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Should We Treat Acute HIV Infection?

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Abstract

Critical advances in the early diagnosis of HIV now allow for treatment opportunities during acute infection. It remains unclear whether treatment of acute HIV infection with antiretroviral therapy improves long-term clinical outcomes for the individual and current guidelines are not definitive in recommending therapy at this stage of infection. However, treatment of acute HIV infection may have short-term benefit on viral set point when compared to delayed therapy as well as reducing the risk of transmission to others. Herein we review the immunological and clinical literature to discuss whether we should treat acute HIV infection, both from the perspective of the individual HIV-infected patient and from the public health perspective. As transmission of drug-resistant HIV variants are of concern, we also review recent clinical trial data to provide recommendations for which specific antiretroviral treatment regimens should be considered for the treatment of acute HIV infection.

Keywords

HIV; Antiretroviral therapy; Clinical trials; Observational studies; Viral load set point; Viral reservoir; Drug-resistant HIV transmission

Introduction

Acute HIV infection is the earliest stage of infection which occurs 1–2 weeks after transmission but before seroconversion. Acute infection lasts for approximately 2–4 weeks, during which the plasma p24 antigen and HIV RNA levels are detectable but the anti-HIV antibodies are not yet detectable [1••]. During this period the virus disseminates widely and viremia reaches very high levels. With the associated cytokines released by innate immune cells in response to the viremia [2], acutely HIV-infected patients often experience a viral syndrome. While peripheral blood CD4+ T-cell counts may remain stable or dip minimally, there is a profound and rapid loss of immune cells in gut-associated lymphoid tissue that is in part irreversible [3, 4].

The question of whether or not to treat acute HIV infection with antiretroviral therapy (ART) remains investigational. There is a paucity of randomized clinical trial data to guide recommendations. The most recent treatment guidelines from the Department of Health and

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Human Services (DHHS) 2011 [5] and International Antiviral Society-USA (IAS-USA) 2010 [6] conclude that there is insufficient data to routinely recommend treatment of acute HIV infection, but that treatment should be considered optional. In this review we will therefore summarize pertinent data to inform this critical decision: both from the perspective of potential individual benefit and also in terms of public health considerations.

Acute HIV Clinical Presentation and Diagnostics

Acute HIV infection is difficult to diagnose because the symptoms are transient and protean. However, making the correct diagnosis is critical because 1) treatment during acute HIV infection may provide benefit and 2) acutely HIV-infected patients are at increased risk of transmitting. During acute and early HIV infection the risk of transmission appears to be much higher than during chronic infection [7]. In the rhesus macaque model of SIV infection, plasma is up to 750 times more infectious, per-virion, in the acutely infected animals as compared to the chronically infected animals [8]. It has been hypothesized that this increased infectiousness is due to high viral loads, often in excess of one million RNA molecules per mL and homogeneity of highly infectious transmitted/founder viral variants at the time of acute infection [9, 10].

The diagnosis of acute HIV infection requires astute clinical acumen and correct use of specific diagnostic tests. It has been estimated that 40–90% of acutely HIV infected patients are symptomatic within days to weeks of initial exposure [11]. However, the most common symptoms are nonspecific and could be confused with symptoms of infectious mononucleosis, influenza, malaria, and rickettsial diseases, including fever, fatigue, rash, headache, lymphadenopathy, pharyngitis, myalgia, arthralgia, nausea, vomiting, and diarrhea. Additionally, meningoencephalitis and oral or genital mucocutaneous ulcers have been reported [12–15]. Symptoms have been reported to last up to 10 weeks, but most commonly they last less than 14 days [12]. Severe and prolonged symptoms portend rapid disease progression [16, 17]. Testing for acute HIV should be performed in anyone with these viral symptoms, particularly those with sexual contact with a person who is known to be HIV-infected or who is at high risk for having HIV infection (ie, men who have sex with men, sex workers, or persons who have recently had sex with anyone from highly endemic areas like sub-Saharan Africa) or those presenting with a sexually transmitted infection. Additionally, anyone who is found to have acute HIV infection should also be screened for other sexually transmitted infections.

Whether HIV is transmitted through the mucosal, percutaneous, or intravenous route, the virus is not immediately detectable in plasma. This "eclipse" phase lasts from 7 to 21 days [18, 19]. Subsequently, virus can be detected in the plasma, either using nucleic acid amplification when HIV RNA is detectable at 1–5 copies per mL [20] or using clinically available HIV RNA viral loads when HIV RNA is detectable at ≥ 50 copies per mL [21]. Notably, false positives have been reported when HIV RNA < 10,000 [22, 23]; therefore, repeat testing of HIV RNA within 24 h is advisable, as the dynamics of HIV replication during acute infection are very rapid with doubling times of 10 h [24]. Gag p24 antigen appears next by about 14–21 days and lastly antibody responses become detectable after 21 days in plasma [25]. The enzyme-linked immunosorbent assay (ELISA) is the most common immunoassay used for the detection of HIV-1 and HIV-2 antibody. It has evolved from the first-generation viral lysate-based immunoglobulin G (IgG) tests, to the second-generation tests incorporating recombinant and/or synthetic peptide antigens, to the third-generation tests which detect IgG and IgM (antigen sandwich techniques), and to the third-generation-plus assays which also detect HIV-1 group O [26]. Antibody is detected in most individuals within 6–12 weeks after infection with the earlier generation assays, but antibody levels can be detected within 3–4 weeks after infection with third-generation antigen sandwich assays. The newest fourth-generation ELISAs incorporate p24 antigen testing, so that the window

period for diagnosis can be shortened to about 2–3 weeks from the time of initial infection (Fig. 1) [27–30]. Because the highest viral loads occur between 2 weeks and 2 months [24], the diagnosis of acute HIV infection during this time provides a critical opportunity for the health care provider to offer both education and treatment.

Rationale for the Treatment of Acute HIV Infection: For the Individual

The principal rationales to treat acute HIV with ART, when considering the individual patient, are 1) to treat highly symptomatic patients as they are more likely to progress rapidly, 2) to preserve CD4 T + cell counts and reduce the viral set point, 3) to limit the size of viral reservoirs, 4) to preserve HIV-specific immunity, and 5) time to CD4 T + cell count ≤ 500 is short, why wait?

1. Treat Symptomatic Acute HIV Infection—Acutely HIV-infected patients who are symptomatic tend to progress more rapidly than those without symptoms. Antiviral therapy in acute infection rapidly reduces viral loads and alleviates symptoms as well [31–33]. The most recent IAS-USA guidelines recommend considering ART in the setting of symptomatic acute HIV [6].

2. Preserve CD4 T-Cell Counts and Reduce Viral Set Point (Table 1)

A. Randomized Controlled Clinical Trials of ART During Acute HIV: There have been a paucity of clinical trials addressing the question of whether acute HIV should be treated with ART. To date, there have only been two published placebo-controlled randomized clinical trials (RCTs). The first, reported in 1995, showed that there were significantly fewer opportunistic infections in acutely HIV-infected patients randomized to receive zidovudine (ZDV) monotherapy for 24 weeks as compared to placebo [34]. In 1998, another RCTcomparing ZDV monotherapy for 24 weeks to placebo showed improved CD4+ T cell counts at 1 year but no difference in viral load or clinical events, suggesting that there was early development of ZDV resistance when monotherapy was used in acute infection [35].

The results of the randomized controlled SETPOINT study were recently published in which early versus delayed ART in early (< 6 months) HIV infection was studied to determine whether viral load set point could be altered after treatment interruption [36••]. Early HIV-infected patients were randomized to receive 36 weeks of three-drug ART or to defer therapy until they met predefined criteria. Predefined criteria included having a CD4+ T-cell count ≤ 350 cells/mm^3 at two consecutive determinations ≥ 4 weeks apart, having a CD4+ T-cell count ≤ 200 cells/mm^3 or 14%, HIV RNA level ≥ 750,000 copies/mL plasma 4 weeks into the study or ≥ 200,000 copies/mL at 12 weeks into the study, or CDC category B or C diagnosis. This study was halted prematurely by the Data Safety Monitoring Board due to futility. The deferred treatment arm experienced more rapid disease progression than expected. Notably, by week 72, 50% of subjects in the deferred therapy arm met immunologic or virologic criteria, 20% within the first 36 weeks. Because of this higher than anticipated rate of disease progression, the virologic set point differences between the two groups could not be statistically evaluated. Guidelines have changed since this study began, with a recommendation to start ART during chronic infection once CD4+ T-cell counts drop ≤ 500 cells/mm^3. It would be important to know what number of subjects in the deferred arm reached a CD4+ T-cell count ≤ 500 cells/mm^3 within 36 weeks.

Recently, the preliminary findings of a Dutch open-label randomized three-arm study were reported, which compared 173 acutely HIV-infected subjects who were either untreated, treated with ART for 24 weeks or 60 weeks followed by a treatment interruption. The primary endpoint of needing to start/re-start ART if CD4+ T-cell counts fell below 350 cells/mm^3 or if subjects had an AIDS-defining condition was reached at 0.7 years, 3.1 years,

and 2.1 years respectively. Additionally, viral load set points (log_{10} c/mL) were reported at 36 weeks after randomization or treatment interruption as 4.8 in the untreated arm, and 3.9 and 4.2 in the 24-week and 60-week treated arms. Authors concluded that early and temporary ART lowered the viral set point and delayed treatment initiation during chronic HIV infection [37].

Results of a randomized controlled trial, SPARTAC, were reported at IAS 2011 [38]. Subjects with acute HIV infection were randomized to receive three-drug ART within 6 months of infection for 48 weeks (ART-48), 12 weeks (ART-12), or no therapy (standard of care, SOC). The primary endpoint was time to CD4+ T-cell counts < 350 cells/mm^3 or long-term ART initiation after treatment interruption. Fifty percent of ART-48 participants reached the primary endpoint compared to 61% in each of ART-12 and SOC groups. ART-48 conferred a significant delay in time to reach primary end point compared with SOC, a median of 65 weeks longer, while ART-12 had no effect compared with SOC. ART-48 conferred a reduction in HIV RNA of 36 weeks after interrupting therapy compared with SOC. There were no significant differences between groups in progression rates to AIDS, death, or the incidence of serious adverse events. These investigators concluded that 48 weeks of ART in acute/early HIV infection delayed disease progression.

B. Observational Studies Evaluating Treatment Interruption After ART in Acute HIV: There have been a number of observational studies that have evaluated whether there is benefit to short-term ART initiated during acute HIV infection followed by treatment interruption. One 2006 study prospectively assessed whether initiation of three-drug ART during acute infection and given for 24 weeks would improve adaptive immune responses after treatment interruption. They compared 12 treated subjects to 6 untreated acutely HIV-infected controls. Treatment resulted in suppression of viremia, an increase in the $CD4^+$ T-cell count, enhanced differentiation of HIV-specific $CD8^+$ T cells from effector memory to effector cells at week 24 of treatment, and significantly higher virus-specific interferon-γ^+ $CD8^+$ T-cell responses after viral rebound (at week 48). However, no differences in viremia or in $CD4^+$ T-cell counts were found 6 months after ART was stopped [39]. However, in a 2006 study, initiation of ART within 2 weeks of HIV infection and treatment for at least 12 weeks was associated with sustained viral load and CD4 cell count benefits for up to 72 weeks after termination of therapy [40]. In 2007, another study found that in patients who received 3 months of antiretroviral therapy during acute infection, the subsequent CD4+ T-cell count decline over 3 years was slower than in patients who did not receive acute therapy [41]. Similarly, in subjects treated during acute infection in the Swiss cohort study, treatment was interrupted after 18 months of ART and it appeared that viral loads was were lower in the first year but not 3 years after treatment interruption as compared to untreated control subjects, suggesting that treatment of acute HIV effects are likely transiently beneficial [42].

C. QUEST Study: Largest Prospective Observational Study: In 2007, the largest prospective trial of ART during acute infection, QUEST, showed that acutely HIV-infected patients treated with four-drug ART for 1 year experienced a significant improvement in CD4+ T-cell counts, decreased markers of immune activation (CD38 + CD8+ T cells), and decreased proviral DNA levels as compared to untreated acutely HIV infected controls [43, 44]. Notably, there was a high incidence of clinical depression (11%), of treatment non-adherence (36%), and of grade 3 or 4 liver function test elevations (12%–19%) in the treated patients.

D. Lack of Complete Mucosal Immune Reconstitution Despite ART in Acute and Early HIV: Although blood CD4+ T-cell counts are preserved when acute HIV is treated with ART, investigators evaluated whether gut-associated lymphoid tissue (GALT) similarly

reconstitutes. They performed colonoscopies on acutely HIV-infected subjects who initiated ART during acute infection. Colon biopsies were performed 1–7 years following acute infection. As compared to uninfected control patients, blood CD4 T-cell counts and markers of immune activation normalized but gut lymphocyte populations were persistently 50%–60% depleted at 1–7 years on fully suppressive ART [4].

3. Decreased Viral Reservoir, Future Opportunities for Functional Cure—Cells latently infected with integrated HIV DNA serve as a viral reservoir that persists during ART and contributes to viral rebound after treatment discontinuation. Treating with ART during acute/early HIV infection may reduce the size of the latent reservoir. As new therapeutic vaccines and immunotherapies are developed, it is possible that a smaller viral reservoir may increase chances for successful HIV eradication, particularly as early proof of concept clinical trials of compounds such as histone deacetylase (HDAC) inhibitors are being performed.

At CROI 2011, Jain et al. presented data showing that subjects with acute/early HIV infection (< 6 months) who started ART early (< 6 months after estimated date of HIV infection) versus later (≥ 2 years) and who maintained ≥ 2 years of subsequent virologic suppression had lower levels of activated CD4+ and CD8+ T cells as compared to the group treated later, but still higher than uninfected control subjects [45]. Deferred therapy was also associated with a 4.8-fold higher level of proviral DNA and also higher cell-associated RNA levels. The size of the viral reservoir during ART was associated with the percentage of activated (CD38, HLADR, CCR5, PD1) CD4 and CD8+ T cells. Also at CROI 2011, Ananworanich et al. presented data of 20 Thai subjects with acute HIV infection who were treated within 3 weeks of infection with a four-drug regimen [46]. After 6 months of ART their colon and blood evidenced undetectable levels of HIV RNA (< 50 copies/mL). Colon and blood T-cell subsets were comparable to uninfected controls.

At the Fifth International Workshop of HIV Persistence during Therapy 2011 meeting, Buzon et al. presented data from a cohort of subjects who were treated with ART during acute HIV infection and followed for 10 years while fully suppressed on ART [47]. CD4+ T cells were isolated from these subjects and compared to that from treatment-naïve elite controllers (EC: undetectable viral load in the absence of ART) and subjects who initiated ART in the chronic phase of infection. In comparison to chronic treated patients, levels of integrated HIV DNA and total HIV DNA were significantly lower in EC and acutely treated, while no differences were seen between EC and acute treated, contributing to increasing evidence that prolonged ART initiated during acute HIV may result in reduced levels of HIV residing in established latent reservoirs.

4. Treatment During Acute Infection Preserves HIV-Specific Immunity—There is evidence that treatment during acute infection may preserve HIV-specific adaptive immune responses. Oxenius et al. evaluated HIV-specific CD4+ and CD8+ T cells responses in HIV-infected subjects who received ART within the first 6 months of infection as compared to those who deferred therapy [48]. They found that delayed initiation of ART is associated with a progressive loss of HIV-specific CD8+ T cells and absent HIV-specific CD4+ T cell responses, whereas even transient ART given early during acute infection preserved HIV-specific adaptive immune responses. Similarly, Rosenberg et al. showed that subjects treated early during infection maintained HIV-specific CD8+ and CD4+ T-cell responses, which correlated with a much decreased viral load set point after treatment interruption [49]. These studies have encouraged researchers to test immunomodulatory agents and to develop therapeutic vaccines to enhance immunologic control of HIV [32, 50–56].

5. Why Wait to Treat? Time to CD4 ≤ 500. After Seroconversion—The most recent HIV treatment guidelines recommend earlier therapy—advising initiation with ART when CD4+ T cell counts fall to levels at or below 500 cells/mm^3, so as to reduce the development of co-morbidities such as cardiovascular, kidney, and liver disease, and non-AIDS malignancies [57, 58]. New data asks the intriguing question of how long it takes for patients to reach a CD4+ T cell count ≤ 500 after acute HIV infection. Using Concerted Action on Seroconversion to AIDS and Death in Europe (CASCADE) data, where 25 cohorts of subjects with well-estimated dates of HIV seroconversion are followed prospectively, mixed models were fitted to estimate time from seroconversion to CD4+ T cell counts below 500 cells/mm^3. A total of 18,495 subjects were evaluated with the median time to CD4+ T cell counts to below 500 cells/mm^3 being only 1.19 years, to below 350 cells/mm^3 was 4.19 years, and to below 200 cells/mm^3 was 7.93 years [59]. Notably, this CASCADE cohort was also investigated to understand whether time to start ART after seroconversion affected AIDS or death outcomes. They found that CD4+ T-cell counts less than 500 but not 500–799 cells/mm^3 were associated with slower disease progression and increased mortality [60••]. Similarly, investigators compared the PRIMO Beijing MSM cohort to the MSM component of the CASCADE cohort. They showed that median CD4+ T-cell counts at diagnosis in the PRIMO cohort were 504/uL and in the CASCADE cohort were 554/ mm^3. By 2 years following acute HIV, median CD4 T cell counts were 194 cells/ mm^3 lower in the PRIMO cohort and 149 cells/mm^3 lower in the CASCADE cohort [61]. These data suggest that the time to development of CD4+ T cell counts to levels below 500 cells/mm^3 may be more accelerated than presumed, and that the additional time on therapy represents a small percentage of the total time on ART for most patients.

Rationale Against Treatment of Acute HIV Infection: For the Individual

Although there are potential benefits associated with initiation of ART during acute HIV, there are also limitations to this approach. Concerns about long-term toxicity and the development of ART resistance have served as a rationale for the deferral of HIV therapy during acute HIV. Although newer ART regimens are generally better tolerated, more convenient, and more potent than older regimens, there are fewer longer-term safety data for the newer drugs. Earlier initiation of ART may extend exposure to ART by several years. The D:A:D study found an increased incidence of cardiovascular disease associated with cumulative exposure to some drugs within the nucleoside reverse transcriptase inhibitor (NRTI) and protease inhibitor (PI) classes [62, 63]. In the SMART study, continuous exposure to ART was associated with significantly greater loss of bone density compared with interruption or deferral of therapy [57].

Initiating ART during acute HIV may lead to an earlier onset of drug resistance selection in non-adherent patients. Consequently, patients may have limited options for future drug regimens and, importantly, may be more likely to transmit drug-resistant virus to others. Although studies support decreased development of drug resistance when ART is started at higher CD4+ T cell counts [64], patient "readiness" to start ART during acute HIV infection is of utmost importance. Patients must fully understand that absolute treatment adherence is necessary to prevent drug resistance before they initiate lifelong ART.

Although ART is costly, several modeling studies actually support the cost effectiveness of HIV therapy initiated soon after diagnosis [65–67]. It has been reported that the annual cost of care is 2.5 times higher for patients with CD4+ T-cell counts below 50 cells/mm^3 compared with patients with CD4+ T-cell counts above 350 cells/mm^3 [68]. However, no cost comparisons have been reported between those starting ART with a CD4+ T cell counts between 350 and 500 cells/mm^3 as compared to CD4+ T cell counts above 500 cells/mm^3.

Rationale for the Treatment of Acute HIV Infection: Public Health Implications

New data strongly support an evolving paradigm of "treatment as prevention," such that treating HIV-infected individuals will decrease transmission to others. This principle strongly applies to the acutely HIV infected patient. The efficiency of HIV transmission is proportional to the amount of blood and genital viral load in the individual and acutely HIV infected patients have tremendously high viral loads in their blood and genital secretions [69–71].

Although it is biologically probable that acute HIV contributes strongly to sexual transmission, the proportion of transmission events attributable to acute HIV infection are challenging to study. Increased rates of transmission in early and late HIV were observed in the Rakai cohort in Uganda, with (8.2/1000) events of transmission per coital act during the first 2.5 months of infection, (0.7/1000) events during chronic infection, and (2.8/1000) in the last 6–24 months of life [7]. During acute HIV the hazard ratio was calculated to be 26 times higher when compared to chronic HIV infection [72].

In Quebec, related transmission clusters were investigated by evaluating phylogenies reconstructed from sampled viral gene sequences of persons who had seroconverted in the most recent 6 months [73]. Approximately half of the persons who seroconverted in the previous 6 months co-segregated into 75 transmission clusters, while the remaining individuals had unique sequences, suggesting that early HIV infection was responsible for approximately half of HIV transmission events. In related studies, about 30–35% of patients with acute HIV infection cosegregated into phylogenetically related clusters [74, 75].

Using mathematical modeling, sexual transmission events during the epidemic phase of HIV may be more influenced by acutely infected individuals than during the endemic phase [76–82]. All together, however, it is likely that acutely HIV-infected persons contribute disproportionately to sexual transmission. As "test and treat" strategies are being evaluated [83], it will be important to understand whether treating acutely HIV-infected persons will aid in curbing transmission.

Revisions to Clinical Practice Guidelines in 2010–2011

The HIV treatment guidelines from the Department of Health and Human Services (DHHS) [5] and International Antiviral Society-USA (IAS-USA) [6] have recently been revised in 2011 and 2010, respectively. Regarding acute/ primary HIV infection, both the older and the revised guidelines recommend starting ART if acute HIV is symptomatic (rated A1a; strongly recommended). For asymptomatic individuals, the revised guidelines recommend treating during acute HIV if CD4+ T cell count ≤ 500 whereas the earlier guidelines recommended treating when CD4 T + cell count ≤ 350. This change reflects changes in the guidelines to begin treating chronic HIV infection when CD4+ Tcell count ≤ 500. Both old and new guidelines recommend treatment of all HIV-infected pregnant women (A1) because acute or recent HIV infection is associated with a high risk of mother-to-child transmission of HIV [84]. Both older and revised guidelines conclude that there is insufficient data to recommend treatment of acute HIV infection at this time, but that treatment of acute HIV infection should be considered optional and that any potential benefits must be weighed against the risks of potential drug toxicities, development of drug resistance, and need for continuous therapy with strict adherence.

Choosing the Best ART Regimen for Treatment of Acute HIV Infection

Transmitted Drug Resistance—Transmitted drug resistance has been reported in 6%–16% of newly acquired HIV infections [85, 86]. For example, in a European multi-cohort study, 10,056 subjects were evaluated for drug resistance mutations prior to starting their

first ART regimen. A total of 9.5% had evidence of transmitted drug resistance, with 15% experiencing treatment failure at 1 year, with the hazard ratio for the risk of failing their initial treatment regimen being twofold higher for those with a NNRTI-containing regimen [87]. Notably, clinically relevant transmitted PI resistance is quite uncommon [88–90]. Therefore, if ART is begun before genotype testing is available, a non-NNRTI, ie, a PI-based regimen should be chosen. Though an integrase inhibitor-based regimen could be considered as empiric therapy in the setting of acute infection there is little data regarding the durable antiviral efficacy of this regimen in patients with plasma HIV-1 RNA levels in excess of 10^6 copies/mL [91].

Conclusions

Acute HIV infection represents a unique treatment opportunity in the course of infection both for the individual and from a public health perspective. Given current treatment guideline recommendations regarding earlier therapy as well as improvements in safety and tolerability of current preferred first-line regimens and the promise of future immunologic interventions, it would appear that the benefits of early therapy are likely to outweigh the risks (Table 2). That said, if possible, when the diagnosis is made providers should consider enrolling patients with acute HIV infection in a clinical trial. From the evidence that we have presented in this review, it is paramount that we more clearly determine the role of ART in this setting. Information regarding such trials can be obtained at www.clinicaltrials.gov or from local HIV treatment experts.

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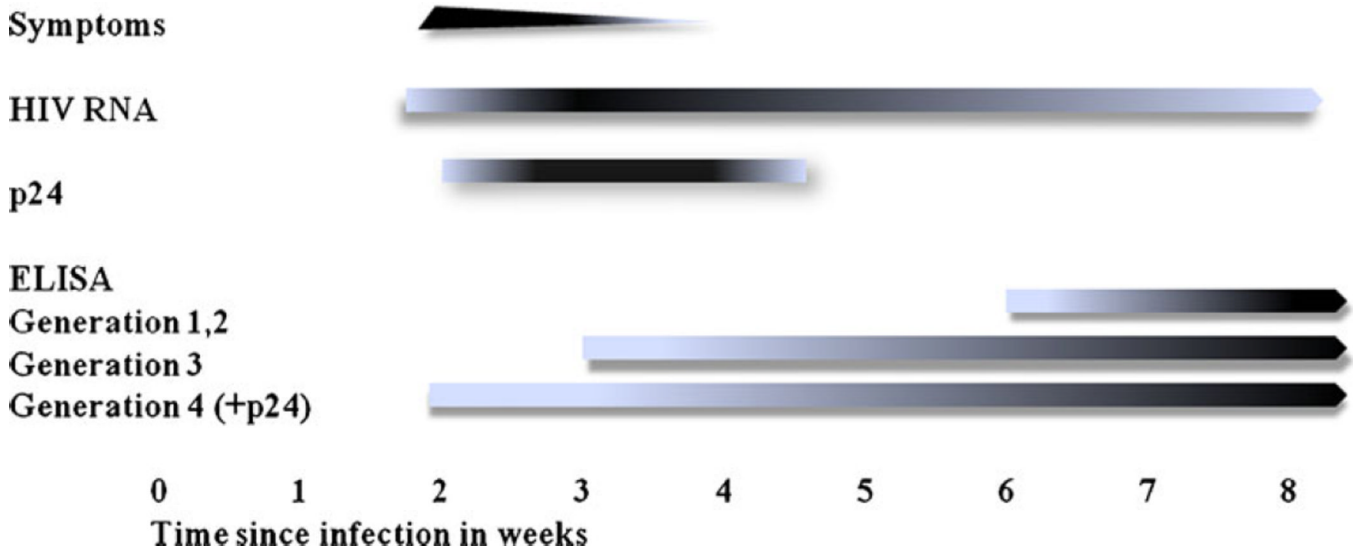

Fig. 1.
Timeline of acute HIV presentation and diagnostics

Table 1

Summary of clinical trials of treatment of acute HIV with ART

Study	Time to ART from diagnosis	Duration of ART	Outcome, as compared to untreated
Kinloch-De Loes (1995) [34] Placebo-controlled RCT	25 days	24 weeks	Less opportunistic infections during treatment
AZT monotherapy			
Niu (1995) [35] Placebo-controlled RCT AZT monotherapy	18 days	24 weeks	Improved CD4+ T cell counts at 1 year after treatment interruption (TI) but no difference in viral load (VL) or clinical events
Hogan, SETPOINT (2011) [36••] RCT	Within 6 months	36 weeks	Delayed time to CD4+ T cell counts ≤ 350 cells/mm^3 after TI
3-drug ART			
Streeck (2006) [39] Observational prospective	25 days	24 weeks	Improved HIV-specific CD8+ T cell responses, no improved VL for 6 months after TI
3-drug ART			
Hecht (2006) [40] Observational prospective	14 days	12 weeks	Decreased VL, improved CD4+ T cell count for 72 weeks after TI
3-drug ART			
Fidler (2007) [41] Retrospective	"During primary infection"	12 weeks	Slower CD4+ T-cell decline after TI
3-drug ART			
Von Wyl (2011) [42] Observational prospective	16 weeks	18 months	Decreased VL for 1 y but not 3 y after TI
3-drug ART			
Grijsen (2011) [37] Randomized 3-arm	"During primary infection"	24 or 60 weeks	Decreased VL and decreased time to start ART 36 wk after TI
3-drug ART			
Fidler, SPARTAC (2011) [41] RCT	Within 6 months	12 or 48 weeks	Delayed time to CD4 T-cell count < 350 cells/mm^3 after TI
3-drug ART			
Hoen, QUEST (2007) [43] Observational prospective	"During primary infection"	48 weeks	During treatment, improved CD4+ T-cell counts, decreased markers of immune activation (CD38 + CD8+ T cells), and decreased proviral DNA
4-drug ART			

Table 2

Rationale for and against starting ART during acute HIV

Rationale for ART in acute HIV
• To reduce the risk of viral transmission
• To decrease viral reservoir for future therapeutic vaccines or immunotherapies
• As earlier ART is indicated, why wait?
Disadvantages of ART in acute HIV
• Potential development of drug resistance if patient is non-adherent
• Earlier commitment to lifelong therapy
• Less time to educate patient about ART
• Insufficient data regarding effectiveness of early treatment