Genetic and Immunologic Heterogeneity among Persons Who Control HIV Infection in the Absence of Therapy

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Background. Spontaneous control of human immunodeficiency virus (HIV) infection has been documented in a minority of HIV-infected individuals. The mechanisms behind this outcome remain largely unknown, and a better understanding of them will likely influence future vaccine strategies.

Methods. HIV-specific T cell and antibody responses as well as host genetics were examined in untreated HIV-infected patients who maintain comparatively low plasma HIV RNA levels (hereafter, controllers), including those with levels of < 50 RNA copies/mL (elite controllers, n = 64), those with levels of 50–2000 copies/mL (viremic controllers, n = 60); we also examined HIV-specific T cell and antibody responses as well as host genetics for patients with levels of >10,000 copies/mL (chronic progressors, n = 30).

Results. CD8+ T cells from both controller groups preferentially target Gag over other proteins in the context of diverse HLA class I alleles, whereas responses are more broadly distributed in persons with progressive infection. Elite controllers represent a distinct group of individuals who have significantly more CD4 and CD8 T cells that secrete interferon-γ and interleukin-2 and lower levels of HIV-neutralizing antibodies. Individual responses were quite heterogeneous, and none of the parameters evaluated was uniquely associated with the ability to control viremia.

Conclusions. Elite controllers are a distinct group, even when compared to persons with low level viremia, but they exhibit marked genetic and immunologic heterogeneity. Even low-level viremia among HIV controllers was associated with measurable T cell dysfunction, which has implications for current prophylactic vaccine strategies.

After more than 25 years of HIV infection, some persons remain asymptomatic with normal CD4 T cell counts and undetectable plasma viral loads, despite having never been treated with antiretroviral medications [1]. This extraordinary outcome provides hope that HIV infection may be durably controlled and that the development of a vaccine that prevents disease progression may be possible. Indeed, the accepted strategy for first-generation HIV vaccines is to provide protection from disease progression rather than to provide sterilizing immunity [2], because induction of broadly cross-reactive neutralizing antibodies (NAb) to prevent infection remains an elusive goal [3]. A major question for current vaccine strategies is the level of viremia that would be an acceptable goal following subsequent infection, to prevent transmission and disease progression.

Insight into this question can be derived from HIV transmission studies [4–6]. Among a cohort of 415 discordant couples, none of the 51 subjects with serum viral loads of <1500 RNA copies/mL transmitted virus to their partners [7]. Viral load is the major independent risk factor for maternal-fetal transmission; a viral load of >1000 copies/mL is associated with a 12-fold increased risk of transmission. Viral load also clearly impacts disease progression; viral loads of less than 1000–2000 RNA copies/mL are associated with long-term AIDS-
for the available ultrasensitive assays (e.g., therapy—plasma HIV RNA levels below the level of detection) view board approval and written informed consent. Elite clinicians at local Boston hospitals; they were also referred from low and were recruited on the basis of viral load from outpatient clinics of 16 years. We classified subjects into 2 controller subgroups: a group that maintains viral loads below the level of detection as measured by currently available ultrasensitive assays (<50 or <75 copies/mL; hereafter, “elite controllers”); and a second group that maintains viral loads between 50 and 2000 copies/mL, whom we call “viremic controllers.” We compared these individuals to untreated persons with progressive infection, with the goal of defining immunologic and host genetic factors associated with control of HIV infection.

**METHODS**

**Study subjects.** HIV controllers were defined as described below and were recruited on the basis of viral load from outpatient clinics at local Boston hospitals; they were also referred from providers throughout the United States, after institutional review board approval and written informed consent. Elite controllers were defined as having—without antiretroviral (ARV) therapy—plasma HIV RNA levels below the level of detection for the available ultrasensitive assays (e.g., < 75 copies/mL by bDNA or < 50 copies/mL by ultrasensitive PCR). Viremic controllers were defined as having—without ARV therapy—plasma HIV RNA levels between 50 and 2000 copies/mL; chronic progressors were recruited locally on the basis of viral load and were defined as having—without ARV therapy—plasma HIV RNA levels above 10,000 copies/mL (table 1). To qualify for the study, all subjects had to have a minimum of 3 determinations of plasma HIV RNA spanning at least a 12-month period. For elite controllers, isolated episodes of viremia with plasma levels up to 1,000 copies/mL were allowed if there were no consecutive viremia episodes and such episodes represented the minority of all available determinations. For viremic controllers, isolated episodes of viremia >2,000 copies/mL were allowed if such episodes represented the minority of all available determinations. For chronic progressors, episodes of viremia <10,000 copies/mL were allowed as long as such episodes represented the minority of all available determinations.

**HLA typing and determination of CCR5Δ32 and CCR2-64I genotypes.** Intermediate to high resolution HLA class I–typing was performed for all patients by sequence-specific primer polymerase chain reaction as described elsewhere [16]. The presence of CCR5Δ32 and CCR2-64I was determined for all HIV controllers (i.e., both elite and viremic); reverse transcriptase–polymerase chain reaction was performed as described elsewhere [17, 18].

**Assessment of HIV-specific CD8 T cell responses.** Interferon (IFN)-γ enzyme-linked immunospot (Elispot) assays performed with peripheral blood mononuclear cells (PBMC) were performed as described elsewhere [16, 19]; these assays included 410 peptides 16–19 amino acids in length and overlapping by 10 amino acids, which spanned the entire HIV proteome. All positive responses were confirmed in a second assay. Responses were regarded as positive if they had at least 3 times the mean number of spot-forming cells (sfc) in the 3 negative control wells; positive responses also had to have >50 sfc/10^6 PBMCs. Responses to peptides had previously been shown to be largely mediated by CD8 T cells [19, 20].

**Flow cytometric detection of antigen-induced intracellular IFN-γ and interleukin (IL)-2.** Intracellular cytokine staining assays were performed as described elsewhere [21]. PBMC were incubated with HIV–1 Gag, Nef, Pol, and Env peptide pools and a combination pool of Tat, Rev, Vif, Vpr, and Vpu (TRVVV) peptides. For analysis, between 70,000 and 125,000 CD4+ and CD8+ cells were collected. Ten HIV-seronegative donors were screened for T cell responses by use of the same protocol. Among these individuals, <0.01% of CD4 or CD8 T cells responded to all HIV peptide pools (0.0092% for IL-2+, 0.0014% for IL-2+ IFN–γ +, and 0.0028% for IFN–γ +). Responses were considered positive if they were >0.01% and at least 2 times the value of the unstimulated control.

**Neutralizing antibody assay.** The antibody neutralization assay is a modification of the Monogram Biosciences HIV coreceptor tropism assay [22]. Briefly, HIV envelope sequences were amplified from plasma and transferred to an expression vector; pseudotyped viruses were generated by transfection of HEK-293 cells with the envelope expression vector and a genomically HIV vector which contains a luciferase gene in place of env. Virus infectivity was determined by measuring the amount of luciferase activity expressed in infected cells. Neutralizing activity was reported as the concentration or dilution of each plasma required to inhibit the virus by 50%.

**Statistical analysis.** Statistical analyses and graphical presentations were performed using Prism (version 3.0, GraphPad). When the 3 groups were compared, determinations of significance were made on the basis of 1-way analysis of variance by use of a nonparametric Kruskal-Wallis test; when 2 groups were
compared, a 2-tailed nonparametric Mann-Whitney test was used. A nonparametric Spearman test was used to calculate correlations.

RESULTS

Heterogeneity of host genetic factors associated with delayed disease progression among elite and viremic controllers. A total of 66 elite controllers and 60 viremic controllers were compared to 30 chronic progressors recruited over the same period (table 1). The absolute CD4 count differed among the 3 groups and was higher in elite controllers, compared with viremic controllers (median, 884 vs. 602 cells/mm$^3$, $P < .001$). The frequency of HLA-B*57 alleles differed among the groups ($P < .005$), but there was no difference in B*57 carriage between elite and viremic controllers ($P = .223$; table 1), and only 44% of elite and 33% of viremic controller groups carried this allele, a frequency much less than that previously reported among smaller cohorts [13, 23]. Including other HLA alleles that have been associated with delayed disease progression [24, 25] in the analysis (B*5801, HLA-B*27, B*1503, B13, and B51), 68% of elite controllers and 60% of viremic controllers carry at least one HLA allele that has been associated with better prognosis, compared with 37% of chronic progressors ($P = .025$), leaving almost one-third of HIV controllers without any known relatively protective HLA alleles.

We also evaluated the frequency of CCR5 and CCR2 polymorphisms that are associated with slower disease progression (table 1) [17, 26]. No controllers, either elite or viremic, were homozygous for CCR5Δ32, whereas heterozygosity was present in 14% of elite controllers and 22% of viremic controllers ($P = .44$), a frequency that is not significantly different from that reported among the population of individuals not infected with HIV [27]. Homozygosity for the CCR2-64I genotype also did not differ among the groups ($P = .84$). These data indicate that although some HLA alleles are enriched in HIV controllers, neither HLA class I alleles nor well-characterized chemokine receptor polymorphisms are predictive of the control of viremia in the absence of therapy.

Elite control is associated with the lowest breadth and magnitude of HIV-specific CD8 T cells. We next evaluated CD8 T cell responses in a randomly selected subgroup of 45 elite

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Elite controllers</th>
<th>Viremic controllers</th>
<th>Chronic progressors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects, no.</td>
<td>66</td>
<td>60</td>
<td>30</td>
</tr>
<tr>
<td>Age, mean (range), years</td>
<td>47 (22–75)</td>
<td>48 (32–67)</td>
<td>36 (18–70)</td>
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<tr>
<td>Sex</td>
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<td></td>
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</tr>
<tr>
<td>Male</td>
<td>42 (64)</td>
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<tr>
<td>Female</td>
<td>24 (36)</td>
<td>13 (22)</td>
<td>6 (20)</td>
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<tr>
<td>Race</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>36 (54)</td>
<td>35 (58)</td>
<td>17 (57)</td>
</tr>
<tr>
<td>Black</td>
<td>19 (29)</td>
<td>13 (22)</td>
<td>3 (10)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>9 (14)</td>
<td>5 (8)</td>
<td>8 (27)</td>
</tr>
<tr>
<td>Other</td>
<td>2 (3)</td>
<td>7 (12)</td>
<td>2 (6)</td>
</tr>
<tr>
<td>Plasma HIV RNA level, median (IQR), copies/mL</td>
<td>Below detection</td>
<td>770 (348–1500)</td>
<td>152,000 (67,050–278,000)</td>
</tr>
<tr>
<td>CD4 cell count, median (IQR), cells/mm$^3$</td>
<td>884 (641–1149)</td>
<td>602 (451–786)</td>
<td>295 (203–455)</td>
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<tr>
<td>Duration of HIV diagnosis, median (IQR), years</td>
<td>15 (9–22)</td>
<td>17 (13–25)</td>
<td>5.5 (1–17)</td>
</tr>
</tbody>
</table>

NOTE. Data are no. (%) of subjects, unless otherwise indicated. See Methods for details about the 3 study groups. WT, wild type; HT, heterozygous; HM, homozygous; NA, not applicable.

$^a$ Elite controllers compared to viremic controllers, $P < .001$ by nonparametric Mann-Whitney test.

$^b$ Includes B*57, 27, 5801, 1503, 13 and 51.
controllers, 25 viremic controllers, and 25 chronic progressors, by use of a panel of overlapping HIV peptides that spanned all viral proteins in an IFN-γ Elispot assay [28]. HIV-specific, IFN-γ producing T cells were detected in all subjects. The magnitude and breadth of T cell responses differed among elite controllers, viremic controllers, and chronic progressors (median magnitude, 5428, 6253, and 8300 sfc/10⁶ PBMC, respectively; median breadth, 15, 19, and 27 responses, respectively; \( P = .007 \) and \( .009 \), respectively) (figure 1A and 1B). Elite controllers demonstrated lower magnitude and breadth of responses, compared with chronic progressors (\( P = .003 \) and \( .004 \), respectively), and there was a trend suggesting differences in magnitude and breadth between elite controllers and viremic controllers (\( P = .053 \) and \( .067 \), respectively), but not between viremic controllers and chronic progressors. These relationships persisted even when individuals carrying HLA-B*57 were removed from the analysis (figure 1C and 1D). Remarkably, both the strongest and weakest HIV-specific T cell responses were detected in the elite controllers, with the magnitude of responses ranging from <500 to >25,000 sfc/10⁶ PBMC, and breadth ranging from 2 peptides to 101 peptides. Comparing elite and viremic controllers with favorable and unfavorable HLA alleles and/or coreceptor polymorphisms, we found no difference in breadth (\( P = .149 \)) or magnitude of responses (\( P = .101 \)) between the 2 groups (data not shown).

Overall, these data show that although elite control is typically associated with less robust CD8 T cell responses as measured by IFN-γ Elispot assay, compared with those with even low-level viremia, there is marked heterogeneity in the breadth and magnitude of these responses among HIV controllers.

**Gag is preferentially targeted by CD8 T cell responses in HIV controllers.** We next determined the relative contribution of responses to individual proteins to the total virus-specific CD8 T cell activity. These analyses demonstrated significant differences in the responses to the protein subunits among the groups (figure 2A and B). Both elite and viremic controller groups were distinguished from chronic progressors by preferential targeting of Gag. In contrast, there was comparable targeting of Gag, Pol, and Nef in persons with progressive infection, and significantly more targeting of Env. In elite and viremic controllers, Gag responses contributed most to the total magnitude (median, 42% and 48%, respectively) and total breadth (median, 41% in both groups), values that were significantly more than those observed in chronic progressors (Gag contribution to magnitude, 27%; \( P = .01 \) and \( .003 \), respectively; Gag contribution to breadth, 27%; \( P = .001 \) and \( 0.004 \), respectively). Similar results were also found when we analyzed just non-B*57 expressing individuals (figure 2 panels C and D). These data indicate that preferential targeting of Gag, rather than total magnitude or breadth of responses or specific HLA class I alleles, is
associated with the control of HIV infection, which is similar to recent findings with respect to chronic untreated clade C infection [29].

Higher frequency of HIV-specific CD4 and CD8 T cells producing IFN-γ and IL-2 in elite controllers. We next analyzed the qualitative function of HIV-specific CD4 and CD8 T cell responses as measured by their ability to secrete IFN-γ and/or IL-2. For this analysis, 14 elite controllers and 11 viremic controllers were randomly selected and compared with 12 chronic progressors who were selected on the basis of relatively preserved CD4 cell counts, to limit the potential bias that low peripheral CD4 counts might have on measurement of T cell function. Median CD4 counts were 884, 776, and 436 cells/mm³, respectively; median viral load was 50, 985, and 86,000 copies, respectively. Although elite controllers had a higher percentage of circulating CD4 cells that secrete both IL-2 and IFN-γ (median, 0.06%; range, 0.01–1.2), compared with viremic controllers (median, 0.02%; range, 0–0.44; P = .03) and chronic progressors (median, 0.01%; range, 0–0.38; P = .02), there was marked heterogeneity among the subjects, with some entirely lacking these responses (figure 3A). No difference was found in CD4 cells that secrete IFN-γ alone among the 3 groups (data not shown). Elite controllers also had a higher percentage of circulating CD8 T cells that secreted both IL-2 and IFN-γ (median, 0.05%; range, 0.01–0.23), compared with viremic controllers (median, 0%; range, 0–0.08; P = .02) and progressors (median, 0%; range, 0–0.19; P = .02) (figure 3B). In line with the Elispot data, there was a trend for a lower percentage of circulating CD8 cells that secrete IFN-γ alone in elite controllers, compared with viremic controllers and chronic progressors; this difference did not reach statistical significance in this smaller subset (median percentage, 0.75%, 1.7%, and 2.4%, respectively; P = .06; data not shown). Thus, despite significantly lower CD8 T cell responses in elite controllers by Elispot assay, CD4 and CD8 T cell responses that produced both IL-2 and IFN-γ were higher, indicating enhanced T cell function in these persons.

Paucity of broadly cross-reactive NAb in elite controllers. We next quantified autologous and/or heterologous NAb among 17 elite controllers, 17 viremic controllers, and 20 chronic progressors, randomly selected. Plasma was tested against 2 laboratory HIV-1 strains, 14 viruses isolated from the viremic controllers, and 15 viruses isolated from the chronic
progressors. Plasma from viremic controllers and chronic progressors exhibited extensive cross-neutralization of nearly all of the viruses from both viremic controllers and chronic progressors (figure 4) as well as high-level inhibition of JRCSF and laboratory strains NL43 and SF162 (data not shown). Despite the dramatic differences in viral load and CD4 counts between these 2 groups, there was no statistically significant difference between them in terms of NAb titers ($P = .50$). In contrast, as a group, elite controllers had significantly lower-level NAb responses to primary viruses from viremic controllers and JRCSF, as well as lower-level responses to laboratory strains ($P = .001$). However, once again there was marked heterogeneity among elite controllers, some individuals having broad NAb responses, and others having minimal or no NAb. Neutralization of autologous virus was consistently present and was equally strong in viremic controllers and chronic progressors. These data indicate that there is marked heterogeneity in not only cellular immune responses but also in humoral immune responses among elite and viremic controllers.

DISCUSSION

Current HIV vaccine strategies are focused on the induction of immune responses that will protect from disease progression rather than prevent infection, and thus it is critical to understand the immune parameters associated with persistent control of HIV. At a level of viremia of $<2000$ HIV RNA copies/mL, both transmission and progression would be expected to be markedly diminished, suggesting a target level for current vaccine efforts, and indicating a need to understand the immunologic and host genetic features associated with this level of control. Our results indicate that, as a group, persons who control viremia to $<2000$ RNA copies/mL in the absence of ARV therapy are distinct from persons with progressive infection, with preferential targeting of the HIV Gag protein and enrichment for specific HLA B alleles in both controller groups. Moreover, elite controllers are more likely than viremic controllers and chronic progressors to have CD4 and CD8 T cells that secrete IFN-$\gamma$ and IL-2 and to have significantly less robust HIV-specific CD8 T cell responses by IFN-$\gamma$ Elispot and less robust NAb. However, individual responses were quite heterogeneous, and none of these parameters was predictive of this phenotype. Moreover, responses were not simply driven by viral load, because the elite controller group included persons that had both the strongest and the weakest, as well as the broadest and the narrowest, CD8 T cell responses. Potential explanations for these differences might be the sequence of the infecting virus and immunologic escape due to viral mutations, which were not assessed in this study.

Compared to previous smaller studies [30], one striking finding in the present study is that the majority of HIV controllers did not carry HLA-B*57; likewise specific chemokine polymorphisms associated with slower disease progression were not...
more pronounced. If the carriage of HLA alleles reported to be protective are considered in combination with the presence of chemokine receptor polymorphisms associated with delayed disease progression, more than 25% of elite and viremic controllers lack these host genetic factors, which might be anticipated to at least partially contribute to their improved disease outcome. Moreover, the preferential targeting of Gag was independent of the presence of the HLA-B*57 allele, suggesting the key role of Gag targeting in durable immune control of HIV, perhaps as a result of selection for mutations that alter viral fitness [31] or of early targeting of infected cells due to immediate processing of preformed Gag protein on viral entry [32]. Given that Gag is the preferred antigen produced by the virus and incorporated into virions, one could hypothesize that increased levels of viremia result in an increased number of immune responses targeting non-Gag proteins. This seems an unlikely explanation for our findings, given that the overall breadth and magnitude of responses, as well as the ability to secrete multiple cytokines, is not different between viremic controllers and chronic progressors, yet the former clearly target Gag preferentially.

Figure 4. Summary of antibody neutralization titers and relationship between breadth and potency of antibody responses and viral load among study groups. Pseudovirions isolated from viremic controllers (VC) and chronic progressors (CP) were used in neutralization assay against plasma from all study groups. The median concentration or dilution of each plasma required to inhibit the virus by 50% (IC₅₀) from each plasma tested with VC and CP viruses is shown in A. Elite controllers (EC) group had significantly lower neutralization of all viruses than viremic controllers (VC) and chronic progressors (CP) (*** P < .001). P values shown with asterisks were calculated using a 2-tailed Mann-Whitney test; viruses from chronic progressors are equally susceptible to neutralization, compared with viruses from viremic controllers. Breadth and potency of antibody responses does not correlate directly with viral load. B, Viral load is graphed with the median neutralizing antibody IC₅₀ for each plasma tested with viruses from viremic controllers and chronic infected individuals; black circles, plasma from each group of patients. Viral load is graphed with the median IC₅₀ for plasma of chronic progressors (C) and viremic controllers (D). Correlations are calculated using a nonparametric Spearman test.
Many recent studies have focused on identifying the functional characteristics of CD8 and CD4 T cell-mediated immune control [11, 14, 33–35], including the ability of T cells to proliferate as a result of stimulation and secrete multiple cytokines [33, 34, 36] and the presence of IL-2–secreting CD4 and CD8 T cells of a central memory phenotype [35, 37, 38]. Our data in the present study show that elite controllers, despite having lower overall IFN-γ secretion, have higher numbers of HIV-specific CD4 and CD8 T cells that secrete both IL-2 and IFN-γ, compared to both viremic controllers and chronic progressors. These responses may contribute to the enhanced ability of CD8 T cells from elite controllers to inhibit virus replication in vitro [39]. In addition, elite controllers have the highest ratio of functional CD4 to CD8 T cells and chronic progressors have the lowest ratio (figure 3C). These data confirm and extend the results of previously published studies [11, 14, 37] in which T cell polyfunctionality, as measured by secretion of multiple cytokines, was found to be higher among individuals who had lower levels of HIV replication, and suggest that even low-level viremia has a negative effect on T cell function. However, whether this association between T cell function and HIV control is cause or effect cannot be addressed by these or other human studies [11, 14]. In previous studies, HIV elite controllers were compared to noncontrollers and, therefore, the effects of chronic viremia on T cells could account for the differences observed [14]. Even when the effects of viremia are controlled in studies that compare elite controllers to successfully treated individuals [11], one cannot rule out that the differences seen are a consequence of immunologic damage during the viremic period that usually leads to initiation of ARV therapy.

The role of NAb in the control of viral replication has been controversial. Some [10, 40–42], but not all [43], early studies showed higher titers of heterologous NAb in long-term nonprogressors, compared with individuals who had chronic progressive disease. More recently, in studies largely focused on persons who expressed HLA-B*57, their heterologous NAb levels were shown to be significantly lower than those observed in individuals with viremia >10,000 copies, but no difference was found in NAb titers against autologous, contemporaneous plasma viruses [44]. Our findings of lower NAb activity among elite controllers are in agreement with these data [44], which suggests that NAb do not play a major role in the maintenance of viral suppression in individuals who spontaneously control viral replication. Our findings among viremic controllers and chronic progressors suggest that any level of viremia maintains broad autologous and heterologous cross-neutralizing antibodies.

In summary, this study of 126 persons who controlled HIV viremia to levels that may be expected to reduce transmission and disease progression indicates that, although elite and viremic controllers share some immunologic features and are distinct from persons with chronic progressive infection, the elite controllers are a distinct subgroup. However, even within these groups there is substantial heterogeneity in all of the parameters studied, which suggests that there are as-yet-undefined viral or host factors or combinations of factors that contribute to this remarkable phenotype. The lack of a definable immunologic marker for durable control and the limitations that small cohorts pose in defining host genetics provides a rationale for the use of newer approaches in defining this phenotype. Such studies, including extensive viral and host genetic analyses, are currently underway through the HIV Controller Consortium, which seeks to enroll 1000 elite controllers and 1000 viremic controllers in order to perform a whole-genome association study to define the genetic basis for this remarkable phenotype. This collaborative effort will extend the current study in the hope of defining disease pathways that not only predict durable control of infection but can also lead to new interventions to achieve this state in persons with otherwise-progressive HIV infection.

References


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