Clinical Management of Acute HIV Infection: Best Practice Remains Unknown

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Best practice for the clinical management of acute human immunodeficiency virus (HIV) infection remains unknown. Although some data suggest possible immunologic, virologic, or clinical benefit of early treatment, other studies show no difference in these outcomes over time, after early treatment is discontinued. The literature on acute HIV infection is predominantly small nonrandomized studies, which further limits interpretation. As a result, the physician is left to grapple with these uncertainties while making clinical decisions for patients with acute HIV infection. Here we review the literature, focusing on the potential advantages and disadvantages of treating acute HIV infection outlined in treatment guidelines, and summarize the presentations on clinical management of acute HIV infection from the 2009 Acute HIV Infection Meeting in Boston, Massachusetts.

Despite ongoing investigation, the optimal clinical management of acute human immunodeficiency virus (HIV) infection remains unknown. The potential benefits and disadvantages of initiating antiretroviral therapy (ART) during acute or early infection are the subject of debate. How can practicing clinicians make sense of current uncertainties and best advise patients during this important time? Here we review the literature, summarize the presentations on clinical management of acute HIV infection from the 2009 Acute HIV Infection Meeting in Boston, Massachusetts, and offer a rational approach to this unanswered clinical question.

The 2009 Department of Health Services guidelines recommend consideration of ART for individuals with acute HIV infection or with HIV seroconversion within the antecedent 6 months [1]. This recommendation is based on several potential benefits, including improved laboratory markers of disease progression, decreased severity of acute illness, preservation of immune function, a favorable alteration of viral set point, decreased viral evolution and mutagenesis based on suppression of viral replication, and reduced risk of viral transmission. The guidelines also indicate that early therapy may mitigate the early and profound loss of T cells within gastrointestinal lymphoid tissue. Such potential benefits should be weighed against the potential risks of early therapy, including unknown long-term clinical benefit, drug toxicity, development of resistance, and adverse effect on quality of life.

The literature on acute HIV infection is limited by the paucity of randomized controlled trials (RCTs). To date, 4 RCTs of treatment in acute or early infection have been published. The first, in 1995, showed a statistically significant decrease in HIV-related opportunistic infections in subjects randomized to receive treatment with zidovudine monotherapy or placebo during primary HIV infection [2]. The subsequent trials also examined zidovudine monotherapy [3] or compared ART with or without immunomodulatory therapy [4, 5]. An RCT that compared conventional ART with deferred therapy in early infection was presented at the 2010 Conference on Retroviruses and Opportunistic Infections, showing a modest delay in the subsequent...
need for ART in the treatment arm [6]. Although other RCTs comparing conventional ART with delayed therapy in acute infection are now under way in Europe and the United States [7–10], data from these studies are not currently available to guide today’s clinical decisions.

Existing data from observational cohorts of treated subjects with acute HIV infection are largely skewed toward more symptomatic individuals, because these are the persons who present for medical evaluation and are most likely to be diagnosed with acute HIV infection. Physicians may favor earlier therapy for patients who have particularly severe symptoms, such as meningitis. Because increased severity of the acute retroviral syndrome has been associated with a potential for greater risk of disease progression [11, 12], longer-term outcomes from these studies may represent those for a “sicker” subpopulation of acutely infected individuals and may underestimate the potential benefit of early treatment.

Interpretation of acute infection studies is further hampered by the lack of standardized definitions for acute and early infection. Many studies use different definitions and criteria, often including treatment within 3–6 months after infection, seroconversion, or trial enrollment as treatment during “acute” infection.

**POTENTIAL ADVANTAGES OF EARLY TREATMENT**

**Clinical markers of disease.** In the QUEST study, a prospective observational multicenter international trial, 148 participants initiated treatment with twice-daily zidovudine, lamivudine, abacavir, and amprenavir during acute HIV infection and were followed up for 48 weeks [13]. Of the 115 subjects still receiving treatment at 48 weeks, 84.2% had a viral load of <50 RNA copies/mL. The investigators noted a decrease in median cell-associated DNA levels and immune activation compared with baseline values.

The CASCADE investigators studied a prospective observational international cohort of >1000 HIV-positive patients from Canada, Europe, and Australia who were identified during acute infection [14]. A follow-up CASCADE study focused on an early-treatment group of 348 subjects for whom therapy was initiated within 6 months after seroconversion [15]. Of these, 147 stopped ART: 38 of them after 6 months, 40 of them after 6–12 months, and 69 of them after >12 months. CD4 cell counts and HIV viral load measurements for early-treatment patients after treatment cessation were compared with the corresponding treatment-free period for participants in the deferred-treatment group (n = 675). Notably, those with ≥2 CD4 cell measurements of <350 cells/mm³ or a diagnosis of AIDS within the first 6 months after seroconversion were excluded. Six months after treatment cessation, subjects who had been treated for >12 months appeared to maintain significantly higher CD4 cell counts (mean, 430 cells/mm³), but those treated for shorter durations had CD4 cell counts comparable to those in the deferred-treatment group (mean CD4 cell counts, 304 cells/mm³ for those treated for 6–12 months, 241 cells/mm³ for those treated for <6 months, and 234 cells/mm³ for the deferred-treatment group). AIDS rates were similar in early-treatment (followed by cessation) and deferred-treatment groups (~3%), but the death rate was higher in the deferred-treatment group (0.6 vs 1.8%), largely owing to causes not related to HIV infection.

For subjects treated during acute infection who continue to receive therapy, longitudinal studies have shown durable virologic suppression and improved levels of immunologic markers (CD4 T lymphocyte counts) after early treatment. In a group of 64 patients with symptomatic acute HIV infection who received ART, 72% achieved virologic suppression by 21 months in an intention-to-treat analysis [16]. In another group of 102 subjects with acute and early infection, 91% had undetectable viral loads at 12 months; at 3 years, 86% continued to receive therapy, with virologic suppression maintained in all of these subjects. The mean CD4 increase after 1 year of ART was ≥200 cells/mm³ for the first year of treatment. Study subjects who continued to receive ART demonstrated ongoing incremental CD4 T lymphocyte recovery gains over 5 years of follow-up (to a mean of 842 cells/mm³) [17]. Adherence to ART was exceptionally good in this cohort, and this may not be generalized outside an intensively monitored study cohort.

In an observational study of 356 participants with acute and early infection from 8 study sites in North America initiating highly active ART (HAART), 56% modified their initial ART regimen, with 51% of these changes attributed to ART toxicity [18]. Alteration of the initial HAART regimen in this study, for any reason, was predictive of future virologic failure. Of note, the rates of ART regimen changes were associated with a shorter time from HIV seroconversion to start of ART and were comparable between patients receiving nonnucleoside reverse-transcriptase inhibitor–based regimens and patients receiving protease inhibitor–based regimens, and for all years of HAART initiation (2002–2005). Similar high rates of ART nonadherence in acutely treated persons have been associated with suboptimal outcomes [19–21]. Initiation of therapy in acute and early HIV infection can have a positive effect on disease markers [13, 15–17, 22–24], but whether this has long-lasting clinical significance remains unclear.

**Decreased severity of acute retroviral syndrome.** The acute retroviral syndrome is characterized by mononucleosis-like symptoms and signs, typically lasting 2 weeks but potentially continuing for ≥10 weeks [25]. The sudden onset of symptoms, including ≥10 symptoms in the first 24 h in some cases, can be debilitating [26]. Whether the etiology of acute retroviral syndrome involves direct viral pathogenesis or the host immune
response is unknown; a contribution of both is likely. Initiation of early treatment can rapidly suppress viral load, thereby lessening both direct viral effect and host immune response to circulating virus. Consideration of treatment of acute infection for the purposes of lessening the acute retroviral syndrome was one of the few indications initially included in the British HIV Association guidelines [27]. Early involvement of the central nervous system has since been added as a separate indication meriting consideration of treatment in these guidelines. Because up to a quarter of patients may present with aseptic meningitis [25, 28], treatment for this indication may affect a substantial subset of acutely infected individuals.

**Preservation of immune function.** Early enthusiasm about treatment of acute HIV infection stemmed from studies showing that early treatment preserved HIV-specific T-helper cell function [29–33] and that delay of therapy resulted in CD4 T lymphocyte depletion [31, 34, 35]. This and other work, providing the rationale for using ART to mitigate the natural sequence of T lymphocyte activation by HIV infection, followed by infection and depletion, offered promise [35].

CD4 T lymphocyte depletion in the gut occurs very early in the course of HIV infection and may mark an early and critical event in the pathogenesis of HIV infection. Investigators have recently queried whether early therapy could preserve this vulnerable population of cells. Experiments in a simian immunodeficiency virus (SIV) animal model suggested that early treatment may allow CD4 T lymphocyte restoration in the gut [36]. However, in a study of 54 human subjects with acute and early HIV infection, a 50%–60% persistent depletion of lamina propria lymphocytes was seen in 70.7% of patients studied longitudinally, despite 1–7 years of HAART [37]. Additional studies are needed to clarify the relationship between early treatment and preservation of gut-associated T lymphocyte depletion and the clinical significance of these findings.

The functional capacity of HAART-restored CD4 T lymphocytes remains another area of uncertainty [36]. Studies from SIV-infected macaques treated with HAART suggest that polyfunctional CD8 T lymphocyte responses (dual interferon-γ/interleukin-2) were not found in animals treated during primary stages of infection, suggesting that even in the face of HAART-associated CD4 T lymphocyte depletion there may be persistent immune dysfunction. Using microarray-based gene expression analyses, George and colleagues demonstrated that among SIV-infected macaques receiving ART, CD4 T lymphocyte recovery in gut-associated lymphoid tissue was associated with enhanced repair and regeneration of the mucosal epithelium not observed in untreated SIV-infected animals [38]. These studies and others offer a potential rationale in support of earlier ART with the hypothesis that treatment might reduce the magnitude of mucosal inflammation and enhance tissue repair critical to restoring the mucosal immune system.

**Viral set point.** Natural history studies indicate that the viral set point—established early in the course of infection—is prognostic of disease progression [39]. Whether initiation of therapy during acute infection affords patients the opportunity to establish a lower viral set point remains unproved. Because treatment during acute infection occurs before establishment of viral set point, it is not possible to determine which subset of individuals would spontaneously control viral replication without antiretroviral medication. Randomized controlled studies evaluating the effect of early treatment on the viral set point are limited, and the literature therefore largely represents varying findings from nonrandomized studies [40].

An early example of favorable virologic control after early ART was described in the “Berlin patient,” a subject who was treated during acute infection and had several treatment discontinuations followed by spontaneous control of viral replication for years after stopping HIV medications [41]. This was the first reported case demonstrating that durable immune control after short-course therapy during acute infection may be possible. At the time, investigators hypothesized that autologous exposure to viral antigen during bursts of viremia after treatment interruptions could augment host immune responses and promote longer-term control of viral replication.

**Effects of treatment followed by cessation.** Multiple studies have examined the effects of early treatment followed by cessation, with varying outcomes (Table 1). Several investigations have concluded that early treatment of acute HIV infection does not have a lasting effect on the viral set point [14, 15, 42, 44, 47, 53]. Other studies report more prolonged virologic control or possible CD4 cell count benefit after early treatment followed by cessation [6, 46, 50, 52]. Some studies report mixed or time-dependent effects on immunologic and/or virologic outcomes [45, 47]. Here we review a few such representative studies.

Early experience with treatment interruption in a pilot study suggested that a few individuals were able to control viral replication short term on discontinuation of medications [30]. In a follow-up study of this small cohort, long-term control was limited, and investigators found no predictable way to determine which subjects would achieve control despite extensive immunologic and host factor analysis [43]. The ability to predict and potentially elicit host factors associated with durable virologic control among patients treated during acute HIV infection remains a major unanswered challenge.

The SETPOINT trial (AIDERP 503/ACTG5217) randomized recently infected subjects to receive immediate ART with tenofovir, emtricitabine, and lopinavir-ritonavir for 9 months or to receive no therapy; it was stopped prematurely by the Data Safety and Monitoring Board because of more rapid disease progression in the untreated arm [6]. The authors note that early treatment “modestly delayed” the need to start ART.
Table 1. Summary of Studies on the Effects on Virologic Control and/or Disease Progression of Early Antiretroviral Therapy (ART) during Acute or Early Infection with Human Immunodeficiency Virus (HIV) Followed by Treatment Cessation

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<thead>
<tr>
<th>Reference</th>
<th>Year</th>
<th>Study type</th>
<th>Study details</th>
<th>Outcome</th>
<th>Net clinical effect</th>
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<tr>
<td>Rosenberg et al</td>
<td>2000</td>
<td>Prospective observational</td>
<td>8 acutely infected patients who started treatment during acute infection, followed by structured treatment interruptions</td>
<td>Short-term virologic control seen in 5 of 8 patients a median of 6.5 months after cessation of therapy (range, 5–8.7 months)</td>
<td>Virologic control</td>
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<tr>
<td>Desquilet et al</td>
<td>2004</td>
<td>Comparison of 2 prospective observational cohorts</td>
<td>58 PRIMO cohort subjects who started ART within 3.5 months after acute infection (median time to treatment, 45 days) and continued ART for a median of 17.3 months with sustained virologic suppression, who were then followed for up to 3 years, compared with 116 untreated seroconverters in the SEROCO cohort</td>
<td>Early treatment did not affect the viral set point 12 months after ART cessation, in the treatment group, compared with time-matched assessments in the no-treatment group</td>
<td>No difference in virologic control</td>
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<tr>
<td>Kaufmann et al</td>
<td>2004</td>
<td>Prospective observational</td>
<td>14 acutely infected subjects who started ART during acute infection, followed by structured treatment interruptions</td>
<td>8 (57%) of 14 patients maintained virologic control for 180 days: 6 (43%) of 14 for 360 days, and 5 (21%) of 14 for 720 days. There was no predictable way to determine which subjects would achieve control</td>
<td>Limited virologic control</td>
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<td>Streeck et al</td>
<td>2006</td>
<td>Prospective observational</td>
<td>12 acutely infected subjects treated within 25 days for 24 weeks, compared with 8 untreated seroconverters</td>
<td>All treated subjects achieved virologic suppression by 24 weeks (when treatment was stopped), but CD4 cell count and viral load outcomes at 1 year showed no difference between treated and untreated subjects</td>
<td>No difference in virologic control</td>
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<tr>
<td>Hecht et al</td>
<td>2006</td>
<td>Prospective observational</td>
<td>International cohort of subjects with acute infection (n = 131) or early infection (n = 45) who received treatment for ≥12 weeks, compared with a deferred-treatment group (n = 337)</td>
<td>Acute group demonstrated lower viral loads and higher CD4 cell counts 24 weeks after cessation of therapy; early group demonstrated persistent but decreasing CD4 T cell count benefit over time and loss of the viral load benefit by week 72 after discontinuation of ART</td>
<td>Mixed outcomes</td>
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<td>Lampe et al</td>
<td>2007</td>
<td>Comparison of 2 prospective observational cohorts</td>
<td>385 subjects in the CASCADE deferred-treatment cohort, compared with 79 treated subjects in the QUEST cohort, who continued therapy for a mean of 2.6 years</td>
<td>Viral load was &lt;1000 copies/mL in 10.1% of CASCADE subjects 3 years after seroconversion and in 17.7% of QUEST subjects 24 weeks after treatment cessation</td>
<td>Virologic control</td>
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<td>Fidler et al</td>
<td>2007</td>
<td>Comparison of 2 prospective observational cohorts</td>
<td>89 patients who started treatment within 6 months after acute infection (median time to treatment, 1.5 months) and received highly active ART for a median of 3.3 months, compared with 179 matched untreated controls in the CASCADE cohort</td>
<td>Treated subjects showed a less steep estimated rate of CD4 cell count decline (decrease of 51 cells/mm³ per year) compared with untreated subjects (decrease of 77 cells/mm³ per year). There was no significant difference in viral loads between the groups 6 months after ART cessation</td>
<td>Mixed outcomes</td>
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<td>Steingrover et al</td>
<td>2008</td>
<td>Comparison of 2 prospective observational cohorts</td>
<td>24 subjects who started ART during primary HIV infection, compared with 46 chronically infected subjects who started ART with a CD4 cell count of &gt;350 cells/mm³; all subjects underwent a single treatment interruption</td>
<td>Steeper CD4 cell count decline after treatment interruption in the chronic infection group over the first 4 weeks; no difference between groups from 4 to 48 weeks. The median time to viral rebound was shorter in the chronic infection group than in the acute infection group (4 vs 8 weeks); 2 (8.3%) of 24 subjects with acute infection maintained viral loads of &lt;50 copies/mL for up to 48 weeks of follow-up</td>
<td>Mixed outcomes</td>
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<td>Pantazis et al</td>
<td>2008</td>
<td>Prospective observational</td>
<td>348 subjects in the CASCADE cohort who started ART within 6 months after infection, compared with 675 subjects identified at seroconversion who had deferred treatment</td>
<td>No difference in viral load set point between the early-treatment and the deferred-treatment groups; significant CD4 cell count benefit 6 months after treatment cessation in the early-treatment group, compared with the deferred-treatment group, but only for subjects who had continued to receive treatment for ≥12 months. The death rate was higher in the deferred-treatment group, largely owing to causes not related to HIV infection</td>
<td>Mixed outcomes</td>
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because the rate of disease progression necessitating ART was greater than expected, there was inadequate virologic data to assess differences in viral set point.

The effect of early treatment on disease progression was also demonstrated by Koegl et al [53] in a study of 100 subjects who underwent transient early treatment during acute infection (median duration, 9.5 months) compared with 56 subjects who deferred therapy. The median viral load 12 months after cessation of therapy in the treatment group was not significantly different from that in untreated subjects 12 months after seroconversion. However, the median time to a CD4 cell count of <350 cells/mm³ was significantly longer in the treatment group: 20.7 months after treatment cessation, compared with 8.3 months after seroconversion in untreated patents.

Fidler et al [47] compared 89 subjects treated with HAART (median duration, 3.3 months; initiated within 6 months of acute infection; median time to treatment, 1.5 months) with 179 matched untreated control subjects in the CASCADE cohort. At 3 years after seroconversion, the estimated rate of CD4 cell loss was significantly slower in the treated group than in the untreated group (mean decrease, 51 vs 77 cells/mm³ per year, respectively). There was no statistically significant difference in mean viral load between the 2 groups after 2 years of follow-up, but extrapolated data suggested significantly lower viral loads in the treated group at 3 years after seroconversion. Untreated seroconverters were more likely to reach CD4 cell counts of <350 cells/mm³ or initiate clinically indicated ART.

Some studies suggest that, in addition to delaying CD4 cell

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<td>Goujard et al [51]</td>
<td>2009</td>
<td>Prospective observational</td>
<td>223 subjects who started treatment within 3 months after seroconversion and continued it for &gt;3 months and who stopped treatment for &gt;12 months were studied to determine factors associated with virologic control</td>
<td>Virologic control</td>
<td>12% (223 subjects maintained viral loads of &lt;500 copies/mL after treatment interruption (median duration, 19.3 months; median duration of virologic control, 27 months).</td>
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<td>Volberding et al [52]</td>
<td>2009</td>
<td>Prospective observational</td>
<td>121 subjects were enrolled with acute infection (≤14 days after infection) or early infection (14–180 days after infection) and started therapy within 3 days of enrollment; 73 subjects had virologic suppression for 1 year, followed by treatment interruption</td>
<td>Virologic control</td>
<td>40% of 73 treated subjects with acute infection or early infection sustained viral loads of &lt;5,000 copies/mL after 24 weeks of treatment interruption</td>
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<tr>
<td>Koegl et al [53]</td>
<td>2009</td>
<td>Comparison of 2 prospective observational cohorts</td>
<td>100 subjects with acute infection who were treated for a median of 9.5 months, compared with 56 subjects with acute infection who had deferred treatment</td>
<td>Mixed outcomes</td>
<td>No difference in median viral load 12 months after ART cessation in the treatment group, compared with the median viral load 12 months after seroconversion in the deferred-treatment group; median time to CD4 cell count &lt;350 cells/mm³ was 20.7 months after ART cessation in treated group vs 8.3 months after seroconversion in deferred-treatment group</td>
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<tr>
<td>Hogan et al [8]</td>
<td>2010</td>
<td>Randomized controlled trial</td>
<td>130 (of an intended 150) subjects randomized to start ART immediately and continue it for 9 months or to defer therapy</td>
<td>Slower disease progression</td>
<td>The study was stopped early by DSMB because of more rapid disease progression in the deferred-treatment group; virologic data were inadequate to assess differences between groups in the viral set point.</td>
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**NOTE.** CD4 cell, CD4 T lymphocyte; DSMB, Data Safety and Monitoring Board; HIV, human immunodeficiency virus.
count decline and the subsequent need for long-term ART, early therapy followed by cessation can increase virologic control. At the Boston Acute HIV Infection meeting, Goujard et al [51] presented data from the French National Research Agency for AIDS Research (ANRS) group, a multicenter observational cohort in which 1089 patients have been enrolled since 1996 during acute or early HIV-1 infection. Patients who initiated ART within the first 3 months after infection, were treated for >3 months, and experienced a treatment interruption of ≥12 months were studied to determine factors associated with sustained virologic control [51]. In 26 (12%) of 223 treated patients, HIV RNA levels remained <500 copies/mL after treatment interruption (median treatment duration, 19.3 months). Low levels of replication (<500 copies/mL) were sustained for a median period of 27 months. In 13 (50%) of 26 patients, HIV RNA levels remained <50 copies/mL for a median of 42 months, with high CD4 cell counts (median count, 946 cells/mm$^3$).

Predictive factors for HIV control after ART interruption were lower HIV RNA and HIV DNA levels and higher CD4 cell counts at the time of acute infection, and female sex [51]. Age, symptomatic acute HIV infection, characteristics of viruses (subtype, resistance profile, and X4-tropism), treatment duration, and delay between acute infection and treatment initiation did not influence viral control after treatment interruption. HLA genotyping in white patients showed no overrepresentation of protecting alleles (HLA B57 or B27).

In comparison, these researchers also reported on 8 (3.8%) of 211 untreated patients from the ANRS PRIMO cohort in whom viral control was established a median of 6.2 months after acute infection and lasted a median of 4.1 years. Seven of the patients initially had detectable viral replication. For 4 patients, loss of viral control was noted during follow-up [54]. Although the direct comparison was not made, these additional data suggest that the rate of virologic control achieved with early ART followed by cessation is greater than that of spontaneous controllers seen in the general acute HIV infection population.

Other studies demonstrate similar virologic benefit. In a prospective nonrandomized multicenter study by Volberding et al [52], subjects with acute infection (<14 days after infection) or early infection (14–180 days after infection) who began receiving therapy and had viral suppression for 1 year underwent treatment interruption. The researchers report that 40% maintained viral loads of <5000 copies/mL after 24 weeks of treatment interruption. Lampe et al [46] compared sustained virologic control between 385 subjects in the deferred-treatment group of the CASCADE cohort and 79 subjects who received early treatment in the QUEST cohort (and continued therapy for an average of 2.6 years). In this study, 10.1% of CASCADE participants had viral load measurements of ≤1000 copies/mL 3 years after seroconversion, and 17.7% of QUEST subjects showed viral load values of ≤1000 copies/mL 24 weeks after treatment cessation. Lampe et al [46] note that women and subjects with asymptomatic infection (which was much less prevalent among QUEST subjects than among CASCADE subjects) were more likely to achieve sustained virologic control, potentially causing the effect of early treatment to be underestimated.

Finally, researchers have also found that time to virologic rebound may be delayed in subjects who start ART during acute infection rather than during chronic infection. In another prospective study, subjects from 2 prospective studies who underwent a single treatment interruption while having well-suppressed viral levels and receiving HAART were compared. One group started HAART during primary HIV infection (n = 24), and the other during chronic HIV infection, with CD4 cell counts of >350 cells/mm$^3$ [48]. The median time to viral rebound was shorter for the chronically infected group than for the acute infection group (4 vs 8 weeks). In 2 (8.3%) of the acutely infected patients, no rebound of the plasma HIV-1 RNA load to a level of >50 copies/mL occurred during up to 48 weeks of follow-up.

Although these data suggest a possible delay in CD4 cell count decline, or increased frequency of sustained viral control after early ART compared with that observed in untreated patients, additional studies are needed to further resolve this question. It is unclear whether sustained virologic control (with low viral loads) after early treatment followed by cessation represents the immediate effects of treatment and a delay in the natural history, rather than a long-term benefit or an unmasking of the patient’s “natural” immunologic control mechanisms in the absence of ART. Taken together, these data suggest a possible role for early ART, although the precise timing and duration of treatment has not been established, and a long-term benefit has not yet been proved.

**Transmission.** After documentation of a >10-fold increased risk of transmission during the window of acute HIV infection [55, 56] and genetic analyses linking ~50% of new infections to other sequences identified during the acute infection period and occurring in transmission clusters [57, 58], treatment as a mechanism of secondary transmission reduction has gained increased attention. A large RCT of ART to prevent sexual transmission of HIV in serodiscordant couples is in progress (HPTN 052), with enrollment expected to be completed in spring 2010 (M. Cohen, personal communication).

The dynamics of HIV RNA rebound after cessation of short-course ART initiated in acute infection have implications both for the individual index patient and for the risk of HIV transmission to uninfected persons. Fidler presented data at the Boston meeting from a study of 315 subjects in a combined cohort from the prospective observational UK Register of HIV
detectable HIV RNA level (≥1000 copies/mL), using survival methods [59]. All subjects had well-estimated dates of HIV seroconversion and started ART within 6 months of the first positive result of an HIV test, for a median ART duration of 4 months. The median pretreatment RNA level was 4.7 log_{10} copies/mL. The investigators considered rebound outcomes in subjects with high baseline RNA levels and subjects with low baseline RNA levels (≥5 vs <5 log_{10} copies/mL). Overall, for the 81% of subjects who achieved an undetectable HIV RNA level (<400 copies/mL) during ART, the median time to a detectable HIV RNA level (>1000 copies/mL) after stopping treatment was 1.2 months. By 3 months after ART cessation, 75% of subjects had detectable HIV RNA. The absolute levels of viral rebound up to 6 months after stopping ART correlated with pretreatment RNA levels and reached magnitudes that may confer a potential increased risk of transmission. In a fully adjusted Cox model, a greater risk of detectable HIV RNA was associated with being male and higher pretreatment RNA levels. Adherence data were not presented. There was no evidence that the timing of ART initiation had an effect on virologic outcomes [59].

Another study by Fidler et al [60] (and S. Fidler, personal communication) compared virologic rebound after treatment cessation in patients with early infection (within 6 months after seroconversion) (n = 228) and patients with chronic infection (n = 2225), using data from the SPARTAC and SMART trials, respectively. Viral rebound was lower in the early-treatment group, although still of sufficient magnitude to permit transmission as early as 4 weeks after ART cessation. The proportion of subjects with detectable virus at 4 weeks did not differ between early and chronic infection groups (78% vs 79%, respectively). The nadir CD4 cell count in the chronically infected (SMART trial) participants was associated with the level of viremia after stopping ART.

These data suggest that individuals starting ART during acute infection may need to continue therapy to maintain the benefit of treatment as a mechanism of reduced onward transmission. However, diagnosis of acute HIV infection, coupled with early patient support, education, and counseling, can provide a public health benefit through behavioral change, irrespective of whether early treatment is initiated, because acute infection marks the stage of greatest transmission [55–58, 61, 62].

**POTENTIAL DISADVANTAGES OF EARLY TREATMENT**

**Toxicity.** Despite the many adverse experiences that used to significantly limit tolerability of ART, many regimens are now well tolerated, with few or well-managed side effects. The marked improvement in ART pill burden and adverse effects is a major success of the past 15 years. Nonetheless, several potential short-term and long-term complications accompany the use of these medications. Because no schedule of terminal treatment interruption has been proved to maintain virologic control, initiation of therapy during acute infection (other than as part of specified trial protocols) generally means lifelong therapy. Some clinicians are understandably reluctant to initiate treatment with drugs that may otherwise be deferred for years.

Treatment is complicated by high rates of premature discontinuation in some studies, depression in the period after diagnosis, and substantial drug-related toxic effects (although these may be regimen specific), each limiting adherence and therefore efficacy. Published toxicity rates range in scope and magnitude: the QUEST investigators reported depression in 11% of patients, grade 3–4 elevations in the alanine transferase level in 20%, and serious adverse events overall in 56% (83 of 148 patients) [13]. Other studies report 19%–50% rates of treatment discontinuation at 1 year [20, 63, 64].

**Drug resistance.** Primary resistance of HIV to antiretroviral drugs is not infrequent [65] and has been associated with an increased risk of virologic treatment failure in some studies [66, 67] and comparable outcomes in others [68]. Overall, untreated persons with transmitted drug resistance have more rapid rates of immunologic disease progression in the first year after infection [69], though initial CD4 T lymphocyte counts are higher in persons with transmitted drug resistance at a given plasma viral load [66, 69]. Rates of transmitted drug resistance may vary widely, depending on geography, the demographics of the population, the year of study, and the definition of resistance. More recently, a consensus genotypic definition of transmitted HIV-1 drug resistance has been developed (the surveillance drug resistance mutation list) to facilitate comparison between studies [70]. Population-based sequencing studies show remarkably consistently higher rates of transmitted drug resistance in North America than in Europe: 14%–24% in North America [68, 71, 72] and 3%–11% in Europe [72–76].

Persistence of transmitted drug resistance has been well documented for >4 years using consensus-based sequencing to detect resistant variants. Conservative estimates of the time to complete reversion to wild type suggest that this process may require many decades (ie, longer than the life of the infected person [77]). In response to different selection pressures (eg, drug penetration or host immune responses), virus with transmitted drug resistance may also persist in the genital compartment longer than in the blood plasma, raising potential concerns about onward transmission, despite the detection of wild-type virus as the predominant strain in plasma [13]. Given the relatively high rates of transmitted drug resistance and durable persistence, consensus guideline panels routinely recommend genotypic drug resistance testing at the time of HIV infection.
diagnosis and before initiation of ART [27, 78, 80]. In the case of more immediate initiation of ART during acute HIV infection, empiric treatment should probably include a boosted protease inhibitor–based regimen until resistance testing results are available [1].

The detection of a transmitted drug resistance variant depends on the sensitivity of the detection method and the amount of resistant virus present in the viral population being tested. Methods to detect minority variants that represent <1% of the population are now available [81], though the clinical significance of minor variants identified at concentrations that may emerge as a result of natural variation remains unresolved. Johnson and colleagues [61] assessed the frequency of certain minor drug resistant variants in treatment-naive persons to determine the possible clinical significance of these minority resistant variants among patients initiating ART. This study showed that low-frequency drug resistance mutations at baseline were more common in patients experiencing subsequent virologic failure than in those who experienced treatment success [61]. Additional studies are needed to determine under which circumstances the transmission of drug-resistant minor variants will affect the clinical outcome in recently infected individuals initiating immediate or deferred ART.

Quality of life. Other than the tangible improvements in pill burden and adverse effect profile, we know very little about quality-of-life implications of ART for patients. Some patients believe that each dose of medication, even if only a single pill once daily, is a reminder of their HIV infection and—for some—the associated stigma. Although the DHHS treatment guidelines list “quality of life” as a potential disadvantage of therapy, others may view early treatment as having a positive effect, because they feel they are “doing something” about the infection, rather than “knowingly allowing” viral replication. Because initiation of therapy may well imply lifelong therapy at this point in time, such “unmeasured” effects on quality of life can be considerable. Potential physician-patient discrepancies in perceptions related to HIV treatment have been demonstrated [82] and underscore the importance of learning more about patient preferences, tending to the psychological state of patients facing a new diagnosis and the prospect of lifelong therapy, and partnering with patients to maximizing shared decision making concerning treatment initiation.

Just as acute infection may be a unique period immunologically, it is also a unique period physically and psychologically. The types of supports needed by acutely infected patients may be different from those needed during any other stage of infection. Optimizing therapy for those starting treatment will no doubt involve optimizing adherence, support, and integration back into the patient’s usual life, at a time of typically great confusion and stress.

FUTURE DIRECTIONS

Overall treatment trends. The approach to treatment of HIV infection has been characterized by pendulum swings, oscillating between a “hit early hit hard” approach [83] and delaying therapy in the hope of preserving future choices and avoiding cumulative toxicity, resistance, and medication burden. Recent data are increasingly pushing the pendulum back toward earlier initiation of therapy [84, 85], and guidelines have been modified to recommend initiation of therapy at higher CD4 count thresholds to reflect this thinking [1]. Although management of acute HIV infection may represent strategies for a “special patient population” [1], taken in context these trends raise the question of whether the push for earlier treatment echoes possible benefits that may be amplified in the case of acute infection. Further studies are needed. Recent data suggesting sex or racial differences in disease progression after acute infection also highlight the need to better understand which subsets of individuals may benefit most from early therapy [86].

Treatment options. Treatment choices for acute HIV infection have historically been extrapolated from regimens used for chronic HIV infection, but might there be a unique (though yet unproved) role for some HIV medications in acute infection? Because most viruses are chemokine (C-C motif) receptor 5 (CCR5)–tropic at the time of acute infection, use of a CCR5 inhibitor to block cell entry is enticing, even though the role for CCR5 inhibitors to date has predominantly been in salvage regimens. Also inviting is an approach that combines medications from different classes at the start of therapy for a concerted robust effort to paralyze viral cell entry and replication. A lower toxicity profile and lack of observed transmitted resistance suggest a possible role for integrase inhibitors (now approved for use in treatment-naive patients [1]) as first-line therapy in patients with acute infection—a potential role now under investigation [79]. A more intensive “induction” regimen might also need to be studied, given the extraordinarily high viremia in patients with acute HIV infection and the low genetic barrier to resistance for this class of medications. Although no definitive evidence has yet emerged regarding the potential benefit of combining antiretroviral medications with immune modulators, this approach remains intriguing from basic scientific principles. Finally, coupling early ART with therapeutic vaccination remains an area of ongoing investigation.

A rational approach. Until more definitive data emerge from RCTs, clinicians are left with a set of conflicting outcomes from largely observational cohorts to guide their decisions. How can the practicing clinician integrate these data in real time?

Unless patients are being enrolled in an RCT, the decision to start therapy should be made on a case-by-case basis after a careful review of potential advantages and disadvantages with the patient. Psychological assessment as part of an overall eval-
ulation of the patient’s potential to adhere to the treatment regimen (as well as support to maximize adherence) is time well spent. Underscoring for the patient the importance of adherence to therapy is also critical, because incomplete adherence to early treatment can be worse—from a resistance standpoint—than no treatment at all, given rapid the replication of HIV at extremely high levels of viremia under the selection pressure of medications.

For those patients who are ready, willing, and able to commit to treatment, doing so may leave the door open for future adjunctive therapies, such as vaccines, immunomodulators, or even more effective antiretroviral medications or combinations yet to be discovered, while preserving the immune system so that it can maximally benefit from these interventions. Regardless of treatment decisions, referring patients with acute infection to a clinical trial can help us learn from the collective experience of patients and hopefully address future treatment decisions from the vantage point of a stronger evidence base.

References


