HLA-B\text{(*)}57 versus HLA-B\text{(*)}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).

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

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value for group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SCs (n = 538)</td>
</tr>
<tr>
<td>No. of subjects (%) from the following country:</td>
<td></td>
</tr>
<tr>
<td>Kenya</td>
<td>106 (19.7)</td>
</tr>
<tr>
<td>Rwanda</td>
<td>85 (15.8)</td>
</tr>
<tr>
<td>Uganda</td>
<td>128 (23.8)</td>
</tr>
<tr>
<td>Zambia</td>
<td>219 (40.7)</td>
</tr>
<tr>
<td>Sex ratio, M/F (no. of individuals)</td>
<td>1.7 (336/202)</td>
</tr>
<tr>
<td>Age at enrollment in study (mean ± SD) (yr)</td>
<td>31.1 ± 8.3</td>
</tr>
<tr>
<td>Age ≥ 40 years, no. of subjects (%)</td>
<td>84 (15.6)</td>
</tr>
<tr>
<td>Estimated dates of infection</td>
<td></td>
</tr>
<tr>
<td>Earliest</td>
<td>May 2005</td>
</tr>
<tr>
<td>Latest</td>
<td>Aug 2011</td>
</tr>
<tr>
<td>No. of subjects (%) with the following HIV-1 subtype:</td>
<td></td>
</tr>
<tr>
<td>A1</td>
<td>179 (33.3)</td>
</tr>
<tr>
<td>C</td>
<td>211 (39.2)</td>
</tr>
<tr>
<td>D</td>
<td>73 (13.6)</td>
</tr>
<tr>
<td>Other (B and recombinants) d</td>
<td>20 (3.7)</td>
</tr>
<tr>
<td>Unknown (no viral sequencing)</td>
<td>55 (10.2)</td>
</tr>
<tr>
<td>Viral load measure per patient, median (IQR)</td>
<td>8 (7–10)</td>
</tr>
<tr>
<td>Total person visits with viral load data</td>
<td>4,615</td>
</tr>
<tr>
<td>Viral load (mean ± SD)</td>
<td>3.3 ± 1.3</td>
</tr>
<tr>
<td>CD4 T-cell count per patient, median (IQR)</td>
<td>9 (7–10)</td>
</tr>
<tr>
<td>Total person visits with CD4 count</td>
<td>4,676</td>
</tr>
<tr>
<td>CD4 count (mean ± SD)</td>
<td>534 ± 239</td>
</tr>
</tbody>
</table>

a Chronically infected subjects (seroprevalent subjects) with <200 CD4+ T cells/μl are excluded from this study.

b M, male; F, female; SD, standard deviation of the mean; IQR, interquartile range.

c SCs, seroconverters; SPs, serorepolitical 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.

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

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

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

**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.
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

<table>
<thead>
<tr>
<th>Model</th>
<th>Analysis of HLA-B*57&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Analysis of HLA-B*81&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>Δ (mean ± SE) or pOR (95% CI)&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Generalized linear models for VL SCs</td>
<td>49</td>
<td>−0.38 ± 0.12</td>
</tr>
<tr>
<td>Peak (n = 538)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>49</td>
<td>−0.31 ± 0.14</td>
</tr>
<tr>
<td>Set point (n = 538)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>49</td>
<td>−0.51 ± 0.12</td>
</tr>
<tr>
<td>Repeated measures (3 to 24 mo)&lt;sup&gt;d&lt;/sup&gt;</td>
<td>38</td>
<td>−0.39 ± 0.22</td>
</tr>
<tr>
<td>SPs at the only available visit (n = 292)&lt;sup&gt;d&lt;/sup&gt;</td>
<td>49</td>
<td>26 ± 34</td>
</tr>
<tr>
<td>VL peak (n = 538)&lt;sup&gt;e&lt;/sup&gt;</td>
<td>49</td>
<td>28 ± 35</td>
</tr>
<tr>
<td>VL set point (n = 538)&lt;sup&gt;e&lt;/sup&gt;</td>
<td>49</td>
<td>39 ± 30</td>
</tr>
<tr>
<td>Repeated measures (3 to 24 mo)&lt;sup&gt;d&lt;/sup&gt;</td>
<td>38</td>
<td>80 ± 38</td>
</tr>
<tr>
<td>SPs at the only available visit (n = 292)&lt;sup&gt;d&lt;/sup&gt;</td>
<td>49</td>
<td>0.38 (0.21–0.66)</td>
</tr>
<tr>
<td>Ordinal logistic regression for VL SCs</td>
<td>49</td>
<td>0.54 (0.31–0.95)</td>
</tr>
<tr>
<td>Peak (n = 538)&lt;sup&gt;e&lt;/sup&gt;</td>
<td>49</td>
<td>0.47 (0.25–0.91)</td>
</tr>
<tr>
<td>Set point (n = 538)&lt;sup&gt;e&lt;/sup&gt;</td>
<td>49</td>
<td>0.38 (0.21–0.66)</td>
</tr>
<tr>
<td>SPs at the only available visit (n = 292)&lt;sup&gt;d&lt;/sup&gt;</td>
<td>49</td>
<td>0.38 (0.21–0.66)</td>
</tr>
</tbody>
</table>

<sup>a</sup> 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).

<sup>b</sup> 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.

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

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

<sup>e</sup> Three VL categories, i.e., high (>10<sup>5</sup> copies/ml), medium (10<sup>4</sup> to 10<sup>5</sup> copies/ml), and low (<10<sup>4</sup> copies/ml), are defined according to their differential impact on HIV-1 transmission (9, 26).

Virologic and CD4 count measures across the first 24-month period of infection. On average, B*81<sup>+</sup> SCs had 92 ± 40 more CD4 cells per µl of blood than did B*81<sup>+</sup> SCs in the 3 to 24 months after infection (P = 0.02 in analyses of repeated measures) (Table 2). B*57<sup>+</sup> SCs, on the other hand, did not demonstrate clear advantage in CD4 count compared with B*57<sup>+</sup> SCs (beta estimate = 39 ± 30 cells/µl; adjusted P = 0.19) (Table 2). The slight trend for higher CD4 count in B*57<sup>+</sup> 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<sup>+</sup> and B*81<sup>+</sup> SCs (P < 0.001), but HIV-1 VLs were similar in B*81<sup>+</sup> and B*81<sup>+</sup> SCs (P = 0.25). For comparisons between B*57<sup>+</sup> and B*57<sup>+</sup> SCs, the difference in the CD4 count was 80 ± 38 cells/µl, in favor of B*57<sup>+</sup> (P = 0.03), while the difference in HIV-1 VL (0.39 ± 0.22 log<sub>10</sub>) 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 SCs, but with-
date of infection, respectively. (C) In SPs with a CD4 count of
based on measurements at
(A and B) In SCs, the acute-phase (peak) CD4 (A) and nadir CD4 count (B) are
and 292 seroprevalent subjects (SPs) stratified by HLA-B*57 and HLA-B*81.

Both B*57 and B*81. Subjects without B*57 or B*87 (B*57
als) serve as the reference group. The mean (horizontal black line)
deviation (error bars) for each subgroup are indicated. The dotted lines in
panels B and C indicate a CD4 count of 200 cells/
l.

Separate analyses of subjects from southern and eastern Af-
ica to assess regional consistency. HLA-related, discordant rela-
tionship between VL and immunodeficiency was evident in sub-
group analyses (Table 4 and Fig. 4). Among 219 southern African
(Zambian) SCs, the association of HLA-B*57 with lower VL (ad-
justed 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 = 0.17). 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). Nonethe-
less, the adjusted effect size attributable to HLA-B*81 was more
substantial in Zambian SPs (Δ = 219 ± 72 cells/μl; P < 0.01) than
eastern African SPs (Δ = 161 ± 63 cells/μl; P = 0.01).

FIG 2 Progression to severe immunodeficiency among 538 HIV-1 sero-
verters (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.
HIV-1 viral load (VL) (SCs) from southern Africa (Zambia) (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/µl, 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/µl. 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-
uation 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-1 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 compensated “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 mangabeys, 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-positve 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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REFERENCES


HIV RNA level on rate of CD4 T-cell decline in untreated HIV infection. JAMA 296:1498–1506.


