We investigated the effect of HLA class I alleles on clinical parameters for HIV-1 disease progression in the Japanese population, where two strongly protective alleles, HLA-B*57 and HLA-B*27, are virtually nonexistent. HLA-B alleles showed a dominant role, primarily through HLA-B*67:01 and the HLA-B*52:01-C*12:02 haplotype. Neither a rare-allele nor a heterozygote advantage was found, suggesting that the effect of HLA alleles in the Japanese population is either different from those observed in Africans and Caucasians or undetectable due to limited power.
ians, in which this allele was more commonly observed among HIV noncontrollers (5). On the other hand, HLA-B*35:02 and -B*35:03 associate with rapid disease progression in Caucasians, whereas HLA-B*35:01 does not (6), highlighting distinctions across allelic associations depending on the clinical outcome being considered. HLA-A*02:07 (frequency = 0.073), an allele that is missing in Caucasians and Africans, also associated with susceptibility.

An advantage of rare HLA alleles in HIV-1 disease progression has been reported previously (13). Therefore, we investigated the effect of HLA frequency on VL or CD4 count in our cohort by comparing these clinical measurements first to the sum of the frequencies of the two alleles at each HLA locus individually (HLA-A, -B, and -C separately) and second to the sum of the frequencies of all HLA class I alleles (HLA-A, -B, and -C combined) for each subject. No significant correlation was observed between the overall HLA allele frequency and VL or CD4 count (Fig. 2A and B), nor was there a correlation between HLA-A allele frequencies or HLA-C allele frequencies with these clinical measurements (Fig. 2C, D, G, and H). In contrast to previous observations, the frequencies of HLA-B alleles were positively and negatively associated with CD4 count and VL, respectively (Fig. 2E and F). We also analyzed the effect of HLA supertype frequency on VL and found no effect (see Fig. S1 in the supplemental material).

These results indicate no advantage of rare alleles on VL and CD4 count in the Japanese cohort. Further, we detected no significant

<table>
<thead>
<tr>
<th>Allele (n)</th>
<th>VL P</th>
<th>H</th>
<th>CD4 cell count P</th>
<th>H</th>
</tr>
</thead>
<tbody>
<tr>
<td>HLA-A (504)</td>
<td>0.006</td>
<td>37</td>
<td>0.43</td>
<td>18</td>
</tr>
<tr>
<td>HLA-B (504)</td>
<td>0.0005</td>
<td>81</td>
<td>0.004</td>
<td>71</td>
</tr>
<tr>
<td>HLA-C (503)</td>
<td>0.0001</td>
<td>52</td>
<td>0.084</td>
<td>29</td>
</tr>
</tbody>
</table>

a Values in bold are statistically significant.

FIG 1 Association of HLA allele expression with viral load and absolute CD4 count in Japanese individuals chronically infected with HIV-1. All HLA alleles occurring at a phenotypic frequency greater than 1% were examined for their associations with viral load (A) and absolute CD4 count (B) in a cohort of 504 chronically HIV-1-infected Japanese individuals recruited from 2000 to 2010. Associations with a P value of <0.05 are highlighted in gray.

FIG 2 HLA frequency-dependent effects on viral load and CD4 counts. The correlations between VL or CD4 count with combined frequencies for all subjects (n = 504) are shown. HLA frequencies used to calculate the combined frequencies for each individual were derived from the overall allele frequencies in the entire cohort of 504 subjects. Linear regression lines are included in the plots. The distribution of HLA class I frequencies among 504 chronically HIV-1-infected Japanese individuals used in this analysis is shown in Table S4 in the supplemental material.
AIDS represents an effective breakdown of the immune response, a putative association observed in the non-AIDS group would not be comparable to that in the AIDS group even if HLA class I alleles had an effect on VL and CD4 count.

In summary, the HLA-B locus appears to have the strongest allelic effects on VL and CD4 counts in this Japanese cohort, with the HLA-B*52:01-C*12:02 haplotype showing the greatest significance. These findings in a Japanese cohort highlight the differences of the effects of HLA class I alleles on HIV-1 control between Japanese and Africans/Caucasians.

ACKNOWLEDGMENTS

This research was supported by the Global COE program “Global Education and Research Center Aiming at the Control of AIDS,” launched as a project commissioned by the Ministry of Education, Science, Sports, and Culture, Japan, and by a grant-in-aid for scientific research from the Ministry of Health (no. H21-AIDS-010 and H24-AIDS-007), Japan. This project was funded in part with federal funds from the National Cancer Institute, National Institutes of Health, under contract no. HHSN261200800001E. This research was supported in part by the Intramural Research Program of the NIH, National Cancer Institute, Center for Cancer Research.

The content of this publication does not necessarily reflect the views or policies of the Department of Health and Human Services, nor does mention of trade names, commercial products, or organizations imply endorsement by the U.S. Government.

We have no conflicting financial interests.

We thank Sachiko Sakai for her secretarial assistance.

REFERENCES