With >33 million individuals infected with human immunodeficiency virus type 1 (HIV-1) worldwide, and with >2 million more individuals infected every year [1], the need for an effective HIV-1 vaccine has never been greater. With the recent failure of a T cell immunity vaccine to prevent HIV-1 infection, and with the suggestion that the vaccine actually increased the risk of HIV-1 infection in important population subgroups [2], the human immunodeficiency virus (HIV) research community is reexamining the mechanisms mediating both natural protection against HIV-1 in seronegative individuals exposed to HIV-1 and natural viral control among HIV-infected individuals.

A critical reassessment of the goals of vaccination is also ongoing. The ideal HIV-1 vaccine should prevent HIV acquisition; however, if this is not possible, reduction in the plasma HIV RNA level “set point” in vaccinated individuals is an important secondary goal. Indeed, HIV-1 transmission is uncommon when the plasma HIV RNA level of the source partner is <2000 copies/mL [3]. Reduction of the viral load set point as a goal of vaccination has spurred interest in a rare group of HIV-infected individuals who naturally control HIV replication in the absence of therapy. These untreated HIV-infected “elite controllers” (ie, patients with plasma HIV RNA levels of <50 copies/mL) and “viremic controllers” (ie, patients with plasma HIV RNA levels of 50–2000 copies/mL) are highly enriched for several host factors associated with T cell–mediated control, including the protective HLA B57 allele [4, 5]; these observations have motivated the development of T cell immunity vaccines for HIV-1. Would decreasing the viral load set point to the levels observed in HIV-infected elite and viremic controllers necessarily prevent clinical progression?

Not all HIV controllers have long-term nonprogression. Many have assumed that HIV controllers represent a “functional cure” and are simply an elite subset of long-term nonprogressors (LTNPs; ie, patients who maintain CD4+ T cell counts in the normal range and AIDS-free survival indefinitely). However, as we and others have reported, the control of viral replication and the lack of clinical progression are really distinct clinical phenotypes. Some HIV-1 controllers experience significant CD4+ T cell count depletion and AIDS events, despite maintaining low to undetectable levels of viremia [6–10]. In this issue of the Journal, Okulicz and colleagues [11] reinforce this point by describing rates of disease progression among 25 elite and 153 viremic controllers in the longitudinal US Department of Defense HIV Natural History Study of >4586 HIV-infected individuals, most of whom had a defined date of seroconversion. A previous study from the seroincident CASCADE (Concerted Action on SeroConversion to AIDS and Death in Europe) cohort established that some individuals who were maintaining plasma HIV RNA levels of <400 copies/mL in the absence of antiretroviral therapy experienced clinically significant decreases in the CD4+ T cell count and that 7% eventually experienced progression to AIDS [6]. However, it has remained unclear how much of this disease progression was driven by individuals with low-level viremia detectable by modern assays.

In their article, Okulicz and colleagues establish that, although HIV controllers have much slower rates of disease progression than noncontrollers, viremic controllers with plasma HIV RNA levels of 50–2000 copies/mL have much more rapid rates of progression to AIDS (P = .048) and reduction in the CD4+ T cell...
count to <350 cells/mm³ (P = .009) than do elite controllers maintaining plasma HIV RNA levels of <50 copies/mL. The striking differences between elite and viremic controllers, in terms of CD4+ T cell count trajectories, suggest that even a relatively small increase in viremia (on an absolute scale) can result in very significant differences in clinical progression. Indeed, only 1 of 25 elite controllers in their cohort exhibited a decrease in the CD4+ T cell count to <350 cells/mm³ over a median of nearly 8 years of observation, and none developed AIDS during this time (although 3 subsequently started receiving antiretroviral therapy, for reasons that are unclear). Although receipt of antiretroviral therapy may have altered the natural history of HIV infection in some of these elite controllers (32% had received early antiretroviral therapy before commercial plasma HIV RNA testing became available), the lack of disease progression and increasing CD4+ T cell counts during several years of undetectable viremia in the absence of therapy is striking. Extremely low rates of clinical progression in elite controllers have also been described in another recently reported longitudinal study occurring over a similar observation period [12]. These observations suggest that the majority of HIV controllers experiencing clinical progression in the earlier CASCADE report were likely to have had low, but persistently detectable, viremia of 50–400 copies/mL.

However, evaluation of these seroincident cohorts cannot adequately determine the long-term risk of clinical progression in elite controllers, because observation times are typically <10 years. Assessment of HIV-seroprevalent cohorts suggests that if elite controllers are followed long enough, significant decreases in the CD4+ T cell count and opportunistic diseases may be observed. For example, in our elite controller cohort in San Francisco, which was infected for a median of >16 years, 15% of subjects had a CD4+ T cell count of <350 cells/mm³, and 7% met the clinical definition of AIDS [8]. Similarly, only 32 (46%) of 69 elite controllers who were infected for ≥8 years in the recently reported French Hospital Database on HIV study were maintaining stable CD4+ T cell counts of >500 cells/mm³ [10]. Taken together, these observations suggest that, although the vast majority of HIV controllers remain healthy with normal CD4+ T cell counts for many years, many will eventually develop measurable immunodeficiency, and some will experience opportunistic diseases. Thus, even elite control of HIV replication does not always result in a functional cure.

Not all LTNP are HIV controllers. Okulicz and colleagues also provide us with evidence that not all LTNPs maintain control of HIV replication. Although LTNP’s maintaining CD4+ T cell counts of >500 cells/mm³ for at least 10 years had significantly lower plasma HIV RNA levels than did individuals with typical progression, most had plasma HIV RNA levels of >2000 copies/mL. This finding is consistent with earlier observations suggesting that plasma HIV RNA levels explain <50% of the variability in rates of clinical progression [13, 14]. Okulicz and colleagues also provide us with a tantalizing report of an HIV-infected individual with plasma HIV RNA levels of >150,000 copies/mL who continued to maintain normal CD4+ T cell counts of >500 cells/mm³ in the absence of antiretroviral therapy for >10 years. This “viremic nonprogressor” phenotype is reminiscent of sooty mangabeys and African green monkeys, the natural hosts of simian immunodeficiency virus (SIV) infection, which, unlike SIV-infected rhesus macaques, rarely develop immunodeficiency or simian AIDS despite having high plasma SIV RNA levels [15].

The nonprogressive nature of SIV infection in sooty mangabeys and African green monkeys appears to be explained by a lack of generalized immune activation in the chronic phase of infection [16]. Interestingly, the only other report of HIV-infected viremic nonprogressors suggests that these individuals also maintain low levels of generalized immune activation [17]. This viremic nonprogressor phenotype is, in many ways, the exact opposite of the phenotype of elite controllers who experience a progressive decrease in the CD4+ T cell count, despite viral control; this latter phenotype is one that we and other investigators have associated with abnormally high T cell activation [8, 9]. Collectively, these observations suggest an important role of immune activation in HIV pathogenesis; however, further research is needed to better define the precise mechanisms responsible for nonprogression, despite the high levels of viremia in this rare but fascinating patient population.

Importance of stringent case definitions for rare clinical phenotypes. Another strength of the current report by Okulicz and colleagues is their demonstration that subtle differences in the definitions for rare clinical phenotypes can have a major effect on disease outcomes. Just as viremic controllers had much more rapid disease progression than elite controllers, LTNP’s who were defined as individuals having maintained CD4+ T cell counts of >500 cells/mm³ for 7 years had much higher mortality rates than did LTNPs who maintained high CD4+ T cell counts for 10 years, even when the analysis was restricted to those surviving for at least 10 years. These observations suggest that loose case definitions for viral control (plasma HIV RNA level, <2000 copies/mL) and LTNP (just 7 years of CD4+ T cell counts >500 cells/mm³) may result in heterogeneous groups of patients with widely divergent clinical outcomes. This finding is particularly important in translational research studies investigating the mechanisms mediating the natural control of viral replication and LTNP. For example, genomewide association studies require extremely large numbers of individuals for adequate statistical power. Consequently, looser case definitions for rare clinical phenotypes (i.e., defining control of HIV replication as <2000 copies/mL) are often used.
However, this may introduce significant heterogeneity in the rare phenotype population, making it more difficult to identify rare but biologically important mediators. This may be one reason why the genomewide association studies performed to date have failed to identify more than 3 or 4 consistent genetic variants associated with the natural control of HIV replication [18–21]. One wonders whether pooled analyses across cohorts restricted to much more specific phenotypic case definitions would identify novel mechanisms of viral control and/or nonprogression to be exploited in future vaccine and therapeutic strategies.

In summary, the current report by Okulicz and colleagues reinforces that control of HIV replication and LTNP are overlapping but distinct clinical phenotypes. Some HIV controllers experience progression despite viral control, and some LTNP maintain high levels of viremia. Immune activation may well play an important role in explaining these apparently discordant clinical phenotypes. Last, understanding the mechanisms responsible for these rare, but biologically important, phenotypes of HIV-infected individuals will require careful attention to clinical case definitions and collaborations among many cohorts and investigators.

References