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Editorial

Treating primary HIV infection — is your HAART in it?

Don E. Smith[A,B] *and Derek J. Chan*[A]

[A]Albion Street Centre, South Eastern Sydney Area Health Service, NSW 2010, Australia.
[B]Author for correspondence; email: smithdo@sesahs.gov.nsw.au

Introduction

One of the more controversial areas in the era of combination antiretroviral therapy is whether to treat patients identified during primary human immunodeficiency virus (HIV) infection (PHI) or delay therapy until otherwise clinically indicated. Adding to this confusion is the suggestion in recent treatment guidelines to delay treatment in persons with chronic infection but to consider treating patients presenting with acute infection.[1]

In the absence of good clinical data, a case may be made for or against treating patients presenting with PHI. The potential benefits of immediate therapy are based on theoretical grounds and some small case series. In principle highly active antiretroviral therapy (HAART) may:

- Prevent the destruction of the accumulating HIV-specific CD4+ host response (thought to be critical in the immune control of viral replication);
- Lower the viral set-point by preserving HIV-specific responses (set-point being prognostic of disease progression);[2]
- Reduce the severity and duration of symptoms associated with the acute retroviral syndrome, known to be an important prognostic indicator;[3,4]
- Reduce the likelihood of viral evolution and escape at a time of high viral turnover (so that emerging immune responses can more effectively control viral replication in the future);
- Reduce the early dissemination of HIV to potential sanctuary sites, such as the CSF; and
- Reduce HIV transmission to others (approximately half of all new infections are though to have originated from newly infected source patients).[5]

On the other hand, the disadvantages of treating during PHI include:

- Prolonged exposure to toxicity associated with HAART; and
- Development of viral resistance resulting from poor compliance as patients grapple with the emotional and/or physical aspects of a positive diagnosis and the perceived need to start therapy as a medical emergency.

So why is primary infection such an important phase of HIV infection? In most situations, this is when a small amount of homogeneous virus encounters an otherwise healthy immune system, so the chances of influencing long-term prognosis are greatest at this early stage. PHI may be marked by the acute retroviral syndrome (fever, headaches, myalgia, pharyngitis, lymphadenopathy and rash etc.)[6] which stems from an evolving immune response aimed at clearing HIV from the body.

The persistent generation of HIV-specific CD4+ responses is associated with the control of viremia following PHI in a minority of patients.[7] Unfortunately, for most patients these initial HIV-specific CD4+ cells are preferentially activated, infected and destroyed. Thereafter the immune response could be considered a second rate effort. Thus, preserving these specific cells and allowing them time to co-stimulate the appropriate cytotoxic CD8+ T-cells, seems an eminently sensible approach.

Treating PHI in theory

Theoretically, HAART taken during PHI may influence HIV disease progression, since the duration and severity of the acute retroviral syndrome, and the level of viral replication 6–12 months following resolution of the acute infection (viral set-point), are both strong predictors of long-term disease progression rates.[2,3,8–13] Viral loads in untreated chronically infected patients are one of the most important prognostic indictors.[14] Altering these residual replication levels with a transient period of initial therapy is therefore an appealing concept.

HAART during PHI results in improvements in surrogate markers of disease progression similar to that seen in chronic infection[15–25] and importantly seems to preserve HIV-specific immune responses. In addition, recovery of the various sub-populations of CD4+ T-cells occurs faster and appears to be more complete if HAART is commenced in early stages of HIV-1 infection.[26]

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The preservation of these HIV-specific cellular immune responses may increase the likelihood that viral suppression will be maintained if treatment is stopped. In primates, initial exposure to viral DNA, followed by viral antigen exposure results in the generation of protective immune responses.[27] In small series, disease progression rate is reduced in newly infected patients using a similar strategy based on exposure and subsequent antigen stimulation.[28,29]

From primate studies it appears that antiretroviral therapy can have a significant impact on HIV disease, but timing appears to be critical. If antiretroviral therapy is initiated early enough following exposure, then HIV infection can be aborted[30] or significantly ameliorated.[31] Unfortunately, patients are rarely identified so soon after exposure. Most patients present for care 1–2 weeks after symptoms have first appeared, so may have passed beyond any window period in which the pathogenic course of infection could potentially be significantly influenced.

Treating PHI in practice

Studies suggest that continuous HAART during and following PHI improves disease progression rates when compared to no or sub-optimal therapy.[32] However, this is also the case for continuous therapy initiated during chronic infection and thus it is unclear whether there is any greater benefit in therapy initiated during PHI *v.* chronic infection.

Comparative studies in this area are limited. One non-randomised study of two PHI cohorts compared disease progression rates in 47 subjects not on treatment with 20 subjects treated with zidovudine, lamivudine and indinavir.[32] Over 78 weeks of follow up, there were no treated patients who progressed to acquired immunodeficiency syndrome (AIDS) compared with 13% untreated patients who progressed to AIDS ($P < 0.01$). Other studies of antiretroviral therapy initiated during PHI also show no progression to symptomatic HIV disease, but are mostly of limited duration.[15,19,33,34]

So how well does transient therapy during PHI match these theoretical goals?

When compared to seroconverters in the natural history cohorts CASCADE[9] and MACS,[13] studies suggest that transient treatment during PHI does not significantly influence viral replication levels. However, both the CASCADE and MACS natural history cohorts comprised more asymptomatic seroconvertors (with lower viral loads) than symptomatic seroconverters who make up the majority of treated cohorts.

The first randomised trial of a 6-month course of zidovudine monotherapy during PHI initially suggested a significant delay in early symptomatic disease progression.[35] However, longer follow-up of this cohort failed to confirm any delay in progression to AIDS.[36] A second study using a similar treatment schedule failed to confirm any clinical benefit.[37]

The most compelling evidence for treating PHI comes from two small cohort studies and a case report. The most well publicised of these comes from Bruce Walker's group in Boston, USA, where the introduction of triple therapy in eight subjects, (ranging from 383 to 1081 days duration), resulted in a viral load (VL) of <5000 copies/mL in three subjects after their first treatment interruption and in another three subjects after their second interruption.[28] After 2.5 years of follow-up, five of these eight patients maintained low levels of replicating virus (in stark contrast to the outcomes seen in the MACS cohort); however, longer follow-up of this PHI cohort reveals ongoing relapses in viral control [Kaufmann *et al*. Limited durability of immune control following treated acute HIV infection. 11th conference on retroviruses and opportunistic infections. San Francisco, February 2004. (Abstract 24)].

In a French study, four out of nine subjects treated for 1 year maintained a low VL (500–12 395 copies/mL) out to 18 months off therapy.[29] Finally, widespread mainstream media reporting of the 'Berlin patient', who was able to achieve persistently undetectable VLs following unstructured treatment interruptions during PHI, has had undue influence in determining what might routinely be achieved with treatment during PHI.[38]

Conversely, viral set points were unaffected in a number of other open label studies of transient therapy during PHI. In one study of 16 patients (treated for 931–1822 days before discontinuing therapy), VL reached <5000 copies/mL in only four subjects — an identical VL distribution to that described in the MACS cohort.[39] Similarly, 37 patients in a UK study received short-term therapy (for 3 months or until VL <50 copies/mL) before stopping.[33] After 48 weeks off therapy the mean VL was 4.25 $\log_{10}$, comparable with a mean VL of 4.3 $\log_{10}$ in untreated seroconverters from the CASCADE cohort.

Despite the high levels of plasma viraemia during PHI, rapid reduction in VL does occur with treatment at a viral decay rate identical to that seen during treatment of established HIV-1 infection.[34] Whilst studies suggest that induced viral suppression in PHI is similar or greater to that seen during treated chronic infection, VL declines of ≥ 1 $\log_{10}$ during *untreated* seroconversion illness (following induction of cytotoxic T lymphocyte responses) are documented. Therefore, the apparently impressive effects noted with therapy during PHI in some studies may not be related solely to the potency of the medications used.[26,35,37]

Conclusion

The justification for therapy during PHI is based on the theoretical grounds of preserving immune response against HIV, which may be beneficial should that patient discontinue therapy in the future. Specific immune responses do appear

to be preserved with the early introduction of HAART but are unfortunately preferentially destroyed when therapy is stopped. Patients with a severe retroviral syndrome (usually a poor prognostic group) can, while on therapy, have surrogate markers akin to long-term non-progressors, but tend to lose these benefits once therapy is stopped.

Arguments against the use of HAART during PHI have generally flowed from the belief that persons will unnecessarily be on therapy for prolonged periods, thus increasing their exposure to long-term drug toxicities. This would certainly be the case where the toxicities associated with therapy are significant.[40] However, with the increasing awareness of the long-term limitations of certain combinations, more selective choices are being made based on long-term toxicity concerns.[41] In addition, it must be remembered that persons with symptomatic PHI are more likely to be rapid progressors, who may not be able to wait 5–6 years before therapy is clinically indicated and are thus burdened with the need for more immediate intervention.[3]

An additional complicating factor in discussions of the merits of PHI therapy has often been based around the near normalisation of immune parameters observed while patients remain on ART. This potentially allows patients to benefit from future therapies that rely on baseline immune competence. Some immune-modulating therapies appear to induce more positive responses in patients with higher baseline CD4+ cell counts, for example CD4+ nadir is an important predictor of CD4+ recovery with interleukin-2 therapy.[42] Similarly, 'therapeutic immunisations' are most commonly undertaken in patients treated shortly after seroconversion, as it is thought that these patients will have the most favourable outcomes. However, these arguments often confuse the debate of clinical benefit of PHI therapy, more accurately addressing the question of the relative benefits of early *v.* deferred chronic therapy using immunological modifiers.

Using HAART during PHI has significant short-term immunological and virological efficacy, compared to no therapy. Compared to never being treated, remaining on PHI-initiated therapy may delay clinical progression. Limited data suggest significantly greater virological suppression and immune recovery following treatment during PHI rather than chronic infection. However, there is no evidence that short-term therapy during PHI delays or alters clinical progression compared to using HAART later in the disease course.

Where does this leave the clinician who has identified a patient seroconverting to HIV? Despite numerous intervention studies, there is no compelling evidence that transient therapy during PHI affects the long-term prognosis associated with HIV infection and we conclude that treatment of PHI outside of a research setting is not warranted. Fortunately there are currently 2 PHI intervention studies about to start that now include no treatment comparator arms (M. Markowitz, ADARC, NY; I Weller, MRC, UK; personal communication), so that any confusion over the benefit of immediate therapy will hopefully be resolved.

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