Acute HIV-1 Infection: What’s New? Where Are We Going?

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This supplemental issue of the Journal of Infectious Diseases is devoted to the important topic of primary human immunodeficiency virus type 1 (HIV-1) infection. It was prompted by the planning of the Acute HIV-1 Infection Meeting in Boston in September 2009, at which leading scientists and practitioners gathered to discuss new insights into the early, critical events of HIV-1 infection. The reviews that follow underline the current state of the field with regard to transmission biology of HIV-1; the clinical presentation, diagnosis, and management of primary HIV-1 infection; the pathogenesis of primary HIV-1 infection; and innate and adaptive immune responses to the virus. We trust that these findings have the potential to influence the development of effective vaccine strategies.

This supplemental issue of the Journal is devoted to the important topic of primary human immunodeficiency virus type 1 (HIV-1) infection, including reviews of the transmission biology of HIV-1; the clinical presentation, diagnosis, and management of primary HIV-1 infection; its pathogenesis; and innate and adaptive immune responses. The decision to review these aspects of primary HIV-1 infection was triggered by planning the September 2009 Acute HIV-1 Infection Meeting in Boston, which addressed the continuing high incidence rates of HIV-1, new approaches to identifying individuals with acute HIV-1 infection, persistent controversies regarding the optimal management of individuals with primary infection, new insights into the role of innate and adaptive immune responses in mediating control of viral replication, and the potentially important impact of these findings in guiding the development of a protective HIV-1 vaccine.

In 2008, an estimated 2.7 million new cases of HIV-1 infection occurred [1], and recent data suggest high HIV-1 transmission rates by individuals with primary HIV-1 infection, fueling the epidemic. New studies discussed at the Boston meeting suggest that this period is especially infectious, not only because it is characterized by high viral loads but also because lack of protective antibodies may substantially increase infectivity independent of viral load. Early diagnosis of HIV-1 infection is thus a potentially critical step for the prevention of forward transmissions. Acutely infected individuals are difficult to identify, however, because standard rapid tests relying on the detection of antibodies against the virus can yield false-negative results before or early after seroconversion. Moreover, they can also yield false-positive results in uninfected HIV-1 vaccine recipients and infants with passive maternal antibodies derived from HIV-1-seropositive mothers. In their review, Cohen et al discuss the various technical approaches to early detection of HIV-1 infection [2]. Although prospective high-risk cohorts and cross-sectional screening have been shown to be limited in their ability to identify large numbers of individuals with acute infection, newer fourth-generation enzyme immunoassays are aimed at enhancing early diagnosis and promise to change acute HIV-1 detection in typical testing settings. These assays combine sensitive p24 antigen enzyme immunoassays with detection of antibodies against HIV-1, and they are thus capable of detecting infection before antibodies appear. These tests are already available in much of the world, and a test manufactured by Abbott Laboratories was recently approved by the US Food and Drug Administration for potential use in the United States.

Once individuals with acute or early HIV-1 infection are identified and linked to care, perhaps the most pressing decision...
confronting them and their treating clinicians is whether or not to start antiretroviral treatment at this early time. At present, the field offers conflicting evidence regarding whether treatment during primary HIV-1 infection confers a long-term benefit, be it immunologic, virologic, or clinical. Bell et al [3] review the data on both sides of the argument and conclude that although increasing evidence points to the advantages of earlier treatment, decisions regarding treatment initiation should be made on a patient-by-patient basis until results from ongoing randomized clinical trials offer more definitive answers.

The initial transmission events of HIV-1 may represent the most vulnerable phase for the virus. Estimates of the rate of HIV-1 transmission per single sexual exposure are wide ranging, but it is clear that HIV-1 transmission is not highly efficient and only a minority of exposures typically result in infection. Recent data indicate that when transmission does occur, only a single virion typically establishes the infection, at least during heterosexual transmission, resulting in a homogeneous viral population in early infection [4]. In his review, Sagar highlights the importance of understanding the nature of these transmitted viruses and their initial target cells and deciphering the biological mechanisms responsible for productive clinical infection by only a restricted subset of viral variants [5]. It is unclear at this point whether the apparent transmission bottleneck is a result of random or active selection of specific viral variants, but there is increasing hope that a vaccine could potentially be most effective at blocking HIV-1 acquisition during the period between exposure and the onset of quantifiable, sustained viremia.

Once infection is established, innate immune responses kick into high gear, and increasing evidence suggests that these first immune responses may be critical in predicting the quality of subsequent adaptive immunity and disease progression in the host. Chang and Alfheid review our present understanding of innate immunity in HIV-1 infection, drawing particular attention to recent data supporting the roles of type I interferons and natural killer cells in driving potent immune responses during the acute phase. Identifying and harnessing antiviral innate immune responses for vaccine design might therefore represent an avenue to enhance the efficacy of future HIV-1 vaccines [6].

Since HIV-1 was first isolated, virus-specific CD8+ T cells have been studied extensively in the context of HIV-1 infection [7]. The accumulation of two decades of research clearly points to their important role in control of viremia during the acute phase of infection. In their review, Streeck and Nixon contrast the major contribution of HIV-1–specific CD8+ T cells to the reduction of peak viremia during early infection with their apparent exhaustion in the setting of chronic viremic HIV-1 infection [8]. In addition, they suggest that CD4+ T cell help may play a supportive role in the persistence of robust adaptive immune responses and resulting control of viremia observed in a minority of HIV-1–infected individuals termed HIV-1 “controllers.”

The exceptional genetic variability of HIV-1 presents a barrier to vaccine development that has yet to be overcome. Studying the diversity and evolution of HIV-1 during the acute phase of infection might help guide effective vaccine design by identifying conserved and/or vulnerable regions within the virus. Boutwell et al review recent investigations of the genetic diversity of HIV-1 at the time of transmission and the subsequent evolution of the virus in response to the host immune environment [9]. The authors highlight the fact that some viral escape mutations in response to immune pressure come at a fitness cost to the virus, as evidenced by reversions to wild-type sequences commonly observed after transmission into a new host. Next-generation deep sequencing of HIV-1 promises a rapid and cost-effective way to characterize viral evolution and its common pathways of escape. Knowledge gained by these studies might translate into the design of rational vaccine approaches capable of inducing enhanced immune control of HIV-1.

Another significant barrier to the development of a protective HIV-1 vaccine is that no vaccine candidate to date has been able to induce in humans potent neutralizing antibody responses that were able to protect against the viral quasispecies diversity. An envelope immunogen with the ability to induce broadly reactive protective antibodies will probably be an essential component of any successful HIV/AIDS vaccine. Given the recent disappointing results from the Merck adenovirus serotype 5 (Ad5) vaccine aimed at eliciting T cell responses, the need to identify envelope immunogens that can elicit broadly reactive neutralizing antibodies has never been greater. In their review, Alter and Moody evaluate the evidence as to why this might be the case and suggest that recent advances in understanding the kinetics, specificity, and function of early humoral responses offer new hope that an HIV-1 vaccine could one day generate potent antibodies [10]. The authors also discuss the results of the 2009 Thai trial [11], which suggest that the weak protection against HIV-1 acquisition observed in vaccinees may have been associated with an early nonneutralizing antibody response in those individuals and that protection was prominent in the first year after vaccination. These results have undoubtedly drawn attention back to the enduring question: how can protective humoral immune responses be reliably induced by a vaccine? Moreover, it suggests the need to expand the scope of immunogenesis and efficacy testing platforms research to include diverse types of antibody responses when candidate HIV-1 vaccines are evaluated.

Although treatment regimens have advanced enormously in efficacy and reduced side effects, lifelong treatment remains an impractical global solution owing to expense, long-term toxic effects,
poor health care infrastructure in resource-limited settings, and increasing drug resistance. The development of an effective HIV-1 vaccine remains our best hope for curbing this global health challenge. Will these new findings resulting from studies of acute HIV-1 infection help the research community to develop an efficacious HIV-1 vaccine that will protect from infection, or at least allow for persistent immune control of HIV-1 replication in individuals that become infected? This important question is discussed in a commentary by McElrath [12]. The recent Step Study evaluated the MRKAd5–HIV-1 gag/pol/nef vaccine, which to date is the most immunogenic vaccine developed against HIV-1 [13, 14]. The vaccine generated high-frequency and high-magnitude T cell responses in the majority of subjects, as measured by enzyme-linked immunospot and intracellular cytokine assays; however, its failure to protect against HIV-1 infection suggests that the magnitude of T cell responses alone does not predict antiviral activity. Rather, the quality of Ad5–HIV-1–induced CD8+ T cells may not have been sufficient to confer immunity. Moreover, it is unclear whether other vaccines currently in development—such as recombinant DNA, pox vectors, or alternate serotype adenovirus vectors—induce fundamentally different qualities of T cell responses, which responses will predict vaccine efficacy, and whether a T cell–based vaccine will require a protein boost to protect against HIV-1 infection or disease.

The articles in this supplement underscore the critical front that primary infection represents in the battle against HIV-1 and suggest some of the next areas that need to be addressed in future research. Improved understanding of the important role that this stage of infection plays in transmission highlights the continued need to detect more early infections and understand the most effective ways to prevent transmission. The role of treatment in this period continues to be debated; it is hoped that studies currently underway and soon to be reported will better clarify the benefits of treatment, though a definitive answer may not come soon. A series of elegant and detailed investigations have improved our understanding of early transmission events and begun to identify some of the potential vulnerabilities of HIV-1 to vaccine strategies. The data presented in this supplement aim to summarize many aspects of the current state of the field. With a global health problem as complex as HIV-1, summaries are necessarily incomplete. Important topics related to primary HIV-1 infection such as social behavior, prevention measures, and the interplay between host genetics, acutely transmitted envelopes, and immunogen design are not extensively covered in this issue and deserve further consideration in other forums. We hope the reviews included here will help advance efforts to prevent transmission of HIV-1, provide optimal care early in infection, and develop vaccine strategies to elicit immune responses that exploit the well-concealed vulnerabilities of HIV-1.

References