DEBATE

HIV/TB: WHEN IS IT SAFE TO START HAART?

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South Africa has the fourth highest burden of tuberculosis (TB) worldwide after China, India and Indonesia and has the highest TB notification rate of any country. The World Health Organization (WHO) estimated that in 2006 South Africa had 303 114 incident TB cases; of these patients, 32% were tested for HIV and 53% were found to be HIV infected.[1] HIV testing of TB cases has been encouraged by the WHO and testing has resulted in identification of increasing numbers of HIV-infected individuals in the TB control programme. The success of this policy has been demonstrated in the Cape Town Gugulethu antiretroviral clinic, where referrals directly from the local TB clinics have increased from 15% to 30% within the past 2 years. The national TB control programme has therefore become an increasingly important pathway to HIV care and access to highly active antiretroviral therapy (HAART). An additional 15 - 20% of patients in the Gugulethu programme have a diagnosis of TB made during the HAART screening period, further increasing the number of individuals on TB medication who require HAART. Mortality after referral is very high. The HIV/TB case mortality has been reported to be as high as 16 - 35%[2] prior to the introduction of HAART, with both HIV and TB contributing to this mortality. Optimal timing of HAART is currently unknown and there is an urgent need for development of evidence-based protocols for HAART initiation and immune reconstitution disease (IRD) management.

Tuberculous meningitis occurring in HIV-infected individuals (HIV/TBM) exemplifies the dilemmas facing clinicians when addressing potentially preventable mortality. HIV/TBM has a devastating clinical impact with a median time from onset of symptoms to presentation of 10 days, 67% mortality and a median time to death of 20 days.[3] Expert opinion on when to start HAART in HIV-infected patients with TB meningitis varied between 2 weeks and 12 months after starting TB medications.[4] This uncertainty of expert opinion reflects the present lack of randomised clinical trial data with which to inform clinical management. A clinical trial specifically addressing immediate initiation versus deferring HAART (zidovudine/lamivudine/efavirenz) for 8 weeks has been conducted at two hospital sites in Ho Chi Minh city, Vietnam. Results of this study should become available in late 2008 or early 2009.[5] A study demonstrating proof of the concept that earlier initiation of antiretroviral therapy may impact on mortality of HIV patients with active opportunistic infections (OIs) was recently presented.[6] The AIDS Clinical Trials Group study 5164 (ACTG 5164) was a randomised strategy trial of immediate versus delayed ART in the setting of acute OI. At the time of inclusion study subjects had pneumocystis pneumonia (63%), cryptococcal meningitis (13%), other acute pneumonic illnesses (10%) or multiple opportunistic infections (30%). Patients were randomised to immediate or delayed initiation of HAART, a median of 12 days or 45 days after starting OI treatment, respectively. After 48 weeks, deaths in the early treatment group were significantly lower with no difference in drug toxicities, adherence or hospitalisation. Somewhat counter-intuitively, IRD was also less frequent in the earlier treatment group. The conclusion from this study was that in the absence of contraindications very early use of HAART should be considered in patients with acute OIs. However, it should be noted that TB cases were not included in this study population.

CONSIDERATIONS DETERMINING EARLIER VERSUS LATER INITIATION OF HAART

The decision when to initiate HAART after TB treatment is complex, involving a number of variables including treatment tolerance, drug co-toxicities, pharmacokinetic drug interactions and impact of polypharmacy on adherence (Fig. 1). However, of over-riding importance is the mortality associated with delays in ART initiation versus mortality associated with IRD when HAART is initiated early. The frequency of IRD in cohort studies describing co-infected patients varies markedly between 8% and 43%.[7,8] The mean interval to IRD after HAART initiation also varies widely (1 - 180 days) with most cases occurring within the first 28 days.[7] However, cross-cohort comparisons are complicated by differing mortality in cohorts from high- and low-resourced settings and

differing incidences of TB-associated IRD in TB patients starting HAART in different settings. Furthermore, while variable rates of IRD may represent differences between cohorts, analysis is complicated by variable ascertainment and lack of a standardised IRD definition. A consensus document with proposed definitions of IRD for use in resource-constrained settings may help address the problem of differing case definitions.[8] IRD is characterised by worsening of systemic symptoms, transient enlargement of pre-existing lesions, onset of new lesions including lymphadenopathy, and worsening of radiographic changes. Life-threatening conditions are rare but include tracheal and bronchial obstruction, pulmonary adult respiratory distress syndrome (ARDS), central nervous system tuberculomas and cerebral oedema.[7-13] The management of life-threatening IRD includes use of high-dose steroid therapy and may necessitate interruption of HAART, although there are no randomised controlled studies to inform policy. The precise pathological processes responsible for IRD are not clearly defined, but the condition is associated with an expansion of CD4 cells in the peripheral blood[8,14] and increased macrophage activity.[15] Fig. 2 illustrates a proposal that clinical manifestations result from an interplay between cellular events and mycobacterial antigen load.[16] The risk factors for development of IRD are predominantly a low CD4 cell count and a short interval between starting TB therapy and HAART initiation.[9,13,17] In a prospective Cape Town cohort, IRD occurred in 100% and 70% of patients commencing HAART within 30 days with CD4 counts of <50 cells/µl and 50 - 100 cells/µl respectively[13] (Fig. 3). Extrapulmonary TB and black ethnic group have been identified as additional risk factors for IRD.[9] Severe TB-associated IRD therefore tends to develop in those patients who have a high mortality risk, manifested by low CD4 cell counts and a high mycobacterial burden associated with disseminated TB. Several studies reporting considerable morbidity associated with IRD have not shown an excess mortality.[13,17-21] Similar findings were also reported in a South African cohort where 10.5% who developed TB-IRD died; however, 9.9% of TB patients who did not develop IRD also died.[9] Development of IRD and IRD-associated mortality in these studies was therefore not associated with significant excess overall mortality.

Variations in IRD frequency and associated mortality indicate that the optimal timing of ART initiation may differ between settings. In lower income countries, the risk of mortality associated with delays in ART initiation is likely to outweigh the excess mortality of TB-associated IRD. The optimal timing of ART initiation may therefore be earlier in the course of TB treatment for patients in resource-limited settings compared with those in high-income settings. Current guidelines for the timing of HAART in patients with TB are shown in Table I. All these guidelines reflect an increased urgency to commence HAART at lower CD4 cell counts with variable

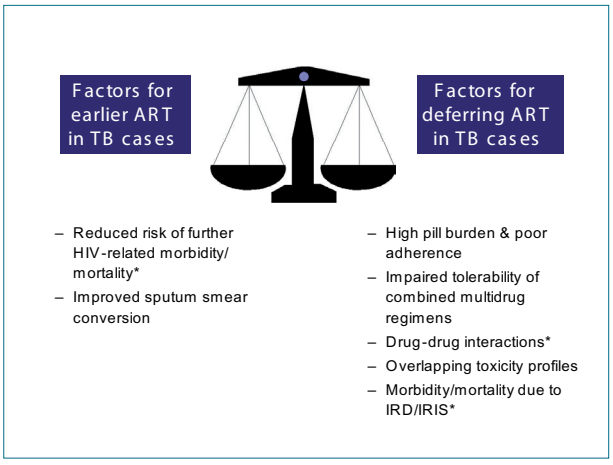

Fig. 1. Factors influencing the decision of timing of commencement of HAART after starting TB therapy in HIV-infected individuals.

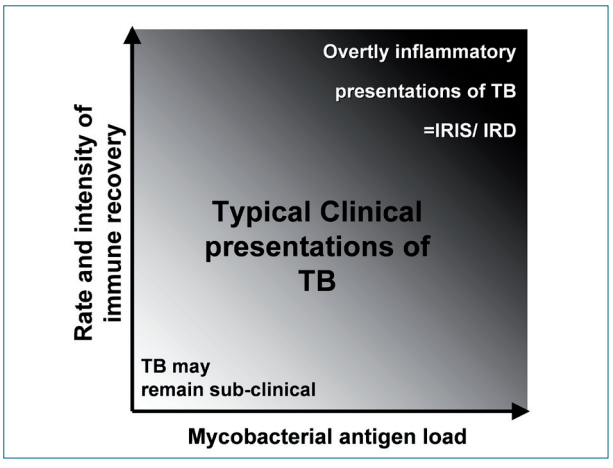

Fig. 2. The proposed interaction between Mycobacterium tuberculosis *antigen load and rate and intensity of immune recovery after initiating HAART (adapted from Lawn* et al.[16]*).*

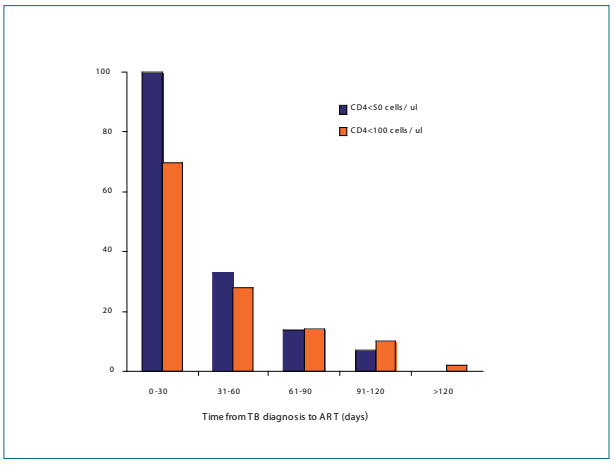

Fig. 3. The impact of baseline CD4 cell count and timing of initiation of HAART on risk of TB-immune recovery disease in the Gugulethu cohort, Cape Town (adapted from Lawn et al.[13]*).*

timing recommendations due to a lack of data from randomised controlled trials. This lack of informative data is clearly reflected in the recommendations of the International AIDS Society (IAS), USA. Several guidelines focus on 8 weeks as a key time point in TB therapy when simplification of TB medications occurs. In South Africa schedule 1 TB therapy consists of an intensive four-

TABLE I. CURRENT INTERNATIONAL AND SOUTH AFRICAN GUIDELINES FOR THE TIMING OF INITIATION OF HAART IN HIV-INFECTED PATIENTS ON TB THERAPY

Year	Organisation	CD4 count	Recommendations
2003	American Thoracic Society*	CD4 <350 CD4 >350	Individualise between 4 and 8 wks Defer HAART
2004	MMWR† (Pediatrics)		Defer 4 - 8 wks
2004	WHO 'Scaling up ART in resource-limited settings'‡	CD4 <200 CD4 200 - 350 CD4 >350	2 wks - 8 wks Start at 2mo. Defer HAART
2004	South African National ART Programme§	CD4 < 50 CD4 <200 CD4 >200	2 wks - 8 wks 8 wks 6 mo.
2006	IAS/USA panel¶		Individualise as there are no RCTs
2008	DHHS: Guidelines**	CD4 <100 CD4 100 - 200 CD4 200 - 350 CD4 >350	2 wks 8 wks 8 wks 8 - 24 wks or defer

Guidelines available at: *http://www.thoracic.org; †htpp://www.cdc.gov/mmwr/; ‡http://www.doh.gov.za; §http:// www.iasusa.org/pub/; ¶http:// www.aidsinfo.nih.gov/Guidelines/; **http://www.who.int/3BYS/publications/documents/ARV_guidelines/en/

drug therapy (isoniazid, rifampicin, pyrazinamide and ethambutol) which is reduced to two-drug maintenance (RIF/INH) after 8 weeks.[22] The South African TB control programme promotes use of fixed-dose combination tablets which results in identical pill burdens before and after the 8-week treatment time point. Rifampicin, the anti-TB agent with the greatest potential for drug-drug interactions with non-nucleoside and protease inhibitor antiretrovirals, is continued throughout the whole 6 months of treatment. Similarly isoniazid, with a potential for peripheral neuropathy co-toxicity with stavudine, is also continued throughout TB therapy. The main co-toxicity shared between TB and HAART is hepatotoxicity, and some staggering of initiation of the two treatment regimens may simplify clinical management of drug-induced hepatitis. Although pyrazinamide, which is routinely discontinued after 8 weeks of TB treatment, may contribute somewhat to hepatic co-toxicity, it is unproven whether the optimal deferring time period is 8 weeks,

STUDY DATA ADDRESSING WHEN TO START HAART

Randomised controlled trials addressing the optimal timing of ART initiation in patients with TB are awaited, but meanwhile data from observational cohorts and modelling studies may help inform policy. Cohort studies have reported a markedly variable impact of HAART on TB mortality.[19,23-26] Three cohort studies describing outcomes in patients starting HAART at different time points after TB therapy reported at the International AIDS Society 2008 Conference meeting in August 2008 highlight the difficulties in interpreting cohort data. A Brazilian clinic-based cohort study of 662 patients found no significant difference in survival between patients starting HAART in the first 2 months, 2 - 6 months or more than 6 months after commencement of TB treatment.[24] In contrast, an Iranian study of 69 hospitalised patients showed significant increases in TB cure rate and survival in patients who started HAART within 2 weeks compared with 8 weeks of TB treatment.[25] A third study, from Argentina, showed similar differences in TB cure rate and survival with early initiation of HAART.[26] However, this last study also reported significant differences in baseline characteristics between the groups, demonstrating that cohort studies may be subject to considerable selection bias. A South African cohort study of the International Epidemiological Databases to Evaluate AIDS Group (IeDEA) retrospective analysis of 4 000 HIV/TB patients from multiple sites in the Free State and Cape Town will be completed and is planned for reporting during 2009.[27]

A decision analysis model, based on published cohort data, examined three treatment strategies in patients with AIDS and TB; early initiation of HAART (<2 months), deferred HAART (>2 months), and no HAART strategy.[28] The model indicated that earlier HAART could reduce mortality at 1 year by 30% and 80% compared with the deferred and no HAART strategies, respectively.

Several randomised controlled studies addressing the timing of HAART after starting TB treatment are currently enrolling.[5,29-32] Of these ongoing studies only

TABLE II. ONGOING TRIALS OF HAART IN HIV-INFECTED INDIVIDUALS ON TB THERAPY[5,29–32]

Trial (sponsor)	CD4 (/µl)	Time (design)	Study design	End-points
CAMELIA (NIH/ANRS)	<200	12 mo. (ROL*)	2 wks v. 8 wks after TB initiation (*N*=660, accruing results 2009/10)	Survival
ACTG 5221 (NIAID)	<200	12 mo. (ROL*)	2 wks v. 12 wks after TB initiation (*N*=200 of 800 accrued)	AIDS-free survival
SAPIT (NIAID)	>50	18 mo. (ROL*)	<2 mo. v. >2 mo. v. post 6 - 8 mo. TB Rx (*N*=645, DSMB stopped 3rd arm)	Survival AIDS
TB-HAART (WHO/TDR)	>200 <500	6 mo. (RPC†)	HAART at 2 wks v. placebo at 2 wks (*N*=1 900 accruing results 2011)	Survival, TB failure
TB meningitis (Wellcome Trust)	All	9 mo. (RPC†)	Immediate v. 8 wks ART + steroids (*N*=247, accrued results Dec 2008)	Survival

*Randomised open-label study.
†Randomised placebo-controlled study.
NIH = National Institute of Health; ANRS = Agence Nationale Recherche sur Le Sida; NIAID = National Institute of Allergy and Infectious Disease; WHO = World Health Organization; TDR = Tropical Disease Research.

the Vietnamese TB meningitis study is expected to be able to report outcomes in the near future (Table II). The Cambodian Early versus Late Introduction of Antiretrovirals (CAMELIA), a large randomised open-labelled study conducted in five sites in Cambodia, should be the first of these studies to report outcomes, some time during 2009 or 2010.[29] Unexpectedly, preliminary data from the Starting Antiretroviral therapy in three Time Points in Tuberculosis (SAPIT) study conducted in KwaZulu-Natal became available in September 2008 owing to the data safety and monitoring board (DSMB) discontinuing the third randomisation arm of the study because of a 55% increased mortality in subjects deferring HAART for 6 - 8 months.[31]

DISCUSSION

Determination of the optimal timing of initiation of ART in patients with TB is urgently needed in South Africa, where HIV/TB is extremely common and availability of HAART is rapidly expanding. HIV/TB case fatality rates are high and the optimal deferral time will therefore be determined predominantly by mortality rather than morbidity. Unfortunately the results of several randomised controlled trials addressing when to start HAART in TB, with a primary endpoint of survival, will not be available until 2009/2010. Meanwhile, preliminary data from the SAPIT study indicate that deferring treatment for 6 months is associated with significantly increased mortality.[31] The Vietnamese study results of immediate initiation of HAART in TBM should become available in the next few months.[5] The results of this study may not necessarily be generalisable to other forms of TB; however, any significant mortality benefit of immediate initiation of HAART will bolster support for earlier treatment in other severe forms of TB.

The present status of information concerning the most important factors that may impact on the optimal timing of HAART in TB are shown in Fig. 4. Reduction of ongoing HIV-related mortality by HAART is counterbalanced by TB/IRD-associated mortality and a clinical need to stagger the initiation of both treatments for ease of clinical management of co-toxicity. Those at highest risk of HIV progression also have the highest risk of co-toxicity and IRD. The ACTG 5164 study has demonstrated improved survival with very early initiation of HAART in patients co-infected with acute OIs.[6] Treatment of TB requires prolonged treatment and is complicated by frequent occurrence of IRD. However, published reports indicate that while TB/IRD is a common cause of morbidity it is a less frequent cause of death.

Much interest has rightly focused on the optimal timing of HAART in relation to TB treatment. In low-income settings TB in HIV-infected patients is often only

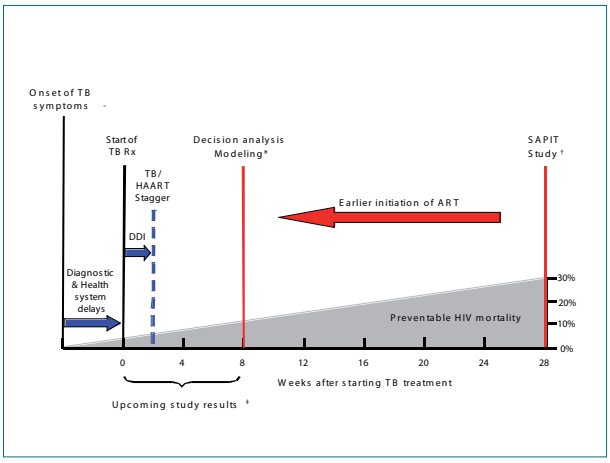

*Fig. 4. Data from present and future studies that affect the timing of initiation of HAART and are likely to impact on preventable HIV mortality in individuals already on TB treatment (*ref. 28, †ref. 31, ‡refs 29, 32).*

diagnosed after prolonged delay, and yet the mortality associated with even short delays in accessing HAART is unacceptably high. Furthermore, the potentially more important problem of delays in the care pathway has received little attention.

While the results of randomised controlled studies addressing the timing of initiation of HAART are eagerly awaited, the results may still not be generalisable to all types of TB, HIV progression, race and health systems. In the meantime it is important to recognise that time delays between the onset of TB symptoms and starting HAART in those eligible for HAART are associated with potentially preventable HIV-related mortality and that all delays should be minimised.

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