Treatment Strategies for HIV-Infected Patients with Tuberculosis: Ongoing and Planned Clinical Trials

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Currently, there are limited data to guide the management of highly active antiretroviral therapy (HAART) for human immunodeficiency virus type 1 (HIV-1)–infected patients with active tuberculosis (TB), the leading cause of death among individuals with acquired immunodeficiency syndrome (AIDS) in resource-limited areas. Four trials to take place in Southeast Asian, African, and South American countries will address the unresolved question of the optimal timing for initiation of HAART in patients with AIDS and TB: (1) Cambodian Early versus Late Introduction of Antiretrovirals (CAMELIA [ANRS 1295/NIH-CIPRA KH001]), (2) Adult AIDS Clinical Trials Group A5221, (3) START, and (4) a trial sponsored by the World Health Organization/Special Programme for Research and Training in Tropical Diseases. Two other clinical questions regarding patients with TB and HIV-1 coinfection are also undergoing evaluation: (1) the benefits of short-term HAART when CD4 cell counts are >350 cells/mm³ (PART [NIH 1 R01 AI051219-01A2]) and (2) the efficacy of a once-daily HAART regimen in treatment-naive patients (BKVIR [ANRS 129]). Here, we present an overview of these ongoing or planned clinical studies, which are supported by international agencies.

Despite the fact that, globally, tuberculosis (TB) has been and continues to be the major coinfection among individuals with AIDS, it is remarkable that basic aspects of the management of these diseases are still not established. This lack of knowledge can partially be attributed to the fact that access to highly active antiretroviral therapy (HAART) in resource-limited areas where both diseases are particularly prevalent has been extremely limited. Given the magnitude of the problem and the current increased access to HAART in areas of high TB prevalence and incidence [1], the urgency of establishing optimal approaches to cotreatment cannot be overstated. Strikingly, at the time of writing, in 2006, even the optimal time to initiate HAART in patients with TB remains a point of debate [2]. Currently, the indication to start antiretroviral therapy in patients with TB and HIV coinfection depends on several factors—most importantly, clinical status and CD4 cell count in absolute and percentage values. In itself, HIV-1 load does not provide a major determinant [3]. Because of the lack of data on the optimal timing to initiate HAART in HIV-infected patients with diagnoses of TB, the decision to initiate HAART in such patients is, thus, often made on clinical grounds on a case-by-case basis.

The major beneficial effects of HAART result from gradual restoration of Mycobacterium tuberculosis–specific CD4 cell immune responses [4]. However, during the initial months of HAART, the reconstitution of immune function can also result in a transient worsening or appearance of new signs, symptoms, or radiographic manifestations of TB [4–6]. Such immune reconstitut-
tion inflammatory syndrome (IRIS) has been reported to occur in 7%–36% of HIV-infected patients with TB receiving TB treatment and HAART [6, 7], and it has been suggested that these reactions may be particularly severe when HAART is initiated soon after the initiation of TB treatment. Thus, there is a theoretical trade-off between prolonged immunosuppression when initiating HAART late and concomitant opportunistic infections, versus the risk of immune-mediated inflammatory syndromes and additive drug-related toxicity of HAART combined with TB treatment [6, 8]. High pill burden, overlapping drug toxicities, and drug-drug interactions are generally regarded as the main points that complicate the simultaneous management of both TB treatment and HAART [8]. Although some recommendations have been published in past years [9–13], there currently are no published prospective controlled studies examining the optimal timing of HAART after the initiation of TB treatment [14, 15]. The question thus remains: when should HAART be started after initiation of TB treatment?

**ONGOING OR PLANNED CLINICAL TRIALS FOCUSING ON TB/HIV-1 THERAPY**

Clinical trials that started enrollment after 1 July 2005 are required to register in a public trials registry to satisfy later consideration for publication [16]. On the basis of information accessed on 2 April 2006, 15 trials listed in the National Institutes of Health (NIH) clinical trials database (http://www.clinicaltrials.gov/) indicated, as diseases or conditions of interest, both TB and HIV infection. In June 2006, a World Health Organization (WHO)/Special Programme for Research and Training in Tropical Diseases (TDR)–sponsored trial was also registered in the controlled-trials database (http://www.controlled-trials.com/), adding to the list of trials addressing the management of HIV-associated TB. Of these trials, 6 specifically focus on the treatment of TB and HIV coinfection. Four trials—(1) Cambodian Early versus Late Introduction of Antiretrovirals (CAMELIA), (2) Adult AIDS Clinical Trials Group [AACTG] A5221, (3) START, and (4) the TB-HAART WHO/TDR–sponsored trial mentioned above—are designed to answer the question of the optimal timing of HAART initiation in patients with TB and HIV coinfection, whereas the 2 others (PART and BKVIR) address the potential benefits of short-term HAART when CD4 cell counts are >350 cells/mm² and the efficacy of a once-daily HAART regimen, respectively. These trials are summarized in table 1.

**The best timing for HAART initiation in patients with TB/ HIV-1 coinfection.** The CAMELIA (“Early vs. late introduction of antiretroviral therapy in treatment-naive HIV-infected patients with TB in Cambodia”) trial, jointly sponsored by the Agence Nationale de Recherches sur le Sida et les Hépatites Virales (ANRS 1295) and the NIH (Comprehensive International Program of Research on AIDS [CIPRA] KH 001), is a randomized, open-label, active-control, parallel-assignment, safety/efficacy study designed to show that outcomes in the “early arm” (HAART initiated 2 weeks after TB treatment initiation) are superior to those in the reference “late arm” (HAART initiated 2 months after TB treatment initiation). This trial is being spearheaded by the Cambodian Health Committee, a local nongovernmental organization that has an extensive community-based TB and AIDS clinical and research network in Cambodia [17, 18]. The CAMELIA, which began patient enrollment in January 2006, will include 660 TB treatment–naive and HAART-naive patients who are $\geq$18 years of age and have CD4 cell counts <200 cells/mm² and culture-proven *M. tuberculosis* infection from 5 sites in rural and urban Cambodia (table 1). The TB treatment regimen being employed is 2 months of rifampin, isoniazid, ethambutol, and pyrazinamide, followed by 4 months of rifampin and isoniazid (2EHRZ/4HR). The HAART regimen is a fixed-dose combination of WHO-validated generic stavudine/lamivudine plus efavirenz, in accordance with Cambodian national policy. The primary study end point is the survival rate at the end of the trial. Secondary objectives include the evaluation of (1) the safety of early initiation of HAART; in terms of drug interactions or IRIS; (2) the occurrence of opportunistic infections; (3) patients’ adherence to TB treatment and HAART; (4) the rate of hospitalization for any cause during the trial; (5) the effectiveness of TB treatment and HAART; and (6) the predictive factors for the survival and the response to TB/HIV therapy. In this study, stavudine was chosen because of its superior toxicity profile with regard to hematological parameters.

The AACTG A5221 trial (“A strategy study of immediate versus deferred initiation of antiretroviral therapy for HIV-infected persons treated for TB with CD4 less than 200 cells/mm³”), for which patient recruitment was scheduled to start in September 2006, is a randomized, open-label study of 800 HIV-1–infected participants treated for TB in 8 resource-poor countries (table 1). It is designed to determine whether initiating HAART within ~2 weeks after initiating TB treatment reduces mortality and the incidence of other AIDS-defining events, compared with later initiation. This study will include patients who are at least 13 years of age and have CD4 cell counts <200 cells/mm³. Culture-positive TB is not mandatory for enrollment; an acid-fast bacilli (AFB)–positive smear or a diagnosis of TB based on clinical criteria is sufficient. The TB regimen to be used will contain rifampin or rifabutin, in accordance with the WHO and national treatment guidelines of the 8 countries involved in the study. The HAART regimen to be used is the fixed drug combination of tenofovir/emtricitabine (Truvada; Gilead) plus efavirenz. The primary study end point is the proportion of participants who have survived without AIDS progression at the end of the trial. Secondary objectives will evaluate drug-associated toxicities, pharmacokinetic
<table>
<thead>
<tr>
<th>Trial</th>
<th>Sponsor(s)</th>
<th>Country or countries (sample size)</th>
<th>Culture-confirmed TB at entry</th>
<th>CD4 cell count at entry, cells/mm³</th>
<th>TB treatment regimen</th>
<th>HAART regimen</th>
<th>Arms</th>
<th>Duration, months</th>
<th>Primary outcome(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAMELIAᵃ</td>
<td>ANRS (France) and NIAID/ CIPRA (US)</td>
<td>Cambodia (N = 660)</td>
<td>Mandatory</td>
<td>&lt;200</td>
<td>Standard 2EHRZ/4HR</td>
<td>d4T/3TC (generic) + EFV</td>
<td>Early: HAART 2 weeks after initiation of TB treatment. Late: HAART 8 weeks after initiation of TB treatment.</td>
<td>12</td>
<td>Survival</td>
</tr>
<tr>
<td>AACTG A5221ᵇ</td>
<td>NIAID (US)</td>
<td>Brazil, Haiti, India, Malawi, Peru, South Africa, Thailand, Zimbabwe (N = 800)</td>
<td>Not mandatory</td>
<td>&lt;200</td>
<td>RIF- or RIB-based regimen</td>
<td>TDF/FTC (Truvada; Gilead) + EFV</td>
<td>Early: HAART within 2 weeks after initiating TB treatment. Late: HAART 8 to 12 weeks after initiating TB treatment.</td>
<td>12</td>
<td>Survival without AIDS progression</td>
</tr>
<tr>
<td>STARTᵈ</td>
<td>NIAID (US)</td>
<td>South Africa (N = 592)</td>
<td>Not mandatory</td>
<td>&gt;50</td>
<td>Standard 2EHRZ/4HR</td>
<td>ddI/3TC + EFV</td>
<td>Integrated: HAART concurrent with standard TB treatment through DOT. Sequential: after completion of TB treatment, HAART without DOT.</td>
<td>18</td>
<td>Diagnosis of an AIDS-defining illness; mortality at 18 months</td>
</tr>
<tr>
<td>TB-HAART¹</td>
<td>WHO/TDR</td>
<td>South Africa, Tanzania, Uganda, Zambia (N = 1900)</td>
<td>Mandatory</td>
<td>&gt;200</td>
<td>Standard 2EHRZ/4HR</td>
<td>ZDV/3TC (Combivir; GlaxoSmitKline) + EFV or placebo</td>
<td>1: HAART initiated 2 weeks after initiation of TB treatment, concomitant with TB treatment until 6 months, then continuation with ART alone. 2: HAART placebo initiated 2 weeks after initiation of TB treatment, concomitant with TB treatment until 6 months, then HAART initiated.</td>
<td>24</td>
<td>Composite end point of TB treatment failure or death at 6 months after initiation of TB treatment</td>
</tr>
<tr>
<td>PARTᵍ</td>
<td>NIAID (US) and Makerere University (Uganda)</td>
<td>Uganda</td>
<td>Not mandatory</td>
<td>&gt;350</td>
<td>Standard 2EHRZ/4HR</td>
<td>ZDV/3TC/ABV (Trizivir; GlaxoSmithKline)</td>
<td>1: Initial HAART. 2: Delay HAART until CD4 cell count decreases to &lt;200 cells/mm³.</td>
<td>24</td>
<td>CD4 cell count decrease (slope); time to AIDS diagnosis</td>
</tr>
<tr>
<td>BKVIRʰ</td>
<td>ANRS (France)</td>
<td>France</td>
<td>Mandatory</td>
<td>...</td>
<td>Standard 2EHRZ/4HR</td>
<td>TDF/FTC (Truvada) + EFV</td>
<td>NA</td>
<td>12</td>
<td>Treatment success rate; plasma HIV-1 RNA level &lt;50 copies/mL; TB cured</td>
</tr>
</tbody>
</table>

**NOTE.** A table with regularly updated information can be found at http://www.hivforum.org and http://www.tbhiv-create.org. 2EHRZ/4HR, 2 months of ethambutol, isoniazid, rifampin, and pyrazinamide, followed by 4 months of isoniazid and rifampin; 3TC, lamivudine; ABV, abacavir; AFB, acid-fast bacilli; ANRS, Agence Nationale de Recherches sur le Sida et les Hépatites Virales; CIPRA, Comprehensive International Program of Research on AIDS; d4T, stavudine; ddI, didanosine; DOT, directly observed therapy; EFV, efavirenz; FTC, emtricitabine; HAART, highly active antiretroviral therapy; NA, not applicable; NIAID, National Institute of Allergy and Infectious Diseases; NIH, National Institutes of Health; RIB, rifabutin; RIF, rifampin; TDF, tenofovir; WHO, World Health Organization; ZDV, zidovudine.

ᵃ ANRS 1295, CIPRA KH 001: “Early vs. late introduction of antiretroviral therapy in naive HIV-infected patients with TB in Cambodia” (trial registration, NCT 00226434).
ᵇ A strategy study of immediate versus deferred initiation of antiretroviral therapy for HIV infected persons treated for TB with CD4 less than 200 cells/mm³” (trial registration, NCT 00108862).
ᶜ AFB-positive smear results or probable TB on the basis of clinical judgment.
ᵈ “Implementing anti-retroviral therapy in resource-constrained settings: a randomized controlled trial to assess the effect of integrated TB and HIV care on the incidence of AIDS-defining conditions or mortality in subjects co-infected with TB and HIV” (trial registration, NCT 00091936).
ᵉ AFB-positive smear results.
ᶠ “An evaluation of the impact of early initiation of HAART on TB treatment outcomes for TB patients coinfected with HIV” (trial registration, ISRCTN77861053).
ᵍ NIH 1 R01 AI051219-01A2: “Punctuated antiretroviral therapy in HIV-associated TB” (trial registration, NCT 00078247).
ʰ ANRS 129: “Efficacy of a once-daily HAART regimen associating tenofovir-emtricitabine and efavirenz in HIV-1 infected patients with active TB: a pilot study” (trial registration, NCT 00115609).
drug interactions, occurrence and predictors of other AIDS-defining illnesses, mortality, IRIS, TB treatment outcome, rates of viral suppression, increases in CD4 cell count, and HIV drug resistance.

The START study (“Implementing anti-retroviral therapy in resource-constrained settings: a randomized controlled trial to assess the effect of integrated TB and HIV care on the incidence of AIDS-defining conditions or mortality in subjects co-infected with TB and HIV”), for which patient recruitment commenced in May 2006, is a randomized, open-label, parallel-assignment, safety/efficacy study comparing 2 treatment strategies in 592 patients with CD4 cell counts >50 cells/mm^3 in South Africa (table 1). TB and HIV medications will be given concurrently to patients receiving TB medications (integrated arm) within an existing TB treatment program, or TB treatment will be completed first within the TB program, followed by HIV treatment (sequential arm) in an HIV program and will continue for 24 months after patient randomization. Diagnosis of TB will be made on the basis of AFB-positive sputum smear results or clinical criteria, in accordance with standards established in the national TB program. In the integrated arm, participants will receive once-daily didanosine, lamivudine, and efavirenz concurrently with standard TB therapy (2EHRZ/4HR) by directly observed therapy (DOT) on weekdays and by self-administration on weekends. In the sequential arm, participants will first receive DOT-provided TB treatment alone; after completion of TB treatment, participants will receive the same once-daily HAART regimen as in the integrated arm without DOT. Primary outcomes include 18-month mortality and diagnosis of an AIDS-defining illness. Secondary outcomes include clinical HIV disease progression, HIV viral loads, CD4 cell counts, levels of medication adherence, IRIS, toxicities, quality of life, and TB outcomes. A small pilot study demonstrating the feasibility of the strategy within the TB program and the acceptability and effectiveness of the once-daily antiretroviral regimen has been published [19].

A fourth study, a multicenter, WHO/TDR-sponsored trial (“An evaluation of the impact of early initiation of HAART on TB treatment outcomes for TB patients coinfected HIV”) designed to provide evidence of the efficacy, safety, and feasibility of the concomitant use of drugs to treat TB and HIV infection in 1900 coinfected patients in 4 African countries (Zambia, South Africa, Uganda, and Tanzania) commenced recruitment in March 2007. This randomized, placebo-controlled, double-blind trial will also address the question of whether the optimal timing of HAART initiation is early (2 weeks after TB treatment initiation). This TB-HAART trial differs from the ones described above, in that it is designed to establish whether significant benefits accrue from initiating HAART in less immunosuppressed patients—that is, those with CD4 cell counts of 200–349 or 350–500 cells/mm^3 [20]. The HAART regimen to be used is lamivudine/zidovudine plus efavirenz, and the TB regimen is 2EHRZ/4HR. The primary outcome measure is the composite end point of TB treatment failure or death evaluated at 6 months after initiation of short-course chemotherapy. Secondary outcomes include information on drug interactions and the potential influence of levels of immune suppression on drug absorption in different populations of African ancestry and distinct ethnicity. This study is expected to be completed in 2011.

Together, these trials will provide critical data needed to decide the best timing of HAART initiation in HIV–1–infected patients with clinical TB with different levels of immunosuppression. Because these trials are being conducted in populations with ethnic differences, parallel findings will be robust and will not be ethnicity specific. Given, for example, that T cell responses to TB antigens in patients with pulmonary TB, as measured by delayed-type hypersensitivity to purified protein derivative, are ethnicity specific [21], it is possible that the rate of TB cure or the incidence of IRIS may vary between patients of different ethnicities. Moreover, the whole range of immunodepression will be covered by these studies, because they include both patients with severe immunosuppression (CAMELIA and AACTG A5221) and individuals with CD4 cell counts >200 cells/mm^3 (the WHO/TDR-sponsored trial [20]), although a limitation of these studies is that they are taking place or will take place in low-income countries and do not include European and North American patients. Another limitation is that these trials have different end points; however, they will together provide critical information about the major end point, survival. Further studies—in, for example, pediatric populations—should be considered once the results of these trials are known. Similarly, studies including patients for whom the use of second-line TB medications is necessary are also urgently needed: overlapping drug toxicities and drug-drug interactions will likely be different in the pediatric population and when second-line drugs are employed. Future trials will also have to deal with the severity of IRIS and the predictive factors associated with that condition.

**Nontiming trials of TB/HIV-1 cotherapy.** The PART study (NIH 1 R01 AI051219-01A2), which initiated patient recruitment in Uganda in 2004, is assessing the benefits of short-term HAART given when CD4 cell counts are still high. This randomized, open-label, active-control, parallel-assignment, safety/efficacy study is being conducted to determine whether short-term HAART (abacavir, lamivudine, and zidovudine) given during TB treatment will slow the progression of HIV disease in 350 coinfected patients 13–60 years of age who have pulmonary TB (AFB-positive smear or culture-positive) and CD4 cell counts >350 cells/mm^3 (table 1). Participants are randomly assigned either to receive 6 months of HAART or to delay HAART until their CD4 cell count drops below 200 cells/mm^3. The participants will be followed for 2 years, and CD4 cell
counts will be compared between groups. Primary outcomes are the rate of CD4 cell count decline and the time to the development of clinical AIDS. The study also assesses the possible risks (e.g., drug toxicities and resistance) and benefits (e.g., more rapid clearance of *M. tuberculosis* and reduced rate of TB relapse) of punctuated HAART.

The BKVIR (ANRS 129) study, which began patient recruitment in January 2006, is assessing the efficacy and safety of once-daily HAART in HAART-naïve HIV-1–infected patients with TB. Specifically, this multicenter pilot study will follow 100 patients for 21 months and will address the efficacy and safety of tenofovir/emtricitabine (Truvada) plus efavirenz taken once daily during active TB (table 1). This is a noncomparative phase 3 trial that will take place in France: immigrants are expected to be the majority of enrollees. The focus of this study will be to determine the efficacy of this HAART regimen in achieving virologic (viral load, <50 copies/mL) and bacteriological (smear and culture negative for *M. tuberculosis*) success at week 48 of TB treatment. Secondary outcomes include tolerance of and adherence to medication, quality of life, occurrence of IRIS, CD4 cell counts, viral load, and proviral DNA evolution.

**CONCLUSION**

With regard to treatment-naïve patients with TB and HIV-1 infection, the studies detailed here will help to answer 2 types of therapeutic questions by the end of 2008 or during 2009. For those patients who have severe immunosuppression when TB is diagnosed, with CD4 cell counts <200 cells/mm³, data will be provided to determine whether mortality will be reduced by early initiation of HAART at 2 weeks versus 2 months after the initiation of TB treatment. Furthermore, information on the efficacy of the 2 timings of HAART as they relate to drug-drug interactions, overlapping drug toxicities, and IRIS will be available. For patients who have less immunosuppression when TB is diagnosed, the question of the benefit of concomitant HAART and the optimal regimen to be utilized will be answered. Some of these trials will also explore the benefits of once-daily HAART regimens, which allow for concomitant administration with standard once-daily TB regimens in HIV-infected patients with TB. No trial is designed to shorten the duration of TB treatment.

Despite the escalating global burden of TB and HIV-1 infection, the issues that are the focus of this review have not yet been answered. Why? Globally, HIV-associated TB disproportionately affects the poorest countries and has not been a prominent feature of the AIDS epidemic in industrialized countries. To conduct a clinical trial in a resource-poor setting first requires an established clinical network on the ground, with a commitment to research and deep community links, as is exemplified by the Cambodian Health Committee. Furthermore, significant investment by the international community in all the trials presented here has been critical for establishing the infrastructure necessary for the initiation of studies involving a large enough number of patients to adequately address the question posed. To ensure the integration of TB and AIDS efforts and the translation of trial results to improved clinical care and guideline development, there is also a critical need to engage national TB and AIDS programs early in the development of such clinical trials. Finally, it is important to emphasize that, over and above the resolution of the clinical controversies presented, the implementation of such trials in low-income countries results in an enhancement of medical, laboratory, and research capacity, resulting in significant benefits to patients who might otherwise not have access to drugs or to quality care.

**Acknowledgments**

We thank S. S. A. Karim and O. Lortholary for providing unpublished data.

**Supplement sponsorships.** This article was published as part of a supplement entitled “Tuberculosis and HIV Coinfection: Current State of Knowledge and Research Priorities,” sponsored by the National Institutes of Health Division of AIDS, the Centers for Disease Control and Prevention Division of TB Elimination, the World Bank, the Agence Nationale de Recherches sur le Sida et les Hepatites Virales, and the Forum for Collaborative HIV Research (including special contributions from the World Health Organization Stop TB Department, the International AIDS Society, and GlaxoSmithKline).

**References**


Note added in proof. Since this article was accepted for publication, the START trial was terminated, after only 58 patients enrolled, as a result of a lack of funding and slower-than-anticipated enrollment.