TB and HIV co-infection: when to start antiretroviral therapy

Guidelines on when to start therapy in TB and HIV co-infection.

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South African reports to the World Health Organization (WHO) indicate that its tuberculosis (TB) notifications have increased fivefold over the last 20 years; in 2008, South Africa (SA) had the third-highest TB burden, after India and China.[1] SA and Swaziland now have the highest TB notification rates in the world, with about 1% of their populations developing TB annually.[1,2] South Africa also has the greatest number of HIV-infected individuals in any country in the world, estimated at 5.5 million. South Africa was responsible for approximately 25% of the global burden of HIV-associated TB cases in 2007.[2]

Furthermore, the South African national TB control programme has become an increasingly important pathway to HIV care and access to antiretroviral therapy (ART).[3] Given the synergistic epidemics of HIV and TB in southern Africa, the question of how and when to integrate HIV and TB treatment in co-infected patients is a critical one.

Given the synergistic epidemics of HIV and TB in southern Africa, the question of how and when to integrate HIV and TB treatment in co-infected patients is a critical one.

Previously, TB therapy has been prioritised over ART and ART has been delayed in many co-infected patients until after the completion of TB therapy. This strategy reflected concerns about ongoing transmission of TB, as well as drug-drug interactions, high pill burden, overlapping drug toxicities, and immune reconstitution inflammatory syndrome (IRIS). Delaying initiation of antiretroviral therapy until 4 - 8 weeks after starting antituberculosis therapy has the potential advantages of allowing better determination of a specific cause for a drug-related adverse effect, decreasing the severity of paradoxical reactions, and decreasing adherence difficulties for the patient.4 However, of overriding priority is to balance the mortality associated with delaying ART initiation with mortality associated with immune reconstitution inflammatory syndrome (IRIS) when ART is initiated early (Figs 1 and 2).[4]

The need for ART

Indications for ART are based on an assessment of individual risk-benefit analysis of treatment versus no-treatment for patients at different stages of HIV disease progression. Guidelines have evolved considerably over recent years. The WHO guidelines for scaling up ART in resource-poor settings were first published in 2002 and recommended initiation of ART for those with AIDS or a CD4 count less than 200 cells/mm^3. The guidelines were subsequently updated in 2003 to extend therapy to those with WHO stage 3 disease and CD4 counts less than 350 cells/mm^3.[5] The South African public sector ART programme was based on the WHO 2002 initiation criteria until 2010 but was extended to <350 cells/mm3 in pregnant patients and patients with TB, and most recently includes all patients with CD4 T cell counts <350 cells/mm^3. [6,7]

Indications for ART are based on an assessment of individual risk-benefit analysis of treatment versus no-treatment for patients at different stages of HIV disease progression.

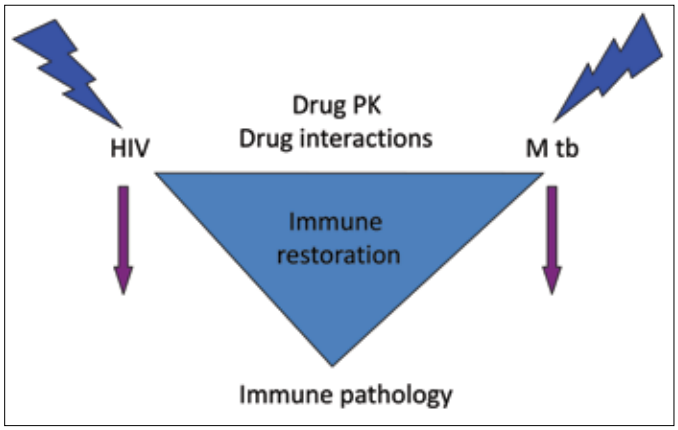

Fig. 1. HIV and TB treatment.

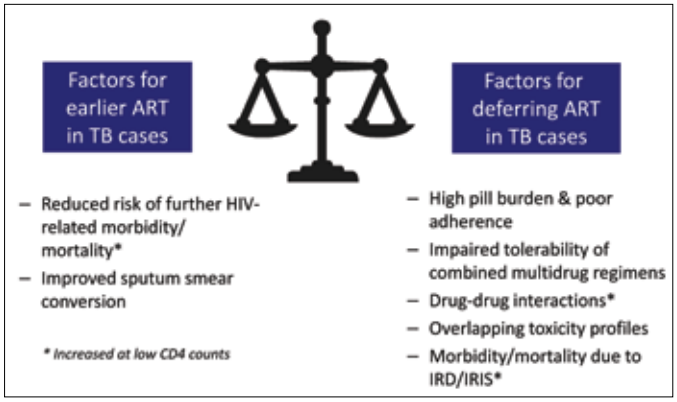

Fig. 2. Risk analysis of early v. delayed ART.

Mortality risk of HIV

At the moment the greatest proportion of HIV disease burden occurs prior to starting ART.[8] Pre-ART mortality increases markedly with both decreasing CD4 count and increasing clinical stage.[9] Progression to AIDS and death appears to be higher in South African patients compared with Europeans at all CD4 count strata.[10,11] This increased

risk may be due to increased exposure to pathogenic organisms such as *Mycobacterium tuberculosis*, and gastrointestinal pathogens that can cause disease prior to the development of profound immune suppression. Among patients with HIV, TB mortality is highest in those with low CD4+ T cell counts and advanced clinical stage.[12] Localised pulmonary TB is a WHO stage 3 AIDS diagnosis and disseminated TB a WHO stage 4 AIDS diagnosis. South African observational cohort data indicate that 6-month mortality of patients with CD4+ cell counts <200 cells/mm^3 and WHO stage 3 disease is 10.8 per 100 patient-years (95% confidence interval (CI): 7.5 - 13.2), whereas mortality for those with WHO stage 4 is 22.2 per 100 patient years (95% CI: 17.9 - 27.1) in the absence of ART.[12] The hazard of death is reduced by ART to 0.24(95% CI: 0.11 - 0.56) and 0.11 (95% CI: 0.01 - 0.61) for those with WHO stage 3 or 4 disease, respectively (Fig. 3).[13,14]

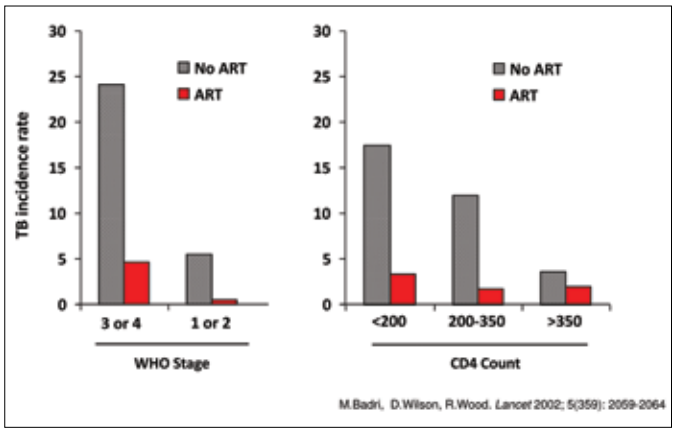

Fig. 3. TB incidence with and without HAART – cases/100 person years.

Morbidity and mortality during early ART

Mortality is high during early ART and is a reflection of the high mortality preceding the start of ART, together with immune restoration disease, as increased immune surveillance recognises occult pathogens or antigens. Although death rates rapidly decrease from those prior to the start of ART approximately 66% of ART programme deaths occur in the first 4 months of therapy.[8] These deaths, together with associated morbidity, result in considerable strain on medical resources allocated to ART programmes. Deaths occur predominantly in those with advanced disease, with risk factors for death being CD4 counts >100 cells/mm^3 and a prior AIDS diagnosis.[9] Although the efficacy of ART as measured by viral suppression appears similar in resource-rich and resource-poor settings, early deaths on ART are more frequent in resource-poor settings, particularly when ART is commenced at very low CD4 counts.[11] The risk/benefit of ART for individuals commencing treatment in developing countries therefore does not favour later initiation of therapy than that recommended in developed settings (Fig 4).

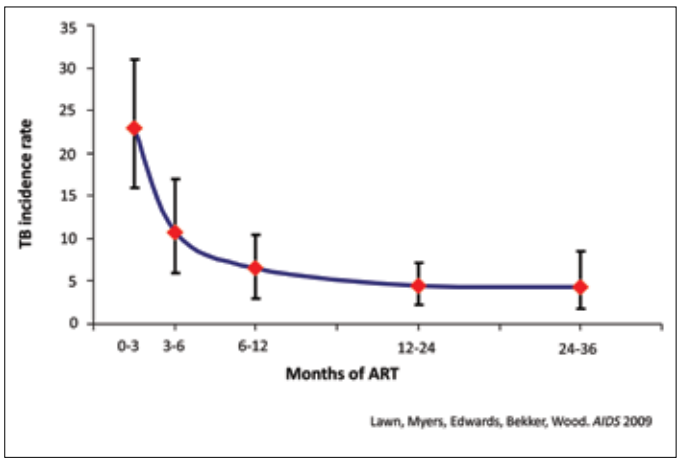

Fig. 4. TB incidence after initiation of HAART – cases/100 pys.

Risk of IRIS

The frequency of IRIS in cohort studies describing HIV/TB-coinfected patients varies markedly between 8% and 43% because of variable ascertainment and lack of a standardised IRIS definition.[15] IRIS may infrequently be life-threatening because of tracheal and bronchial obstruction, pulmonary adult respiratory distress syndrome, central nervous system tuberculomas, or cerebral oedema. The mean interval to an IRIS event after ART initiation also varies widely (1 - 180 days) with most cases occurring within the first 28 days. However, cross-cohort comparisons are complicated by differing mortality in cohorts from high- and low-resourced settings and differing incidences of TB-associated IRIS in TB patients starting ART in different 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 IRIS. 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.[16-18]

Localised pulmonary TB is a WHO stage 3 AIDS diagnosis and disseminated TB a WHO stage 4 AIDS diagnosis.

Drug-drug interactions

In South Africa schedule 1 anti-TB therapy consists of an intensive four-drug therapy (isoniazid, rifampicin, pyrazinamide and ethambutol) which is reduced to two-drug maintenance (RIF/INH) after 8 weeks. The South African TB control programme promotes the 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 ART 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 has been the question in RCTs to assess whether the optimal deferring time period is 8 weeks.

Drug interactions are discussed elsewhere in this edition, but ART options that are compatible with South African TB treatments are limited. If patients cannot take an efavirenz-based ART regimen, boosted protease regimens are indicated with inherent interactions with rifampicin.

Guidelines of when to start ART in TB/HIV patients

Since 2003, all treatment guidelines for the timing of ART in patients with TB reflected an increased urgency to commence ART at lower CD4 cell counts with variable timing recommendations around the 2 - 8-week interval. The World Health Organization and US guidelines now recommend that ART should be started during rather than after TB treatment as soon as possible after the commencement of TB therapy. Several guidelines focus on 8 weeks as a key time point in TB therapy when simplification of TB medications occurs. It is important to note that in the SA setting where pill burden is unaffected at 8 weeks, this simplification refers more to potential drug-drug interactions rather than pill burden *per se*.

The World Health Organization and US guidelines now recommend that ART should be started during rather than after TB treatment as soon as possible after the commencement of TB therapy.

The current guidelines for SA, USA Dept of Health and British recommendations are shown in Table I.

Table I. Guidelines

Guideline/ Recommendation	CD4 count strata	Interval
SA national ART programme 2004	CD4 <200	2 wks – 8 wks
	CD4 200 – 350	8 wks
	CD >350	6 mo
DHHS (USA) 2008	CD4 <100	2 wks
	CD4 100 – 200	8 wks
	CD4 200 – 350	8 wks
	CD4 >350	8 – 24 wks or defer
British 2010	CD4 <100	2 wks
	CD4 100 – 200	8 wks
	CD4 >200	6 mo

Observational cohort data

Data from observational cohorts and modelling studies have helped to inform policy. Cohort studies have reported a markedly variable impact of ART on TB mortality.[19,20-22]

A decision analysis model, based on published cohort data, examined three treatment strategies in patients with AIDS and TB; early initiation of ART (<2 months), deferred ART (>2 months), and no ART strategy. The model indicated that earlier ART could reduce mortality at 1 year by 30% and 80% compared with the deferred and no ART strategies, respectively.[23]

Randomised controlled trials

Randomised controlled studies are usually considered to provide the best quality of data to inform clinical practice because the randomisation process equally distributes unforeseen confounding biases between the experimental strategy arms.

When to start ART and opportunistic infections

The AIDS Clinical Trials Group study 5164 (ACTG 5164) was a randomised strategy trial of immediate versus delayed ART in the setting of acute opportunistic infections (OIs). 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 ART, 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, IRIS 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 ART should be considered in patients with acute OIs. However, it should be noted that TB cases were not included in this study population. Treatment of TB requires prolonged treatment and is complicated by frequent occurrence of IRD. However, published reports indicate that while TB/IRIS is a common cause of morbidity it is a less frequent cause of death.[24]

The TB meningitis study

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. Expert opinion on when to start ART in HIV-infected patients with TB meningitis varied between 2 weeks and 12 months after starting TB medications. A clinical trial specifically addressing immediate initiation versus deferring ART (zidovudine/lamivudine/efavirenz) for 8 weeks (early treatment) was conducted at two hospital sites in Ho Chi Minh city, Vietnam. The median CD4 T cell count in the study was 40 (range 16 - 100) and 60% of the patients had a positive culture for TB in cerebro-spinal fluid, so this was a study population with *particularly* advanced HIV and TBM. The Kaplan Meier survival estimates at 9 months were 35.2% in the immediate treatment arm and 40.3% in the early treatment arm (see Fig. 5). These results didn't change in the per protocol analysis. Grade 3 adverse events were common but similar in both arms of the study with significantly more Grade 4 adverse events in the immediate v. the early treatment arms (Fig. 6).[25]

Non-CNS tuberculosis

Three RCTs have recently been reported for general TB and are described in Table II.

ART commencement POST TB treatment completion

The Starting Antiretroviral therapy in three Time Points in Tuberculosis (SAPIT) study was an open- label study conducted in KwaZulu-Natal, South Africa. ART was offered either as an integrated (TB and ART

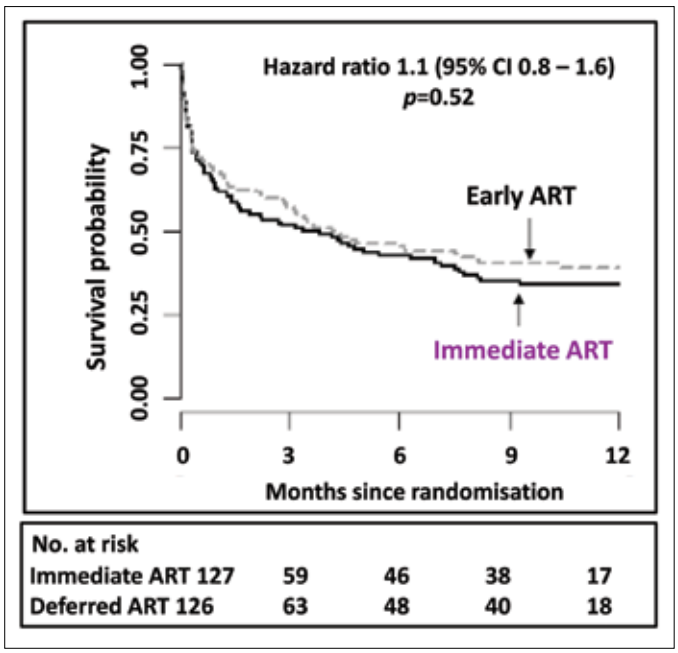

Fig. 5. Effect of ART timing in TB meningitis.

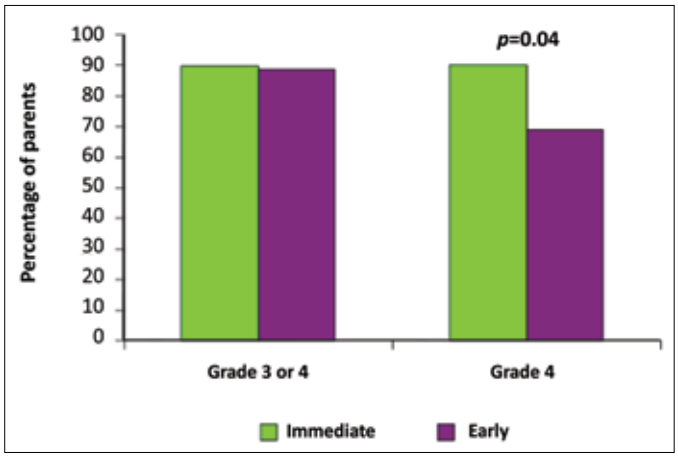

Fig. 6. Effects of ART timing on adverse events in TB meningitis.

Table II – RCT key characteristics

Study	Setting	Key enrollment criteria	Median CD4 (IQR)	Primary endpoint
CAMELIA	Cambodia	Smear +, CD4 <200	25 (10 – 56)	Death
STRIDE	Multi-national	Clinical TB, CD4 <250	77 (36 – 145)	AIDS or death
SAPIT	South Africa	Smear +, CD4 <500	150 (77 – 254)	AIDS or death

given concurrently) or in a sequential (ART started after TB treatment was completed) way with integrated treatment further divided into immediate (within 1 - 2 weeks after TB treatment commencement) or early (within 2 months). Doctors could modify treatment options after randomisation. The schema and outcomes of the study are shown in Fig. 7.

The SAPIT data safety and monitoring board (DSMB) at an interim review proposed an early stoppage of the sequential treatment arm of the study because of a 55% increased mortality in deferring ART for 6 - 8 months (Fig. 8). The increased mortality was seen in both low and higher CD4 count strata (Fig. 8). Urgent initiation of ART for all patients remaining in the sequential therapy group was proposed and initiated. It was confirmed by this arm of the SAPIT study that ART

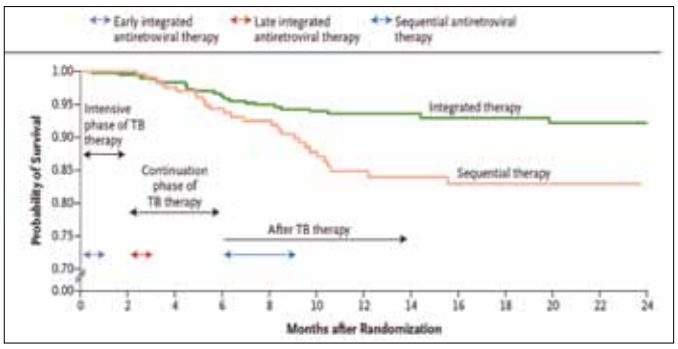

Fig. 7. SAPIT study outcomes.

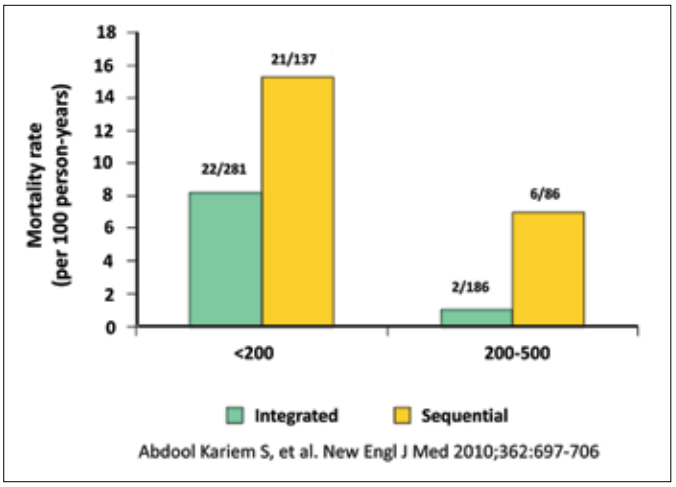

Fig. 8. Effect of ART timing on mortality by baseline CD4 count: SAPIT.

during TB treatment decreases the high case fatality rate seen in HIV/TB among patients with a broad range of baseline CD4 counts. Earlier ART resulted in more IRIS but these cases were manageable. WHO now recommends ART should be started during TB therapy in all HIV/TB patients regardless of CD4 count.[26]

Immediate v. early integrated treatment

Two other randomised clinical trials have recently reported on outcomes in patients started immediately or early during the period

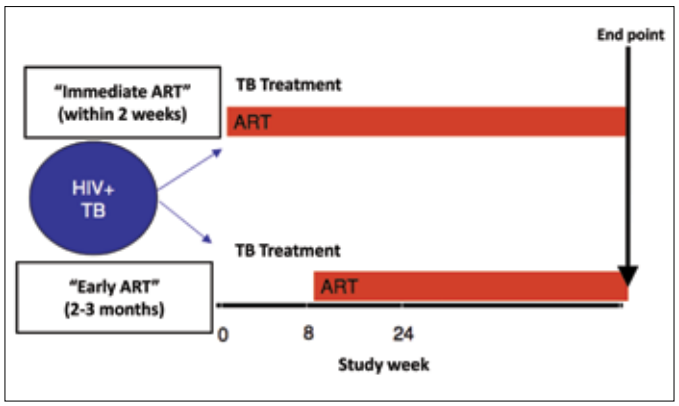

Fig. 9. Schema for 3 RCTS: CAMELIA, STRIDE, integrated arms of SAPIT.

of TB therapy: they are known as CAMELIA and STRIDE. The characteristics of all three clinical trials is shown in Table II. The General schema for CAMELIA, STRIDE and integrated arms of SAPIT is given in Fig. 9.

The Cambodian Early versus Late Introduction of Antiretrovirals (CAMELIA), a large randomised open-labelled study conducted in five sites in Cambodia, was the first of these studies to report outcomes and also had the most advanced patients with a median CD4 of 25. The endpoint reported in this study was death.

The STRIDE study was a multinational ACTG study of patients with clinical diagnosed TB and the endpoint in this study was AIDs or death. This was similar to the ongoing integrated arms of the SAPIT study in which TB diagnosis was confirmed on smear. All three studies reported

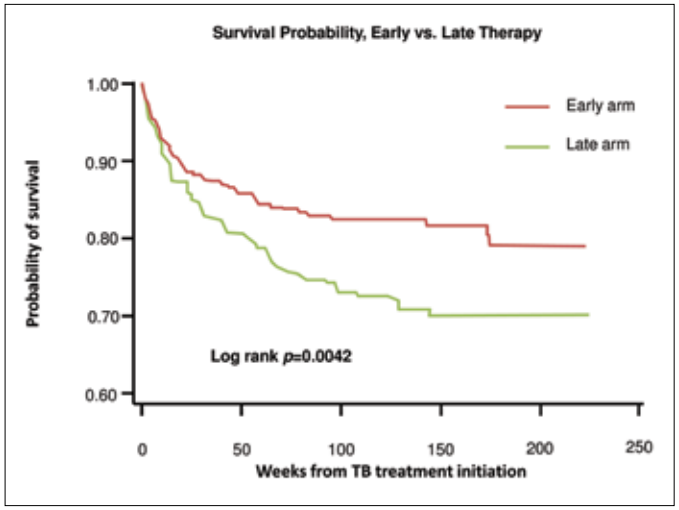

Fig. 10a. CAMELIA: survival probability.

Week	Survival Probability, % (95% CI)		*p*-value
	Early Arm	Late Arm	
50	86.1 (81.8 - 89.4)	80.7 (76.0 - 84.6)	0.07
100	82.6 (78.0 - 86.4)	73.0 (67.7 - 77.6)	0.006
150	82.0 (77.2 - 85.9)	70.2 (64.5 -75.2)	0.002

Fig. 10b. CAMELIA: survival probability.

less death or death/AIDS overall with a significant 34% reduction in the immediate v. early arms of CAMELIA (Figs 10 a and b).

All three studies showed significant reduction in death and death/AIDS in patients with CD4 <50 cells/mm^3. CAMELIA: 34% reduction (p=0.004), STRIDE: 42% reduction (p=0.02), SAPIT: 68% reduction (p=0.06) (Figs 11 and 12). This effect was lost in patients with CD4 >50 cells/mm^3 in both STRIDE and SAPIT (Fig. 13).

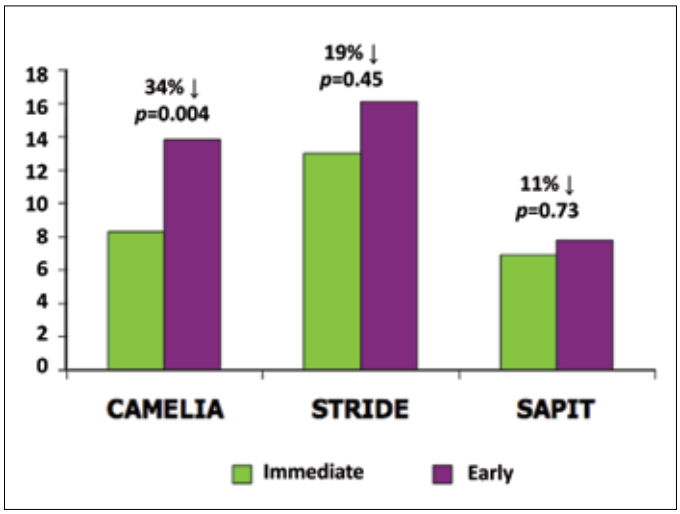

Fig. 11. Effect of ART timing: death (CAMELIA) or death/AIDS (STRIDE, SAPIT).

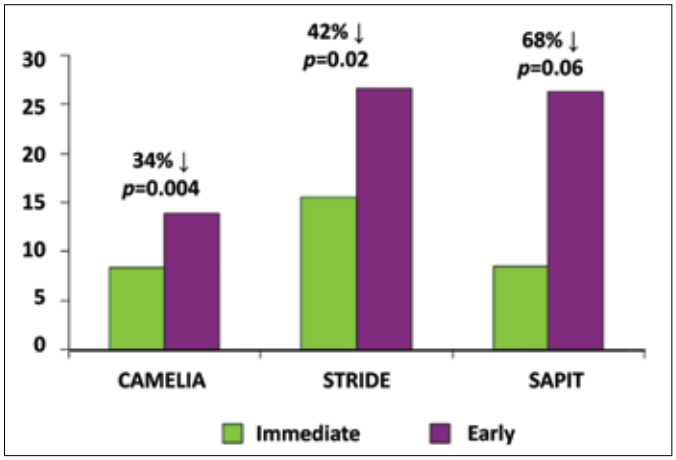

Fig. 12. Effects of ART timing in all patients with baseline CD4 counts >50.

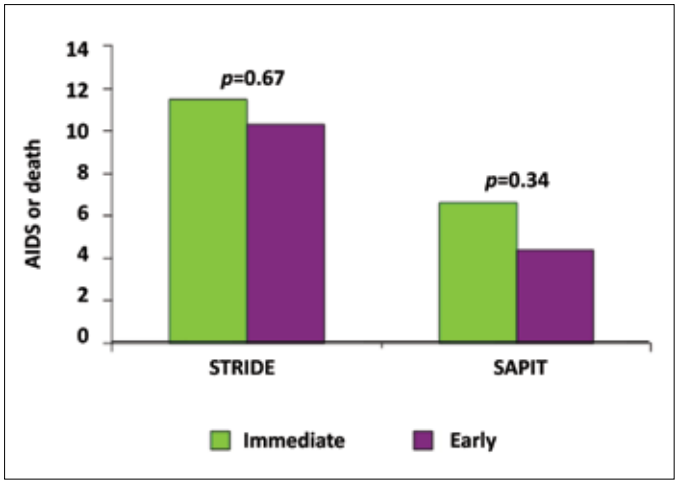

Fig. 13. Effects of ART timing in all patients with baseline CD4 counts >50.

However, there was significantly higher incidence of IRIS with early v. late ART in CAMELIA: 4.03 v. 1.44 cases per 100 person-months, respectively ($p<0.0001$) Similarly, there was also significantly more IRIS reported among patients with baseline CD4 >50 in both STRIDE and SAPIT (Fig. 14). The risk factors described in STRIDE for IRIS included immediate ART, low CD4 count and confirmed TB. No deaths were attributed to IRIS but 'excess TB deaths' were reported in the immediate arm of SAPIT. In all three studies there was no discernible effect of ART timing on viral suppression outcomes at the end of TB treatment in all three studies.[27-29]

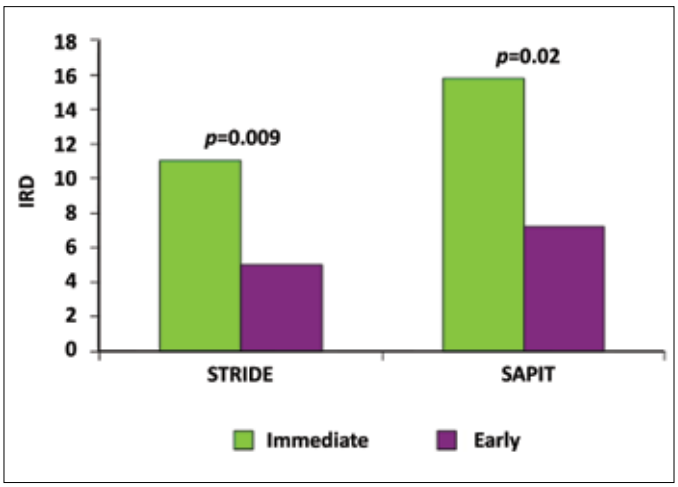

Fig. 14. Effects of ART timing on IRIS: SAPIT and STRIDE.

A clinical problem

A 35-year-old woman arrived in casualty with a 2-week history of fever and one day of confusion. The accompanying family informed you that she had lost weight over many months. On examination you found that she was confused and had no central neurological deficits but had absent ankle jerks. She had a high temperature of 38.6°C, her pulse was 110 beats/min, blood pressure was 130/70 and oxygen saturation was 100%. She had oral candidiasis, a submental and axillary lymph nodes. Abdominal examination revealed possible hepatosplenomegaly. The rest of her exam was normal. An HIV test was positive, a lumbar puncture was acellular with a slightly raised protein, her CD4 T cell count was 35 cells/mm^3 and she had +AFB on sputum. Lab confirmed this was *M. tuberculosis* and TB drug sensitive. You commenced isoniazid, rifampicin, ethambutol and pyrazinamide and witnessed clearing of her confusional state and settling of her temperature in days.

The mortality associated with even short delays in accessing ART is unacceptably high.

Your diagnosis: a patient with advanced HIV and concomitant TB, pulmonary with possible extrapulmonary involvement. The +AFB on sputum suggests there is a reasonable bacillary load and the hepatosplenomegaly may suggest some extrapulmonary TB. It does not appear that she has TB meningitis but may well have HIV-related nervous system involvement with a raised CSF protein and peripheral neuropathy.

Problem: When is the best time to start her ART?

Discussion

Given the facts above, there is no doubt that this patient requires ART. Her low CD4 count and stage 3 HIV disease means she has a mortality of 10.8 per 100 patient-years, and should her hepatosplenomegaly indicate extrapulmonary TB, her mortality rate is 22.2 per 100 patient years. With a baseline CD4 count <50 cells/mm^3, CAMELIA, SAPIT and STRIDE would all suggest that she should start ART within 2 weeks. She does not appear to have neurological TB and so the caveats of the Vietnamese TB meningitis study should not apply. The patients in this study were extremely ill but immediate therapy was not useful in this setting. The risk in this patient is that with her low CD4 count and smear-positive TB, she is almost certain to have evidence of TB IRIS. Commencement of ART within 2 weeks will enhance this risk, but if the precautions discussed elsewhere in this edition are adopted, this complication of ART is manageable. It is also important to note that this patient already has HIV-related peripheral neuropathy, INH may make this worse and this may be further exacerbated by the initiation of nucleoside reverse transcriptase inhibitors, especially stavudine. Routine administration of vitamin B_6 may give some protection, and control of HIV viral load may also have a positive effect. Should the hepatosplenomegaly indicate hepatic extrapulmonary TB, IRIS may also result in liver function abnormalities involving both hepatic and bile duct components.

On balance: this patient should start ART within 2 weeks of TB treatment, to offset her high risk of HIV mortality, but should be closely observed and monitored for IRIS and drug toxicities which may well cause significant morbidity in the first few weeks to months of treatment.

Conclusion

Determination of the optimal timing of initiation of ART in patients with TB is important in South Africa, where HIV/TB is extremely common and availability of ART is rapidly expanding. HIV/TB case fatality rates are high and the optimal deferral time must therefore be determined predominantly by mortality rather than morbidity. The results of several randomised controlled trials addressing when to start ART in TB, with a primary endpoint of survival, have indicated that immediate ART (within 2 weeks) improves survival in patients with advanced AIDS (CD4 <50). Despite increased risk of IRIS, there is still a survival benefit to immediate therapy. In those patients with CD4 >50, then early ART (within 2 months) provides a good balance of competing risks of death/AIDS v. IRIS. However, the Vietnamese TB meningitis study indicates no benefit to immediate therapy when there is CNS involvement with the added possibility of harm in these very sick patients. The SAPIT study has also confirmed that deferring treatment for sequential ART in 6 months is associated with significantly increased mortality and should not be practised.

The present status of information concerning the most important factors that may impact on the optimal timing of ART in TB are shown in Fig. 15. Reduction of ongoing HIV-related mortality by ART

is counterbalanced by TB/IRIS-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 IRIS. The ACTG 5164 study has demonstrated improved survival with very early initiation of ART in patients co-infected with acute OIs. Treatment of TB requires prolonged treatment and is complicated by frequent occurrence of IRIS. TB/IRIS is a common cause of morbidity but is a less frequent cause of death.

In low-income settings TB in HIV-infected patients is often only diagnosed after prolonged delay, and yet the mortality associated with even short delays in accessing ART is unacceptably high. Furthermore, the potentially more important problem of delays in the care pathway has received little attention.

In a study from India of 396 HIV/TB patients all eligible for ART, only 68% of patients were referred, 56% reached the ART clinic and only 26% were finally commenced on ART. Among 893 TB patients studied in Cape Town (median CD4 count, 81 cells/μl), the delay between starting TB treatment and starting ART was prolonged (median, 95 days; IQR=49 - 155). The median delay was almost three-fold longer for patients referred from separate TB clinics compared with patients whose TB was diagnosed in the ART clinic (116 days versus 41 days, respectively; $p<0.001$).[30] Health system challenges to immediate or even early commencement of ART in TB/HIV patients require rapid diagnoses of TB and HIV, CD4 cell counts, ART availability where TB is diagnosed and training in the diagnosis and management of TB, HIV and IRIS at all health facilities where these diseases are managed. It is important to recognise that time delays between the onset of TB symptoms and starting ART in those eligible for ART are associated with potentially preventable HIV-related mortality and that all delays should be minimised.

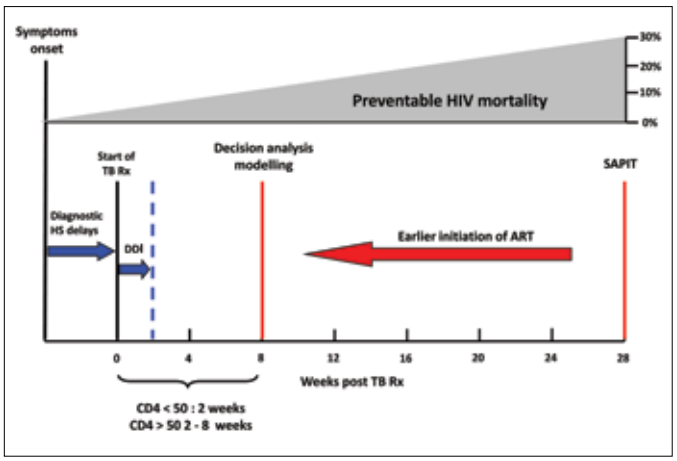

Fig. 15. Summary of when to start ART in TB/HIV.

Acknowledgement
With thanks to Dr William Burman, Denver Public Health.

References available at www.cmej.org.za

In a nutshell

- Indications for antiretroviral therapy are based on an assessment of individual risk-benefit analysis of treatment versus no-treatment for patients at different stages of HIV disease progression.
- Mortality is high during early ART and is a reflection of the high mortality preceding the start of ART, together with immune restoration disease, as increased immune surveillance recognises occult pathogens or antigens.
- The risk/benefit of ART for individuals commencing treatment in developing countries therefore does not favour later initiation of therapy than that recommended in developed settings.
- The mean interval to an IRIS event after ART initiation also varies widely (1 - 180 days) with most cases occurring within the first 28 days.
- In lower income countries, the risk of mortality associated with delays in ART initiation is likely to outweigh the excess mortality of TB-associated IRIS.
- 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.
- ART options that are compatible with South African TB treatments are limited.
- If patients cannot take an efavirenz based ART regimen, boosted protease regimens are indicated with inherent interactions with rifampicin.
- The World Health Organization and US guidelines now recommend that ART should be started during rather than after TB treatment as soon as possible after the commencement of TB therapy.
- Several guidelines focus on 8 weeks as a key time point in TB therapy when simplification of TB medications occurs.

Single suture

A nose for the time of death

Tiny finger-like projections lining the nose continue to beat after death. Since the beating of these cillia slows at a predictable rate, forensic teams should be able to estimate time of death more accurately.

Pinpointing precisely when someone died can be a challenge for investigators. They can look at body temperature or decomposition rate, but these indicators can be confounded by temperature or whether the person was involved in struggle, say, shortly before death. The beating rate of cillia could add an additional tool to help decide the time of death, especially if it was within the previous 24 hours.

Nasal cillia are tiny projections that waft mucus, dust and bacteria out of the nose and into the throat. Biagio Solarino of the University of Bari in Italy and his colleagues suspected that cillia continue to beat after death. So they took a scraping from the inside of the nose of 100 cadavers to examine the cillia.

'Motility was observed as long as 20 hours after death,' say Solarino, who presented his results at the International Symposium on Advances in Legal Medicine in Frankfurt, Germany, recently. They hope to use the cillia to judge time of death since not only does the beating slow gradually, but it also seems relatively immune to environmental factors.

New Scientist, 1 October 2011, p.19.