

The gastrointestinal tract is critical to the pathogenesis of acute HIV-1 infection

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It has become evident that the gastrointestinal tract is preferentially and profoundly depleted of CD4⁺ T cells during acute HIV-1 infection. The enhanced susceptibility of gastrointestinal lymphoid tissue to HIV-1 is in part due to the large complement of CCR5⁺ memory CD4⁺ T cells resident at this site. Here we summarize the recent findings demonstrating that the gastrointestinal tract plays a critical role in the pathogenesis of acute HIV-1 and simian immunodeficiency virus infections. Ongoing work in this field is likely to have a significant effect on HIV research in the near future. (J Allergy Clin Immunol 2005;116:419-22.)

Key words: Acute HIV-1, gastrointestinal tract, CD4⁺ T cells

Acute infection is a critical time in the course of HIV-1 infection. During this phase, the virus gains access to its target cells, infects, replicates, disseminates, and simultaneously establishes a pool of latently infected cells. As evidenced by the explosive growth of the epidemic in the last 2 decades, it is clear that HIV-1 is extremely adept at accomplishing these tasks. Once established, untreated HIV-1 infection culminates in profound immunodeficiency and death in the majority of individuals. Recent evidence derived from human subjects with acute HIV-1 infection and macaques with acute simian immunodeficiency virus (SIV) infection suggests that the course of these infections might be determined during the acute phase of infection. Because the virus entering a new host must negotiate a series of obstacles between entry, amplification, and dissemination, it is plausible that interventions made during acute HIV-1 infection have the potential to change the natural history of this disease. To date, much work has focused on understanding these events and have described changes exclusively within the peripheral blood. Until recently, mucosal sites, such as the gastrointestinal (GI) tract, have been relatively under-

Abbreviations used

GI: Gastrointestinal
SIV: Simian immunodeficiency virus

emphasized in the study of acute HIV-1 infection. Here we will summarize the recent findings suggesting the critical role of the lymphoid system of the GI tract during acute HIV and SIV infection.

It has been well established that the GI tract harbors the majority of the body's complement of immune cells.¹ GI tract lymphocytes, placed in close proximity to the external environment, are phenotypically distinct from peripheral blood lymphocytes; the majority of the intestinal lymphocytes (>90%) exhibit a memory phenotype.² In addition, because of constant exposure to a myriad of food and microbial antigens, GI tract lymphocytes are significantly more activated than peripheral blood lymphocytes.² Furthermore, up to 70% of GI tract lymphocytes express CCR5, a chemokine receptor that serves as an essential coreceptor for the entry of CCR5-tropic HIV-1 into CD4⁺ T cells.³ (In contrast, approximately 20% of peripheral blood lymphocytes express CCR5.) Thus the vast population of activated memory CD4⁺ T cells with abundant expression of chemokine receptors provides HIV-1 with an ideal environment to establish infection.

Unfortunately, the study of the human GI tract during acute HIV-1 infection is challenging. It is fraught with difficulties in identifying individuals during acute infection and the added complexity of obtaining GI tract biopsy specimens in the face of psychological and physical complications associated with acute HIV-1 infection. Consequently, initial work in this area emerged from the SIV macaque model. A striking depletion of intestinal CD4⁺ T cells was noted in macaques within days of SIV infection, at a time when little or no CD4⁺ T-cell depletion was evident in the peripheral blood.^{4,5} Furthermore, intestinal CD4⁺ T-cell depletion occurred regardless of whether viral inoculum was delivered intrarectally or intravenously.⁵ These studies were subsequently extended to demonstrate that GI tract lymphocyte depletion occurs in all stages of SIV infection, including acute infection.⁴ Studies conducted during the 1990s indicated that intestinal CD4⁺ T-cell depletion might be an early feature of HIV-1 infection as well⁶ and that intestinal CD4⁺ T-cell

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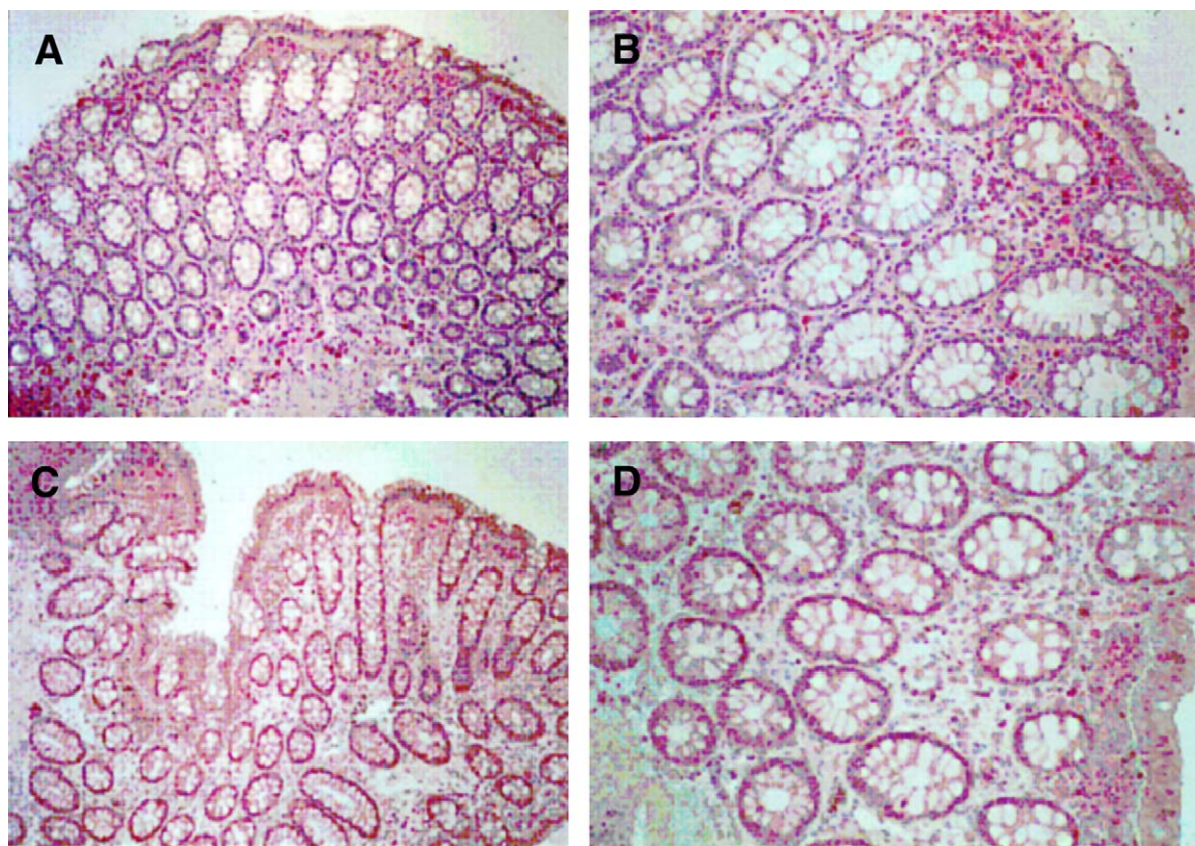


FIG 1. Effector sites (lamina propria) of the GI tract show pronounced CD4⁺ T-cell depletion in acute and early HIV-1 infection. At magnifications of 25 $\times$ (**A**) and 80 $\times$ (**B**), CD4⁺ T cells (stained red) are seen in a representative biopsy specimen from an HIV-uninfected individual. In comparison, profound CD4⁺ T-cell depletion is noted in low-power (**C**, 25 $\times$) and high-power (**D**, 80 $\times$) views in a specimen from a subject with acute HIV-1 infection.

depletion is more significant than depletion of CD4⁺ T cells in the peripheral blood.⁷ However, such studies were not conducted in patients identified during acute infection.

Along with 2 other groups, we have recently demonstrated that during acute HIV-1 infection, a preferential and profound depletion of CD4⁺ T cells occurs within the GI tract.⁸⁻¹⁰ In the first of these studies, Guadalupe et al⁸ described 2 individuals with acute HIV-1 infection in which significant CD4⁺ T-cell depletion occurred within approximately 4 to 6 weeks of infection. Brenchley et al¹⁰ studied one individual with acute HIV-1 infection (infected for <1 month) and 4 individuals with early HIV-1 infection (duration of infection was 4-9 months). In all 5 subjects, a preferential CD4⁺ T-cell depletion was noted in the intestines. In fact, significant GI tract CD4⁺ T-cell depletion was characteristic of all stages of HIV-1 infection.^{9,10}

Our initial focus was to describe changes within the GI tract of individuals with acute and early HIV-1 infection. To this end, we studied 13 individuals identified during acute (n = 7) and early (n = 6) infection. Mean CD4⁺ T-cell percentage in the GI tract was 15.7% $\pm$ 3.6% compared with a mean of 42.3% $\pm$ 14.7% in the blood (P < .001). Thus in all of our subjects, profound CD4⁺

T-cell depletion was observed in the GI tract and was significantly greater than depletion in the peripheral blood (Fig 1). Since then, we have extended our studies to 26 subjects with acute and early HIV-1 infection and have observed far greater CD4⁺ T-cell depletion in the intestines compared with in the peripheral blood (unpublished data). Having demonstrated a striking CD4⁺ T-cell depletion within the GI tract, we have examined the subsets of CD4⁺ T cells in which this depletion was most prominent. Because a majority of intestinal CD4⁺ T cells express CCR5³ and given that viruses during the early stages of HIV-1 infection are predominantly CCR5-tropic,¹¹ it was not surprising that Brenchley et al¹⁰ and we⁹ both observed that GI tract lymphocyte depletion was most significant among the CCR5⁺ subsets of CD4⁺ T cells. In addition, we have observed marked CD4⁺ T-cell depletion in the effector sites (lamina propria) of the GI tract, with relative sparing of the inductive sites (organized lymphoid tissue). In contrast, however, HIV-1 RNA was localized to the inductive sites. We believe that this discrepancy is best explained by loss of target cells in the effector compartment. We hypothesize that if we could examine a subject within the first 7 to 10 days of infection, viral RNA would be evident in the effector compartment

as well before the annihilation of the resident CD4⁺ cells. In a small cross-sectional cohort, we have observed that in contrast to the peripheral blood, restoration of CD4⁺ T cells in the GI compartment with highly active antiretroviral therapy is incomplete. We are currently examining patients longitudinally to determine whether the timing of onset of antiretroviral therapy is associated with better GI tract CD4⁺ T-cell reconstitution, as has been suggested by Guadalupe et al⁸ in a limited cohort comprised of 2 subjects.

Recent data obtained from the SIV macaque model provide startling insights into the degree of GI tract CD4⁺ T-cell infection and depletion as well. Studies by Mattapallil et al¹² and Li et al¹³ demonstrate rapid infection and destruction of GI tract memory CD4⁺ T cells within days of infection with SIV. The study by Mattapallil et al¹² suggests that at peak viremia (day 10), as many as 60% of GI tract memory CD4⁺ T cells might be infected with SIV and that these cells are lost within 14 days of infection. This results in profound immunodeficiency that begins within days of infection, not months to years as was previously thought. The authors put forth the notion that memory CD4⁺ T cells are killed by means of direct, virus-mediated destruction rather than bystander effects or suppression of CD4⁺ T-cell production.

Li et al¹³ showed, somewhat surprisingly, that GI tract cells infected initially with SIV have a nonactivated (CD69[−]CD25[−]Ki67[−]) phenotype. Peak infection of memory CD4⁺ T cells within the GI tract corresponded to peak viremia, and depletion of GI tract CD4⁺ T cells coincided with a decrease in the peripheral viral load. Li et al therefore suggested the concept of “substrate depletion,” resulting in viral load reduction in the host. In contrast to Mattapallil et al,¹² Li et al¹³ propose that CD4⁺ T-cell depletion is caused by virus-triggered, Fas–Fas ligand–mediated apoptosis. It is likely that CD4⁺ T-cell destruction is multifactorial, caused by virus-induced cytolysis, apoptosis, and the host’s own cytotoxic T-lymphocyte, natural killer cell responses. Further work needs to be done to resolve this issue.

Concurrent studies in our laboratory have focused on determining virologic and immunologic correlates of GI tract CD4⁺ T-cell depletion. Our data (unpublished) suggest that acute HIV-1 infection results in immunologic activation and proliferation of GI tract CD4⁺ T cells, creating a local niche of viral replication. We have observed a highly significant difference between the level of CD4⁺ T-cell infection in the GI tract and peripheral blood. In addition, we have observed a striking difference in HIV-1 viral RNA production within CD4⁺ T cells derived from the GI tract compared with from the peripheral blood. Thus we hypothesize that during acute infection, HIV-1 encounters a vast population of susceptible cells within the GI tract and preferentially infects them. Viral infection results in immune activation and CD4⁺ T-cell proliferation, both of which augment viral production, setting up the next round of infection. The end result is profound CD4⁺ T-cell depletion within the GI tract. Combined, the results from recent studies in human

subjects and SIV-infected macaques suggest an emerging model for the pathogenesis of HIV-1 infection. The large complement of resident memory cells in mucosal surfaces get preferentially infected and fuel subsequent rounds of replication and infection. Therefore in acute stages mucosal sites appear to propel the infection forward.

What are the implications of these findings? A number of significant issues emerge from these studies:

1. By demonstrating that significant viral replication and immune depletion occurs at mucosal sites during acute infection, these findings provide compelling evidence to the argument that mucosal sites should be the focus of further examination and should be considered in the monitoring of patients on therapy.
2. These findings shatter the dogma that during acute HIV-1 infection, there is little CD4⁺ T-cell depletion in the body.
3. These findings reinvigorate the debate regarding the timing of therapy in HIV-1 infection. Guidelines recommending that treatment need not be initiated until CD4⁺ T-cell count decreases to less than 350 cells/mm³ or until plasma viral load is more than 100,000 copies/mL¹⁴ should take into account these recent data demonstrating severe mucosal CD4⁺ T-cell depletion in acute and early HIV-1 infection. This said, however, it must be mentioned that the clinical significance of mucosal immune depletion remains uncertain. Redundancy in our immune system might prevent long-term consequences, yet the possibility of early immune senescence exists, and the long-term consequences are not clear.
4. These findings suggest a potential for the use of immunomodulators, such as cyclosporine, during acute HIV-1 infection with the goal of curtailing successive rounds of viral infection and CD4⁺ T-cell depletion within the GI tract.
5. With regard to preventive efforts directed against HIV-1, recent data underscore the need to develop strategies to protect mucosal surfaces from infection. The use of microbicides and CCR5 blockers would represent such interventions.
6. Finally and perhaps most importantly, these findings reemphasize the fact that mucosal immune responses must be targeted in the development of effective HIV-1 vaccines.

The weight of current evidence places mucosal lymphoid tissue as pivotal in HIV-1 pathogenesis. These findings are likely to have a significant effect on HIV research in the near future.

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