ELSEVIER
SAUNDERS

Infect Dis Clin N Am
21 (2007) 19–48

INFECTIOUS
DISEASE CLINICS
OF NORTH AMERICA

Diagnosis and Management of Acute HIV Infection

Nicola M. Zetola, MD[a],
Christopher D. Pilcher, MD[b,*]

[a]*Division of Infectious Diseases, University of California-San Francisco, 1360 Mission St., Suite 401, San Francisco, CA 94103, USA*
[b]*HIV/AIDS Division, San Francisco General Hospital, University of California-San Francisco, Building 80, Ward 84, Box 0874, 995 Potrero Avenue, San Francisco, CA 94143–0874, USA*

HIV infection starts as an acute, systemic infection; as the natural history of HIV continues, acute HIV infection is followed by chronic period of clinical latency, usually lasting 3 to 10 years, which precedes the eventual collapse of the immune system. It is increasingly recognized that events occurring during acute infection may determine the natural course of the disease. Acute HIV infection is the phase during which standard antibody tests are rapidly evolving; this lasts about 2 months for most patients. Recent HIV infection is used to describe HIV infections that may not be clearly acute, but have likely occurred within 6 to 12 months. Primary HIV infection is a somewhat looser term that describes all acute and recent patients equally well. The very dynamic events of acute HIV infection provide multiple opportunities for biologic interventions, such as antiretroviral or immune-based therapies, and the implementation of public health measures during acute HIV infection could help control epidemics or outbreaks. Many of the dramatic possibilities for intervention in acute HIV infection remain unproved, not the least because of traditional difficulty of diagnosing acute disease. This article covers in some detail the natural history and pathogenesis of acute HIV infection; its clinical aspects; and some new diagnostic strategies with promise greatly to increase recognition of this common syndrome.

This paper was supported in part by the Universitywide AIDS Research Program (UARP), the San Francisco Department of Public Health, and the National Institutes of Health/National Institute of Mental Health (R01-MH068686).

* Corresponding author.
E-mail address: cpilcher@php.ucsf.edu (C.D. Pilcher).

0891-5520/07/$ - see front matter
doi:10.1016/j.idc.2007.01.008

Pathogenesis and natural history

Transmission, selection, and expansion of R5 HIV variants

In HIV infection resulting from sexual exposure, intact mucosal surfaces represent a significant barrier to HIV infection, and very few cells are initially infected [1]. Several mechanisms have been proposed for traversal of mucosal surfaces by cell-free or cell-associated virus particles [2,3]. Whatever the true mechanism, pre-existing inflammation or breaks in the integrity of mucosal architecture at the site of inoculation (eg, from sexually transmitted diseases) can clearly increase the efficiency of this process [4,5]. Once the virus crosses the epithelial layers, infection is established by replicating within target cells at the point of entry [6]. Entry of HIV to any cell depends on interactions of HIV envelope proteins gp120 and gp41 with cell surface CD4 receptors, but also with the co-receptors CXC chemokine receptor 4 or CC chemokine receptor 5 (CCR5) [7]. Interestingly, the HIV variants that first appear in more than 90% of acute HIV infections use CCR5 exclusively, regardless of route of infection [8–13]. This is also seen in acute simian immunodeficiency virus infections [11,14,15]. Whether this is caused by selection by innate immune responses around the time of transmission, or to later, more efficient outgrowth of CCR5-using populations in mucosal tissues of the new host, is not known [6,7,16–18].

Within 72 hours of a transmission event, local virus replication results in infection at the site of entry and the draining lymph nodes [19]. Infection becomes systemic by the end of the first week, as the virus disseminates to other lymphoid tissue compartments [1,20]. By day 10 after infection, most extra-lymphoid tissue $CCR5^+$ $CD4^+$ effector-memory T cells has been either infected or has interacted with HIV [1,18,20]. Secondary to viral infection or to coreceptor-dependent induced apoptosis, a dramatic depletion of such $CCR5^+$ $CD4^+$ effector memory T cells occurs between days 10 and 21, which is much more pronounced in the gut (the largest lymphoid organ) than is reflected in peripheral blood CD4 cell counts, which decrease only modestly [20–26].

The availability and rapid consumption of targets during this early period leads to massive viral replication, accounting in part for the peak levels of viremia and genital shedding achieved by the end of the first month [20,23,27–31]. Once infection has become truly systemic, virus loads grow exponentially, becoming detectable in blood around day 8 postinfection and expanding with a doubling time of approximately 0.3 days during the first 2 to 3 weeks of infection [1,19,20,28,32–36].

Establishment of long-lived reservoirs

Long-lived reservoirs of HIV are established within the first month of acute infection [37]. Perhaps the largest site for virus propagation in vivo is the large number of follicular dendritic cells, which trap and retain

infectious HIV particles and protect them from degradation for many months [38]. Much smaller numbers of (predominantly resting) $CD4^+$ T cells with memory phenotype integrate the virus into their chromosome. These latently infected cells do not spontaneously produce virus unless activated [39,40]. Their long lifespan (44 months) constitutes one of the main barriers to HIV eradication with current antiretroviral therapies [37,38].

Induction of immune activation

As viremia is rising toward its peak and resting $CD4^+$ T-cell populations are depleted (in the second to third week of infection), the immune system transitions to a state of hyperactivation and the patient may develop symptoms of the acute retroviral syndrome. Proliferation and activation of $CCR5^+$ T cells in this milieu provide further fuel for viral replication, because T cells with an activated phenotype are more susceptible to HIV infection [18,41]. Systemic exposure to bacterial endotoxin following disruption of gut mucosal immune integrity has been suggested as one trigger for this process [42]; however, it remains unclear what sustains this hyperactivated state indefinitely. In natural simian immunodeficiency virus infection of sooty mangabeys, for instance, initial T-cell depletion occurs without any persistent immune activation, and animals do not progress to AIDS [43]. In people with HIV infection, high levels of immune activation are among the strongest predictors of progression to AIDS [44].

Emergence of controlling host responses

Anti–HIV-1 antibodies begin to be detected by IgM-sensitive ELISAs 2 to 4 weeks after infection [28,45,46]. These low-titer antibodies bind with low avidity or affinity, however, and exert little if any selective pressure on circulating virus populations [47–49]. They also fail to slow the increase in viral loads in blood, genital secretions, or other compartments, until around 4 weeks after infection (Fig. 1) [27,29,50].

The downward deflection in virus levels that finally occurs at this time may reflect exhaustion of $CCR5^+$ $CD4^+$ target cells but may also be determined by the first appearance of specific anti-HIV cytotoxic $CD8^+$ T lymphocytes, which accumulate in significant numbers at mucosal sites after the viral load peak [20,22,23,36,51–55]. Virus loads then drop precipitously (see Fig. 1), and generally attain their lowest levels by week 10 postinfection in both blood and genital secretions.

Further viral load oscillations may occur but a balance between viral replication and immune control eventually produces a steady ‘‘set point’’ in viral load at sometime between weeks 8 and 24 [36]. During this interval, initially narrow cytotoxic T lymphocyte responses may start to broaden, targeting an increasing variety of epitopes and exerting selective pressure on virus populations [56–59]. The first neutralizing antibodies against glycosylated epitopes in envelope also appear in this time period, accompanied by

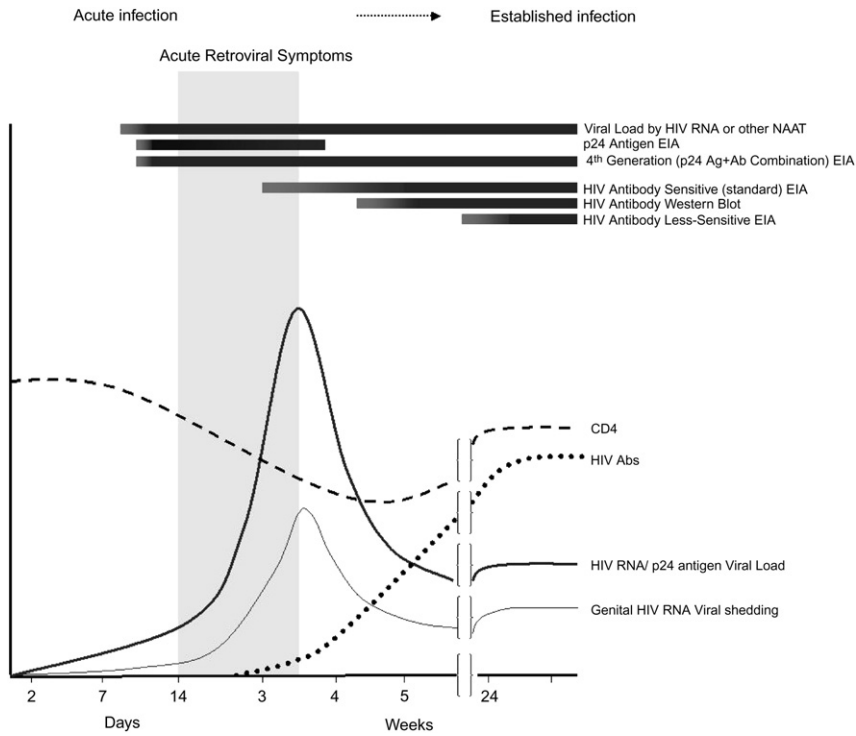

Fig. 1. HIV viral load. CD4 cell count and antibody dynamics during an idealized primary HIV infection, and their correlation with diagnostic tests and the acute retroviral syndrome. Windows in which various tests are likely to be positive are shown by dark bars. The symptomatic period is light gray. Ab, antibody; Ag, antigen; EIA, enzyme immunoassay; NAAT, nucleic acid amplification test. (*From* Fiebig EW, Wright DJ, Rawal BD, et al. Dynamics of HIV viremia and antibody seroconversion in plasma donors: implications for diagnosis and staging of primary HIV infection. AIDS 2003;17:1876; with permission; and Bernard M. Branson, personal communication, June 13, 2006.)

an explosion in viral diversity [45,47–49,60]. As escape variants appear, the HIV-specific antibody response further broadens, exerting a selective pressure that drives continuous evolution of neutralization escape mutants from this point forward [60,61] Another group of functional antibodies, although unable to neutralize the virus, induce potent antibody-dependent cytotoxicity [62].

The degree to which these emerging adaptive immune responses control viral replication varies greatly. Individual-to-individual variation in set-point viremia is partially explained by viral factors or by host genetics determining CCR5 expression levels, but is also influenced strongly by differences in certain HLA types, supporting the key role of cellular responses in establishing immune control [63–67]. Strong and broadly targeted cellular and humoral responses have each been associated with lower set-point

viremia, and with slowing of $CD4^+$ T-cell loss, immune collapse, and clinical progression [45,61,64–70]. One important determinant of the strength and breadth of these responses is the availability of HIV-specific $CD4^+$ T-cell help; because HIV-specific $CD4^+$ lymphocytes must proliferate in the face of massive viral replication, protection of nascent $CD4^+$ cell populations is considered one theoretical indication for early antiretroviral therapy in acute HIV infection [71–74].

Summary

As a general rule, mature, controlling immune responses first emerge between weeks 8 and 24 of acute HIV infection, accompanied by loss of viral homogeneity as viruses rapidly evolve to escape immune pressure. Long-lived reservoirs are probably fully established by around week 8, and the transition to persistent immune hyperactivation probably also takes place around this time. For these reasons, acute interventions (eg, antiretroviral or immunomodulatory therapies) attempting to modify these phenomena are expected to have their greatest effects if instituted in the first 2 months of infection, and acute or primary HIV infection is considered to be over for practical purposes by 24 weeks.

Diagnosis

The acute retroviral syndrome

Following infection by HIV, approximately two thirds of patients have some symptoms attributable to an acute retroviral syndrome, whereas about one third of patients are asymptomatic [21,75–78]. For those with symptoms, their onset is usually abrupt following an incubation period of 10 to 14 days (incubation periods ranging from 5–35 days have been reported) [21,75,76,78–81]. The most common manifestations of acute infection (Table 1) include fever up to 40°C (present in 80%–90% of symptomatic patients), malaise, anorexia or weight loss, myalgias, and arthralgias; about half or fewer patients complain of headache (with or without meningeal signs), pharyngitis (with or without tonsillar exudates), or rash; occasionally, patients may complain of diarrhea or oral, esophageal, and genital ulcers [21,75,76,78–81].

The physical examination may reveal rash; meningeal signs; pharyngitis; oral, vaginal, or anal ulcers; and diffuse lymphadenopathy (see Table 1). The rash can involve face, trunk, palms, and soles. Oral or vaginal thrush is occasionally present and sometimes resolves without treatment. In addition to meningeal signs, rare neurologic findings have been reported in association with acute HIV infection, including cranial nerve palsies (especially involving cranial nerve VII); radiculopathy; encephalopathy; and Guillain-Barré syndrome [82]. Because it is both readily diagnosable and life threatening,

Table 1
Signs and symptoms associated with having acute HIV infection

Sign or symptom	Approximate prevalence (%)[a]	Reported odds ratios[b,c]
Fever[d]	>70	2.8, 3.4, 4.5, 7.0, 10.6
Lymphadenopathy[d]	35–70	1.9, 3.3
Sore throat[d]	40–70	1.7, 2.0, 3.3
Rash[d]	20–70	2.1, 4.0
Joint pain[d]	30–60	1.6, 2.1, 2.6, 3.8, 6.4
Diarrhea	25–50	3.1
Anorexia or weight loss[d]	15–70	2.5, 2.8, 9.5, 9.9
Night sweats[d]	50	2.2, 11.2
Myalgia[d]	40–70	2.1, 2.8, 4.2, 6.8
Malaise or fatigue[d]	>70	1.6, 2.2, 6.3, 8.0
Headache[d]	30–40	2.0, 3.0
Vomiting	10–30	4.8
Too sick to work	60	4.0
Hospitalized	10–20	7.4
Oral or genital ulcer disease	10–20	2.1, 2.6

[a] Among symptomatic patients; approximately one third of patients are asymptomatic.
[b] Data obtained from case-control studies [21,78,79,81].
[c] Data obtained from case series [75–77,80].
[d] Statistically significant in two or more studies.

acute HIV should be in the differential diagnosis for all cases of aseptic meningitis in sexually active adults.

A few of the previously mentioned acute signs and symptoms (eg, generalized lymphadenopathy, rash, mucosal ulceration, or thrush) are uncommon enough in other common adult febrile illnesses that they should raise suspicion of acute HIV infection. Oral and genital examinations and a brief survey of axillary and inguinal nodes can be extremely helpful in assessing risk of having acute HIV infection.

Laboratory findings in acute infection typically include general leukopenia with $CD4^+$ lymphopenia and atypical lymphocytosis, mild thrombocytopenia, and abnormal liver function tests [82,83]. Cerebrospinal fluid examination typically shows lymphocytic pleocytosis [27]. Although most of the signs and symptoms of acute HIV infection typically resolve after less than 2 weeks, laboratory manifestations including $CD4^+$ lymphopenia may persist for several months (as may malaise and diffuse adenopathy).

The presence or absence of symptoms during acute HIV infection may have great prognostic importance. Cohort studies enrolling seroconverting patients have consistently shown that both the number and duration of acute retroviral symptoms each independently increase the likelihood of later disease progression [55,84–87]. For instance, Lindback and colleagues [88] found that seroconverting patients reporting >14 days' acute illness had a 78% likelihood of progressing to AIDS within 3 years, versus a 10% likelihood of progression for asymptomatic seroconverters in the same study.

Risk factors for acute HIV infection

A number of key risk factors can be identified that have been strongly associated with acute HIV infection in multiple studies. These include traumatic sex; anal intercourse (especially receptive anal intercourse); active genital ulcer disease (in self or in a sexual partner); having sex in exchange for drugs or money; regular recreational drug use; or having multiple sexual partners [89–93]. For men, uncircumcised status and use of sildenafil citrate have been shown in studies to increase risk; for women, douching before sex is an independent risk factor [94–97]. Injection drug use or needle-sharing confer especially high risk [98–100].

There are several settings where single sexual exposures may merit screening for acute HIV infection; where the source patient has known acute HIV, single sexual exposures carry transmission risks similar to deep needlesticks, and directed acute HIV screening is absolutely indicated in the evaluation of exposed patients. When there is history of occupational exposure, it is important to inquire about the type of bodily fluid, type of exposure, type of needle (hollow or solid), presence of blood in the needle, deepness of the injury, and history of postexposure prophylaxis, and the HIV status and clinical stage of the index patient [101]. Screening for acute HIV infection may be necessary for both the source patient (at the time of exposure) and for the exposed patient (in follow-up of exposure).

Overview of the approach to screening

Acute HIV infection is most often diagnosed by infectious disease specialists [21,102]. Although rarely considered, it is a rarely diagnosed, moderately prevalent, but life-threatening primary care disease. Ideally, the presence of one or more key symptoms (see Table 1) plus a key risk factor or convincing HIV exposure history would lead to assessment for acute HIV infection in the primary care setting. Acute HIV is a much more likely explanation for flu-like symptoms than is usually appreciated: in one study, 1% of patients undergoing evaluation for mononucleosis (and heterophile antibody negative) at Massachusetts General Hospital proved to have acute HIV infection [103]. Another study found similar rates of acute HIV in Boston urgent care patients with flu-like symptoms [104]. Given the nonspecific nature of the syndrome, a low threshold for acute HIV testing is warranted. The approach to HIV testing in acute HIV is different depending on whether one screens symptomatic, high-risk, or lower-risk populations.

Use of HIV tests

Tests for acute HIV infection are chosen based on the dynamic natural history of HIV biomarkers in acute infection (see Fig. 1) [28]. The least recommended, but most common, way to diagnose acute infection is simply documenting antibody seroconversion (making the diagnosis in retrospect).

Two types of results are needed to diagnose acute HIV infection in real time (Fig. 2). The first is a positive screening test result, indicating HIV infection. This can be HIV nucleic acid amplification, HIV p24 antigen, HIV antibody, or combined p24 antigen-antibody screening test. The second is a negative, indeterminate HIV antibody test result suggesting incomplete seroconversion.

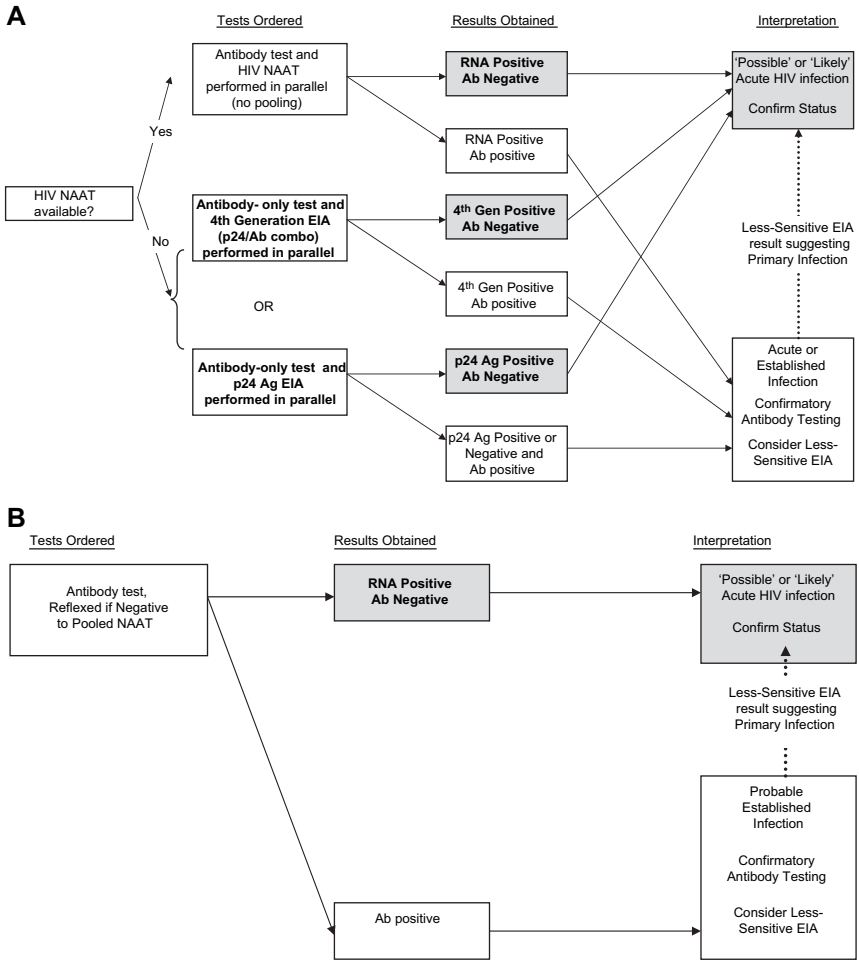

Fig. 2. Clinical decision tree for acute HIV diagnostic testing. (*A*) Assessment of symptomatic patients or patients with high suspicion for acute HIV infection. HIV NAAT may not be readily available in some resource-limited settings. (*B*) Assessment of asymptomatic patients or patients with low suspicion for acute HIV infection. Ab, antibody; Ag, antigen; EIA, enzyme immunoassay; NAAT, nucleic acid amplification test.

One common misconception is that the window period for HIV tests lasts 3 to 6 months. Although at one time true, modern antibody tests are highly sensitive to the presence of low-level, immature, IgM-class antibodies. This is true for modern Western blot assays and for HIV rapid tests [30,105].

Rapid HIV antibody tests can be used as part of an acute testing algorithm, and the most successful acute programs have used a rapid testing-based approach [105,106]. At the time of this writing, however, no point-of-care rapid tests are yet available that can detect HIV antigens or nucleic acids in acute infection. If a rapid test is used for antibody screening, additional acute HIV testing requires (1) storing an appropriate blood specimen for additional nucleic acid or antigen testing, (2) providing follow-up for these confirmatory results, and (3) emphasis on the preliminary nature of both negative and positive rapid test results at the time of rapid test results notification.

Modern antibody tests usually become positive within the first 4 weeks after infection; it is not unusual for individuals to test antibody positive when evaluated for possible acute retroviral symptoms. For such patients, some experts and research programs supplement a positive standard antibody result with a less-sensitive (so-called "detuned") antibody test when acute HIV infection is suspected (see Fig. 2). Less-sensitive antibody assays are engineered to have reduced affinity or avidity for early HIV antibodies. In the proper setting, a confirmed positive sensitive antibody test and a negative less-sensitive antibody test can strongly support a clinically suspected diagnosis of acute HIV infection.

To identify or confirm HIV infection in patients with incomplete seroconversion, nucleic acid amplification tests for HIV RNA are the screening test of choice (see Fig. 2). This assay is the first to become reliably positive (in the second week of HIV infection); they also remain positive through to antibody seroconversion in virtually all patients. Disadvantages to RNA include higher cost than other tests and imperfect specificity, both problems that can be addressed by ordering RNA testing using a specimen pooling approach (see later).

Assays to detect viral core antigens (p24 antigen or combined p24 antigen and antibody enzyme immunoassay [EIAs]) become positive 3 to 6 days after HIV RNA tests; these assays are technologically simpler, cheaper, and more specific than HIV RNA tests, but specimens cannot be pooled. In chronic HIV infection, fewer than half of patients are positive by p24 antigen EIA tests: viral loads are sometimes low, and antibodies in the patient sample can bind and complex with available antigen, interfering with detection [107,108]. In symptomatic acute HIV infection, however, such early antibodies are rare and viral loads are high. An HIV p24 antigen assay may be substituted for the HIV RNA test in evaluation of acutely symptomatic patients (see Fig. 2). Trials of p24 screening of lower-risk populations have demonstrated 77% to 91% sensitivity for acute HIV infection [21,30,75,109].

The dual HIV p24 antigen–HIV antibody combination assays (so-called "fourth-generation" HIV EIAs) have comparable sensitivity in early acute HIV infection to standard p24 assays. Confirmatory testing for positive results on such fourth-generation EIAs typically involves antibody-only reflex testing of the original specimen, with discordant results (fourth-generation EIA plus antibody-only EIA) taken to indicate possible acute HIV infection.

Screening patients with symptoms or risk factors to suggest acute HIV infection

Up to 13% of patients with a plausible exposure history and compatible symptoms may have acute infection [21,75]. For evaluation of patients with acute retroviral symptoms, viral loads are usually >100,000 copies/mL (see Fig. 2). One should consider the following:

- A simultaneous HIV RNA test and standard antibody test are appropriate. Low-positive viral load results (eg, <10,000 RNA copies/mL) in this setting should raise concerns for a false-positive result, which in the worst case can occur with rates up to 2.6% depending on the assay used [75].
- If both RNA and antibody tests are positive, a less-sensitive antibody test can be used to discern acute from chronic HIV infection.
- If RNA testing is unavailable, p24 antigen testing may be substituted.
- Fourth-generation EIAs (combination Ag-Ab assays) can be used for initial screening of symptomatic patients. Confirm positive results with reflex antibody testing of original specimen.
- If acute infection screening is done for a high-risk recent exposure in an asymptomatic individual, testing should be repeated at least once (and 1 month or longer out from exposure) to exclude infection.

Screening for acute HIV infection with routine HIV testing: role of specimen pooling algorithms

Both cost and the adverse impact of false-positive screening tests are potentially important in lower-risk testing situations (eg, for patients with symptoms but no risk factors, or risk factors but no symptoms). To identify acutely HIV-infected patients for prevention purposes, several public health departments have experimented with adding tests capable of identifying acute infection to their testing algorithms for routine HIV voluntary counseling and testing (algorithms depicted in Fig. 2B). To overcome the costs, labor, and false-positive results that limit the use of nucleic acid amplification tests (NAATs) for testing individual antibody-negative samples, a pooled-sample, group-testing approach has been used. Initially used by blood donor programs in the United States to screen donated blood for acute HIV-1 infection, group testing screens multiple antibody-negative specimens pooled into screening pools [110]. A negative screening pool ends the testing protocol; in the event of a positive NAAT result, the pool

is deconstructed and either smaller pools or individual blood samples are then tested to identify the specimen-source of the positive result [110]. In settings with a low yield of acute infection, most pools are declared negative. This greatly reduces the number of tests used, improving efficiency and making sporadic false-positive results unlikely.

Initial experience with this approach (Table 2) has been extremely promising: during the first year after the incorporation of NAAT screening of pooled HIV antibody–negative samples into a routine public HIV voluntary counseling and testing program in North Carolina, 109,250 patients were screened and 23 cases of acute HIV infection were detected [111]. These cases represented 4% of all HIV cases identified and were captured with an additional cost per test of $3.63 [111]. Only two false-positive HIV NAAT results were reported during this period, because of the use of group testing [111]. Currently, North Carolina and Maryland, jurisdictions of Seattle-King County and Washington DC, and the cities of Atlanta, Los Angeles, and San Francisco have used or are using group testing approaches to screen for acute HIV infection with similar results [106,112–115].

Clinical management

Acute HIV infection is the setting for important individual clinical and public health interventions. It is possible, for instance, that acute HIV infection might represent a unique window of opportunity to change the course of the disease [116]. For patients with particularly severe CD4 lymphopenia in acute HIV infection, or with prolonged or severe acute retroviral symptoms, early treatment might provide short-term clinical improvements. Stopping or decreasing viral replication early in the course of acute HIV infection, however, might theoretically serve many important goals in the management of HIV infection: if instituted very early, such treatment might limit the establishment of latent reservoirs [82,116]. By preventing infection of HIV-specific CD4 cells and allowing virus clearance, antiretroviral therapy might also protect the developing host immune response, reduce immune activation, and limit the HIV diversification that emerges toward the end of acute HIV infection as a consequence of sustained viral replication.

There is some preliminary evidence to suggest that emergent treatment can provide such benefits. To study the effect of early antiretroviral therapy on the course of HIV infection, 77 patients presenting with acute retroviral syndrome (mean time from the onset of symptoms was 25 days) were enrolled in a seminal multicenter, double-blind trial to receive zidovudine or placebo for 6 months. During a mean follow-up period of 15 months, the group of patients that received zidovudine showed lower incidence of opportunistic infection and greater increase of CD4 [117]. These results were reproduced by a similar controlled trial of 28 patients with acute HIV infection randomized to receive zidovudine or placebo for 6 months [118].

Table 2
Nucleic acid amplification testing in publicly funded federal, state, county, and city HIV testing programs in the United States

	Blood Donor Program			California					
	All	Red Cross Only	North Carolina	Los Angeles	San Francisco	Seattle King County	Maryland	Atlanta	Washington DC
Population description	98% of US blood donations	All American Red Cross donations	All voluntary counseling and testing clients, all 110 publicly funded sites in North Carolina	All men seeking HIV testing at three STD clinics in Los Angeles	All persons seeking HIV testing at San Francisco municipal STD clinic	All MSM seeking HIV testing through Seattle-King County public health facilities	All persons seeking HIV testing at publicly funded sites in Maryland (not Baltimore)	All persons seeking HIV testing at the municipal STD clinic, community testing site, or drug treatment clinic	All consenting persons seeking HIV testing at a municipal STD clinic
HIV prevalence per 1000	0.01554	0.01554	2.13	4.47	17.52	16.4	5.34	3.0	4.1
Year on initiation	1999	1999	2002	2003	2003	2003	2004	2004	2004
Pooling strategy	16:1	16:1 128:1	90:10:1	90:10:1	50:10:1 10:1	30:10:1	20:1	48:8:1	20:1
Subjects tested (N)	37,164,054	13,200,000	109,250	1712	3075	3525	NA	2212	1553
EIA-positive (%)[a]	NA	NA	583 (0.5)	14 (0.8)	105 (3.4)	81 (2.3)	534 (NA)	66 (2.9)	64 (4.1)

NAAT-positive (%)[a]	12 (3×10^{-5})	6 (5×10^{-5})	23 (0.02)	1 (0.58)	11 (0.36)	7 (0.2)	0 (NA)	4 (0.18)	6 (0.39)
Increase in diagnostic yield from adding NAAT (%)	NA	NA	4	7.1	10.5	6.2	0	5	10
Indications of cost or cost-effectiveness	$1.5 to $4.3 million per QALY	$1.5 to $4.3 million per QALY	$3.63 per HIV-1 Ab (-) specimen (equipment, kits, labor and admin), $3935 per QALY [171]	NA	$12.78 per specimen, $2314 per case	NA	$0.81 per specimen (test kit only)	NA	$2350 per case

Abbreviations: MSM, men who have sex with men; NAAT, nucleic acid amplification testing; QALY; quality-adjusted life year; STD, sexually transmitted disease.

[a] Percent positive out of the total population tested.

Higher CD4 cell counts were found in the treatment arm 1 year after starting therapy [118]. Although the results of these studies were encouraging, none of these studies showed a significant viral load reduction and long-term follow-up failed to decrease progression to AIDS [117–119].

Multiple reports of significant improvement of virologic and immunologic markers associated with early therapy followed these two trials. Stronger HIV-specific and sustained T-cell responses, decreased frequency of opportunistic infections, and reduced progression to AIDS were documented among acutely infected persons treated with antiviral therapy when compared with untreated patients [59,72,120–124]. The viremic control achieved by antiretroviral treatment before seroconversion was also found to be associated with a more narrow cytotoxic T-cell response and a less diverse virus population [125]. Furthermore, HIV-specific cytotoxic T-cell responses seem to be preserved in patients experiencing HIV antibody seroreversion after initiation of antiretroviral therapy during early HIV infection [126].

Initiation of continuous antiretroviral treatment during acute HIV infection

The goal of initiating continuous treatment in acute HIV infection is broadly to halt the natural evolution of HIV infection and clear HIV (with all its immunosuppressive and oncogenic potential) from tissues, allowing optimal restoration and preservation of overall immune system function. In a prospective cohort of 102 patients treated during acute and early HIV infection, Kassutto and colleagues [126] analyzed the potential long-term benefits of early treatment with regard to virologic suppression and absolute $CD4^+$ cell count. The cohort was divided into patients receiving treatment before seroconversion and within the first year after seroconversion. Most patients achieved sustained virologic suppression within the first 3 months of treatment that lasted at 18 months of follow-up. The mean nadir $CD4^+$ cell count of 422 cells/mm^3 increased to 702 cells/mm^3 at the end of the first year and continued to increase over 60 months in patients who continued therapy. This gain in the $CD4^+$ cell count was significantly higher when compared with untreated historical controls. Preseroconversion and postseroconversion groups had similar virologic and immunologic outcomes. Half of the patients discontinued at least one drug secondary to side effects [124]. In this and other studies of highly active antiretroviral therapy (HAART) in acute HIV infection, rates of reported antiretroviral toxicity have been generally similar to those in chronically infected patients treated with similar regimens. Acquired resistance from continuous antiretroviral therapy initiated in acute HIV infection is rare.

Most current treatment guidelines emphasize that in early chronic infection, the potential benefits of early therapy must be carefully balanced with the adverse reactions, metabolic effects, and potential unknown long-term toxicities; potential for drug resistance; high cost; and adherence issues

inherent to antiretroviral treatment [82,116]. As the guidelines themselves acknowledge, acute HIV infection may represent a special case [127]. The long-term costs and benefits of continuous therapy in acute HIV infection have not been well studied. Moreover, many clinicians who choose to use continuous therapy in acute HIV infection view such treatment as a placeholder: freezing virus populations and the immune response at their earliest state of development is seen as a way of preserving future options, in the event that emerging strategies emerge to permit eradication or prolonged viral control following treatment discontinuation [116].

Experience with short-course or discontinuous antiretroviral therapy

Attempts to discontinue therapy following treatment of acute HIV infection have met with mixed results. Hecht and colleagues [128] compared patients initiating HAART within 2 weeks of HIV seroconversion (13 patients) and patients initiating therapy between 2 weeks and 6 months after seroconversion (45 patients) with untreated patients (337 patients). The decision to start therapy was left to the patients and only patients receiving HAART for at least 12 weeks were included in the analysis. Six months after discontinuation of therapy, significant CD4 cell count and viral load benefits were found among patients receiving therapy. Long-term benefits (18 months after discontinuation of therapy) persisted in a subgroup that had started therapy within 2 weeks of seroconversion. Viral rebound occurred in most patients after discontinuation of therapy [129]. In a contrasting report, however, Streeck and colleagues [129] found no major short-term benefit among 20 patients offered a 24-week course of HAART while experiencing acute retroviral syndrome. Although the 12 patients receiving therapy showed significant CD4 response, suppression of viremia, and enhanced differentiation of HIV-specific CD8 T cells from effector memory to effector cells by the end of therapy, no differences in viremia or in the $CD4^+$ T cell count were found 6 months after HAART was stopped [129].

It has been hypothesized that the relative preservation of the integrity of the immune system in patients receiving early treatment might allow the establishment of a stronger HIV-specific response that will enable viremic suppression even after antiretrovirals are discontinued [71]. Earlier in the course of the epidemic, the initial trials with zidovudine monotherapy showed the potential of structured interrupted therapy [118,119]. More recently, in a small study of treatment interruption after a variable duration of HAART started during acute HIV infection, three of eight patients achieved relative short-term viremic control (<5000 copies/mL) after the first interruption and three others after the second one despite an initial viremic rebound [71]. All patients showed increased and maintained virus-specific cytotoxic T-cell response by the end of the follow-up period (median, 6.5 months) [130,131]. These results were not reproduced in two other studies in which viral suppression after discontinuation of therapy was not different than in untreated patients [130,131].

Antiretrovirals were started later in the course of the disease, however, of the patients enrolled in these two studies [132]. Similarly, the results of a recent small prospective trial failed to prove the benefit of structured treatment interruption [132]. In this study, patients detected during symptomatic primary HIV infection were started on HAART for 34 weeks. After achieving viral suppression (<50 copies/mL), HAART was interrupted for 2, 4, and 8 weeks separated by 12 weeks on treatment, and then permanently stopped at week 84. Six months following HAART discontinuation, 7 of 26 met the study-defined measure of success, with viral loads less than 1000 copies/mL [128].

Taken together, these data suggest that treatment of acute HIV could augment host immunity, potentially obviating or delaying the need for lifelong continuous antiretroviral therapy. The long-term risks versus benefits, however, of continuous antiretroviral therapy in acute HIV infection are not well understood [116]. The role of discontinuous therapy in acute HIV infection, or of other treatment strategies using immunomodulatory drugs, eradication agents, or therapeutic vaccines, is not yet defined and awaits the completion of large, randomized clinical trials [116,133–135].

There is a strong basis for believing early antiretroviral therapy might benefit acutely HIV-infected patients. There is also strong theoretical or preliminary evidence supporting use of less conventional approaches: corticosteroids, cyclosporine A, interleukin-2, and hydroxyurea have all been incorporated in previous acute treatment studies. As long as effective treatment strategies are unproved and under active investigation, current United States Public Health Service, Centers for Disease Control and Prevention (USPHS) guidelines (urging consideration for initiation of antiretroviral therapy in patients with less than 6 months of HIV infection, preferably in the context of research studies) are appropriate and urgent research and specialty referral is indicated for all cases of acute HIV infection.

Suggested first steps in the clinical management of suspected acute HIV infection are summarized in Box 1.

Early antiretroviral therapy: special considerations

Interpreting HIV RNA viral load and CD4 cell count

The prognostic value of viral load or CD4 cell count measurements before the establishment of viral set point is highly questionable. An unusually low CD4 cell count (eg, <350 cells/mm^3) might favor treatment in acute HIV infection (and a CD4 cell count <200 cells/mm^3 should merit temporary antibiotic prophylaxis). The acute viral load is very dynamic, however, and has no accepted prognostic value.

Severity of symptoms

One commonly accepted indication for early initiation of antiretroviral therapy is a severe symptomatic acute retroviral syndrome. In this setting, therapy is oriented to decrease the duration and severity of the symptoms.

Noting that the severity and duration of the acute retroviral syndrome correlate with a higher viral load peak, higher subsequent viral set point, and more rapid disease progression, some experts further argue that symptomatic patients might benefit the most from early antiretroviral therapy [88,136–138]. This remains speculative, however, and no duration of treatment has yet been defined for this indication.

Timing of therapy

Given that important events affecting the natural history of HIV disease start within the first few days after infection, the rapidity with which antiretroviral therapy is started during acute infection might affect its impact. Animal and human studies have suggested that early initiation of antiretroviral therapy can significantly limit the size of the initial latent pool and even prevent the establishment of HIV infection [139–143]. Similarly, antiretroviral treatment started after simian immunodeficiency virus inoculation in rhesus macaques prevents many of the events associated with acute infection, including $CD4^+$ T-cell depletion from the intestinal mucosa [143]. Many experts believe that very early treatment might positively interfere with the initial events that determine the future course of the disease, decreasing viral diversity and viral reservoirs [116]; and that the potential effects of antiretroviral therapy on immune function are likely to be greatest if introduced in the first 8 weeks of infection, when first potent responses are developing. Unfortunately, most studies looking into the benefits of early antiretroviral treatment have combined patients starting therapy before and after seroconversion [119,120,130,131,144–146]. Most of these trials support early initiation of therapy, but the window of opportunity is not clearly defined. Most experts do agree, however, that if HAART is to be considered in acute HIV infection, it should be started immediately at, or as soon as possible after, the diagnosis. This is different from standard practice in chronic HIV infection, where many return visits are usually required before initiation of therapy.

Selection of the initial regimen

Although differences in the potency of antiretroviral regimens might affect short- and long-term outcomes, the ideal regimen has not been defined. The available data suggest that even monotherapy can result in immunologic and virologic benefit. Generally speaking, any of the regimens recommended for treatment of established HIV infection are appropriate for acute HIV infection. Special attention should be paid to the possibility of transmitted (primary) drug-resistant HIV. For instance, the high prevalence of transmitted resistance to non-nucleoside reverse transcriptase inhibitor (NNRTI) drugs favors protease inhibitor (PI)-based regimens, or even four-drug regimens, for initial therapy of acute HIV in some locations [147,148].

Box 1. Approach to the patient with suspected acute HIV infection

Counseling
Before testing is performed
- Emphasize behavior change and risk reduction
- Discuss the limitations of the test (false-positive and false-negative results)
- Discuss the preliminary status of any preliminary (eg, rapid antibody testing) results
- Obtain or confirm contact information and arrange follow-up

After the results become available
- *For patient with negative results*
  - Consider retesting in 2 to 4 weeks if screened for risk exposure only
  - Counsel as uninfected if screened for acute retroviral symptoms and HIV NAAT result is negative
- *For patients with positive results*
  - Patients with positive rapid tests should be told that they have a possible or likely HIV infection, but that results need confirmation. Discuss the possibility of false-positive results (particularly in low-risk patients or those without specific clinical findings)

Additional steps for patients with possible acute HIV infection before confirmation
Collect information on partners that may be at risk of infection themselves (potential sources of infection or those exposed to the index patient during the acute risk interval [eg, those exposed during an 8-week window])
For patients with known HIV-infected partners, collect information on the partner's antiretroviral treatment and resistance patterns
Encourage contacting partners regarding the need for testing and evaluation
Immediate public health referral
Supplemental testing
Discuss treatment

Initial tests recommended for possible HIV-infected patients
- CD4 count
- HIV genotype

Confirmatory HIV testing including quantitative HIV RNA viral load and antibody testing (pooled RNA testing not recommended)

Treatment

Discuss treatment options with all patients with possible acute HIV infection; do not wait for confirmation of status

If at all possible, referral to a research center

Patients with highest likelihood to benefit from treatment include patients with severe or unremitting symptoms of acute HIV infection or with CD4 <350 cells/mm^3

Consider *Pneumocystis jiroveci* (*P carinii*) prophylaxis for patients with initial CD4 <200 cells/mm^3

Primary HIV resistance

Establishing whether there is primary HIV antiretroviral resistance is a critical point in the management of acute HIV infection, and should be addressed as part of the initial patient assessment. The patient with suspected acute HIV should be asked about possible antiretroviral drug usage by any sexual partners, and concerted attempts should be made to ascertain specific drugs if source patients are readily identified. Primary resistance is highly prevalent [147–150]. Examining 227 patients diagnosed with acute and recent HIV infection in North Carolina, Frost and colleagues [149] identified 25 (11%) that had primary drug resistance or exhibited revertant mutations at position 215 in reverse transcriptase. In a study of 136 newly identified HIV patients (including 11 acute and 44 recent infections), Truong and colleagues [147] found primary antiretroviral resistance in 13.2% of patients, of which 65% was NNRTI resistance. Currently, most guidelines recommend genotype testing before the initiation of therapy. In the case of acute HIV infection, however, genotyping should not delay the initiation of therapy. Instead, genotype testing results should be used to adjust the antiretroviral regimen when they become available.

Psychologic assessment

Acute HIV infection is often a marker of chaotic events in patients' lives, and depression, bipolar illness, and other major psychiatric diagnoses are common among patients diagnosed with HIV [151–153]. Moreover, the diagnosis of acute HIV itself can be extremely distressing [154]. In addition to the distress of being told they have HIV infection, patients diagnosed with acute infection are often confused by contradictory test results. The need for urgent treatment or public health interventions can also create real or perceived threats to the patient's privacy and to their relationships

[154,155]. For these reasons, psychologic assessment is a critical part of the initial evaluation and a team approach including social workers or psychologists experienced in HIV counseling is highly recommended [155,156]. Given the current uncertainty regarding the benefits of initiating antiretroviral therapy in acute HIV infection, urgent initiation of therapy may be contraindicated by serious mental illness given the important links between such mental illness, nonadherence to antiretroviral therapy, and drug resistance.

Public health management

It has long been hypothesized that acute HIV infection, characterized by high viremia, was likely a period of high transmission potential [157]. Indeed, a number of lines of epidemiologic evidence have converged to support this contention [29,158–163]. Supporting the hypothesis that acutely infected individuals are biologically hypercontagious, Wawer and colleagues [162] examined 235 retrospectively identified monogamous, HIV-discordant couples in a Ugandan cohort. Percoital act transmission rates were approximately 10-fold higher than among couples during the index partner's first 5 months of infection than among couples in which the index partner had longer-term infection, controlling for other important covariates. Among HIV-susceptible partners having sex with recent seroconverters, 43% went on to be infected. Such high rates of infection seem to be explained by greatly increased HIV shedding in genital secretions [29,31,164]. Critically, however, the period of acute shedding is over by 10 weeks postinfection, emphasizing the need for extreme urgency in public health interventions for acute HIV infection.

Mathematical models have emphasized the importance of acute HIV infection in spreading and maintaining HIV epidemics [160,161,165], caused by both elevated infectiousness [29,31] and increased risk behavior among patients with acute HIV infection [160,165,166]. In theory, the identification and counseling (or even treatment) of acutely HIV-infected patients and their partners have the potential to stop outbreaks and control or reduce the spread of the HIV. Because acute HIV infections are so contagious and are detected so close to the actual HIV transmission event, acute case detection makes it possible actively to intervene in risk networks [167].

Focusing outbreak control efforts on the most contagious or recent cases is a model used with great success in both syphilis and tuberculosis control programs. The most dramatic example of such acute HIV-based outbreak control comes from a recent outbreak of HIV in the heterosexual adult film industry [168]. In April 2004, a performer was identified with acute HIV infection through HIV RNA testing, which resulted in 1-month voluntary industry quarantine while other performers were tested. As a result of case management, three additional acute HIV infections were identified. Twenty-three percent (3 of 13) of the index person's sexual contacts in the

30 days before his positive test became infected (he had had a negative HIV RNA test 23 day before his positive test.) [168]. Because of the rapid response by the local health department and industry compliance with the quarantine, further transmission related to these 2004 cases was completely halted.

Because of the clear danger for ongoing HIV transmission (by the acute case or by their source partner) in acute patients' risk networks, public health measures have a very important, even central place in the early management of acute HIV infection. HIV risk reduction counseling should be part of the initial assessment in all patients with suspected acute HIV infection, and should not be delayed until a diagnosis is confirmed (losing a potentially critical prevention opportunity). As part of this counseling, patients need to be informed directly and clearly about the infectious potential of acute HIV infection, and counseled regarding abstention and condom use. Patient-centered, individualized risk reduction counseling has been shown to be highly effective at reducing HIV risk behavior when delivered as part of a brief intervention to patients with HIV [155,169].

Acute patients' partners should be considered to be at real risk of either transmitting the viruses, or of becoming infected themselves. Patients should be encouraged to refer partners for counseling and testing and should be referred promptly to available public health prevention and surveillance programs. Where available, some programs can actively assist with confidential partner notification. In the first 2 years of public acute HIV testing in North Carolina, specialists in disease intervention notified and counseled 41 of 43 acute cases within 72 hours; they were able successfully to interview 102 (78%) of 130 high-risk, named sex partners, of whom 39% proved to be HIV positive. Similar to experience in Uganda and in the Los Angeles outbreak, seroconversion was noted in 6 of the 12 recently HIV-negative partners in this group who were clearly exposed to acute HIV infection.

Together with evidence suggesting cost-effectiveness of pooled HIV NAAT screening (see Table 2) [170], and considering current revisions to United States guidelines for voluntary HIV counseling and testing that encourage much more frequent, routine HIV testing in virtually all health care settings, the North Carolina experience suggests that similar interventions could be effective at the population level. Taking the experience of existing small state or regional programs to scale is among the major challenges in HIV prevention with the potential to decrease the spread of HIV.

Summary

The complex, initial interactions between the virus and the immune system are important in determining the future course of HIV disease and, in large part, the likelihood of onward sexual transmission of HIV. Compelling evidence suggests the potential impact of early interventions at both patient and population level. Until recently, however, difficulty identifying patients

with acute HIV infection has interfered with the development of therapeutic and public health interventions specific for this group of patients. New advances in HIV diagnostic technologies and population-based serosurveillance methods have overcome previous barriers in the detection of acute HIV patients, creating exciting research, clinical, and public health opportunities. Many experts believe it is likely that new vaccines and potentially curative interventions will come from better understanding of the early events in HIV infection [167,171,172]. For acutely infected patients themselves, it may now be possible formally to evaluate the many therapeutic strategies proposed for acute HIV infection in randomized trials. The increased identification of acute infection has provided clear impetus to develop network interventions and other public heath strategies to control HIV outbreaks and improve disease surveillance.

References

[1] Miller CJ, Li Q, Abel K, et al. Propagation and dissemination of infection after vaginal transmission of simian immunodeficiency virus. J Virol 2005;79(14):9217–27.
[2] Cole AM. Innate host defense of human vaginal and cervical mucosae. Curr Top Microbiol Immunol 2006;306:199–230.
[3] Pope M, Haase AT. Transmission, acute HIV-1 infection and the quest for strategies to prevent infection. Nat Med 2003;9(7):847–52.
[4] Fleming DT, Wasserheit JN. From epidemiological synergy to public health policy and practice: the contribution of other sexually transmitted diseases to sexual transmission of HIV infection. Sex Transm Infect 1999;75(1):3–17.
[5] Royce RA, Sena A, Cates W Jr, et al. Sexual transmission of HIV. N Engl J Med 1997; 336(15):1072–8.
[6] Haase AT. Perils at mucosal front lines for HIV and SIV and their hosts. Nat Rev Immunol 2005;5(10):783–92.
[7] Doms RW. Chemokine receptors and HIV entry. AIDS 2001;15(Suppl 1):S34–5.
[8] McNearney T, Hornickova Z, Kloster B, et al. Evolution of sequence divergence among human immunodeficiency virus type 1 isolates derived from a blood donor and a recipient. Pediatr Res 1993;33(1):36–42.
[9] Roos MT, Lange JM, de Goede RE, et al. Viral phenotype and immune response in primary human immunodeficiency virus type 1 infection. J Infect Dis 1992;165(3):427–32.
[10] Zhang LQ, MacKenzie P, Cleland A, et al. Selection for specific sequences in the external envelope protein of human immunodeficiency virus type 1 upon primary infection. J Virol 1993;67(6):3345–56.
[11] Amedee AM, Lacour N, Gierman JL, et al. Genotypic selection of simian immunodeficiency virus in macaque infants infected transplacentally. J Virol 1995;69(12):7982–90.
[12] Wolinsky SM, Korber BT, Neumann AU, et al. Adaptive evolution of human immunodeficiency virus-type 1 during the natural course of infection. Science 1996;272(5261):537–42.
[13] Delwart E, Magierowska M, Royz M, et al. Homogeneous quasispecies in 16 out of 17 individuals during very early HIV-1 primary infection. AIDS 2002;16(2):189–95.
[14] Veazey RS, Mansfield KG, Tham IC, et al. Dynamics of CCR5 expression by CD4(+) T cells in lymphoid tissues during simian immunodeficiency virus infection. J Virol 2000; 74(23):11001–7.
[15] Pandrea I, Apetrei C, Gordon SN, et al. Paucity of CD4+CCR5+ T cells is a typical feature of natural SIV hosts. Blood 2007;109(3):1069–76.

[16] Locher CP, Witt SA, Kassel R, et al. Differential effects of R5 and X4 human immunodeficiency virus type 1 infection on CD4+ cell proliferation and activation. J Gen Virol 2005; 86(Pt 4):1171–9.
[17] Veazey R, Lackner A. The mucosal immune system and HIV-1 infection. AIDS Rev 2003; 5(4):245–52.
[18] Picker LJ. Immunopathogenesis of acute AIDS virus infection. Curr Opin Immunol 2006; 18(4):399–405.
[19] Zhang Z, Schuler T, Zupancic M, et al. Sexual transmission and propagation of SIV and HIV in resting and activated CD4+ T cells. Science 1999;286(5443):1353–7.
[20] Li Q, Duan L, Estes JD, et al. Peak SIV replication in resting memory CD4+ T cells depletes gut lamina propria CD4+ T cells. Nature 2005;434(7037):1148–52.
[21] Daar ES, Little S, Pitt J, et al. Diagnosis of primary HIV-1 infection. Los Angeles County Primary HIV Infection Recruitment Network. Ann Intern Med 2001;134(1):25–9.
[22] Picker LJ, Hagen SI, Lum R, et al. Insufficient production and tissue delivery of CD4+ memory T cells in rapidly progressive simian immunodeficiency virus infection. J Exp Med 2004;200(10):1299–314.
[23] Mattapallil JJ, Douek DC, Hill B, et al. Massive infection and loss of memory CD4+ T cells in multiple tissues during acute SIV infection. Nature 2005;434(7037):1093–7.
[24] Brenchley JM, Schacker TW, Ruff LE, et al. CD4+ T cell depletion during all stages of HIV disease occurs predominantly in the gastrointestinal tract. J Exp Med 2004;200(6):749–59.
[25] Mehandru S, Poles MA, Tenner-Racz K, et al. Primary HIV-1 infection is associated with preferential depletion of CD4+ T lymphocytes from effector sites in the gastrointestinal tract. J Exp Med 2004;200(6):761–70.
[26] Veazey RS, Marx PA, Lackner AA. Vaginal CD4+ T cells express high levels of CCR5 and are rapidly depleted in simian immunodeficiency virus infection. J Infect Dis 2003;187(5): 769–76.
[27] Pilcher CD, Shugars DC, Fiscus SA, et al. HIV in body fluids during primary HIV infection: implications for pathogenesis, treatment and public health. AIDS 2001;15(7):837–45.
[28] Fiebig EW, Wright DJ, Rawal BD, et al. Dynamics of HIV viremia and antibody seroconversion in plasma donors: implications for diagnosis and staging of primary HIV infection. AIDS 2003;17(13):1871–9.
[29] Pilcher CD, Tien HC, Eron JJ Jr, et al. Brief but efficient: acute HIV infection and the sexual transmission of HIV. J Infect Dis 2004;189(10):1785–92.
[30] Fiscus SA, Pilcher CD, Miller W, et al. Real-time detection of patients with acute HIV infection in Africa. Presented at the 12th Conference on Retroviruses and Opportunistic Infections. Boston, February 22–25, 2005.
[31] Stekler J, Sycks B, Holte S, et al. Semen HIV dynamics and effect of ART following primary HIV infection. Presented at the 13th Conference on Retroviruses and Opportunistic Infections. Denver, Colorado, February 5–8, 2006.
[32] Spira AI, Marx PA, Patterson BK, et al. Cellular targets of infection and route of viral dissemination after an intravaginal inoculation of simian immunodeficiency virus into rhesus macaques. J Exp Med 1996;183(1):215–25.
[33] Bogers WM, Koornstra WH, Dubbes RH, et al. Characteristics of primary infection of a European human immunodeficiency virus type 1 clade B isolate in chimpanzees. J Gen Virol 1998;79(Pt 12):2895–903.
[34] Little SJ, McLean AR, Spina CA, et al. Viral dynamics of acute HIV-1 infection. J Exp Med 1999;190(6):841–50.
[35] Lindback S, Karlsson AC, Mittler J, et al. Viral dynamics in primary HIV-1 infection. Karolinska Institutet Primary HIV Infection Study Group. AIDS 2000;14(15):2283–91.
[36] Stafford MA, Corey L, Cao Y, et al. Modeling plasma virus concentration during primary HIV infection. J Theor Biol 2000;203(3):285–301.
[37] Finzi D, Hermankova M, Pierson T, et al. Identification of a reservoir for HIV-1 in patients on highly active antiretroviral therapy. Science 1997;278(5341):1295–300.

[38] Smith BA, Gartner S, Liu Y, et al. Persistence of infectious HIV on follicular dendritic cells. J Immunol 2001;166(1):690–6.
[39] Zhang L, Ramratnam B, Tenner-Racz K, et al. Quantifying residual HIV-1 replication in patients receiving combination antiretroviral therapy. N Engl J Med 1999;340(21): 1605–13.
[40] Furtado MR, Callaway DS, Phair JP, et al. Persistence of HIV-1 transcription in peripheral-blood mononuclear cells in patients receiving potent antiretroviral therapy. N Engl J Med 1999;340(21):1614–22.
[41] Weber J, Piontkivska H, Quinones-Mateu ME. HIV type 1 tropism and inhibitors of viral entry: clinical implications. AIDS Rev 2006;8(2):60–77.
[42] Brenchley JM, Price DA, Douek DC. HIV disease: fallout from a mucosal catastrophe? Nat Immun 2006;7(3):235–9.
[43] Kornfeld C, Ploquin MJ, Pandrea I, et al. Antiinflammatory profiles during primary SIV infection in African green monkeys are associated with protection against AIDS. J Clin Invest 2005;115(4):1082–91.
[44] Deeks SG, Kitchen CM, Liu L, et al. Immune activation set point during early HIV infection predicts subsequent CD4+ T-cell changes independent of viral load. Blood 2004; 104(4):942–7.
[45] Rybarczyk BJ, Montefiori D, Johnson PR, et al. Correlation between env V1/V2 region diversification and neutralizing antibodies during primary infection by simian immunodeficiency virus sm in rhesus macaques. J Virol 2004;78(7):3561–71.
[46] Henrard DR, Daar E, Farzadegan H, et al. Virologic and immunologic characterization of symptomatic and asymptomatic primary HIV-1 infection. J Acquir Immune Defic Syndr Hum Retrovirol 1995;9(3):305–10.
[47] Pilgrim AK, Pantaleo G, Cohen OJ, et al. Neutralizing antibody responses to human immunodeficiency virus type 1 in primary infection and long-term-nonprogressive infection. J Infect Dis 1997;176(4):924–32.
[48] Wei X, Decker JM, Wang S, et al. Antibody neutralization and escape by HIV-1. Nature 2003;422(6929):307–12.
[49] Pellegrin I, Legrand E, Neau D, et al. Kinetics of appearance of neutralizing antibodies in 12 patients with primary or recent HIV-1 infection and relationship with plasma and cellular viral loads. J Acquir Immune Defic Syndr Hum Retrovirol 1996;11(5):438–47.
[50] Pullium JK, Adams DR, Jackson E, et al. Pig-tailed macaques infected with human immunodeficiency virus (HIV) type 2GB122 or simian/HIV89.6p express virus in semen during primary infection: new model for genital tract shedding and transmission. J Infect Dis 2001;183(7):1023–30.
[51] Mattapallil JJ, Letvin NL, Roederer M. T-cell dynamics during acute SIV infection. AIDS 2004;18(1):13–23.
[52] Borrow P, Lewicki H, Wei X, et al. Antiviral pressure exerted by HIV-1-specific cytotoxic T lymphocytes (CTLs) during primary infection demonstrated by rapid selection of CTL escape virus. Nat Med 1997;3(2):205–11.
[53] Letvin NL, Walker BD. Immunopathogenesis and immunotherapy in AIDS virus infections. Nat Med 2003;9(7):861–6.
[54] Schmitz JE, Kuroda MJ, Santra S, et al. Control of viremia in simian immunodeficiency virus infection by CD8+ lymphocytes. Science 1999;283(5403):857–60.
[55] Koup RA, Safrit JT, Cao Y, et al. Temporal association of cellular immune responses with the initial control of viremia in primary human immunodeficiency virus type 1 syndrome. J Virol 1994;68(7):4650–5.
[56] Goulder PJ, Brander C, Tang Y, et al. Evolution and transmission of stable CTL escape mutations in HIV infection. Nature 2001;412(6844):334–8.
[57] Yu XG, Addo MM, Rosenberg ES, et al. Consistent patterns in the development and immunodominance of human immunodeficiency virus type 1 (HIV-1)-specific CD8+ T-cell responses following acute HIV-1 infection. J Virol 2002;76(17):8690–701.

[58] Goulder PJ, Altfeld MA, Rosenberg ES, et al. Substantial differences in specificity of HIV-specific cytotoxic T cells in acute and chronic HIV infection. J Exp Med 2001;193(2): 181–94.
[59] Malhotra U, Berrey MM, Huang Y, et al. Effect of combination antiretroviral therapy on T-cell immunity in acute human immunodeficiency virus type 1 infection. J Infect Dis 2000; 181(1):121–31.
[60] Richman DD, Wrin T, Little SJ, et al. Rapid evolution of the neutralizing antibody response to HIV type 1 infection. Proc Natl Acad Sci USA 2003;100(7):4144–9.
[61] Frost SD, Wrin T, Smith DM, et al. Neutralizing antibody responses drive the evolution of human immunodeficiency virus type 1 envelope during recent HIV infection. Proc Natl Acad Sci USA 2005;102(51):18514–9.
[62] Srivastava IK, Ulmer JB, Barnett SW. Role of neutralizing antibodies in protective immunity against HIV. Hum Vaccin 2005;1(2):45–60.
[63] Gonzalez E, Kulkarni H, Bolivar H, et al. The influence of CCL3L1 gene-containing segmental duplications on HIV-1/AIDS susceptibility. Science 2005;307(5714):1434–40.
[64] Kaslow RA, Carrington M, Apple R, et al. Influence of combinations of human major histocompatibility complex genes on the course of HIV-1 infection. Nat Med 1996;2(4): 405–11.
[65] Malhotra U, Holte S, Dutta S, et al. Role for HLA class II molecules in HIV-1 suppression and cellular immunity following antiretroviral treatment. J Clin Invest 2001;107(4): 505–17.
[66] Goulder PJ, Pasquier C, Holmes EC, et al. Mother-to-child transmission of HIV infection and CTL escape through HLA-A2-SLYNTVATL epitope sequence variation. Immunol Lett 2001;79(1–2):109–16.
[67] Migueles SA, Sabbaghian MS, Shupert WL, et al. HLA B*5701 is highly associated with restriction of virus replication in a subgroup of HIV-infected long term nonprogressors. Proc Natl Acad Sci USA 2000;97(6):2709–14.
[68] Connick E, Marr DG, Zhang XQ, et al. HIV-specific cellular and humoral immune responses in primary HIV infection. AIDS Res Hum Retroviruses 1996;12(12):1129–40.
[69] Mellors JW, Kingsley LA, Rinaldo CR Jr, et al. Quantitation of HIV-1 RNA in plasma predicts outcome after seroconversion. Ann Intern Med 1995;122(8):573–9.
[70] Gao X, Nelson GW, Karacki P, et al. Effect of a single amino acid change in MHC class I molecules on the rate of progression to AIDS. N Engl J Med 2001;344(22):1668–75.
[71] Rosenberg ES, Altfeld M, Poon SH, et al. Immune control of HIV-1 after early treatment of acute infection. Nature 2000;407(6803):523–6.
[72] Rosenberg ES, Billingsley JM, Caliendo AM, et al. Vigorous HIV-1-specific CD4+ T cell responses associated with control of viremia. Science 1997;278(5342):1447–50.
[73] Pitcher CJ, Quittner C, Peterson DM, et al. HIV-1-specific CD4+ T cells are detectable in most individuals with active HIV-1 infection, but decline with prolonged viral suppression. Nat Med 1999;5(5):518–25.
[74] Kalams SA, Buchbinder SP, Rosenberg ES, et al. Association between virus-specific cytotoxic T-lymphocyte and helper responses in human immunodeficiency virus type 1 infection. J Virol 1999;73(8):6715–20.
[75] Hecht FM, Busch MP, Rawal B, et al. Use of laboratory tests and clinical symptoms for identification of primary HIV infection. AIDS 2002;16(8):1119–29.
[76] Celum CL, Buchbinder SP, Donnell D, et al. Early human immunodeficiency virus (HIV) infection in the HIV Network for Prevention Trials Vaccine Preparedness Cohort: risk behaviors, symptoms, and early plasma and genital tract virus load. J Infect Dis 2001;183(1): 23–35.
[77] Schacker T, Collier AC, Hughes J, et al. Clinical and epidemiologic features of primary HIV infection. Ann Intern Med 1996;125(4):257–64.
[78] Bollinger RC, Brookmeyer RS, Mehendale SM, et al. Risk factors and clinical presentation of acute primary HIV infection in India. JAMA 1997;278(23):2085–9.

[79] Lavreys L, Thompson ML, Martin HL Jr, et al. Primary human immunodeficiency virus type 1 infection: clinical manifestations among women in Mombasa, Kenya. Clin Infect Dis 2000;30(3):486–90.
[80] Kinloch-de Loes S, de Saussure P, Saurat JH, et al. Symptomatic primary infection due to human immunodeficiency virus type 1: review of 31 cases. Clin Infect Dis 1993;17(1):59–65.
[81] Tindall B, Barker S, Donovan B, et al. Characterization of the acute clinical illness associated with human immunodeficiency virus infection. Arch Intern Med 1988;148(4):945–9.
[82] Kassutto S, Rosenberg ES. Primary HIV type 1 infection. Clin Infect Dis 2004;38(10): 1447–53.
[83] Kahn JO, Walker BD. Acute human immunodeficiency virus type 1 infection. N Engl J Med 1998;339(1):33–9.
[84] Borrow P, Lewicki H, Hahn BH, et al. Virus-specific CD8+ cytotoxic T-lymphocyte activity associated with control of viremia in primary human immunodeficiency virus type 1 infection. J Virol 1994;68(9):6103–10.
[85] Douek DC. Disrupting T-cell homeostasis: how HIV-1 infection causes disease. AIDS Rev 2003;5(3):172–7.
[86] Zaunders JJ, Moutouh-de Parseval L, Kitada S, et al. Polyclonal proliferation and apoptosis of CCR5+ T lymphocytes during primary human immunodeficiency virus type 1 infection: regulation by interleukin (IL)-2, IL-15, and Bcl-2. J Infect Dis 2003;187(11): 1735–47.
[87] Zaunders JJ, Kaufmann GR, Cunningham PH, et al. Increased turnover of CCR5+ and redistribution of CCR5- CD4 T lymphocytes during primary human immunodeficiency virus type 1 infection. J Infect Dis 2001;183(5):736–43.
[88] Lindback S, Brostrom C, Karlsson A, et al. Does symptomatic primary HIV-1 infection accelerate progression to CDC stage IV disease, CD4 count below 200 x 10(6)/l, AIDS, and death from AIDS? BMJ 1994;309(6968):1535–7.
[89] Chan DJ. Fatal attraction: sex, sexually transmitted infections and HIV-1. Int J STD AIDS 2006;17(10):643–51.
[90] Osmond DH, Page K, Wiley J, et al. HIV infection in homosexual and bisexual men 18 to 29 years of age: the San Francisco Young Men's Health Study. Am J Public Health 1994; 84(12):1933–7.
[91] Kim AA, Kent CK, Klausner JD. Increased risk of HIV and sexually transmitted disease transmission among gay or bisexual men who use Viagra, San Francisco 2000–2001. AIDS 2002;16(10):1425–8.
[92] Buchacz K, McFarland W, Kellogg TA, et al. Amphetamine use is associated with increased HIV incidence among men who have sex with men in San Francisco. AIDS 2005; 19(13):1423–4.
[93] Reynolds SJ, Quinn TC. Developments in STD/HIV interactions: the intertwining epidemics of HIV and HSV-2. Infect Dis Clin North Am 2005;19(2):415–25.
[94] Gray RH, Li X, Kigozi G, et al. Increased risk of incident HIV during pregnancy in Rakai, Uganda: a prospective study. Lancet 2005;366(9492):1182–8.
[95] Quinn TC. Circumcision and HIV transmission. Curr Opin Infect Dis 2007;20(1):33–8.
[96] Drain PK, Halperin DT, Hughes JP, et al. Male circumcision, religion, and infectious diseases: an ecologic analysis of 118 developing countries. BMC Infect Dis 2006;6(1):172.
[97] Rosen RC, Catania JA, Ehrhardt AA, et al. The Bolger conference on PDE-5 inhibition and HIV risk: implications for health policy and prevention. J Sex Med 2006;3(6):960–75 [discussion 973–65].
[98] Elder A, Paterson C. Sharps injuries in UK health care: a review of injury rates, viral transmission and potential efficacy of safety devices. Occup Med (Lond) 2006;56(8):566–74.
[99] Moss AR, Vranizan K, Gorter R, et al. HIV seroconversion in intravenous drug users in San Francisco, 1985-1990. AIDS 1994;8(2):223–31.
[100] Sarkar S, Mookerjee P, Roy A, et al. Descriptive epidemiology of intravenous heroin users: a new risk group for transmission of HIV in India. J Infect 1991;23(2):201–7.

[101] Cardo DM, Culver DH, Ciesielski CA, et al. A case-control study of HIV seroconversion in health care workers after percutaneous exposure. Centers for Disease Control and Prevention Needlestick Surveillance Group. N Engl J Med 1997;337(21):1485–90.
[102] Weintrob AC, Giner J, Menezes P, et al. Infrequent diagnosis of primary human immunodeficiency virus infection: missed opportunities in acute care settings. Arch Intern Med 2003;163(17):2097–100.
[103] Rosenberg ES, Caliendo AM, Walker BD. Acute HIV infection among patients tested for mononucleosis. N Engl J Med 1999;340(12):969.
[104] Pincus JM, Crosby SS, Losina E, et al. Acute human immunodeficiency virus infection in patients presenting to an urban urgent care center. Clin Infect Dis 2003;37(12):1699–704.
[105] Fiscus SA, Pilcher CD, Miller WC, et al. Rapid, real-time detection of acute HIV infection in patients in Africa. J Infect Dis 2007;195(3):416–24.
[106] Stekler J, Swenson PD, Wood RW, et al. Targeted screening for primary HIV infection through pooled HIV-RNA testing in men who have sex with men. AIDS 2005;19(12):1323–5.
[107] Schupbach J. Measurement of HIV-1 p24 antigen by signal-amplification-boosted ELISA of heat-denatured plasma is a simple and inexpensive alternative to tests for viral RNA. AIDS Rev 2002;4(2):83–92.
[108] Schupbach J. Viral RNA and p24 antigen as markers of HIV disease and antiretroviral treatment success. Int Arch Allergy Immunol 2003;132(3):196–209.
[109] Pilcher CD, McPherson JT, Leone PA, et al. Real-time, universal screening for acute HIV infection in a routine HIV counseling and testing population. JAMA 2002;288(2):216–21.
[110] Stramer SL, Glynn SA, Kleinman SH, et al. Detection of HIV-1 and HCV infections among antibody-negative blood donors by nucleic acid-amplification testing. N Engl J Med 2004; 351(8):760–8.
[111] Pilcher CD, Fiscus SA, Nguyen TQ, et al. Detection of acute infections during HIV testing in North Carolina. N Engl J Med 2005;352(18):1873–83.
[112] Klausner JD, Grant RM, Kent CK. Detection of acute HIV infections. N Engl J Med 2005; 353(6):631–3 [author reply 631–3].
[113] Quinn TC, Brookmeyer R, Kline R, et al. Feasibility of pooling sera for HIV-1 viral RNA to diagnose acute primary HIV-1 infection and estimate HIV incidence. AIDS 2000;14(17): 2751–7.
[114] Patel P, Klausner JD, Bacon OM, et al. Detection of acute HIV infections in high-risk patients in California. J Acquir Immune Defic Syndr 2006;42(1):75–9.
[115] Priddy FH, Pilcher CD, Moore RH, et al. Detection of Acute HIV Infections in an Urban HIV Counseling and Testing Population in the United States. J Acquir Immune Defic Syndr 2007;44(2):196–202.
[116] Smith DE, Walker BD, Cooper DA, et al. Is antiretroviral treatment of primary HIV infection clinically justified on the basis of current evidence? AIDS 2004;18(5):709–18.
[117] Kinloch-De Loes S, Hirschel BJ, Hoen B, et al. A controlled trial of zidovudine in primary human immunodeficiency virus infection. N Engl J Med 1995;333(7):408–13.
[118] Niu MT, Bethel J, Holodniy M, et al. Zidovudine treatment in patients with primary (acute) human immunodeficiency virus type 1 infection: a randomized, double-blind, placebo-controlled trial. DATRI 002 Study Group. Division of AIDS Treatment Research Initiative. J Infect Dis 1998;178(1):80–91.
[119] Lindback S, Vizzard J, Cooper DA, et al. Long-term prognosis following zidovudine monotherapy in primary human immunodeficiency virus type 1 infection. J Infect Dis 1999; 179(6):1549–52.
[120] Berrey MM, Schacker T, Collier AC, et al. Treatment of primary human immunodeficiency virus type 1 infection with potent antiretroviral therapy reduces frequency of rapid progression to AIDS. J Infect Dis 2001;183(10):1466–75.
[121] Altfeld M, Rosenberg ES, Shankarappa R, et al. Cellular immune responses and viral diversity in individuals treated during acute and early HIV-1 infection. J Exp Med 2001; 193(2):169–80.

[122] Babiker A, Darbyshire J, Pezzotti P, et al. Short-term CD4 cell response after highly active antiretroviral therapy initiated at different times from seroconversion in 1,500 seroconverters. J Acquir Immune Defic Syndr 2003;32(3):303–10.
[123] Lacabaratz-Porret C, Urrutia A, Doisne JM, et al. Impact of antiretroviral therapy and changes in virus load on human immunodeficiency virus (HIV)-specific T cell responses in primary HIV infection. J Infect Dis 2003;187(5):748–57.
[124] Oxenius A, Price DA, Easterbrook PJ, et al. Early highly active antiretroviral therapy for acute HIV-1 infection preserves immune function of CD8+ and CD4+ T lymphocytes. Proc Natl Acad Sci USA 2000;97(7):3382–7.
[125] Hare CB, Pappalardo BL, Busch MP, et al. Seroreversion in subjects receiving antiretroviral therapy during acute/early HIV infection. Clin Infect Dis 2006;42(5):700–8.
[126] Kassutto S, Maghsoudi K, Johnston MN, et al. Longitudinal analysis of clinical markers following antiretroviral therapy initiated during acute or early HIV type 1 infection. Clin Infect Dis 2006;42(7):1024–31.
[127] Hammer SM, Saag MS, Schechter M, et al. Treatment for adult HIV infection: 2006 recommendations of the International AIDS Society-USA panel. JAMA 2006;296(7):827–43.
[128] Hecht FM, Wang L, Collier A, et al. A multicenter observational study of the potential benefits of initiating combination antiretroviral therapy during acute HIV infection. J Infect Dis 2006;194(6):725–33.
[129] Streeck H, Jessen H, Alter G, et al. Immunological and virological impact of highly active antiretroviral therapy initiated during acute HIV-1 infection. J Infect Dis 2006;194(6): 734–9.
[130] Markowitz M, Jin X, Hurley A, et al. Discontinuation of antiretroviral therapy commenced early during the course of human immunodeficiency virus type 1 infection, with or without adjunctive vaccination. J Infect Dis 2002;186(5):634–43.
[131] Fidler S, Oxenius A, Brady M, et al. Virological and immunological effects of short-course antiretroviral therapy in primary HIV infection. AIDS 2002;16(15):2049–54.
[132] Hoen B, Fournier I, Lacabaratz C, et al. Structured treatment interruptions in primary HIV-1 infection: the ANRS 100 PRIMSTOP trial. J Acquir Immune Defic Syndr 2005; 40(3):307–16.
[133] Cohen DE, Walker BD. Human immunodeficiency virus pathogenesis and prospects for immune control in patients with established infection. Clin Infect Dis 2001;32(12):1756–68.
[134] Imami N, Hardy G, Gotch F. Development of immunotherapeutic strategies for HIV-1. Expert Opin Biol Ther 2001;1(5):803–16.
[135] Sereti I, Lane HC. Immunopathogenesis of human immunodeficiency virus: implications for immune-based therapies. Clin Infect Dis 15 2001;32(12):1738–55.
[136] Pedersen C, Lindhardt BO, Jensen BL, et al. Clinical course of primary HIV infection: consequences for subsequent course of infection. BMJ 1989;299(6692):154–7.
[137] Pedersen C, Kolby P, Sindrup J, et al. The development of AIDS or AIDS-related conditions in a cohort of HIV antibody-positive homosexual men during a 3-year follow-up period. J Intern Med 1989;225(6):403–9.
[138] Lavreys L, Baeten JM, Chohan V, et al. Higher set point plasma viral load and more-severe acute HIV type 1 (HIV-1) illness predict mortality among high-risk HIV-1-infected African women. Clin Infect Dis 2006;42(9):1333–9.
[139] Lori F, Lisziewicz J. Targeting HIV reservoirs and reconstituting the immune system. Second annual meeting Research Institute for Genetic and Human Therapy April 18-19, 1999 Washington, DC. AIDS Res Hum Retroviruses 1999;15(18):1597–617.
[140] Lori F, Jessen H, Lieberman J, et al. Treatment of human immunodeficiency virus infection with hydroxyurea, didanosine, and a protease inhibitor before seroconversion is associated with normalized immune parameters and limited viral reservoir. J Infect Dis 1999;180(6): 1827–32.
[141] Lafeuillade A, Poggi C, Hittinger G, et al. Predictors of plasma human immunodeficiency virus type 1 RNA control after discontinuation of highly active antiretroviral therapy

initiated at acute infection combined with structured treatment interruptions and immune-based therapies. J Infect Dis 2003;188(10):1426–32.
[142] Subbarao S, Otten RA, Ramos A, et al. Chemoprophylaxis with tenofovir disoproxil fumarate provided partial protection against infection with simian human immunodeficiency virus in macaques given multiple virus challenges. J Infect Dis 2006;194(7):904–11.
[143] Lifson JD, Piatak M Jr, Cline AN, et al. Transient early post-inoculation anti-retroviral treatment facilitates controlled infection with sparing of CD4+ T cells in gut-associated lymphoid tissues in SIVmac239-infected rhesus macaques, but not resistance to rechallenge. J Med Primatol 2003;32(4-5):201–10.
[144] Kaufmann GR, Zaunders JJ, Cunningham P, et al. Rapid restoration of CD4 T cell subsets in subjects receiving antiretroviral therapy during primary HIV-1 infection. AIDS 2000; 14(17):2643–51.
[145] Ngo-Giang-Huong N, Deveau C, Da Silva I, et al. Proviral HIV-1 DNA in subjects followed since primary HIV-1 infection who suppress plasma viral load after one year of highly active antiretroviral therapy. AIDS 2001;15(6):665–73.
[146] Yerly S, Gunthard HF, Fagard C, et al. Proviral HIV-DNA predicts viral rebound and viral setpoint after structured treatment interruptions. AIDS 2004;18(14):1951–3.
[147] Truong HH, Grant RM, McFarland W, et al. Routine surveillance for the detection of acute and recent HIV infections and transmission of antiretroviral resistance. AIDS 2006;20(17):2193–7.
[148] Grant RM, Hecht FM, Warmerdam M, et al. Time trends in primary HIV-1 drug resistance among recently infected persons. JAMA 2002;288(2):181–8.
[149] Frost S, McCoy S, Hicks C, et al. Tracking molecular epidemiology in North Carolina, USA: The screening and tracing active transmission model. 14th Conference on Retroviruses and Opportunistic Infections 2007, Feb 25–28, Los Angeles, California. Session 56, Abstract# 240.
[150] Little SJ, Daar ES, D'Aquila RT, et al. Reduced antiretroviral drug susceptibility among patients with primary HIV infection. JAMA 1999;282(12):1142–9.
[151] Kessler RC, McGonagle KA, Zhao S, et al. Lifetime and 12-month prevalence of DSM-III-R psychiatric disorders in the United States. Results from the National Comorbidity Survey. Arch Gen Psychiatry 1994;51(1):8–19.
[152] Rabkin JG, Ferrando SJ, Jacobsberg LB, et al. Prevalence of axis I disorders in an AIDS cohort: a cross-sectional, controlled study. Compr Psychiatry 1997;38(3):146–54.
[153] Williams P, Narciso L, Browne G, et al. The prevalence, correlates, and costs of depression in people living with HIV/AIDS in Ontario: implications for service directions. AIDS Educ Prev 2005;17(2):119–30.
[154] Schrooten W, Dreezen C, Fleerackers Y, et al. Receiving a positive HIV test result: the experience of patients in Europe. HIV Med 2001;2(4):250–4.
[155] Department of Health. Guidelines for pre-test discussion on HIV testing. PL/CMO/(96)1 London: Department of Health, 1996.
[156] Stekler J, Collier AC, Holmes KK, et al. Primary HIV infection education: knowledge and attitudes of HIV-negative men who have sex with men attending a public health sexually transmitted disease clinic. J Acquir Immune Defic Syndr 2006;42(1):123–6.
[157] Daar ES, Moudgil T, Meyer RD, et al. Transient high levels of viremia in patients with primary human immunodeficiency virus type 1 infection. N Engl J Med 1991;324(14): 961–4.
[158] Leynaert B, Downs AM, de Vincenzi I. Heterosexual transmission of human immunodeficiency virus: variability of infectivity throughout the course of infection. European Study Group on Heterosexual Transmission of HIV. Am J Epidemiol 1998;148(1):88–96.
[159] Yerly S, Vora S, Rizzardi P, et al. Acute HIV infection: impact on the spread of HIV and transmission of drug resistance. AIDS 2001;15(17):2287–92.
[160] Jacquez JA, Koopman JS, Simon CP, et al. Role of the primary infection in epidemics of HIV infection in gay cohorts. J Acquir Immune Defic Syndr 1994;7(11):1169–84.

[161] Koopman JS, Jacquez JA, Welch GW, et al. The role of early HIV infection in the spread of HIV through populations. J Acquir Immune Defic Syndr Hum Retrovirol 1997;14(3): 249–58.
[162] Wawer MJ, Gray RH, Sewankambo NK, et al. Rates of HIV-1 transmission per coital act, by stage of HIV-1 infection, in Rakai, Uganda. J Infect Dis 2005;191(9):1403–9.
[163] Cohen MS, Pilcher CD. Amplified HIV transmission and new approaches to HIV prevention. J Infect Dis 2005;191(9):1391–3.
[164] Pilcher CD, Eron JJ Jr, Vemazza PL, et al. Sexual transmission during the incubation period of primary HIV infection. JAMA 2001;286(14):1713–4.
[165] Fraser C, Hollingsworth T, Chapman R, Anderson RE. Quantifying the impact of primary infection on HIV transmission and control. 13th Conference on Retroviruses and Opportunistic Infections. Denver, Colorado, February 5–8, 2006.
[166] Colfax GN, Buchbinder SP, Cornelisse PG, et al. Sexual risk behaviors and implications for secondary HIV transmission during and after HIV seroconversion. AIDS 2002;16(11): 1529–35.
[167] Pilcher CD, Eaton L, Kalichman S, et al. Approaching HIV elimination: interventions for acute HIV infection. Curr HIV/AIDS Rep 2006;3(4):160–8.
[168] Brooks JT, Robbins KE, Youngpairoj AS, et al. Molecular analysis of HIV strains from a cluster of worker infections in the adult film industry, Los Angeles 2004. AIDS 2006; 20(6):923–8.
[169] Kelly JA, Kalichman SC. Behavioral research in HIV/AIDS primary and secondary prevention: recent advances and future directions. J Consult Clin Psychol 2002;70(3):626–39.
[170] Simpson K, Biddle A, Leone PA, et al. Cost effectiveness of screening for acute HIV infection: the North Carolina STAT Program. Presented at the 13th Conference on Retroviruses and Opportunistic Infections. 2006; Session 71, Abs# 374.
[171] Center for HIV-AIDS vaccine immunology. Available at: http://www.chavi.org/. Accessed January 14, 2007.
[172] Margolis DM, Archin NM. Attacking HIV provirus: therapeutic strategies to disrupt persistent infection. Infect Disord Drug Targets 2006;6(4):369–76.