IMMUNOPATHOGENESIS OF HIV INFECTION

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ABSTRACT
The rate of progression of HIV disease may be substantially different among HIV-infected individuals. Following infection of the host with any virus, the delicate balance between virus replication and the immune response to the virus determines both the outcome of the infection, i.e. the persistence versus elimination of the virus, and the different rates of progression.

During primary HIV infection, a burst of viremia occurs that disseminates virus to the lymphoid organs. A potent immune response ensues that substantially, but usually not completely, curtails virus replication. This inability of the immune system to completely eliminate the virus leads to establishment of chronic, persistent infection that over time leads to profound immunosuppression. The potential mechanisms of virus escape from an otherwise effective immune response have been investigated. Clonal deletion of HIV-specific cytotoxic T-cell clones and sequestration of virus-specific cytotoxic cells away from the major site of virus replication represent important mechanisms of virus escape from the immune response that favor persistence of HIV. Qualitative differences in the primary immune response to HIV (i.e. mobilization of a restricted versus broader T-cell receptor repertoire) are associated with different rates of disease progression. Therefore, the initial interaction between the virus and immune system of the host is critical for the subsequent clinical outcome.

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INTRODUCTION

Over the past 15 years since the beginning of the AIDS epidemic, a comprehensive understanding of the complexities of the clinical course of human immunodeficiency virus (HIV) disease has been accomplished (68). In addition to the characterization of the different phases of HIV infection, prospective studies on large cohorts of HIV-infected individuals have clearly indicated that the rate of progression of HIV disease may be substantially different among HIV-infected individuals (10, 12, 23, 44, 49, 70, 71, 84, 87, 88). These studies have led to the identification of groups of patients who have experienced unusually rapid disease progression (71, 87) or, alternatively, nonprogressive HIV disease (10, 12, 23, 44, 48, 49, 70, 84, 88) (see below). Although these subgroups are only a relatively small proportion of the total population of HIV-infected individuals, they represent a valuable tool with which to determine the pathogenic mechanisms associated with progressive versus nonprogressive HIV disease.

Both virologic and immunologic events associated with primary HIV infection have been extensively characterized (7, 13, 15, 21, 33, 46, 59, 60, 77, 95). Following the initial peak of viremia, HIV-specific humoral and cell-mediated immune responses are readily detected (7, 33, 46, 59, 60, 77). A variety of anti-HIV antibodies and cytotoxic T lymphocytes (CTLs) specific for different HIV proteins are detected very early during primary infection; in particular, HIV-specific CTLs are thought to play a major role in the initial downregulation of virus replication. Despite the early appearance of a vigorous immune response, this immune response ultimately fails to eliminate the virus since transition to the chronic phase of infection occurs in most individuals (68). Furthermore, although a dramatic downregulation of viremia, i.e. more than 90% of the peak viremia, is observed in most individuals as progression to the chronic phase of infection occurs, virus replication is never completely curtailed. Recent studies have clearly demonstrated that even during the long period of clinical latency, HIV actively and continuously replicates and that lymphoid organs serve as the primary anatomic site of virus sequestration and
replication (24, 65, 66, 73). These observations indicated that HIV disease is active and progressive throughout the course of infection and that clinical latency is not equivalent to disease latency. This persistent virus replication and the chronic immune activation associated with it have been proposed to be responsible for the progressive destruction of lymphoid tissue, and hence the deterioration of the immune system (27, 62).

In favor of this hypothesis, recent studies have demonstrated that virus replication and turnover are extremely high, and precise quantitation of the number of virus particles produced daily has provided a vivid appreciation of the magnitude of virus replication associated with HIV infection (41, 98). In addition, in these same studies a direct relationship between changes in viremia and changes in CD4+ T-cell counts has also been shown. It has been suggested that there is an extremely high turnover of CD4+ T cells and that a large number of CD4+ T cells are depleted and replaced daily. However, the mechanisms responsible for this rapid increase of CD4+ T cells following virus downregulation are still unclear and under considerable discussion.

Taken together these observations have greatly contributed to a better understanding and delineation of the pathogenic mechanisms leading to progression of HIV disease, and they have certainly provided new insights for the appropriate use of antiviral therapy and for the development of alternative, predominantly immune-based, therapeutic strategies. However, a number of crucial issues regarding pathogenesis of HIV disease are still far from being completely delineated. For example, the primary mechanisms of CD4+ T-cell depletion in vivo remain unclear; there is no direct evidence that HIV is cytopathic in vivo, despite the fact that cytopathicity can be readily demonstrated in the artificial milieu of culture. A number of mechanisms have been proposed in order to explain virus escape from the immune response during the chronic phase of infection; however, it is not known how HIV initially evade the vigorous primary immune response. Certain types of immune responses have been found to be associated with stable or nonprogressive HIV disease; however, the quantitative and, more importantly, the qualitative features of antiviral immunity that may result in a more effective immune response are only partially understood.

In the present review, we consider the complex course of HIV infection and the pathogenic events associated with the different stages of HIV disease. Our discussion, however, focuses on the immunologic and virologic events associated with primary HIV infection, on the immunologic and virologic mechanisms that may be responsible for virus escape and that may favor the establishment of chronic infection, and the impact of these early events on the subsequent course of HIV disease.
Clinical Course of HIV Infection

The clinical course of HIV infection generally includes three phases or stages (1): (a) primary infection, (b) clinical latency, and (c) AIDS-defining illness. Such a course of infection is characteristic of the so-called typical progressors who represent the majority of HIV-infected individuals (Figure 1) (see below). The median time from initial infection to progression to AIDS in typical progressors is eight to ten years (10, 28, 49). Based on prospective studies involving large cohorts of HIV-infected individuals, three additional subgroups have been identified (10, 12, 23, 44, 48, 49, 70, 84, 87, 88). These include subjects who have an unusually rapid progression of disease (i.e. rapid progressors) (Figure 1) (71, 87), those who do not experience progressive disease for several years (eight to ten) following primary infection (i.e. long-term nonprogressors) (Figure 1) (10, 12, 23, 44, 48, 49, 70, 84, 88), and those who progress to AIDS within a time frame similar to typical progressors, but in whom both clinical and laboratory parameters remain stable for an unusually long period of time once disease progression has occurred (i.e. long-term survivors) (Figure 1) (84).

Primary infection may be associated with a mononucleosis-like clinical syndrome (15, 21, 95) (see below). Due to the lack of specificity and the variable severity of the clinical syndrome, and to the fact that the diagnostic blood test for HIV infection (detection of HIV antibodies) may be negative early on, primary infection generally goes unnoticed. However, upon retrospective analysis of the clinical history, it is estimated that 50–70% of HIV-infected individuals experience a clinical syndrome of varying severity during primary infection (15, 21, 95). It is unclear, however, if the absence or the presence of symptoms is correlated with the severity of the ultimate clinical course of HIV disease, nor is it clear whether there is a relationship between the severity of the clinical syndrome and the magnitude of the initial burst of viremia. Further studies are necessary to delineate the relationships among the acute viral syndrome, virologic parameters, and immune responses in order to determine more precisely the influence of these events alone or together on the outcome of HIV infection.

Typical Progressors

The majority (70–80%) of HIV-infected individuals belong to the group of typical progressors (Figure 1). Following primary infection, which, as mentioned above, is associated with a clinical syndrome of variable severity in a majority of subjects, typical progressors experience a long period (up to six to eight years) of clinical latency (10, 28, 49). Despite the lack of symptoms, HIV disease is active as is indicated by the persistent replication of virus and by the progressive loss of CD4+ T cells (24, 28, 65, 66, 73). With regard to the relationship between clinical symptoms and the level of CD4+ T cells, individuals
Figure 1: Schematic representation of the different courses of HIV infection on the basis of the changes of CD4+ T-cell counts and viremia overtime.
with CD4+ T-cell counts > 500 per µl generally remain free of symptoms, whereas the appearance of constitutional symptoms is generally more frequent in individuals with CD4+ T-cell counts below 500 per µl. Exceptions to this paradigm are subjects with CD4+ T-cell counts higher than 500 per µl who develop progressive generalized lymphadenopathy (1), Kaposi’s sarcoma (28), or neurologic diseases (76). Progression to clinically apparent disease or AIDS-defining illness generally occurs within eight to ten years in typical progressors (28). When CD4+ T-cell counts are below 200 per µl, the clinical picture may be characterized by severe and persistent constitutional signs and symptoms; at this level of CD4+ T cells, there is an increased susceptibility to opportunistic infections or neoplasms (29).

Rapid Progressors
A significant percentage (10–15%) of HIV-infected individuals experience an unusually rapid progression to AIDS within two to three years of primary infection (Figure 1) (71, 87). As discussed above, it is unknown whether the presence and/or the severity of the acute viral syndrome and a higher peak of viremia are preferentially associated with the category of rapid progression of HIV disease. However, rapid progressors may experience a prolonged acute viral syndrome (see below); in addition, constitutional symptoms of variable severity may persist after transition to the chronic phase of infection. In fact, in rapid progressors the period of true clinical latency may be absent or very brief. Downregulation of the initial burst of viremia may not be very efficient in rapid progressors; even after the initial decrease, the levels of viremia may rise rapidly (see below). Inefficient control of the initial burst of viremia and rapid rise in viremia within the first or second year after primary infection reflect a poor control of HIV infection by the immune system. In this regard, a delay in the appearance of the primary immune response or a rapid disappearance of certain immune functions during the early stages of the chronic phase of infection may be detected in rapid progressors (see below).

Long-Term Nonprogressors
A small percentage (less than 5% on the basis of different cohorts) of HIV-infected individuals do not experience progression of disease for an extended period of time (Figure 1) (10, 12, 23, 44, 48, 49, 70, 71, 84, 87, 88). Long-term nonprogressors by some definitions have CD4+ T-cell counts that are within the normal range and are stable over time; in addition, they generally have low levels of virologic parameters and preservation of lymphoid tissue architecture and immune function (10, 12, 23, 44, 48, 49, 70, 84, 88). From a clinical standpoint, long-term nonprogressors are asymptomatic; it seems that in these individuals, HIV infection has been arrested with regard to disease progression.
It is unknown whether long-term nonprogressors have experienced a primary infection similar to that of other groups of HIV-infected individuals, i.e. associated with an acute viral syndrome and burst of viremia. This latter issue is particularly important since it may provide insights in understanding whether the initial burst of viremia and the systemic dissemination of virus, which are typical of primary infection, are more rapidly and effectively controlled in long-term nonprogressors.

**Long-Term Survivors**

In a small percentage of subjects who experience progression of HIV disease within a period of time similar to typical progressors, both clinical and laboratory parameters, although abnormal, remain stable for an extended period of time (Figure 1) (84). The mechanisms, either virologic or immunologic, that are responsible for preventing further progression of HIV disease are unclear at present; the possibility that changes in virus genotype and/or phenotype, as well as the possibility that preservation of certain HIV-specific immune responses are involved, is being investigated.

**Analysis of Virologic and Immunologic Events Associated with Primary HIV Infection**

**Virologic Events**

As mentioned above, a substantial proportion of HIV-infected individuals experience an acute viral syndrome of variable severity during primary infection (15, 21, 95). The severity of the clinical syndrome is estimated to require hospitalization in only a low percentage (less than 15%) of individuals. On the basis of the clinical history, symptoms generally appear within four weeks from virus exposure in those patients who experience an acute viral syndrome (G Pantaleo, unpublished observations). From a virologic standpoint, a burst of viremia (up to $10^7$ HIV RNA copies per ml of plasma) and high levels of virus expression and HIV DNA copies in peripheral blood mononuclear cells are associated with primary HIV infection (15, 21, 33); these peaks of virologic parameters reflect the systemic dissemination of HIV. In order to determine the primary anatomic sites of the initial localization of virus and the establishment of HIV infection, as well as the dynamics of the systemic dissemination of virus, we have employed two different experimental approaches: (a) longitudinal analysis of virus distribution in lymph node biopsies collected at different time points following inoculation in monkeys infected with simian immunodeficiency virus (SIV) and (b) cross-sectional analysis of virus distribution in lymph node biopsies collected during primary HIV infection prior to or soon after (six to eight months) seroconversion.

Longitudinal analysis performed in the animal model of acute SIV infection has shown that SIV in the form of individual virus-expressing cells is detected
in lymph nodes as early as day 7 following inoculation (63, 64, 67); at this
time the number of individual cells expressing SIV is extremely high in lymph
node (Figure 2). A rapid downregulation of SIV-expressing cells is observed
by day 14; this coincides with the appearance of an HIV-specific immune
response (see below). Of note is the fact that major changes in virus distribution
are observed over time. In contrast to the downregulation in the number of
individual virus-expressing cells, there is a progressive increase in the amount
of virus particles trapped within the follicular dendritic cell (FDC) network
of the lymph node germinal centers (Figure 2). The fact that these virologic
events in the lymphoid organs are truly reflective of the initial establishment
of HIV infection is further supported by their correlation with the changes in
virologic parameters in peripheral blood. In fact, in SIV-infected monkeys the
peak of virus expressing cells in lymph node precedes or is simultaneous with

Figure 2 Virologic and histopathologic events occurring in lymphoid organs and circulation
during acute HIV infection and during the transition to the chronic phase. After entry, HIV
localizes in the lymphoid organs that represent the primary anatomic site for the establishment of
HIV infection. Early on during acute infection, numerous individual virus-expressing cells are
detected in lymph node, and the peak of virus-expressing cells precedes and/or coincides with that
of viremia. Furthermore, early on during acute infection, germinal center formation is minimal or
absent. After the transition to the chronic phase, the number of virus-expressing cells significantly
declines. Simultaneous with the extensive germinal centers formation, virus particles are efficiently
trapped into the FDC network, and viremia is dramatically downregulated.
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the peak of p26 antigenemia in peripheral blood, thus suggesting that the initial burst of virus replication in lymph node accounts for the burst of viremia in the circulation (G Pantaleo, L Martin, AS Fauci, unpublished information). Furthermore, the decrease in virus-expressing cells in lymph node is associated with downregulation of virus in the circulation (Figure 2), further supporting the hypothesis that most of the virus present in the circulation is produced in lymphoid tissue and that a number of mechanisms operating in lymphoid tissue may regulate release of virus in the circulation (see below).

Cross-sectional analysis, performed on lymph node biopsies collected from different HIV-infected individuals during primary infection or within the first year following seroconversion, has indicated that the patterns and changes in virus distribution observed in lymphoid tissue over time are similar to those found in the SIV model of acute infection (Figure 2) (G Pantaleo, AS Fauci, unpublished information). During the early stages of primary infection, individual HIV-expressing cells represent the dominant form of virus found in lymph node. Soon after seroconversion, follicular hyperplasia occurs (see below), and virus particles are effectively trapped in the FDC network that permeates the germinal centers; these trapped virions are the dominant form of virus present in the lymphoid tissue after seroconversion and during the early and intermediate stages of HIV disease (see below). Thus, there is a transition with regard to the dominant form of HIV/SIV within lymphoid tissue from the early stages of primary infection (large numbers of individual cells expressing virus) to the phase of chronic, established infection (large numbers of extracellular virions trapped on the FDCs).

These changes in virus distribution observed in lymphoid tissue reflect histopathologic changes that take place following localization of antigen (in this case, HIV) within lymphoid tissue leading to generation of an immune response. With regard to histopathologic changes, follicular hyperplasia and germinal center formation are essential preludes to efficient virus trapping. Furthermore, the appearance of complement (C)-binding antibodies specific for different HIV proteins may lead to the formation of immune complexes that are trapped in the reticuloendothelial system (63, 64, 67).

The initial burst of virus replication is followed by a dramatic downregulation of viremia and virus expression in peripheral blood mononuclear cells (PBMC) (15, 21, 33). Despite the downregulation of virologic parameters in peripheral blood, a substantial number of virus-expressing cells can be readily detected in lymph node as long as 18 months following primary infection (G Pantaleo, AS Fauci, unpublished information). These data indicate that control of virus expression by the immune response is not very effective over the period of time spanning the transition from acute primary infection to chronic infection.
and for several months thereafter. In contrast, virus-expressing cells are rarely detected in lymph nodes of individuals who are chronically (more than two to three years) and stably infected with HIV prior to the transition to advanced stage disease (see below).

An exception to the general phenomenon of downregulation of virologic parameters during primary HIV infection is the fact that only minor changes are observed over time in the number of HIV DNA copies in PBMC (33). Thus, there is a dissociation between the profound downregulation of virus replication and the minor changes in the total pool of HIV-infected cells. This dichotomy suggests that even during primary infection active virus replication occurs in only a minor percentage of HIV-infected cells at any given time. Alternatively, it may indicate that mechanisms other than elimination by HIV-specific CTLs of cells in which HIV is actively replicating may be responsible of the downregulation of the initial burst of viremia; suppression of virus replication by soluble factors may represent such an alternative mechanism (see below). Furthermore, the formation during primary infection of a large pool of latently infected cells may have important implications with regard to potential mechanisms of virus escape from the immune response and maintenance of HIV infection over time, and implications related to therapy (see below).

Effective downregulation of viremia is associated with resolution of the acute viral syndrome, which generally occurs within six to eight weeks from the onset of symptoms and coincides with the appearance of HIV-specific immune responses (15, 21). Both the sequence of events and the length of primary infection described above are experienced by the majority of HIV-infected individuals. However, downregulation of viremia may not be very effective in individuals who are rapid progressors, and levels of plasma virus may rise again soon after seroconversion. In addition, the duration of the acute viral syndrome may be much more prolonged (up to 16 weeks) in rapid progressors (G Pantaleo, AS Fauci, unpublished information).

IMMUNOLOGIC EVENTS Vigorous HIV-specific humoral and cell-mediated immune responses are detected very early during primary infection (7, 15, 21, 46, 59, 60, 77). The role of these responses in the initial downregulation of virus replication and in its control over time has been subject to considerable debate. However, both the humoral and cellular limbs of the immune response are likely to contribute to the suppression of the initial burst of virus replication. Due to the complexity of the immune response elicited by HIV infection, the different components of this response are discussed separately; in particular, the components that are examined here include HIV-specific antibody responses, HIV-specific cytotoxicity, and cytokine responses.
With regard to the HIV-specific humoral response, high titers of antibody specific for a variety of HIV proteins are a major component of the primary immune response to the virus (15, 21, 59, 95). Indeed, the commonly employed blood tests (ELISA and western blot assays) for the diagnosis of HIV infection are based on the detection of HIV antibodies. In the early stages of HIV infection, anti-HIV antibodies may be barely detected or undetected; however, during the period of seroconversion, high titers of these antibodies are found at the time of peak viremia or at the point of downregulation of viremia (15, 21). Of note is the fact that the HIV antibodies produced during primary infection lack neutralizing activity (46, 59). For these reasons, it is thought that these antibodies have little or no effect on initial virus spreading and dissemination, suggesting that the primary HIV-specific antibody response is nonprotective. However, this antibody response may contribute significantly to the downregulation of viremia, which indeed coincides with the detection of high antibody titers. In particular, these antibodies, which have C-binding ability, could conceivably mediate the formation of immune complexes (antibody plus HIV plus C) that may remain trapped either in the FDC network (FDCs express receptors for C) or in the reticuloendothelial system (Figure 3) (64, 67). Therefore, although the initial antibody response may be nonprotective, it may represent an important mechanism for the removal of large numbers of virus particles from the circulation and for their deposition in the tissue (Figure 3) (64, 67). In this regard, the decline of HIV antigenemia coincides with a rise in titers of C-binding antibodies and with the intensity of virus trapping in lymph node in the SIV model of acute infection (Figure 3) (64, 67). The potential implications of the early trapping of virus in lymphoid tissue are discussed below. In contrast to this nonprotective component of the HIV-specific humoral response, neutralizing antibodies, which are thought to represent the protective component of this response, are detected later in the course of infection, i.e. when the transition from the acute to the chronic phase of infection has already occurred (46). Among the complex array of neutralizing antibodies, neutralizing activity against laboratory strains of HIV such as HIV-IIIB and HIV-MN is most commonly detected. In contrast, neutralizing activity against the autologous virus isolate is rarely detected. It is unclear why neutralizing antibodies are not generated during primary infection and only appear later on, sometimes even several months after seroconversion; these neutralizing antibodies have been suggested to be directed against cryptic epitopes that are not exposed during primary infection (8, 9, 47, 54, 55, 58, 82, 90, 94).

HIV-specific cell-mediated immune responses are detected very early during primary infection (7, 46, 60, 77) and are dominated by large increases in the number of CD8+ T lymphocytes (60; G Pantaleo, unpublished information) that
Figure 3  Schematic representation of the mechanisms of downregulation of viremia mediated by the HIV-specific humoral immune response. Following the appearance of humoral immune response, a large number of antibodies against a variety of HIV proteins are produced, and a fraction of these antibodies may bind C'. These C'-binding antibodies may form IC with virus particles, and these IC may be trapped into the FDC network (FDC express on the cell surface receptors for C') and into the reticuloendothelial system. The above events may significantly contribute to the clearance of virions from the circulation.
may be up to 20-fold above the normal range (i.e. 200–600 per μl of blood). In contrast, a drop of variable magnitude in the number of CD4+ T cells is consistently associated with the peak of viremia. CD4+ T cell–mediated functions are depressed during primary infection (G Pantaleo, unpublished information). CD4+ T-cell responses may already be depressed at the time of the presentation of the patient; this may be the result either of the substantial numerical decrease in CD4+ T cells or of suppression mediated by soluble factors, i.e. cytokines. With regard to CD8+ T cell–mediated function, virus-specific CTLs can be detected as early as five days following infection, as indicated by experiments performed in the SIV model of acute infection (77). Similarly, in most subjects with primary HIV infection, virus-specific CTLs are consistently and readily detected in PBMC during the acute viral syndrome, and their appearance correlates with the downregulation of viremia (7, 46, 60). A delay in the appearance of CTL activity is generally associated with a prolonged acute viral syndrome with persistence of symptoms and high levels of viremia (46). In general, HIV-specific cytotoxic activity may be detected against both structural (env and gag) and regulatory (tat and rev) proteins of HIV; however, during primary infection HIV-specific cytotoxic activity is detected predominantly against structural proteins. Analysis of precursor frequency of HIV-specific CTLs (CTLp) has demonstrated that CTLp frequency may be very high (up to 1 CTLp per 100 cells), although it may vary significantly, ranging from 1:100 to 1:10,000, among different patients (46; G Pantaleo, M Vaccarezza, AS Fauci, unpublished information). In addition to mediating cytotoxic activity, Mackewicz et al demonstrated that CD8+ T cells from subjects with primary HIV infection release a soluble factor with suppressor activity on virus replication in vitro (50). In this regard, a number of substances with suppressor activity produced by CD8+ T lymphocytes have been identified in recent studies (5, 18) (see below). Therefore, CD8+ T lymphocytes may contribute to the down-regulation of viremia either by elimination of virus-expressing cells (i.e. cells in which HIV is actively replicating) via a cytotoxic mechanism or by soluble factor-mediated suppression of virus replication (Figure 4).

With regard to the cytokine response during primary HIV infection, the patterns of cytokine expression in peripheral blood and lymph node of subjects experiencing primary infection have recently been studied, and the relationships between this cytokine response and the other components of the primary HIV immune response have been determined (32). A panel of cytokines including interleukin (IL)-2, IL-4, IL-6, IL-10, tumor necrosis factor alpha (TNF-α), and interferon-gamma (IFN-γ) have been studied. In particular, a longitudinal analysis of the changes in cytokine expression in PBMC samples collected at different time points during primary infection has been performed. This analysis
Figure 4  Schematic representation of the mechanisms of downregulation of viremia mediated by the HIV-specific cell-mediated immune response. Following virus dissemination and generally in coincidence with the peak viremia, oligoclonal expansions of CD8+ T lymphocytes represent the major component of the HIV-specific cell-mediated immune response. These CD8+ T lymphocytes mediate either cytotoxic activity or produce a number of soluble factors that may suppress virus replication. Therefore, HIV-specific cell-mediated immune response may contribute to the downregulation of viremia both by the lysis of virus-expressing cells and by the suppression of virus replication. The HIV-specific cell-mediated immune response may play the primary role in the downregulation of viremia during primary infection.
has demonstrated that the cytokine response during primary HIV infection is dominated by an early peak of IFN-γ expression. IFN-γ expression is observed in all subjects (32); however, in certain subjects the levels of IFN-γ remain constant throughout primary infection and an early peak is not detected. Substantial expression of TNF-α and IL-10 is observed during primary infection (32); however, in contrast to IFN-γ, a peak in the expression of these cytokines is generally detected late during the course of primary infection. Expression of IL-6 is generally very low or absent, and a late peak of IL-6 expression is observed in only a minority of subjects (32). IL-2 and IL-4 expression is barely detected or absent in PBMC; however, analysis of the expression of these cytokines in lymph node mononuclear cells (LNMC) has indicated that significant levels of expression may be detected in some patients at least for IL-2 (32). Similarly, the levels of expression of the other cytokines analyzed are substantially higher in LNMC compared to in PBMC.

Kinetics of expression of the above cytokines were compared with those of the other components of the primary immune response to HIV. The kinetics of IFN-γ expression coincided with those of CD8+ T lymphocytes and in particular with perturbations of proportions of T-cell subsets comprising the T-cell repertoire as determined by T-cell receptor (TCR) analysis (32) (see below). Briefly, T-cell subsets can be identified phenotypically by virtue of the variable (V) region of the β chain (Vβ) of the TCR. There are 24 Vβ families in the human T-cell repertoire. Only those subjects who experienced major expansions of certain Vβ families of CD8+ T cells manifested an early peak of IFN-γ expression, whereas in the absence of major changes in the TCR repertoire, the levels of IFN-γ expression remained constant over time (32). Furthermore, analysis of IFN-γ expression in different T-cell subsets has demonstrated that expression of IFN-γ is predominantly limited to CD8+ T cells (32).

The early peak in IFN-γ expression during viral infections can be very important from a pathophysiologic standpoint. Recent studies in the hepatitis B virus (HBV) experimental system have shown that IFN-γ and TNF-α, but not HBV-specific CTLs, mediate the viricidal effect (35). These observations indicate that CD8+ T cells strongly influence the cytokine response during primary HIV infection. In this regard, the early activation and mobilization of a large number of CD8+ T lymphocytes conceivably also is associated with the production of the putative CD8+ T-cell suppressor factors (RANTES, MIP-1α, MIP-1β and IL-16) of virus replication that have recently been identified (5, 18). However, in addition to CD8+ T cells, other cell types (CD4+ T cells, B cells and macrophages) may also secrete RANTES, MIP-1α, and MIP-1β. Furthermore, these other cell types that are activated late during primary infection
Table 1  Mechanisms of virus escape during the transition from primary HIV infection to the establishment of chronic HIV disease

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<td>Formation of a large pool of latently infected cells</td>
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<td>Deletion of expanded HIV-specific cytotoxic CD8⁺ Vβ clonotypes in the absence of variations in the viral epitope recognized by the CTLs</td>
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may be predominantly responsible for the patterns of expression of the other cytokines mentioned above. These results indicate that different cell types are responsible for the patterns of cytokine response during primary infection and that changes in the kinetics of cytokine expression observed over time reflect the sequential and overlapping contributions of different cell types in influencing and mediating the primary immune response to HIV infection.

Potential Mechanisms Responsible for the Failure of the Primary Immune Response to Eliminate HIV

Vigorous HIV-specific immune responses are detected very early during primary infection; however, in most individuals these responses are not able to completely eliminate HIV from the infected host (7, 15, 21, 46, 59, 60, 77). Two major mechanisms may potentially explain the failure of the immune response (Table 1): virologic and immunologic. With regard to virologic mechanisms, these may include the following: (a) formation of a large pool of latently infected cells that may not be eliminated by virus-specific CTLs, (b) trapping of virus particles in the FDC network that may represent a continuous source of virus for de novo infection of cells that reside in or migrate through the lymphoid tissue (64, 67), and (c) changes in virus phenotype and genotype (56, 72). With regard to immunologic mechanisms, these may include: (a) quantitatively inadequate immune responses, (b) qualitatively inadequate immune responses, (c) accumulation of HIV-specific CTLs in peripheral blood but not in lymph node, and (d) deletion of expanded HIV-specific cytotoxic CD8⁺ Vβ clonotypes in the absence of variations in the viral epitope recognized by the CTLs. Each of these possibilities is discussed in detail below.

As mentioned above, the formation of a large pool of latently infected cells (containing HIV DNA) occurs very early during primary infection (33; G Pantaleo, OJ Cohen, AS Fauci, unpublished information). Coffin has proposed
that most of these latently infected cells contain defective virus (19). On the basis of this hypothesis, the possibility that virus replication may be reactivated in these cells appears to be remote; therefore, these latently infected cells are unlikely to significantly influence the natural course of HIV infection. However, under certain circumstances their presence may become important. This may be the case when the course of HIV infection is complicated by bacterial or other virus infections (22, 39, 40, 43, 102) (D Goletti, AS Fauci, unpublished information); typical examples are influenza and herpes virus infections (39, 40) and tuberculosis (102; D Goletti, AS Fauci, unpublished information). In both cases, levels of HIV viremia rapidly increase coincident with the appearance of symptoms characteristic of these acquired bacterial and virus infections; furthermore, these clinical and virologic events are generally associated with a substantial increase in the percentage of activated CD4$^+$ T cells, which are vulnerable targets for HIV infection and replication. Thus, it is possible that the reactivation of virus replication in latently infected CD4$^+$ T cells may contribute significantly to this burst of viremia. Furthermore, the persistence of a large pool of latently infected cells may have major implications with regard to therapy. In fact, even therapeutic interventions able to completely shut down virus replication would have a minimal impact on the pool of latently infected cells, which in turn may represent the primary mechanism for the failure to completely eliminate HIV.

Trapping of virus particles in the FDC network during primary infection (64, 67) is an important mechanism for the maintenance of HIV infection over time and thus plays a potentially critical role in virus escape from the immune response. Health et al recently demonstrated that this trapped virus is infectious even when coated with antibodies that, under other circumstances, have demonstrable neutralizing activity against HIV (38). Trapping of virus may support the maintenance of HIV infection over time either by representing a continuous source of de novo infection of susceptible target cells or by inducing chronic stimulation and activation of a variety of cell types including CD4$^+$ T cells, thus maintaining a large pool of activated CD4$^+$ T cells that can efficiently support virus replication.

Changes in both virus genotype and phenotype may be important for virus escape from the immune response. With regard to changes in virus genotype, it is obvious that if variations occur in viral epitopes recognized by CTLs, HIV-specific CTLs will be unable to recognize virus mutants, and thus HIV may elude the immune response (72). Furthermore, Meier et al proposed that virus reflecting naturally occurring mutations within the CTL epitopes may act as antagonists in vivo and may prevent T cells from performing their proper effector function (56). With regard to changes in virus phenotype, syncytium-
inducing (SI) strains of HIV generally have higher replicating ability compared to non-syncytium-inducing (NSI) strains, and, more importantly, the transition from NSI to SI has been reported to be associated with a rapid progression of HIV disease (3, 14, 45, 83, 85, 92, 93). The immune response possibly is ineffective in controlling SI strains that have a high replicating ability, or the increase in viremia generally associated with the switch from NSI to SI may have direct and detrimental effects on HIV-specific immune response (see below).

The possibility that the primary immune response to HIV, and in particular to HIV-specific cytotoxicity, is quantitatively inadequate in most patients is highly unlikely. It has been clearly demonstrated that the appearance of HIV-specific CTLs strongly correlates with the downregulation of viremia (7, 46, 60). However, although HIV-specific cytotoxicity is detected in most subjects with primary infection, analysis of CTLp has demonstrated that CTLp frequencies vary greatly among different subjects. Nonetheless, it is still unclear whether there is a relationship between the levels of HIV-specific cytotoxic activity and the extent of virus downregulation (46; G Pantaleo, M Vaccarezza, AS Fauci, unpublished information).

Standard parameters of the immune response such as cytotoxic activity and broad antibody responses are similar in subjects with primary HIV infection (64). However, more precise analysis of the immune response, such as delineation of the kinetics of changes in relative representation of the TCR repertoire, have clearly demonstrated major qualitative differences in the primary immune response to HIV among different individuals (60, 64). In this regard, it has been shown that a major component of the primary HIV immune response is represented by oligo/monoclonal expansion of V\(\beta\) subsets of CD8\(^+\) T cells (60). On the basis of this analysis, three patterns of expansions of certain CD8\(^+\) V\(\beta\) families have been detected (60, 64): (a) expansion of a single V\(\beta\) family where the relative percentage of the expanded V\(\beta\) in peripheral blood is generally > 20%; (b) expansions of two V\(\beta\) families where the relative percentage of the expanded V\(\beta\)s is < 20%; and (c) expansions of multiple (greater than two) or no expansions of V\(\beta\) families where the relative percentage of the V\(\beta\)s is generally below 15%. The importance of these findings relates to the observation that these different patterns of V\(\beta\) family expansions are associated with different clinical outcomes. Those subjects who experience a major expansion of a single V\(\beta\) family (Type 1 pattern) generally have a rapid progression of HIV disease (progression to AIDS occurs within two to four years); those subjects with moderate expansions of two V\(\beta\) families (Type 2 pattern) generally have an intermediate rate of progression of HIV disease; and those subjects with multiple, minor or no expansions of V\(\beta\) families (Type 3 pattern) generally have slow progression of HIV disease.
Progression of HIV disease has been evaluated on the basis of the CD4\(^+\) T-cell counts measured approximately 400 days after primary infection; this analysis has been performed thus far in 21 individuals with primary infection. It is clear from this analysis that the subjects with Type 1 pattern respond to HIV infection with a very limited CD8\(^+\) T-cell repertoire, whereas those with Type 3 pattern respond with a very broad T-cell repertoire. The mechanisms responsible for these qualitative differences in the primary immune response to HIV among different individuals are unclear. An obvious explanation is that these differences are the result of the original selection process that had occurred during thymic ontogeny; however, it cannot be excluded that these differences may be related to the possibility that these subjects may have been previously exposed to, but not obviously infected with, HIV. Thus, these differences in expansions of the responding CD8\(^+\) T-cell repertoire may reflect primary and secondary, and possibly tertiary, immune responses. It is uncertain whether previous exposure to the virus would lead to a more restricted or a more limited expansion of the T-cell repertoire. However, previous priming to an antigen would suggest a more vigorous but restricted secondary or tertiary response to the antigen in question. The observation that the Type 1 pattern (limited expansion of T-cell repertoire) is associated with a rapid progression of HIV disease is consistent with certain preliminary data suggesting that certain expanded cytotoxic clones are rapidly deleted (see below).

Comparative analyses of the frequencies of in vivo activated HIV-specific CTL and CTLp have shown that there is an accumulation of cytotoxic T cells in peripheral blood early during primary infection (G Pantaleo, AS Fauci, unpublished information). This accumulation in the circulation occurs at a time when the levels of viremia are still very high and, more importantly, when a large number of virus-expressing cells are present in the lymph node. The rapid egress of CTLs from lymphoid organs and their concentration in the peripheral blood is a likely physiological event following the localization of antigen in the lymphoid organs and the generation of an immune response. In the case of viruses other than HIV, particularly those that do not primarily infect lymphoid tissue, CTLs are likely to be generated in the lymphoid tissue and to rapidly concentrate in the distal sites of virus replication (lung, brain, other organs) where they carry out their effector function. In the case of HIV, however, the primary site of virus replication is within the lymphoid tissue itself. CTLs may not function adequately and for an extended period of time in the site of their generation; furthermore, the massive amount of virus replication at that very site may contribute to the rapid mobilization and egress of antigen-specific T cells. Indeed, it is possible that these cytotoxic cells leave the lymphoid organs prior to mediating their effector function (i.e., lysis of HIV-expressing cells).
These series of events may be responsible for the persistence of a large number of virus-expressing cells within lymphoid tissue (see above) and thus may largely contribute to the lack of complete elimination of HIV. We have recently observed that disappearance of the expanded HIV-specific CTL clones may occur in the absence of variations in the virus epitope recognized by the CTLs (G Pantaleo, AS Fauci, unpublished observations). Recent studies have shown that the overall size of the TCR repertoire selected by antigen in vivo during a high magnitude CD8 response is comprised of very few clones (15–20) (53). Zinkernagel has hypothesized that only 10–30% of potentially antigen-specific cells are mobilized during a typical virus infection; these cells will die rapidly (within days) after mobilization, usually after eliminating the virus in question (103). However, in the case of an excess of antigen, which is the situation associated with massive virus replication during primary HIV infection, all antigen-specific T cells may be induced and rapidly deleted prior to complete elimination of the antigen, i.e., HIV. The deletion of the expanded CTL clones may occur at a time when high levels of viremia are still detected (G Pantaleo, AS Fauci, unpublished observations). This represents a major mechanism that is potentially responsible, at least in part, for the escape of HIV from an otherwise efficient immune response and the persistence of HIV following primary infection. In this regard, the substantial number of HIV-expressing cells detected in lymph nodes soon after the transition to the chronic phase of infection indicates that the total elimination of virus-expressing cells does not occur, despite the mobilization of a large number of HIV-specific CTL clones.

Analysis of Virologic and Immunologic Events Associated with the Clinically Latent Period of HIV Disease

Virologic Events Downregulation of viremia and resolution of symptoms are the typical events that characterize the transition from the acute to the chronic phase of HIV infection (68). All virologic parameters, including plasma viremia, titers of infectious virus, and virus expression in PBMCs, are generally low during the prolonged clinically latent period of HIV infection. However, recent studies using highly sensitive polymerase chain reaction (PCR) techniques have clearly demonstrated the persistence of viremia in all stages of HIV infection (73); in addition, both the number of HIV DNA containing cells and the levels of virus replication in LNMCs were significantly higher (5- to 100-fold) compared to levels in PBMCs (65, 66). These findings indicate that virus replication is persistent throughout the course of HIV infection and that HIV disease is active and progressive in lymphoid tissue even during the long asymptomatic period of HIV infection (24, 65, 66, 73). Due to the striking
differences in viral load between peripheral blood and lymphoid tissue, this period of HIV infection may be designated as the stage of dichotomy between peripheral blood and lymph node (67). A variety of mechanisms contribute to the dichotomy of viral load between peripheral blood and lymphoid tissue. Among these is increased cell activation (27, 62), which is crucial for effective virus replication (11, 101); mechanical trapping of virus particles in the FDC network associated with the follicular hyperplasia (2, 24, 25, 30, 66–69, 89, 91); and a series of microenvironmental conditions such as close cellular contact, higher concentration of HIV within lymphoid tissue, abnormal trafficking of lymphocytes due either to changes in the expression of adhesion molecules following cellular activation, or slower migration through the lymphoid tissue caused by histopathologic abnormalities (66–69).

The major difference in the levels of viral load between peripheral blood and lymph nodes is generally observed in HIV-infected individuals in early-stage disease with CD4+ T-cell counts greater than 500 per µl (66–69). With progression of HIV disease to the intermediate stage (CD4+ T-cell counts between 200 and 500 per µl), the differences in viral load between peripheral blood and lymph node tend to decrease (66–69), and overall the viral load increases in peripheral blood. These latter events coincide with changes in virus distribution in lymphoid tissue that in turn are the result of the evolving histopathologic picture (Figure 5). Lymphoid tissue shows clear signs of disruption of tissue architecture such as abnormal location of germinal centers in the medulla, larger numbers of germinal centers undergoing follicular involution, and increased vascularity and fibrosis. The above histopathologic changes coincide with changes in virus distribution; these include an increase in the number of virus-expressing cells and a progressive loss of the ability of the involuted germinal centers to trap virus (Figure 5). In this regard, the increase in levels of plasma viremia observed during disease progression may result, at least in part, from the impaired trapping ability of the FDC network (67). Although it has not been directly demonstrated that the levels of plasma viremia are influenced by the efficacy of virus trapping within lymphoid tissue, recent studies have shown that decreases in plasma viremia during antiretroviral therapy correspond to a downregulation of virus replication in lymphoid tissue (20). Thus, the levels of viremia are very likely influenced by the degree of virus replication in lymphoid tissue. Likewise, because trapped virus almost always originates from virus-expressing cells within the lymphoid tissue, it is reasonable to assume that if the mechanism of trapping is impaired, more virus will spill over into the circulation.

IMMUNOLOGIC EVENTS With regard to cell-mediated immunity, HIV-specific CTLs directed either against structural (envelope and gag-pol) or regulatory
(nef, tat) viral proteins are detected in a large percentage of HIV-infected individuals during the clinically latent period (36, 37). The frequency of HIV-specific CTLs as well as their targets may vary among different subjects. Whether these differences are important in the control of virus replication and spreading over time needs to be determined. In addition to the typical HIV-specific cytotoxicity, CD8+ T cell–mediated suppressor activity is also consistently detected during this stage of infection (51). Although the evidence that CTLs, and in general CD8+ T cells, are an important component of the protective anti-HIV immune response is only indirect, several observations strongly support their primary role in the control of virus spreading and disease progression. For example, loss of HIV-specific CTL precedes and/or coincides with disease progression. In this regard, either deletion of HIV-specific T-cell clones in the absence of mutations in the viral epitope recognized by the CTLs

![Figure 5](image)

*Figure 5* Schematic representation of the changes in virus distribution, histopathology, and viremia associated with the progression of HIV disease from early to late stages of disease. In early-stage disease, in lymph node there is extensive germinal centers formation (germinal centers of large size and irregular shape), effective virus trapping into the FDC network (*grey area*), very rare virus-expressing cells, and low levels of viremia. In intermediate stage disease, large areas of the lymphoid tissue undergo involution (i.e. fibrosis and fatty infiltration), and both the number of virus-expressing cells in lymph node and the levels of viremia increase. In late stage disease, most of the lymphoid tissue is replaced by fibrosis and fatty infiltration; virus trapping is generally lost; there are numerous virus-expressing cells and high levels of viremia.
or the occurrence of virus mutations in the CTL epitope may be operative alone or in combination (56, 72; G Pantaleo, AS Fauci, unpublished information). In addition to HIV-specific CD8\(^+\) T cell–mediated immune responses, CD4\(^+\) T-cell responses to a variety of HIV proteins including envelope, gag, and pol have been observed predominantly in HIV-infected individuals in early-stage disease (17, 96).

Due to their immunoregulatory role and ability to modulate the induction of HIV expression from latent or chronic infection to that of active virus expression (reviewed in 74), cytokines have been extensively studied during the chronic phase of HIV infection. On the basis of the effect on virus expression and replication, cytokines may be divided into three groups (75): (a) inducers of virus expression (IL-1, IL-2, IL-3, IL-6, IL-12, granulocyte macrophage-colony stimulating factor, M-CSF, and TNF-\(\alpha/\beta\)); (b) suppressors of virus expression (IFN-\(\alpha\), IFN-\(\beta\), and IL-10); and (c) bifunctional (IFN-\(\gamma\), IL-4, and TGF-\(\beta\)), i.e., depending on the experimental system, they may mediate either induction or suppression of virus replication. These cytokines may modulate virus replication in both T cells and macrophages, and in vivo they may contribute to maintaining a constant level of virus expression and replication, particularly in lymphoid tissue, during the entire course of HIV infection.

With regard to the cytokine response during early and intermediate stages of disease, particular attention has recently been paid to the possibility that cytokines may play a major role in the progression of HIV disease (16). In an initial study, Clerici & Shearer hypothesized that the switch from the TH1 (i.e., IL-2, IFN-\(\gamma\), and TNF-\(\alpha/\beta\)) to the TH2 pattern (i.e., IL-4, IL-5, and IL-10) of cytokine secretion is a critical step in the progression of HIV disease (16). This hypothesis was based on the observations that in certain pathological conditions, different patterns of cytokines were associated with protective, generally TH1, or nonprotective, generally TH2, immune responses (81, 97).

This hypothesis has been subsequently tested in several studies by analyzing both cytokine secretion and expression in peripheral blood and lymph node of HIV-infected individuals at different stages of HIV disease. None of these studies has demonstrated an actual switch from the TH1 to TH2 pattern of cytokine expression and secretion that is associated with disease progression (4, 34, 52, 57, 86). Both cross-sectional and longitudinal analyses of cytokine expression in peripheral blood and lymph node have shown high levels of constitutive expression of pro-inflammatory cytokines such as IFN-\(\gamma\), IL-10, and TNF-\(\alpha\) during the entire course of HIV infection, whereas levels of IL-2, IL-4, and IL-6 were very low and not consistently detected. CD8\(^+\) T cells were predominantly responsible for the expression of IFN-\(\gamma\) and at least in part of IL-10 that was also expressed by non–T cells (i.e., macrophages) (34).
Similarly, studies that have analyzed cytokine secretion have shown a tendency toward a TH0 cytokine phenotype during the progression of HIV disease (4, 52, 57, 86).

Because levels of expression and production of cytokines, which should mediate beneficial (IFN-γ) and detrimental (IL-10 and TNF-α) effects, are elevated throughout the course of HIV disease, it is unlikely that these changes represent a critical step in the progression of HIV disease. However, they do reflect the mobilization and involvement of different effector cells in the immune response to HIV, and the persistence of high levels of expression and secretion of these cytokines may have potential impact on the maintenance of continuous virus replication, may interfere with the generation of the immune response, and/or may have detrimental effects on cellular and tissue trophism.

With regard to humoral immunity, neutralizing antibodies appear after seroconversion and after the initial downregulation of virus after primary infection (see above), and neutralizing activity may be detected for a long period of time during the chronic phase of infection. Neutralizing antibodies are more effective in inhibiting the infectivity of free HIV virions, whereas they seem to be less effective in blocking cell-to-cell transmission (6, 26, 31, 54, 61, 78, 99, 100). In addition to neutralizing antibodies, a variety of antibodies against a number of HIV proteins including p24, Nef, Rev, Vpr, Vpu, and Tat are also detected (reviewed in 36). Furthermore, antibodies that bind NK cells and monocytes via Fc (fragment crystalline) receptors may potentially mediate killing of infected cells that express gp120 on their surface by antibody-dependent cellular cytotoxicity and thus contribute to the elimination of virus infected cells (reviewed in 36). In contrast, antibodies against epitopes of gp41 may enhance HIV infectivity in vitro, and their presence has been correlated with progression to AIDS (42, 79, 80). Both humoral and cell-mediated HIV-specific immune responses tend to decrease with progression of HIV disease from the early to the intermediate stage of disease.

Analysis of Virologic and Immunologic Events Associated with Advanced Stage Disease

Virologic events Included in the category of advanced stage disease are HIV-infected individuals with CD4+ T-cell counts below 200 per µl and/or those with an AIDS-defining clinical illness. From a virologic standpoint, an interesting characteristic of advanced stage disease is the reequilibration of viral load between peripheral blood and lymph nodes (67). This is associated with the increase in all virologic parameters in both peripheral blood and lymph nodes. Furthermore, owing to the complete disruption of the architecture and the destruction of most of the lymphoid tissue, which is replaced by fibrotic
tissue, trapping of virus is markedly diminished and most of the virus that is detected is cell-associated (Figure 5).

IMMUNOLOGIC EVENTS The advanced stage of HIV disease is characterized by profound immunosuppression. HIV-specific cytotoxic activity is generally lost at this stage of disease (36, 37). Similarly, neutralizing antibodies are rarely detected, and the titers of antibodies against a variety of HIV proteins are significantly decreased (36, 37). In contrast, the levels of expression and production of certain cytokines such as IL-10 and IFN-γ remain very high (34); this reflects the fact that CD8+ T cells and monocyte/macrophages account for most of the circulating mononuclear cells after depletion of the majority of CD4+ T cells. The destruction of lymphoid tissue is the primary mechanism responsible for the severe immunosuppression associated with late-stage HIV disease.

CONCLUSIONS Striking differences have been observed in the rate of progression of HIV disease among different individuals. A series of mechanisms, including genetic, virologic, and immunologic types, have been proposed to explain these different rates of progression. A fine balance among these different mechanisms is likely to ultimately determine the course of HIV disease. Lymphoid organs are the major anatomic sites where the initial establishment and spread of HIV infection occurs and from which the virus disseminates. The initial burst of viremia in primary HIV infection is the consequence of the systemic dissemination of HIV throughout the lymphoid systems and its release into the circulation. Downregulation of viremia coincides with the appearance of a vigorous immune response, which fails in most individuals to completely eliminate HIV. This failure is the result of a number of virologic and immunologic mechanisms whereby virus escapes from an HIV-specific immune response that is otherwise quite robust. Virologic mechanisms are predominantly responsible for the propagation of HIV infection over time. Immunologic mechanisms generate unfavorable conditions that prevent this vigorous immune response from completely eliminating HIV.

Therefore, although virologic parameters are generally very low after the transition from primary infection to the chronic phase of HIV disease, virus replication is persistent in lymphoid organs. This continuous virus replication is responsible directly and/or indirectly for a number of pathogenic mechanisms that ultimately lead to the destruction of lymphoid tissue, profound immune dysfunction, and progression of HIV disease.

On the basis of these observations, the primary goal of any therapeutic intervention should be the suppression of virus replication. Due to the detrimental
effects that high levels of HIV replication may have on the virus-specific immune response at the time of primary infection, antiviral therapy should be initiated during primary infection. The precise regimen and duration of therapy remains to be determined by clinical trials.

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