

Primary HIV infection: to treat or not to treat?

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Current Opinion in Infectious Diseases 2008, 21:4–10

Purpose of review

The aim of this article is to review new data on the use of antiretroviral therapy in primary HIV infection.

Recent findings

The concept of 'hit HIV hard and early' supporting the use of antiretroviral therapy to treat the early stages of HIV infection has been revisited. Recent demonstration of massive, rapid and largely irreversible HIV-mediated destruction of memory CD4+ T cells predominantly occurring in the gut suggests that primary HIV infection may be the only time that intervention could confer lasting immunological benefit. There are no data, however, from randomized controlled trials supporting the use of antiretroviral therapy in primary HIV infection, although a number of observational studies have demonstrated limited, transient improvements in measured immunological outcomes. The first randomized controlled trials powered to address whether antiretroviral therapy of a limited duration in primary HIV infection can influence long-term CD4 decline (SPARTAC) is now fully recruited but will report in 2–3 years. In addition, given that individuals with primary HIV infection contribute disproportionately towards onward HIV transmission, there may be an additional public health impetus for earlier diagnosis and intervention in primary HIV infection.

Summary

In the absence of randomized controlled trials data demonstrating clinical benefit of antiretroviral therapy intervention in primary HIV infection, clinical guidelines remain unclear. Intervention seems a logical strategy to counter the high viraemia, enhanced onward transmissibility, and immunological destruction which occurs during primary HIV infection. The nature, duration and timing of that intervention after HIV acquisition remains unknown.

Keywords

antiretroviral therapy (ART), primary HIV infection, seroconverters

Curr Opin Infect Dis 21:4–10
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0951-7375

Introduction

HIV treatment strategies conferring durable virological control, with sustained immunological function in the absence of drug-associated toxicities, are highly desirable. Although effective suppression of HIV using antiretroviral therapy (ART) has remarkably altered the clinical course of HIV disease [1], the optimum timing for treatment initiation is unknown. The goal of early intervention is to preserve immune function ordinarily lost, enhance rapid viral control, and limit the size of the HIV reservoir, with the aim of attenuating long-term outcome. Recent discontinuation of a randomized controlled trial (RCT) evaluating strategies of treatment interruption in chronic HIV infection [2^{*}] in addition to halting an adenovirus vaccine trial [3] has once more refocused the field to interventions in primary HIV infection (PHI), but the nature and timing of that intervention needs reevaluation.

Pathogenesis of HIV infection

PHI refers to the initial phase (up to 6 months following acquisition) of infection characterized by a transient period of massive unchecked viral replication with consequent destruction of memory CD4+ T cells [4]. PHI is followed by partial and variable control of viral replication, chronic immune activation, progressive decline of the naïve and memory T-cell pool, and systemic CD4+ T-cell depletion. Presentation with severe 'seroconversion-like' illness, AIDS defining illnesses, and central nervous system involvement are associated with more rapid disease progression [5–10]. In addition, persistently low CD4 T-cell counts (<200 cells/cm³) and high plasma viral load (pVL) (>500 000 copies HIV RNA/ml) level at PHI diagnosis, and high subsequent viral set-point predict rapid progression in the absence of intervention [11,12].

Upon transmission to a new host, HIV specifically targets CCR5+ CD4+ effector memory T cells, focused in the gut associated lymphatic tissue (GALT) [13,14], resulting in acute, massive high level viral replication leading to major irreversible damage to CD4+ T-cell-mediated immune functions [15]. Due to sparing of naïve and central memory T cells this initial depletion does not immediately compromise the overall capacity of the immune system [16]. Preferential infection of HIV-specific CD4+ T cells [4] reduces their life span *in vivo* thereby compromising the generation of effective immune responses to any antigen challenge as well as to the virus itself [17]. Continual HIV-mediated stimulation of the immune system leads to a perpetual state of heightened immune activation [18], the level of which has been shown to be a better predictor of clinical outcome than pVL [19]. Primate models have demonstrated that healthy animals with high-level SIV replication have low levels of immune activation [20]. Similarly, analysis of three clinically stable individuals with high-level HIV replication demonstrated low levels of immune activation and preserved HIV-specific T-cell responses [21]. Translocation of microbes across an HIV-damaged gut mucosa [14] is one recently postulated source of maintained immune hyperactivation. A marker for microbial translocation is serum level of lipopolysaccharide (LPS) [14,22*], which is low in long-term nonprogressors and diminishes in response to ART [23]. Although early ART intervention in PHI can limit immune activation markers [24] and confer enhanced immune function in peripheral blood and lymph nodes, limited effects were observed on GALT immune activation markers and immune reconstitution [25].

To treat primary HIV infection: the rationale for intervention

It has been proposed that the 'die is cast' for long-term clinical outcome at the time of acute HIV infection [26]. PHI therefore represents a unique window of opportunity where intervention could confer longstanding benefits.

The first RCT of treatment in PHI demonstrated enhanced clinical outcome for participants receiving azidothymidine monotherapy for 6 months over those receiving no therapy [27]. Subsequently, there have been many observational studies investigating, first dual and then triple, therapy in PHI [28]. To date there are no data definitively addressing the role of ART in PHI on long-term clinical outcome.

Observational studies

Although observational studies cannot infer treatment efficacy or superiority over no therapy, their findings clearly signal the need for randomized comparisons. A summary of recent findings from observational and RCT studies of persons treated in PHI is presented in

Table 1. Studies of ART in acute HIV-1 infection demonstrated attenuation of in-vitro immunological function as measured by HIV-specific IFN- γ and IL-2-producing CD4 T cells in treated compared with untreated participants. Immunological preservation, however, was not associated with control of viraemia upon treatment interruption [29]. A multicentre observational study using at least 12-weeks ART for both acute (within 2 weeks of HIV acquisition, $n = 13$) and early (2 weeks to 6 months after infection $n = 45$) infection was compared with 337 untreated controls. The authors reported viral load and CD4+ T-cell count benefits lasting up to 24 weeks after stopping ART with more marked effects the earlier ART was initiated. The observed CD4 count benefits were sustained in the treated group although these diminished over time with no long-term viral load benefits up to 72 weeks after stopping ART [30].

In support of these findings, we have recently reported that the rate of CD4 decline was significantly delayed in volunteers receiving a 12-week course of ART at PHI when compared with matched untreated historical controls from CASCADE, a collaboration of seroconverter cohorts [31]. We failed, however, to identify any significant effect on plasma viral load up to 3 years after stopping therapy between the treated patients and the matched untreated controls. A similar comparison study examined virological control between individuals receiving 18 months ART with or without vaccination in the Quest study with historical matched untreated controls, also from CASCADE [32]. This analysis reported that transient ART in acute infection might increase the probability of low pVL after treatment discontinuation, but that such an effect was likely to be modest. Furthermore, initiating ART during acute infection has been shown to prevent immunological decline and enhance natural killer T-cell subset function during the first year following HIV acquisition [24]. Additional studies demonstrating immunological benefits from safe early ART intervention in PHI [33] support these findings. Hence although transient ART in PHI can confer measurable immunological benefits there are little data to support attenuation of virological control.

Development of resistance to ART is often cited as a reason not to intervene in PHI in the absence of a clear clinical indication, but published findings by the authors [34–36] and others [28] have not identified induction of significant drug resistance following transient ART in PHI.

Randomized ongoing studies

Randomized controlled trials are the only tool that can conclusively address the role of ART intervention in PHI. SPARTAC [37], an international RCT powered to determine the effect of two ART schedules of limited

Table 1 Summary of recently published studies in primary HIV infection

RCT	Publication	Participants (n)	Intervention	Primary endpoints	Conclusion
Quest	[49] JID 2005	79	Intermittent ART + either: ALVAC-HIV	pVL < 1000 copies HIV/RNA/ml 24 weeks after stopping ART	Vaccination conferred no additional virological benefit over placebo HIV-specific immunological benefit was seen
	[78] CID 2007	148	ALVAC-HIV + Remune placebo	In-vitro CD4+ CD8+ T-cell function and % CD8+ CD38 expression	Initiation of ART in PHI was associated with very significant antiretroviral activity and a decrease in immune activation
SPARTAC	[37]	371	12 weeks ART 48 weeks ART No ART	Time to CD4 <350	n/a
ACTG 571	[38]	180		Viral load at week 48 after infection	n/a
Observational studies	[30]	13 treated acute 45 treated early 337 untreated	12 weeks ART		CD4 benefit Short term pVL benefit Acute > early
	[33]	12 treated 8 untreated	24 weeks ART No therapy	Viral load CD4 T-cell counts HIV-specific CD8+ IFN- γ production	CD8+ T-cell benefits of treatment 48 weeks after PHI No CD4 or viral load benefits up to 24 weeks after stopping therapy
	[31]	140 treated PHI 139 CASCADE matched untreated	12 weeks ART		CD4 benefit short-term pVL
	[32]	Quest treated vaccinated CASCADE matched untreated controls	18months ART \pm vaccine		Short-term viral load benefit
	PRIMO	[11]	30% of 565 received ART versus no ART	Time to CD4 <350	

ART, antiretroviral therapy; n/a, not available; PHI, primary HIV infection; pVL, plasma viral load; RCT, randomized controlled trial.

duration in PHI on the rate of CD4 cell decline and, consequently, on the time to initiating clinically indicated anti-HIV therapy is now fully recruited (371 participants) but will not report for a further 2–3 years. An additional RCT, which is currently recruiting, by the ACTG group, is powered to address virological outcomes between two ART interventions in PHI [38].

What antiretroviral therapy regimen to use

Data from ART use in drug naïve chronic HIV disease can be extrapolated to PHI, where both potency and tolerability must be considered when prescribing ART. Avoidance of non-nucleoside reverse transcriptase inhibitors (NNRTI) drugs, in particular nevirapine, is probably advisable for a number of reasons. Firstly, the tendency for skin involvement in PHI makes a rash more likely and, consequently, more difficult to determine if caused by the treatment or the virus. Secondly, variable and unpredictable metabolism of NNRTIs [39] makes it difficult to manage intermittent therapy. Thirdly, the relatively high rates of transmitted drug resistance to NNRTIs make their use less universal. Finally, the reported association of abnormal liver function tests [40] with higher CD4 T-cell counts make hepatotoxicity more of a risk in PHI where

commonly the CD4 count remains higher than in chronic late stage disease.

An observational study comparing virological response to three different ART regimes in PHI demonstrated an enhanced rate of decline of primary viraemia with a four-drug combination (azidothymidine, 3TC, abacavir and efavirenz) but at the cost of toxicity [34]. The continued observed low level of transmitted drug resistance to ritonavir-boosted protease inhibitor agents in the UK [41], in addition to problems with NNRTI-containing regimens in this setting, mean they remain, in our opinion, the agent of choice as part of an initial triple regimen.

When and how long should treatment be for?

Long-term toxicities resulting from extended exposure to ART agents are well recorded [42] and unnecessary drug exposure from the time of PHI is difficult to justify on the basis of current evidence.

Structured treatment interruption studies in chronic HIV infection remain controversial, with some groups reporting encouraging outcomes [43] whilst others report disappointing results. In all structured treatment interruption studies of chronic infection ART initiation was based upon clinical

evidence of immune suppression and CD4 decline. The SMART trial comparing the safety and efficacy of two antiretroviral treatment strategies – CD4-guided intermittent therapy or continuous therapy – was terminated early after an interim analysis reported that participants in the intermittent therapy arm were more likely than those on continuous therapy to experience disease progression or death due to both AIDS related illnesses as well as cardiovascular, liver and kidney disease, irrespective of CD4 count [44]. It is probably inappropriate to extrapolate these findings to PHI given that the use of ART in PHI is prior to the development of severe immunological dysfunction and pathogenesis of PHI differs vastly from chronic disease [14,45^{••}]. Intuitively, the earlier that intervention can be initiated following HIV acquisition, the more enhanced will be the anticipated effect on outcome. Although much of the early immunological work has focused on very acute infection [46,47], a more recent study [30] comparing early intervention (<14 days) with later (2 weeks to 6 months) identified immunological benefit in both groups, but enhanced outcome was only seen with earlier intervention. Primate models have identified, however, that ART initiated ‘too early’ could compromise the development of an HIV-specific immune response [48].

Immunological manipulation in primary HIV infection

Attenuation of the naïve HIV-specific immune response towards ‘protective’ epitopes has been investigated in PHI. Studies including therapeutic vaccination with early ART have had encouraging immunological outcomes. A large scale randomized double blinded placebo controlled trial ‘Quest’ compared quadruple ART in PHI with or without T-cell stimulating additional vaccination arms of either ALVAC-HIV (vCP1452), ALVAC-HIV with Remune or placebo [49]. This trial was powered to determine if addition of a therapeutic vaccine to early intermittent ART in PHI could increase the probability of having a plasma viral load of less than 1000 copies HIV RNA/ml 24 weeks after discontinuation of ART. Subjects receiving active therapeutic vaccination had significantly increased HIV-specific CD4⁺ and CD8⁺ T-cell responses *in vivo* measurable by IFN- γ enzyme-linked immunosorbent spot technology. Disappointingly the addition of either vaccine did not confer any benefit to the virological outcome when compared with placebo. Other therapeutic vaccination strategies in PHI have been similarly discouraging [50].

Immunosuppression

Long-term clinical outcome can be predicted by the measured levels of markers of T-cell activation [19,51–53]. Early modification of T-cell activation using immunosuppressive agents (e.g. cyclosporin) in addition to ART has been investigated [54]. Results of an observational study in nine individuals with PHI treated with ART in addition to cyclosporin A have been encouraging,

reporting significantly enhanced and preserved CD4 T-cell counts up to 104 weeks after stopping ART+ cyclosporin when compared to those individuals receiving ART alone, but the small numbers enrolled in this study mean more work needs to be done in this area [55]. Additional studies employing other immunosuppressive agents such as hydroxyurea [56] or rapamycin [57] in chronic infection have observed limited benefits. More in depth understanding of the early interplay between viral replication and the development of a protective immune response needs to be investigated. Such work is underway in a unique large-scale co-ordinated initiative involving multiple disciplines supported by the Center for HIV-AIDS Vaccine Immunology (CHAVI) [58] prospectively studying viral evolution and HIV-specific and innate immune responses in acute HIV infection.

Antiretroviral therapy in primary HIV infection for public health benefit

Several groups have reported disproportionate rates of onward transmission of HIV from individuals with acute infection [59–65], although this remains controversial [66]. To date HIV prevention efforts have largely focused on HIV-uninfected subjects, but by targeting those contributing most significantly to the propagation of disease, additional success maybe achieved [61,67[•]]. Although the high level viraemia of PHI lasts at most 2–6 months, early identification of PHI enabling short-term interventions could be highly effective in reducing transmission. The introduction of such a scheme on a large scale, although enormously resource intensive, would facilitate both partner notification and the timely implementation of ART and could potentially reach the source of new transmissions and reduce the incidence of new infections [68]. This is under investigation in an RCT of ART comparing ART with no therapy in matched HIV serodiscordant couples (HTPN 052) [69].

Not to treat: the rationale for not intervening

The lack of randomized evidence to support the use of ART in PHI, the risk of drug toxicity and of developing ART resistance, in addition to the cost implications, has led most HIV treatment guidelines not to recommend routine ART in treating PHI [70,71]. Furthermore, concerns of successful ART initiation with sustained adherence to complex regimens, at a time of immense emotional and physical upheaval have been raised. Lessons learnt from the use of single dose nevirapine, whilst a relatively successful tool to prevent mother-to-child HIV transmission, can induce nevirapine resistance in a significant proportion of treated women [72]. Several observational PHI intervention studies, whilst reporting

moderate immunological benefits, have failed to identify any limitation in long-term levels of viral load or set point [73,74]. The French Primo study reported a lack of substantial effect of transient ART in PHI in lowering the virological set point following treatment interruption [75], as did Quest [49].

If ART intervention in PHI is not for life at some point it must be stopped. Viral rebound, the phenomenon in which interruption of ART causes a rapid return to pretreatment viral load, is known to be a potential source of renewed massive immunological destruction. One concern is that the use of intermittent ART in PHI could potentially provide a second assault on the immune system. In a recent report by Seng and colleagues CD4 loss following treatment interruption in PHI was higher than that observed naturally [74], although this is in contrast to a Swiss cohort study in chronic HIV infection [73].

HIV-specific immune responses require the presence of antigen to initiate and perpetuate them optimally. Early ART intervention at a time when an HIV-specific immune response is developing could be detrimental to the overall effective induction of a potent immune response, or at best may delay true 'seroconversion' until ART is stopped. Usually by the time ART is initiated in PHI human studies sufficient viral antigens have been presented to the immune system to stimulate measurable responses. Treatment of very early PHI, however, can delay or even reverse the development of an HIV-specific antibody response: seroreversion [48,76]. In a study of early ART treatment in PHI, HIV antibody seroconversion on second-generation, although not third-generation enzyme immunoassay antibody tests, failed to occur when ART was initiated very early [77]. Antibody seroreversion did not, however, indicate viral eradication.

Conclusion

Although it is unethical to delay the use of ART until irreversible and catastrophic immunological damage to the immune system has occurred, it remains uncertain whether early use of ART in PHI can influence long-term clinical outcome. Whilst the results of SPARTAC are awaited, where does this leave the clinician and their patient presenting with a diagnosis of acute HIV infection? In the presence of profound immunosuppression, an AIDS defining illness or a sustained (> 3 months) CD4 count below 200 cells/cm³ at PHI, ART should be considered. For the vast majority of individuals presenting with asymptomatic PHI, low grade symptoms or CD4 counts above 350 there is still no convincing evidence that ART initiation can confer long-term clinical benefits and entry into a clinical trial, if available, can be the only rational recommendation.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 95).

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