinal VL categories (high, medium, and low) with differential impact on HIV-1 transmission (4, 9, 26). In addition, Kaplan-Meier curves were used to compare time from EDI to severe immunodeficiency (CD4 count < 350 cells/μl) in SCs, with individual plots generated using GraphPad Prism (GraphPad Software, Inc.). Collectively, these analyses aimed at defining the durability and concordance of HLA-I associations with virologic and immunologic manifestations of primary and chronic HIV-1 infection. Separate analyses of two subgroups with subjects from Zambia (southern Africa) and subjects from eastern Africa allowed a partial evaluation of region-specific relationships. The statistical significance was accepted at the level of *P* < 0.05 in multivariable models, i.e., with full adjustment for cofactors and potential confounders.

RESULTS

Overall characteristics of the study population. HIV-1 seroconverters (SCs) available for analysis here included 106 Kenyans, 85 Rwandans, 128 Ugandans, and 219 Zambians, with an overall male-to-female ratio of 1.7 (Table 1). The vast majority (74.4%) of SCs were less than 40 years old at enrollment in the study, and their estimated dates of infection (EDIs) ranged from May 2005 to

Subgroup	HIV-1 seroconverters available at 14 time intervals (0-104 weeks, as shown on the X-axis)													
B*57-/B*81-	466	466	432	403	360	321	303	263	232	222	209	190	178	157
B*57+	25	25	23	23	21	21	21	19	19	19	18	15	15	12
B*81+	47	47	46	42	40	37	36	34	29	27	27	22	20	19

FIG 1 Local regression (LOESS) curves showing the dynamics of virologic manifestations (A) and immunologic manifestations (B) of HIV-1 infection in 538 seroconverters. Measurements for B*57⁺ and B*81⁺ subjects are represented by open circles and dark dots, respectively. Overlap between B*57⁺ and B*81⁺ subgroups is minimal (two SCs in the B*81⁺ subgroup have both B*57 and B*81). Other measurements (gray circles) come from the B*57⁻ B*81⁻ subgroup (treated as the reference group). Thick and thin lines correspond to the expected mean (average) values and 95% confidence intervals for each subgroup. CD4 level at 200 cells/μl is also indicated (dotted line). The numbers of subjects remaining at 14 time intervals are also shown.

August 2011. HIV-1 subtypes C and A1 were dominant among these SCs, accounting for 39.2% and 33.3% of the total, respectively. Other subtypes, i.e., D, B, and recombinant forms, were present at low frequencies. There were a median of 9 follow-up visits (interquartile range, 7 to 10) per patient in the first 2 years after the EDI. HIV-1 viral load (VL) and CD4⁺ T-cell (CD4) count measured at these visits provided longitudinal data for testing.

AIDS-free subjects (SPs) who were seropositive at the first test mostly came from three countries (Rwanda, Uganda, and Zambia), with an overall male-to-female ratio of 0.8. Their ages at enrollment were similar to SCs, but HIV-1 subtypes remained

largely unknown (viral sequencing not done). HIV-1 VL and CD4 count measured at the first available visit were treated as cross-sectional data for analysis.

Two *HLA-B* variants of interest, B*57 (mostly B*57:03) and B*81 (exclusively B*81:01), were found in 49 (9.1%) and 25 (4.6%) SCs, respectively, with two (0.4%) SCs having both (no different from the coexistence frequency expected from a random distribution). In the SP group, the frequency was slightly higher for both, as 38 (13.0%) of them had B*57, 21 (7.2%) had B*81, and two (0.7%) had both.

Relationships between timing of data collection and manifestations of HIV-1 infection. In the SC group, virologic and im-

TABLE 3 Discordant relationships of HLA-B*57 and -B*81 to virologic and immunologic phenotypes in early and chronic HIV-1 infection, as seen in 538 seroconverters and 292 seroprevalent subjects

Model	Analysis of HLA-B*57 ^a			Analysis of HLA-B*81 ^a		
	<i>n</i>	Δ (mean ± SE) or pOR (95% CI) ^b	Adjusted <i>P</i>	<i>n</i>	Δ (mean ± SE) or pOR (95% CI)	Adjusted <i>P</i>
Generalized linear models for VL						
SCs						
Peak (<i>n</i> = 538) ^c	49	−0.38 ± 0.12	0.001	25	−0.05 ± 0.16	0.760
Set point (<i>n</i> = 538)	49	−0.31 ± 0.14	0.032	25	−0.23 ± 0.20	0.241
Repeated measures (3 to 24 mo)	49	−0.51 ± 0.12	<0.001	25	−0.23 ± 0.17	0.178
SPs at the only available visit (<i>n</i> = 292) ^d	38	−0.39 ± 0.22	0.087	21	−0.34 ± 0.29	0.248
Generalized linear models for CD4 count						
SCs						
VL peak (<i>n</i> = 538) ^c	49	26 ± 34	0.443	25	54 ± 46	0.239
VL set point (<i>n</i> = 538)	49	28 ± 35	0.419	25	36 ± 48	0.455
Repeated measures (3 to 24 mo)	49	39 ± 30	0.192	25	92 ± 40	0.023
SPs at the only available visit (<i>n</i> = 292) ^d	38	80 ± 38	0.034	21	183 ± 48	<0.001
Ordinal logistic regression for VL ^e						
SCs						
Peak (<i>n</i> = 538) ^d	49	0.38 (0.21–0.66)	<0.001	25	1.06 (0.47–2.38)	0.893
Set point (<i>n</i> = 538)	49	0.54 (0.31–0.95)	0.031	25	0.68 (0.32–1.44)	0.309
SPs at the only available visit (<i>n</i> = 292) ^d	38	0.47 (0.25–0.91)	0.024	21	0.58 (0.25–1.34)	0.201

^a Tests for three sets of models were performed. Analysis compares subjects with and without the HLA factor. Potential confounders retained as covariates include age, gender, viral subtype, number of outcome measures, and duration of infection (DOI) for SCs, regardless of statistical significance in each model. For SPs, the viral subtype was not available, and time after infection is replaced by duration of follow-up (DOF) after enrollment in the study. The boldface values reach statistical significance (*P* < 0.05).

^b For the generalized linear models for VL and CD4 count, the change or difference (Δ) in the values is shown. For ordinal logistic regression for VL, the proportional odds ratio (pOR) and 95% confidence interval (95% CI) are shown.

^c The highest VL within 90 days of infection is analyzed for the acute phase, as reported elsewhere (6).

^d CD4⁺ T-cell counts exceed 200 cells/μl in all SPs. The time interval in all SCs starts from the estimated date of infection (EDI).

^e Three VL categories, i.e., high (>10⁵ copies/ml), medium (10⁴ to 10⁵ copies/ml), and low (<10⁴ copies/ml), are defined according to their differential impact on HIV-1 transmission (9, 26).

munologic outcomes showed weak and sporadic correlation with duration of infection (DOI) at three major intervals (peak, set point, and nadir) within the first 24 months of infection (Table 2). Correlation with the greatest statistical significance (*P* < 0.0001) was for peak VL and DOI (time elapsed after EDI) (Spearman rho = −0.37). Timing of data collection was not an issue for the SP group, as there was little variation in the duration of follow-up (DOF) until the first VL and CD4 count measurements were taken (Table 2). For consistency, however, DOI and DOF were treated as covariates in all subsequent analyses, regardless of their statistical significance.

Dynamics of viremia and CD4 count during acute and early chronic phases of HIV-1 infection. LOESS curves based on 4,615 person visits (Fig. 1A) revealed that three groups of SCs stratified by the presence and absence of HLA-B*57 and HLA-B*81 had distinct VL profiles that were steady beyond 3 months (13 weeks) of infection. The reference group without these two alleles consistently had the highest VL after infection compared with SCs who were HLA-B*57 positive (B*57⁺) or B*81⁺. In mixed models for testing VL measures in the 3- to 24-month interval, VLs in B*57⁺ SCs were about 0.5 log₁₀ unit lower than in HLA-B*57-negative (B*57[−]) SCs (adjusted *P* < 0.001) (Table 2). VLs differed by about 0.3 log₁₀ unit between B*81⁺ and B*81[−] SCs, but without reaching statistical significance after adjusting for age, sex, and other potential cofactors (DOI and country of origin) (*P* = 0.18) (Table 2).

When CD4 counts corresponding to 4,676 person visits were

plotted for LOESS curves (Fig. 1B), HLA-B*81⁺ SCs showed relatively steady measures across the first 24-month period of infection. On average, B*81⁺ SCs had 92 ± 40 more CD4 cells per μl of blood than did B*81[−] SCs in the 3 to 24 months after infection (*P* = 0.02 in analyses of repeated measures) (Table 2). B*57⁺ SCs, on the other hand, did not demonstrate clear advantage in CD4 count compared with B*57[−] SCs (beta estimate = 39 ± 30 cells/μl; adjusted *P* = 0.19) (Table 2). The slight trend for higher CD4 count in B*57⁺ SCs diminished over time, especially after 72 weeks of infection (Fig. 1B).

Analysis of cross-sectional data from SPs. Cross-sectional data from 292 SPs confirmed the discordance between virologic and immunologic phenotypes associated with HLA-B*57 and -B*81 (Table 3). The adjusted effect size for CD4 count was 183 ± 48 cells per μl of blood for the difference between B*81⁺ and B*81[−] SPs (*P* < 0.001), but HIV-1 VLs were similar in B*81⁺ and B*81[−] SPs (*P* = 0.25). For comparisons between B*57⁺ and B*57[−] SPs, the difference in the CD4 count was 80 ± 38 cells/μl, in favor of B*57 (*P* = 0.03), while the difference in HIV-1 VL (0.39 ± 22 log₁₀) did not reach statistical significance (*P* = 0.09).

Viremia as a categorical phenotype in SCs and SPs. Test for trend was also revealing, as HLA-B*57 was clearly less frequent in the subgroups of SCs and SPs with high VL (>100,000 copies/ml) and medium VL (10,000 to 100,000 copies/ml) than low VL (<10,000 copies/ml) (Table 3). The proportional odds ratio (pOR) across the three ordinal subgroups ranged from 0.24 to 0.54 in analysis of peak, set point, and nadir VL in SCs (adjusted

FIG 2 CD4⁺ T-cell (CD4) count observed in 538 HIV-1 seroconverters (SCs) and 292 seroprevalent subjects (SPs) stratified by HLA-B*57 and HLA-B*81. (A and B) In SCs, the acute-phase (peak) CD4 (A) and nadir CD4 count (B) are based on measurements at <3 months and 3 to 24 months after the estimated date of infection, respectively. (C) In SPs with a CD4 count of >200 cells/μl, the first available CD4 count is tested. Filled circles denote subjects who have both B*57 and B*81. Subjects without B*57 or B*81 (B*57⁻/B*81⁻ individuals) serve as the reference group. The mean (horizontal black line) ± standard deviation (error bars) for each subgroup are indicated. The dotted lines in panels B and C indicate a CD4 count of 200 cells/μl.

$P < 0.04$ for all tests). Estimates for the SP group were similar (pOR = 0.47 and $P = 0.02$). In contrast, HLA-B*81 did not show much differential distribution across the three VL groups (adjusted $P = 0.20$ to 0.89).

Observations from other analyses. In further analyses where subjects without HLA-B*57 and HLA-B*81 served as the reference group, an advantage with CD4 count was persistent for HLA-B*81 beyond the acute phase of infection, with the most dramatic difference seen in the SP group ($P < 0.001$) (Fig. 2). For HLA-B*57⁺ subjects, the CD4 profile was always highly comparable to that of the reference group (Fig. 2).

Kaplan-Meier curve further revealed that time from estimated date of infection to severe immunodeficiency (CD4 count < 350 cells/μl) differed among SCs with or without HLA-B*57 and HLA-B*81 ($P = 0.02$) (Fig. 3). The overall difference was driven by HLA-B*81 (relative hazards [RH] = 0.40; 95% confidence in-

FIG 3 Progression to severe immunodeficiency among 538 HIV-1 seroconverters (SCs) without antiretroviral therapy, as defined by Kaplan-Meier curve. Two SCs with both B*57 and B*81 (B*57⁺/B*81⁺) are kept in the B*81⁺ group (for clarity). The first visit with CD4⁺ T-cell count below 350 cells/μl is counted as the event (outcome). The numbers of subjects remaining at eight time points are all within the 0- to 70-month interval.

terval [95% CI] = 0.19 to 0.86) and not B*57 (RH = 0.82; 95% CI = 0.55 to 1.23). Statistical adjustments for age, gender, and HIV-1 subtype (or country of origin) made no difference to the effects of B*81 or B*57. In sensitivity analysis, the two SCs with both B*57 and B*81 were treated in three ways: (i) left out of the model, (ii) kept in the B*57⁺ subgroup, and (iii) kept in the B*81⁺ subgroup. In each case, statistical significance remained with B*81⁺ SCs (adjusted $P = 0.02$, $P < 0.01$, and $P = 0.02$, respectively). For B*57⁺ SCs, the corresponding P values associated with RH estimates were 0.34, 0.34, and 0.17, respectively (data available from J. Tang).

In our study populations, HLA-B*57 and -B*81 were in strong linkage disequilibrium (LD) with HLA-C*18:01, which is also known to be favorable in Africans (4, 5, 9). Virtually all SCs and SPs with C*18:01 had either B*57 or B*81. The distinct phenotypes in B*57⁺ and B*81⁺ subjects, however, could not be explained by C*18:01 or other companion HLA-C variants. Weak LD between HLA-B and HLA-A variants further ruled out the potential confounding by HLA-A alleles (9).

Separate analyses of subjects from southern and eastern Africa to assess regional consistency. HLA-related, discordant relationship between VL and immunodeficiency was evident in subgroup analyses (Table 4 and Fig. 4). Among 219 southern African (Zambian) SCs, the association of HLA-B*57 with lower VL (adjusted $P < 0.01$) but not higher CD4 count ($P = 0.48$) was in clear contrast with the concordant association of female sex with lower VL and higher CD4 count (Table 4). SCs from eastern Africa ($n = 319$) provided similar results, except that neither CD4 count nor time from infection to a CD4 count of <350 cells/μl reached statistical significance for the subgroup of SCs defined by HLA-B*81 (adjusted $P > 0.25$). In the comparison of cross-sectional data from Zambian SPs ($n = 138$) and eastern African SPs ($n = 154$), HLA-B*81 was unequivocally advantageous in analyses of CD4 count regardless of the country of origin (Table 4). Nonetheless, the adjusted effect size attributable to HLA-B*81 was more substantial in Zambian SPs ($\Delta = 219 \pm 72$ cells/μl; $P < 0.01$) than eastern African SPs ($\Delta = 161 \pm 63$ cells/μl; $P = 0.01$).

TABLE 4 Multivariable analyses of prospective data from seroconverters and cross-sectional data from seroprevalent subjects enrolled in southern Africa (Zambia) and eastern Africa (Kenya, Rwanda, and Uganda)

Factor in model ^a	SCs from Zambia ^{b,c}		SCs from eastern Africa ^{b,c}		SPs from Zambia ^c		SPs from eastern Africa ^c	
	Δ (mean $\pm$ SE)	<i>P</i>	Δ (mean $\pm$ SE)	<i>P</i>	Δ (mean $\pm$ SE)	<i>P</i>	Δ (mean $\pm$ SE)	<i>P</i>
HIV-1 viral load (VL)								
Female gender	-0.43 $\pm$ 0.09	<0.0001	-0.45 $\pm$ 0.10	<0.0001	-0.54 $\pm$ 0.23	0.021	-0.65 $\pm$ 0.22	0.004
DOI (per wk) ^d	0.002 $\pm$ 0.001	0.033	-0.004 $\pm$ 0.001	<0.0001				
HLA-B*57	-0.41 $\pm$ 0.15	0.006	-0.62 $\pm$ 0.17	<0.001	-0.47 $\pm$ 0.31	0.124	-0.31 $\pm$ 0.35	0.381
HLA-B*81	-0.14 $\pm$ 0.20	0.475	-0.46 $\pm$ 0.24	0.059	0.04 $\pm$ 0.43	0.931	-0.73 $\pm$ 0.41	0.079
CD4⁺ T-cell count								
Female gender	69 $\pm$ 23	0.003	89 $\pm$ 25	<0.001	71 $\pm$ 40	0.078	87 $\pm$ 34	0.012
DOI (per wk) ^d	-1 $\pm$ 0	<0.0001	-1 $\pm$ 0	<0.0001				
HLA-B*57	7 $\pm$ 39	0.853	63 $\pm$ 42	0.137	-19 $\pm$ 52	0.719	217 $\pm$ 54	<0.0001
HLA-B*81	140 $\pm$ 51	0.006	64 $\pm$ 59	0.282	219 $\pm$ 72	0.003	161 $\pm$ 63	0.012

^a For consistency, age, viral subtype, and time after infection are always treated as covariates in analysis of SCs. For SPs, viral subtype is not available and time after infection is replaced by time after enrollment.

^b In SCs, analyses test repeated measures of VL and CD4 count in the 3- to 24-month interval after estimated date of infection; cross-sectional data in SPs are defined in Table 2.

^c The boldface values reach statistical significance ($P < 0.05$).

^d The duration of infection (DOI) is relevant to analysis of SCs (Table 2).

FIG 4 Progression to severe immunodeficiency among HIV-1 seroconverters (SCs) from southern Africa (Zambia) ($n = 219$) (A) and eastern Africa (Kenya, Rwanda, and Uganda) ($n = 319$) (B). The analytical strategies are the same as those shown in Fig. 3. The Zambian subgroup has two SCs with both B*57 and B*81 (B*57+/B*81+) kept in the B*81+ group (for clarity). The numbers of subjects remaining at eight time points are all within the 0- to 70-month interval.

DISCUSSION

Spontaneous control of HIV-1 infection is typically manifest by low or undetectable viremia, but our work here provides compelling evidence that virologic control is not always a prerequisite for durable benefit during the first 2 years of infection (when most subjects were available for analysis), as seroconverters (SCs) with HLA-B*81 had relatively steady CD4 count without much advantage in suppressing viral load (VL). The time to a CD4 count of <350 cells/ μ l, a well-recognized threshold for initiation of antiretroviral therapy (27), was delayed so substantially in HLA-B*81+ individuals that this relationship persisted in the cross-sectional analysis of chronically infected subjects (SPs) with a CD4 count over 200 cells/ μ l. Overall, HLA-B*81 may not be the most favorable allele for virologic control, but its steady benefit can become obvious when CD4 counts (immunologic outcomes) are evaluated. HLA-B*57+ subjects showed the inverse to be true, i.e., clear advantage with VL was accompanied by rather limited impact on CD4 count and progression to severe immunodeficiency.

Recognition of HLA-B*57 as a favorable host factor in the course of HIV-1 infection began with cohorts of European ancestry (28–30), with B*57:01 as a single dominating allele highly enriched among elite controllers with undetectable VL or viremic controllers with a VL of $<2,000$ copies/ml and steady CD4 count (31). In cohorts of African ancestry, B*57 is primarily represented by B*57:03, while B*57:02 and B*57:01 are present at much lower frequencies. Recent work does suggest that “micropolymorphisms” within B*57-related alleles have functional consequences in the context of antigen presentation and HIV-1 immune escape (22). While the rarity of B*57:01 in African populations precludes any meaningful analysis of this particular allele here, evidence from comparison of HIV-1-infected African-American controllers and progressors suggests that the effective size (odds ratio) for three B*57 alleles can vary by up to 2-fold (11). Region-specific HIV-1 viruses and HLA alleles (e.g., A*30 and A*74) in strong linkage disequilibrium with HLA-B*57 alleles may offer another explanation for disparity in the relative effects of three alleles in the HLA-B*57 group (9, 32).

Compared with HLA-B*57, B*81 is less common, with popu-

lation frequencies ranging from 2.7% in Kenyans, 4.8% in Rwandans, 5.9% in Zambians, and 7.1% in Ugandans enrolled into this study. Other rare *HLA-B* alleles occasionally associated with advantageous outcomes (e.g., B*13, B*27, and B*39) (10, 33) did not show much differential impact on VL or CD4 count in our cohort, often as a result of limited statistical power. Given the maturity of the HIV/AIDS epidemic in sub-Saharan Africa (34, 35), rare allele advantage is expected to be less obvious because the circulating viruses have had ample opportunities to encounter and adapt to specific HLA-I profiles, especially since these alleles have no reported advantage in delaying or preventing the acquisition of HIV-1 infection (9, 19).

HLA-B*81-restricted, HIV-1-specific cytotoxic T-lymphocyte (CTL) responses are known to induce several mutations in Gag, a matrix protein important to HIV-1 virion assembly and maturation (15, 36). The single amino acid substitution (S186T) in one Gag epitope (TS9) is of particular interest, as HIV-1 subtype C viruses encoding 186S cannot replicate *in vitro* unless compensatory mutations are introduced to neighboring sites (e.g., Q182S plus T190A/I) (16). The biology underlying this rather dramatic “fitness cost” may point to gag codon 186 and neighboring sites as a viral Achilles heel.

HIV-1 infection in HLA-B*81 carriers may resemble simian immunodeficiency virus (SIV) infection in sooty mangabey, a model of nonprogressive infection despite persistency in high viremia for years (37). In study populations where HLA-B*81 or similar alleles are found at high frequencies, the assumed relationship between set point VL and disease progression (38, 39) may become obscured (40). When genetic factors associated with VL are distinct from those important to disease progression, as evident from studies of Africans and African Americans (5, 7, 10), systematic evaluation using open-minded approaches is important (8, 41, 42).

Complication by comorbidity may be relevant (8), as protective alleles like HLA-B*27 (rare in Africans) and -B*57 are known to be unfavorable in the setting of autoimmune diseases, including ankylosing spondylitis and psoriasis (43, 44). Complication from coinfection is also worth noting, as HLA alleles are critical to immunity against all human pathogens.

Future research can benefit from HLA-B*81⁺ individuals in at least two ways. First, B*81-positive subjects and others with steady CD4 count can be ideal for testing therapeutic vaccines, as both CTL and antibody responses depend on regulation by CD4 cells. Second, these individuals may offer an opportunity to examine mechanisms for discordance between VL and immunodeficiency after HIV-1 infection. In particular, assessment of T-cell activation status may provide valuable clues about the unique phenotypes associated with HLA-B*81. These efforts may require close attention to country- or region-specific settings, as findings may vary somewhat from one site to another.

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