IN 2009, THE UNITED NATIONS ESTIMATED THAT 33.2 MILLION PEOPLE worldwide were living with human immunodeficiency virus type 1 (HIV-1) infection and that 2.6 million people had been newly infected. The need for effective HIV-1 prevention has never been greater. In this review, we address recent critical advances in our understanding of HIV-1 transmission and acute HIV-1 infection. Fourth-generation HIV-1 testing, now available worldwide, will allow the diagnosis of infection in many patients and may lead to new treatments and opportunities for prevention.

THE HIV-1 TRANSMISSION EVENT

More than 80% of adults infected with HIV-1 became infected through the exposure of mucosal surfaces to the virus; most of the remaining 20% were infected by percutaneous or intravenous inoculations. The risk of infection associated with different exposure routes varies, but no matter what the transmission route, the timing of the appearance of viral and host markers of infection is generally uniform and follows an orderly pattern. Immediately after exposure and transmission, as HIV-1 is replicating in the mucosa, submucosa, and draining lymphoreticular tissues (Fig. 1), the virus cannot be detected in plasma; this so-called eclipse phase generally lasts 7 to 21 days. Once HIV-1 RNA reaches a concentration of 1 to 5 copies per milliliter in plasma, the virus can be detected with the use of sensitive qualitative methods of nucleic acid amplification; at concentrations of 50 copies per milliliter, HIV-1 can be detected by means of quantitative clinical assays used to monitor viral load. The stages that define acute and early HIV-1 infection are characterized by the sequential appearance of viral markers and antibodies in the blood (Fig. 2). More sensitive, fourth-generation tests, which detect both antigens and antibodies, shrink the virus-positive–antibody-negative window by about 5 days. Testing for viral RNA in plasma closes this gap by an additional 7 days.

The characteristic appearance in the blood of viral markers of acute HIV-1 infection belies an extremely complicated and still poorly understood series of virus–host cell interactions in the tissues (Fig. 1). Given the varied routes of viral transmission — cervicovaginal, penile, rectal, oral, percutaneous, intravenous, in utero — and the distinctly different histologic features of these tissues, it is not surprising that several cell types are candidates for early infection. More is known about vaginal transmission than about other routes, and the study of human tissue explants and the Indian rhesus macaque model of vaginal transmission of the simian immunodeficiency virus (SIV) have been informative (Fig. 1). The preponderance of evidence implicates CD4 T cells and Langerhans’ cells as the first targets of the virus, but other dendritic cells may play an important accessory role. However, recent observations of mucosally transmitted strains of HIV-1 reveal...
that monocyte-derived macrophages are generally poor targets for infection as compared with CD4 T cells.\textsuperscript{20,21}

Regardless of the route of viral transmission and the first cells infected, within a few days, viral replication converges on the lymphoreticular system of the gastrointestinal tract (i.e., gut-associated lymphoid tissue).\textsuperscript{22-25} In this tissue, in both humans and macaques, the phenotype of most productively infected cells appears to be the resting CD4 T cell lacking activation markers and expressing low levels of the chemokine receptor CCR5.\textsuperscript{16-18} Many of these cells express $\alpha_4\beta_7$ integrin receptors and type 17 helper T (Th17)–cell surface markers.\textsuperscript{26,27} (Since these receptors are also detected on T cells harvested from the genital mucosa, they may play an important role in HIV acquisition.)\textsuperscript{29} The rapid expansion of HIV-1, first in gut-associated lymphoid tissue and then systemically,\textsuperscript{25,29} along with a sharp rise in plasma levels of viral RNA, is clinically important because of the coincident irreversible destruction of reservoirs of helper T cells and the establishment of viral latency (defined as the silent integration of HIV-1 DNA into the genomes of resting T cells, an effect that has stymied curative treatment efforts).\textsuperscript{30,31}

Rather than being genetically homogeneous, RNA viruses, including HIV-1, consist of complex mixtures of mutant and recombinant genomes called quasi-species. Genetic studies of the HIV-1 quasi-species in patients with chronic infection as compared with patients with acute infection have brought some clarity to the qualitative and quantitative aspects of HIV-1 transmission.\textsuperscript{8} Figure 3 depicts the HIV-1 transmission event,\textsuperscript{8,5,32,33} in which the inoculum (e.g., semen, cervicovaginal secretions, or blood) contains a complex genetic quasi-species of viruses, of which only a very small number are likely to broach mucosal barriers and establish infection. Lee and colleagues\textsuperscript{9} developed a model that allows transmitted viral genomes to be inferred from a phylogenetic analysis of the viral quasi-species that replicate in the weeks after infection. Empirical analyses based on single-genome amplification of HIV-1 RNA in plasma or HIV-1 DNA in blood lymphocytes have provided robust evidence to support this model.\textsuperscript{8,20,21,33-38} A single virion is responsible for HIV-1 transmission in approximately 80% of heterosexuals but in only about 60% of men who have sex with men and about 40% of injection-drug users.\textsuperscript{8,20,21,33-35} In injection-drug users, as many as 16 transmitted virions have been found to be responsible for productive infection,\textsuperscript{36} which would be consistent with the absence of a mucosal barrier to transmission. The phenotypes of cloned proviruses corresponding to transmitted (or founder) viruses are nearly always CD4 and CCR5 T-cell tropic variants and exhibit neutralization-sensitivity patterns that are typical of primary viral strains. These phenotypic properties are present at the moment of transmission, when the virus encounters the first target cell; they are not the consequence of viral adaptation to the new host.\textsuperscript{8,20,21}

Figure 1 (facing page). Progression from HIV-1 Transmission to Productive Clinical Infection.

HIV-1 must traverse several tissue layers in the female vagina or rectal mucosa to come into contact with appropriate receptive cells (Panel A). The CCR5 (R5) viral strain has selective transmission advantages that remain poorly explained, and R5 variants make up the majority of transmitted and founder viruses. CXCR4 (X4) variants are transmitted only rarely. Founder viruses come into contact with Langerhans’ cells or CD4 T cells in squamous epithelium; CD4 T cells can also be infected by viruses bound to submucosal dendritic cells. It is not clear whether submucosal macrophages are an initial target, since most founder viruses poorly infect macrophages in vitro. The challenge for HIV-1 transmission in the male genital tract differs somewhat from that in the vagina because of differences in anatomy, but the penile foreskin and urethra harbor critical virus-receptive cells (Panel B). Virus–cell interactions in the male submucosa are likely to be similar to those in female submucosa, with viral targets including Langerhans’ cells, other submucosal dendritic cells, and CD4 cells. Removal of the foreskin through elective circumcision can prevent at least 60% of HIV-1 infections in men.\textsuperscript{6} Although the time required for HIV-1 virions or virus-infected cells to traverse epithelial barriers is short (hours), it probably takes as long as 3 to 6 days for HIV-1 infection and propagation to occur and for the virus to spread beyond submucosal CD4 T cells (Panel C). Dissemination into draining lymph nodes and the systemic circulation rapidly follows, with establishment of the CD4 T-cell viral reservoirs. Studies in nonhuman primates of the timing of response to postexposure prophylaxis with antiretroviral drugs suggests that the time to establishment of the CD4 T-cell reservoir may be as short as 24 hours.\textsuperscript{7}

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A HIV-1 translocation through female epithelium

Columnar epithelium in rectum and endocervix

- Mucus layer
- HIV-1-infected cells
- X4
- R5
- CD4 T cell
- Tissue macrophage

Stratified squamous epithelium in vagina and ectocervix

- Mucus layer
- HIV-1 virions
- X4
- R5
- Langerhans' cell
- CD4 T cell
- Tissue macrophage

B HIV-1 translocation through male epithelium

Columnar epithelium in rectum

- Mucus layer
- HIV-1-infected cells
- X4
- R5
- CD4 T cell
- Tissue macrophage

Stratified squamous epithelium of inner side of penile foreskin

- Mucus layer
- HIV-1 virions
- X4
- R5
- Langerhans' cell
- CD4 T cell
- Tissue macrophage

C Timing of HIV-1 infection events

- Virus or virus-infected cells crossing mucosal barrier
- 2–6 hours
- Local propagation of infection on CD4 T cells
- 3–6 days
- Systemic dissemination
- 6–25 days
- Dissemination into draining lymph nodes
- Establishment of CD4 T-cell virus reservoirs (?) earlier
The progression of HIV-1 infection can be depicted as six discrete stages (indicated by Roman numerals). These stages are defined according to the results of standard clinical laboratory tests (listed above the curve for viral load). The stages are based on the sequential appearance in plasma of HIV-1 viral RNA; the gag p24 protein antigen; antibodies specific for recombinant HIV-1 proteins, detected with the use of an enzyme-linked immunosorbent assay (ELISA); and antibodies that bind to fixed viral proteins, including p31, detected on Western immunoblot. A plus sign indicates a positive test result, a minus sign a negative result, and a plus–minus sign a borderline-positive result. The lines below the viral-load curve show the timing of key events and immune responses that cannot be measured with standard clinical laboratory assays, beginning with the establishment of viral latency. Acute-phase reactants include elevated levels of serum amyloid protein A. CD8 T-cell responses lead to the appearance of escape mutants concurrently with inflammatory cytokines in plasma. Immune complexes of antibodies with viral proteins, such as the HIV-1 envelope glycoprotein (gp41), precede the first appearance of free antibodies to gp41. Strain-specific antibodies to gp41 that neutralize the virus do not appear until sometime close to day 80. The portion of the line for viral latency that is dotted reflects uncertainty as to exactly when latency is first established; the dotted line for acute-phase reactants indicates that not all patients have elevated levels of reactants at this early point in the process of infection; the gray segment of the black line for viral load reflects the inability to measure very low viral loads.

NK cells are activated in acute HIV-1 infection and, in vitro, kill cells infected with the virus. NK cells have a range of receptors that either enhance or inhibit their function. NK-cell immunoglobulin-like receptors interact with HLA molecules with some specificity for the peptides they bind. This activity might explain the genetic associations between certain NK-cell immunoglobulin-like receptors and HLA types with more favorable outcomes of infection.

The initial antibody response to the viral envelope is non-neutralizing and does not select for viral escape (Fig. 2). Antibodies that neutralize the transmitted founder virus are not detected until 3 months or more after infection. Although...
Figure 3. Model of HIV-1 Transmission.
A genetically and phenotypically diverse quasi-species of virus is present in the semen, cervicovaginal secretions, or blood of persons with chronic HIV-1 infection, but most often, only a single virion or virally infected cell is transmitted and leads to productive clinical infection. Other viruses may breach the mucosal or cutaneous surfaces, but they generally do not result in productive infection or contribute to it, presumably because such viruses are defective or less fit or simply fail to come into contact with susceptible target cells. \( R_0 \) represents the basic reproductive ratio, which corresponds to the number of secondary infections caused by one infected cell. If this number falls below 1, infection is extinguished. In acute infection, the number of productively infected cells and the concentration of free virus in the plasma increase exponentially, with an estimated \( R_0 \) of 8.32
many of the targets of neutralizing antibodies are on the glycoprotein-120 component of the HIV-1 envelope, the initial antibody response to HIV-1 is focused on non-neutralizing sites of the glycoprotein 41 envelope stalk. It is not known why the initial HIV-1 antibody response is directed (or misdirected) to ineffective envelope sites, but the response may be related in part to the relative abundance of non-native HIV-1 envelope molecules when glycoprotein 41 is exposed, whereas the exposure of functional native envelope trimers is rare. Similarly, other potentially protective antibodies directed against envelope proteins, such as antibodies that neutralize the founder viral strain or those that mediate antibody-dependent cellular cytotoxicity, do not arise until weeks after transmission. By the time a potentially effective antibody response has developed, it is much too late to influence the course of the infection (Fig. 2).

The first CD8 T-cell responses appear days before the peak of viremia and focus on between one and three distinct epitopes (short antigenic peptides bound to HLA molecules that are derived from HIV-1 proteins) most commonly found in HIV-1 proteins nef and gag. These first T-cell responses select escape mutants (which cannot be recognized by killer CD8 T cells), with complete replacement of the original viral amino acid sequence by the new sequence in 10 to 21 days. These initial T-cell responses are followed by new T-cell responses to other epitopes, which often escape as well. A combination of strong T-cell responses, producing chemokine (C-C motif) ligand 4 (CCL4), and a focus on epitopes with high levels of variability (entropy) favors rapid escape. These CD8 T cells also express perforin — a protein closely associated with cell-mediated cytotoxicity — which suggests that they can kill infected cells.

Other CD8 T-cell responses do not appear to select escape mutants — or must do so very slowly. Some of these T cells may be functionally deficient, but most appear to be effective, focusing on regions of the virus that can mutate, but at the cost of making the virus less efficient in replication. These latter T cells are likely to contribute to the control of HIV-1. As this T-cell response evolves, the plasma viral load falls (Fig. 2). The rate of loss of virus containing the epitopes recognized by the early T-cell responses that drive escape provides a measure of the rate of killing (or removal) of virus-infected cells in vivo. Other factors, such as loss of susceptible cells (given the extreme depletion of activated CD4 T cells in gut-associated lymphoid tissue), probably also play a part in lowering the initial peak viral load.

During acute HIV-1 infection, irrevocable depletion of CD4 T lymphocytes from the gastrointestinal tract and some other lymphoid tissues has been observed in humans and rhesus macaques. In humans, adjunctive damage to the mucosal barriers may allow leakage of gut bacterial products into otherwise sterile tissues and to the bloodstream, leading to further immune activation that can promote HIV replication and have other adverse consequences. The rapid, early, and massive loss of CD4 T cells in lymphoid organs (which is poorly reflected in CD4 T-cell counts in blood) probably accounts for the weak CD4 T-cell responses in cases of acute HIV-1 infection.

The importance of CD8 T cells in controlling acute HIV-1 infection is consistent with studies in the rhesus macaque SIV model showing that in vivo depletion of CD8 T cells abrogated viral control in both acute infection and chronic infection. In addition, many studies in macaques have shown that vaccines that stimulate SIV-specific CD8 T-cell responses can attenuate subsequent SIV infection. These data are also consistent with extensive work showing that in patients with certain HLA types, particularly HLA-B57 (and the very closely related HLA-B58) and HLA-B27, viral control is often better than average, with a lower virus set point and longer survival in the absence of antiretroviral therapy. The B27, B57, and B58 molecules present highly conserved parts of the virus to T cells, so that the virus can escape immune control only at the cost of replicative fitness.

In the absence of a high degree of clinical suspicion, the symptoms associated with acute HIV-1 infection are often too vague or nonspecific to lead to a diagnosis. In the absence of antibody seroconversion, confirmation of acute infection requires detection of HIV-1 RNA or p24 antigen, but tests designed for this purpose have heretofore not been routinely available. In public health settings, a cross-sectional screening strategy that
involves searching for HIV RNA in pooled, antibody-negative samples has been used to increase detection.\textsuperscript{61} This approach has been used to detect acute HIV-1 infection, with a prevalence of 0.5 cases detected per 1000 persons tested, in North Carolina, to 4.0 cases per 1000, in San Francisco; acute infection accounted for 5 to 10% of all cases of HIV in both places.

As an alternative and more practical strategy, an enzyme-linked immunosorbent assay that can concomitantly detect viral p24 antigen and antiviral antibodies has been developed and approved for clinical use.\textsuperscript{2,3,61} This test can increase the number of patients with acute HIV-1 infection whose condition is diagnosed at a time when they are most infectious to others.\textsuperscript{9} It is anticipated that a rapid point-of-care test will also be developed for the purpose of detecting acute HIV-1 infection. The implementation of these tests across the United States in public health and commercial laboratories can be expected to dramatically increase the number of patients with acute HIV-1 infection who will require care.

\textbf{PUBLIC HEALTH CONSEQUENCES OF ACUTE HIV-1 INFECTION}

The per-person probability of transmitting HIV-1 is most closely correlated with the viral burden in blood; each time the viral burden in an HIV-1-infected person increases by a factor of 10, the risk of transmission is expected to increase by a factor of 2.5.\textsuperscript{62} The risk of contagion from patients with acute, early infection appears to be much higher than that from patients with established infection,\textsuperscript{63} at least in part because of the high viral load and the homogeneity of viral variants clearly capable of causing infection. In the rhesus macaque SIV model, plasma from animals with acute infection is up to 750 times as infectious, on a per-virion basis, as plasma from animals with chronic infection.\textsuperscript{64} The reduced risk of contagion from patients with chronic infection probably results from the presence of neutralizing antibodies, which are not evident in acute infection.

Mathematical models used to estimate the role of patients with acute infection in the spread of HIV-1 have produced strikingly different results, depending on the population studied and the assumptions used (Fig. 4).\textsuperscript{65-77} The epidemic phase used for modeling has been a critical determinant.\textsuperscript{78} In communities subject to a new epidemic, early infections are held to be responsible for a considerable share of HIV-1 transmission, since a larger proportion of infected persons have acute or early-stage disease rather than late-stage disease.\textsuperscript{79} Sexual behavior plays an important role in rates of infection, with high rates of partner change increasing the chances of contact with a person who has acute HIV-1 infection. In a recent comprehensive study conducted in Lilongwe, Malawi, in which both behavioral and biologic data were used, 38% of cases of HIV-1 were ascribed to sexual exposure to patients in the first 5 months of infection, even though there is a long-established epidemic in Malawi.\textsuperscript{73} The results of the Malawi study may be most relevant to the HIV-1 pandemic in sub-Saharan Africa.

The importance of acute HIV-1 infection can also be seen in studies of phylogenetically related cases, such as the study reported by Brenner and colleagues.\textsuperscript{79} They state that more than half the patients with newly diagnosed early HIV-1 infection in Montreal are infected with viral variants that can be linked through phylogenetic studies, which suggests the presence of clusters of transmission, perhaps from patients with acute and early infection.

\textbf{PREVENTING HIV-1 INFECTION}

Effective HIV preventive strategies must be in place before or immediately after the transmission event. This is a tall order for antiviral prophylaxis, administered before or after exposure, or a vaccine. Indeed, the antibody responses directed against the HIV-1 envelope after the administration of vaccine regimens are not of long duration.\textsuperscript{80,81} Nevertheless, there are several points in the transmission event at which the founder virus may be vulnerable to inhibition by antibodies, ranging from the entry of virus or virus-infected cells into mucus in the genital tract to cell-to-cell transmission in genital tract submucosa (Fig. 1).\textsuperscript{82} Weakly neutralizing antibodies that mediate antibody-dependent, cell-mediated cytotoxicity or antibody-dependent cellular viral inhibition may have a protective effect by stimulating immune cells to produce anti-HIV-1 chemokines, such as CCL3, CCL4, and CCL5.\textsuperscript{83} In a recent vaccine efficacy trial conducted in Thailand, the partial prevention of HIV-1 acquisition observed may have been due to a transient antibody response\textsuperscript{83}; the
results could also be explained by the actions of one or more innate antiviral immune mechanisms.

An alternative prevention strategy that is more readily available is that of offering antiretroviral agents to people at risk before or immediately after HIV exposure or as a means of secondary prevention. Use of the antiretroviral drug tenofovir as a topical prophylactic agent before viral exposure in women at high risk led to a 39% reduction in incident cases of HIV infection that was directly correlated with concentrations of the drug in mucosal tissue. Seven ongoing trials of oral preexposure prophylaxis have been undertaken. A multinational trial focused on men who have sex with men showed that a once-daily pill containing tenofovir plus emtricitabine provided an average of 44% protection over and above that conferred by the provision of comprehensive preventive services, including the provision of condoms and counseling. The level of protection varied widely, depending on how consistently participants used preexposure prophylaxis. The Centers for Disease Control and Prevention has issued preliminary recommendations for the use of preexposure prophylaxis by men who have sex with men. Work with rhesus macaques suggests that achieving high levels of antiviral agents in mucosal tissues shortly after exposure to SIV–HIV viral chimeras is critical for protection from infection. This work, along with the further

Figure 4. Role of Acute and Early HIV-1 Infection in the Spread of HIV-1, According to Population Studies in Sub-Saharan Africa, the United States, and Europe. Acute and early HIV-1 infection is responsible for secondary transmission of HIV-1, which is critical to the epidemic spread of the virus. A variety of models have generated widely varying estimates of the potential importance of acute and early HIV-1 infection, depending on the patient populations studied and the assumptions of the models. These models generally include people in whom the virus was detected before and during seroconversion (acute HIV-1 infection) and for several weeks thereafter (early infection) (see Hayes and White and Salomon and Hogan). The estimates reflect the proportion of all transmissions during an individual patient’s entire infectious period. The extent to which this proportion corresponds to the proportion of all transmissions that occur during acute and early HIV-1 infection at the population level depends on the epidemic phase and the distribution of patterns of sexual contact in the population (see Pinkerton and Abramson, Kretzschmar and Dietz, and Koopman et al.). Transmission probabilities were drawn from the population category shown, but the reported estimates result from a range of hypothetical sexual-behavior variables that do not necessarily reflect a specific population (see Kretzschmar and Dietz and Abu-Raddad and Longini). The range of estimates shown was extracted from the endemic-phase portion of graphs showing the proportion of new infections resulting from early HIV-1 infection over calendar time. I bars represent an estimate of the percentage of new HIV cases caused by people with acute or early HIV infection. MSM denotes men who have sex with men.
exploration of new drug combinations, will probably play a role in the further development of pre-exposure and postexposure prophylaxis.

MANAGING ACUTE HIV-1 INFECTION

The health care provider has three responsibilities with respect to acute HIV-1 infection: detection; secondary prevention, which in some cases must include partner notification (and possibly postexposure prophylaxis with antiretroviral therapy); and initiation of antiretroviral therapy, if it is considered appropriate. Although the fourth-generation HIV tests have the capacity to detect acute HIV-1 infection, algorithms that will reduce the time to diagnosis and linkage to medical care must be put into place.3 Equally important, strategies must be developed to offer the best possible counseling in order to reduce further spread of HIV-1 and to break up the sexual networks that can form around patients with acute HIV-1 infection.91 However, partner notification in the United States has been limited92 and is only now being studied in resource-constrained countries.93 A recent study in Africa has highlighted the difficulty of explaining acute HIV-1 infection to study subjects in a manner that is likely to reduce further transmission.94

Alternatively, antiretroviral therapy could be used to suppress viral replication in order to reduce HIV-1 transmission. What constitutes the optimal use of antiretroviral therapy for patients with acute infection is unclear, in part because the extent of the personal health benefit derived from early use of antiretroviral therapy remains in question.95,96 There have been considerable differences in reported results of the clinical benefits of antiretroviral therapy for patients with primary HIV infection because in many cases antiretroviral therapy was initiated weeks or even months after HIV-1 acquisition — probably much too late to influence the course of disease. A few small studies have shown some benefit when therapy was provided before or during seroconversion, with some degree of immune preservation96 and with sustained reduction of blood viral load after antiretroviral therapy was discontinued. Moir et al. reported that patients treated soon after receiving the diagnosis had improved B-cell function.97 Very early administration of antiretroviral therapy may limit the size of the latent pool of HIV-1–infected CD4 T cells.98,99 Although encouraging, these results underscore the need for well-constructed clinical trials that will provide the basis for determining the overall cost–benefit ratio of antiretroviral therapy for acute HIV-1 infection and for balancing the public health benefits with the benefits for individual patients.

In the most recent treatment guidelines from the International Antiviral Society — USA, the authors argue that potential benefits to public and individual health may even now justify the treatment of patients with acute HIV infection, particularly those who are symptomatic.100 The authors of other guidelines have come to similar conclusions, setting the stage for regular treatment of persons with acute HIV infection. If antiretroviral therapy is to be provided, the treatment regimen might include drugs that concentrate in the genital tract of men and women85 and an integrase inhibitor, the latter because of the rapidity with which this class of drugs lowers the viral load.101 Some pilot studies using multidrug regimens, such as those administered before HIV seroconversion, are in progress.102

CONCLUSIONS

The earliest events in acute HIV-1 infection determine the future health of the individual patient and the extent of transmission in the general population. Recent studies have unraveled many of the initial immune events of acute infection. With improved diagnostic tests, greater numbers of persons with acute HIV-1 infection will come to the attention of practicing physicians and public health officials. Although considerable progress has been made in understanding the HIV-1 transmission event, more studies are needed to develop optimal treatment and prevention strategies for people in the earliest stages of HIV-1 infection.

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