# TLALELETSO

UPDATES IN HIV
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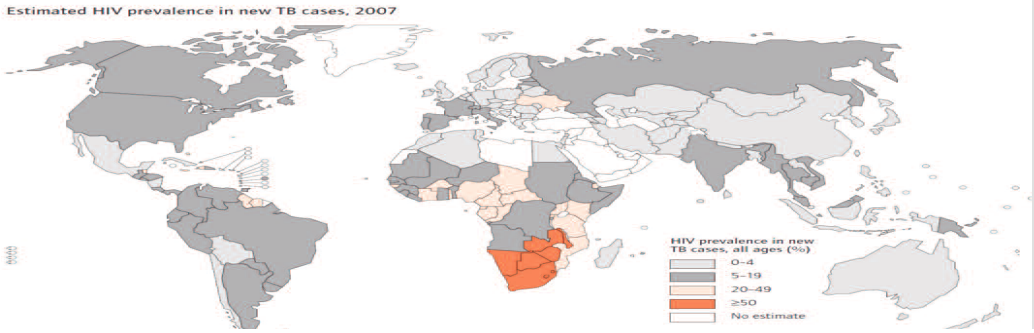



# UPDATES IN HIV:

## TUBERCULOSIS CO-INFECTION

*Tlaleletso is a monthly publication produced by the Botswana UPenn Partnership, in response to your expressed need to have accessible, digestible clinical information. Key clinical issues and challenges identified by doctors across Southern Botswana are explored in Tlaleletso. Each issue will summarize new scientific evidence and highlight recommendations in a user-friendly format.*

*In this month's issue we address the question of when to start antiretroviral treatment in patients with TB/HIV co-infection. We highlight the results of three recent trials, SAPiT, CAMELIA and STRIDE. We underscore the importance of understanding and changing clinical practice accordingly.*

*This is your publication. In this spirit, I encourage you to send ideas, comments, questions and feedback – either on content or format.*

*Respectfully, Mike Reid*

Tuberculosis (TB) is the most common opportunistic infection reported worldwide in HIV-infected patients. People living with HIV are between 20 and 37 times more likely to develop active TB than HIV negative individuals[1]. A quarter of deaths in HIV-infected patients are estimated to be as a result of TB. TB/HIV co-infected patients are four times more likely to die during TB treatment compared to TB patients without HIV.

Prompt initiation of TB treatment in individuals with suspected or confirmed TB is a key priority. Knowledge of HIV status is also critical for all TB patients in order to ensure prompt linkage to HIV care and access to high active antiretroviral therapy. However, the optimal timing of ART initiation in patients with TB and HIV has been unclear for many years. Until recently, guidelines have been largely based on expert opinion and observational data.

Results from three recent trials have clarified that it is very important that patients with HIV and pulmonary TB co-infection should start ART very soon after anti-tuberculous therapy has been commenced.

In this edition of Tlaleletso we review these studies and discuss clinical and programmatic steps to ensuring that patients co-infected with TB and HIV are promptly stated on treatment.

## UPCOMING LECTURES

**August**

Guidelines Update:

Acute Kidney Injury

**September**

Topics in HIV:

HIV and Aging

**October**

Guidelines Update:

Acute Respiratory Distress

**November**

Topics in HIV

HIV and Cancer

**December**

Holiday Quiz 2012!

# WHEN TO INITIATE ARVS IN TB/HIV PATIENTS

**SAPiT '1'**

**Summary:** This trial evaluated the impact of starting ART at the end of TB intensive phase as compared to starting ART after TB treatment had been completed. The study was stopped early because there was a significant reduction in mortality outcomes in those patients that received ART during TB treatment when compared to those that received ART after TB treatment had finished. The study demonstrated that deaths can be more than halved by combining ART with TB treatment.

**CAMELIA**

**Summary:** In this trial those patients that started ART two weeks after beginning TB treatment were 33% less likely to die than those who started ART eight weeks after beginning TB treatment had died. This 33% difference was statistically significant, leading the investigators to conclude that starting ART two weeks after beginning TB treatment boosts the chance of survival for people with HIV-TB co-infection and severely damaged immune systems.

**SAPiT '2'**

**Summary:** This trial, from the same study as the original SAPiT, compared outcomes in those patients initiating ART within 4 weeks of TB treatment and those that initiated ART within 4 weeks of completing the intensive phase of TB treatment. The investigators found no difference in death or AIDS defining illness between the two groups. However, after stratifying for CD4 count, the investigators found a 68% reduction in AIDS defining illness and death in those patients with CD4 counts< 50 cells/mm initiating early compared to those initiating after then end of the intensive phase of TB treatment.

**ACTG STRIDE**

**Summary:** This was a multi-country study, comparing immediate ART initiation after starting TB treatment and early ART initiation. Overall, immediate ART (< 2 weeks) did not reduce AIDS and death compared to early ART (8-12 weeks) after TB treatment commencement. However, for persons with CD4 ≤50 cells/mm3 immediate ART resulted in lower rates of AIDS and death compared to early ART.

**SAPiT**

The SAPiT (Starting Antiretroviral Therapy at three Points in Tuberculosis therapy) trial was designed to test when to initiate antiretroviral therapy after starting TB treatment.

Three years ago the investigators of the SAPiT study reported that starting ART soon after starting TB treatment significantly reduced the risk of death from all causes when compared to delaying the initiation of treatment until after completion of TB treatment (ref). More recently the same study team published results of an analysis comparing patients randomized either to start treatment immediately or to wait until the completion of the intensive phase of TB treatment[2,3].

**Study Design**: Eligible patients were randomized to one of three arms

1. Start ART within 4 weeks of completing the intensive phase of TB treatment
2. Start ART within 4 weeks of starting TB treatment
3. Wait until TB treatment is completed before starting ART (after 6 months)

All participants had confirmed sputum positive TB and HIV with a CD4 count of less than 500 cells/mm. All received standard TB treatment with four drugs during the intensive phase (RHZE) followed by two drugs (RH) during the continuation phase. The end points that the researchers evaluated were (1) all cause mortality and (2) tolerability, toxicity, HIV viral load and TB outcomes.

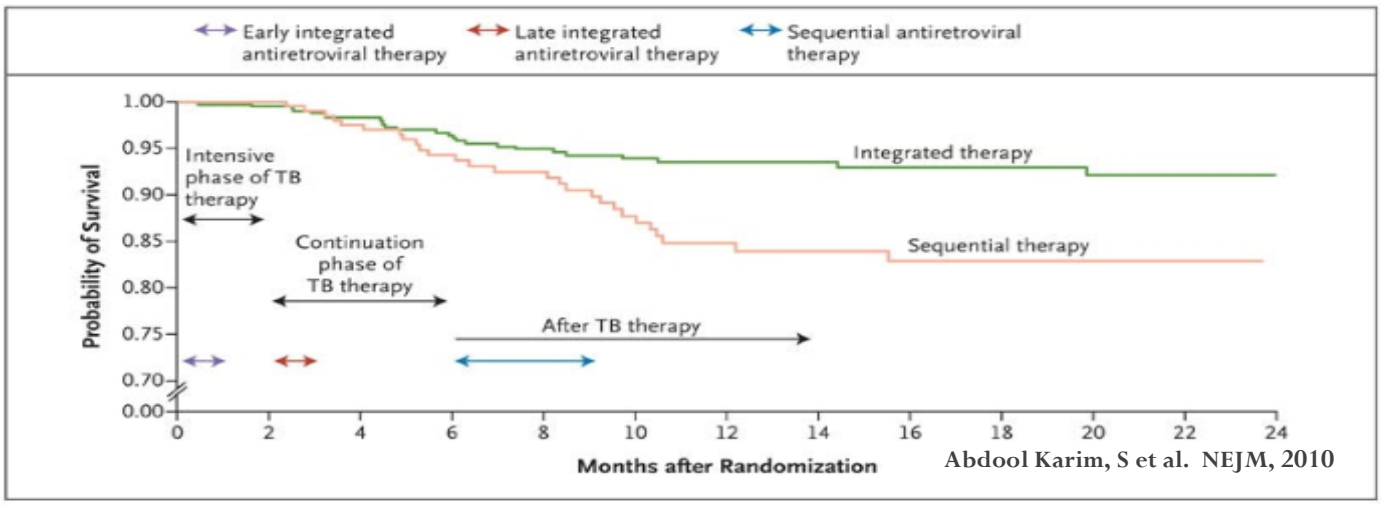
**Results:** A total of 642 patients with TB/HIV were enrolled and followed in the study in Durban South Africa. During the study follow up the data was reviewed by external reviewers who determined that TB/HIV patients who were in the study arms that initiated ART during TB treatment (arms 1 and 2) had significantly better survival that those in the study that received ART only after TB treatment (arm 3).

In the later analysis, released in 2011[3], the researchers compared outcomes for those patients that were randomized to arms 1 and 2.

They did not find a significant difference in AIDS or death in those individuals starting ART within 4 weeks of TB treatment, compared to those individuals starting ART within 4 weeks of completing the intensive phase of TB treatment (incidence rate ratio, 0.89; 95% confidence interval [CI] 0.44 to 1.79, p=0.73). However, among those individuals with CD4 counts of less than 50 cells/mm, the incidence rates of AIDS or death was significantly different between the two arms: those starting ART later had a much high risk of death or AIDS (Incidence rate ratio, 0.32 [CI] 1.48-4.82, P<0.001). There was an increased risk of IRIS in those individuals with lower CD4 counts who start ART within 4 weeks.

**Conclusions:** Early initiation of ART in patients with pulmonary TB and CD4 counts of less than 50 cells/mm increased AIDS free survival. Among patients with CD4 counts of less than 50, the incidence of IRIS was nearly 5 times as high as in the arm 1 (within 4 week so starting ATT) compared to arm 2 (4 weeks after finishing intensive phase).

*The study supports an approach advocating for prompt initiation of ART in patients with pulmonary TB and CD4 counts of less than 50, since the risk of death and AIDS, outweighs the risk of IRIS.*




**SAPiT Conclusions (cont.d)**

In individuals with CD4 counts >50 cells/mm, ART can be deferred until later in TB treatment – *but a long delay in initiating ART should be avoided,* since delaying ART until the end of TB treatment is associated with far worse clinical outcomes.

**CAMELIA**[4]

This study also sought to determine when the optimal time to initiate ART was. It took place in Cambodia and only enrolled people with advanced HIV disease (CD4 cell counts below 200) who had started TB treatment.

**Study Design:** The study randomized 661 participants with HIV and smear positive TB to either initiating ART within 2 weeks of TB diagnosis (n=332) or 8 weeks of TB diagnosis (n=322). The primary endpoint was survival at the end of the trial (when the last participant completed 50 weeks of ART), with an intent to treat analysis. Patient characteristics were similar at baseline. The median CD4 cell count at inclusion was 25mm3, and the body mass index was 17.

**Results**: After a follow-up time of 712.4 person-years, there were 59 deaths in the early arm, a mortality rate of 8.28 (95% confidence interval (CI) 6.42 to 10.69). In the late arm, after 653.7 days follow-up time, there were 90 deaths for a mortality rate of 13.77 (95% CI 11.20 to 16.93). There was a significant reduction in mortality in the early arm (p= 0.02). Only 12 patients (1.8%) were lost to follow-up, and fewer than 2% missed clinic visits. Kaplan-Meier curves showed the survival over time. As noted earlier, the difference in survival between the two arms became more marked with time.

At week 150, survival was more or less stable in the early arm, but it continued to decline in the late arm. IRIS was observed more frequently in the early arm, nearly 2.5 times more common than in the late arm. However it was not severe and no patients received corticosteroids.

**Conclusions:** These findings also support the conclusion that early initiation of ART is associated with a significant reduction in mortality. However, there was an increased risk of IRIS when ART was started early, especially at lower CD4 counts.

**ACTG STRIDE**[5]

This was a multi-country study also evaluating optimal timing of ART in co-infected patients and compared immediate ART initiation (<2 weeks) with early treatment (8-12 weeks after TB treatment initiation) in patients with CD4 counts<250 cells/mm

**Study Design:** This was an open label randomized strategy study comparing immediate ART with early ART among HIV infected subjects with CD4 cells counts<250mm. Researchers sought to determine whether (1) all cause mortality and new AIDS defining illnesses and (2) CD4 counts, TB IRIS and TB outcomes were effected by time of initiation of ART. Subjects received standard TB treatment, cotrimoxazole prophylaxis and an ART regimen that included tenofovir/emtricitabine and efavirenz.

**Results:** Median CD4 count at baseline was 77cells/mm3 and the average time to initiation of ART was 10 days (IQR 7 to 12) for the immediate ART arm and 10 weeks (9.4 to 10.4 weeks) from the start of TB treatment for early ART arms respectively. 13% in the immediate arm and 16% in the early ART arms experienced AIDS or death at 48 weeks (p=0.45, difference CI -1.8 TO 8.1). In the low CD4 stratum (<50, n=285) 15.5% on immediate ART and 26.6% on early ART experienced AIDS or death (p=0.02, difference CI 1.5-20.5).

In the high CD4 stratum (>50, n=521) 11.5% on immediate ART and 10% on early ART experienced events (p=0.67, difference CI -6.7 TO 4.3). IRIS was significantly higher with immediate ART than early ART (11% VS 5%, P=0.009) but no deaths were attributed to IRIS. 50% of those with IRIS required steroids.

**Conclusions:** Immediate initiation of ART was associated with less AIDS defining events and death in those individuals started on ART immediately only if the CD4 count was less than 50.

**Study Summaries**

All of these studies demonstrate that patients pulmonary TB and HIV do better if they are initiated on ART soon after starting TB treatment. The benefit of early initiation is most profound in individuals with the lowest CD 4 counts. CAMELIA and SAPiT also demonstrated that while the benefit was greatest in patients with the lowest CD4 counts, these patients were also at greatest risk for developing Inflammatory Response Immune Syndrome (IRIS)*.

**Managing IRIS:**

In brief, there are several options for management when IRIS

**1. Continuation of ART when IRIS occurs**: Published clinical experience suggests that it is reasonable to continue ART in the majority of cases. In patients with IRIS that is not life-threatening and that is not placing the patient at risk for permanent sequelae, mild or moderate symptoms may be tolerable and patients can be reassured that symptoms will resolve over time. However, ART should be discontinued and hospitalization may be required in patients who experience life-threatening IRIS or in whom localized symptoms threaten to cause permanent sequelae (e.g, airway obstruction from an enlarging mass).[6] These patients can be treated for a period of time for their underlying infection before resuming ART again.

**2. Anti-inflammatory agents:** Although there are no controlled trials evaluating the role of corticosteroids or non-steroidal anti-inflammatory agents (NSAIDS), multiple case reports and case series suggest these ancillary agents may have efficacy in decreasing the inflammatory response associated with IRIS **.** Anti-inflammatory agents may be helpful in the setting of obstructive mass lesions (ie, expanding cervical lymph node secondary), however, use of anti-inflammatory agents, particularly corticosteroids, must be weighed against potential risks and side effects.

**What strategies should be employed to reduce the burden of TB disease among people with HIV?**

**Intensified Case Finding –** It is important that all patients attending IDCC are screened at every visit. Effective baseline screening reduces the risk of unmasking TB immune reconstitution disease in the early weeks of ART[7]. Moreover, rapid effective screening may reduce diagnostic uncertainty, potentially shortening time to initiation of ART. Frequent repeat screening – at every IDCC visit- is especially important in people with very low CD4 counts.

**Symptom Screening –** The Botswana National TB program recommends using the 4 symptom screening tool, recommended by the WHO. Ask every patient about (1) current cough, (2) fever, (3) night sweats, and (4) weight loss. Patients who report any of these symptoms should undergo further testing.

**Rapid Diagnostics –** All TB suspects should undergo further testing. Smear microscopy should be performed on all patients. There is increasing interest in using Gene Xpert MTB/RIF as an alternative to microscopy in settings like Botswana, where TB prevalence is high. This rapid molecular assay uses polymerase chain reaction technology to detect TB. Research to date has shown that it is a very accurate test. While it is not widely available in Botswana, it is likely to be increasingly available over the coming years.

**TB prevention in those who are TB-free –** It is vital to ensure that patients that do not have TB, stay TB-free. ART itself is the key-long term intervention, reducing TB risk by 67%[8]. TB risk is directly related to the current CD4 count and is increased by virological failure. Therefore optimization of adherence and immune recovery are essential. While not currently recommended in Botswana, many HIV programs in Africa are using isoniazid preventive therapy as an intervention to protect people with HIV from getting TB.

**What about people already on ART who develop TB?**

People with HIV reduce their overall risk of tuberculosis by starting ART. Treatment failure should be considered in patients on ART who develop TB after having been on ART for some time. However, note, that risk of TB is increased in the first three months of HIV treatment, especially for older people and those with a low CD4 cell count.

# 2012 BOTSWANA TB/HIV GUIDELINES

All HIV patients with TB are eligible to begin ART regardless of CD4 cell count. TB treatment should be started first, followed by ART as soon as possible and within the first 8 weeks of beginning TB treatment.

- Patients with CD4 counts <100 cells/mm should start ART as soon as the patient is tolerating TB treatment
- Patients with CD4 counts >100 cells/mm should start ART within 8 weeks and at least by the end of the initial phase of TB treatment.
- Patients with CD4 counts <50 cells/mm should start ART as soon as possible. However caution is advised in severely immunosuppressed patients with suspected neurological involvement or deranged LFTs.
- Great care must be taken to monitor these patients for hepatitis and worsening of TB due to IRIS (and seek advice from TB/HIV specialist if necessary)

* None of these studies included patients with TB meningitis (TBM). Studies have shown that there is no mortality benefit to starting ARV before eight weeks in patients with TBM. However, grade three and four toxicities are significantly increased in these patients. Therefore in TBM the recommendation is to wait for eight weeks prior to starting ARVs.

For severely immunosuppressed people, the risk of TB remained increased in the long term.

A recent study in a large cohort of individuals in the US and Europe[9], compared risk of TB in ART-naïve patients with those individuals already on ART. The researchers found that starting HIV therapy was associated with 44% reduction in the risk of TB (HR = 0.56; 95% CI, 0.44-0.72). However, the overall reduction in the risk of TB associated with HIV therapy, the investigators found that people starting ART had an increased risk during the first three months of therapy compared to those who remained ART naïve (HR=1.36, 95% CI, 0.98-1.89). This suggests that unmasking IRIS may be playing a role.

A key message from this research is that it is vital that all patients undergo regular and rigorous screening for TB, especially before initiating ART. Starting patients on ART when clinically indicated and before they develop advanced AIDS is an essential of TB control.

**First line ART patients who develop TB**

Patients on first-line ART who develop TB should continue on first line ART while ATT is initiated, with close monitoring for any potential drug-drug interactions, additive toxicities and TB-related IRIS. Of note, stable patients who are receiving nevirapine, should remain on nevirapine. There is no need to increase the dose or switch to efavirenz or second line drugs unless there is concern that the development of TB may have been a consequence of a priori treatment failure.

**Second line ART patients who develop TB**

Patients on second line ART containing alluvia require dose modification as the effect of rifampicin is significant. Rifampicin can lead to clinical important reductions in alluvia. Therefore, the recommendation is to either double the dose of alluvia or give the standard dose but add 300mg of ritonavir. Always discuss with a specialist!

## SUMMARY

The findings of the studies reviewed in this edition of Tlaleletso highlight the following:

- Knowledge of HIV status for all TB patients is important in order to provide those with HIV infection the needed intervention
- TB/HIV patients should be promptly linked to the IDCC to start ART as soon as possible – ideally within the first two weeks of TB therapy
- TB/HIV patients should all get prompt CD4 count testing.
- Patients with TB/HIV should be closely monitored and receive intensive adherence support.
- Doctors need to monitor closely for signs of IRIS and drug side effects; both of which are more common when ART is started during TB

**Got a clinical question about a complicated medical patient or a patient with HIV?**

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**Want to read more? Check out the references below:**

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