



DOH REVIEWS HIV/TB TREATMENT PROTOCOLS



Caprisa director, Professor Salim Abdool Karim.

The National Tuberculosis Directorate is reviewing the relative cost and staffing implications of earlier ARV treatment for HIV co-infected patients following breakthrough research in Durban that could save up to 10 000 more lives a year.

This was confirmed by directorate chief, Dr Lindiwe Mvusi, who said the trial by the University of KwaZulu-Natal's Centre for the AIDS Programme of Research in South Africa (Caprisa) begged an urgent decision on where to reset the government's current 200 CD4 cell count ART initiation bar. Until now there had been no clinical trial evidence worldwide to prove that treating people concurrently for HIV and TB saves lives.

Caprisa director, Professor Salim Abdool Karim, said the study of 645 patients with CD4 cell counts of less than 500, definitively showed that HIV patients co-infected with TB did worse than those without TB, regardless of their CD4 count.

Traditionally, doctors have first attempted to cure patients of TB and only then start them on ARV medication. This is because one of the TB drugs interacts with some ARVs,

reducing their effectiveness. It also spares patients from taking up to 7 pills a day. However, the Durban study shows that mortality among TB-HIV co-infected patients can be reduced by a remarkable 55% if ART is provided with TB treatment.

The results were welcomed by UNAIDS executive director, Dr Peter Piot, who emphasised that TB was the leading cause of death in people living with HIV, and by Dr Francois Venter, head of the SA HIV Clinicians Society. Venter said the study had 'begun to answer one of the most important questions for the HIV field – when we can start ARVs safely in people with TB'.

Rapid diagnosis of HIV in TB clinics and getting such patients onto ARVs was vital.

'Saving 10 000 lives (nationally) a year by improving a programme that desperately needs strengthening should be a priority,' Venter added.

Trial description and results

Caprisa started the three-arm trial in 2005 to test whether patients with TB

and HIV and CD4 counts of under 500 should:

- be given both TB medicine and ARVs together as soon as possible
- be treated intensively for TB for 2 months and then started on ARVs or
- only be given ARVs after completing TB treatment (a wait of 6 - 8 months).

Twice as many patients died in the group that waited for ARVs until they had completed TB treatment than those in the two groups where ARVs and TB treatment were integrated. As soon as the findings became incontrovertible, the trial's safety committee halted the sequential arm. However, this was not before 26 people had died in the group of 214 – a mortality rate that was 55% higher than the other two groups combined (24 out of 431).

When questioned about the ethics of enrolling advanced-stage patients into the sequential study arm, Karim said any patients could be started on ARVs 'at any time if judged clinically necessary' by the doctors who were monitoring them. Generally patients who died had low CD4 cell counts – in all three study arms.

Mvusi told *Izindaba* that the government's response has been to begin TB treatment and 'then give them up to 2 months before initiating ARVs – using the 200 CD4 cell count as a benchmark. Those with CD counts of less than 100 we'd consider starting immediately on ARVs, but we'd first initiate TB treatment.' She said this had been policy 'since the ARV rollout began in 2001'. People who were HIV

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positive but TB negative would be offered preventive TB therapy.

WHO and local treatment guidelines challenged

The WHO generally recommends starting ARVs at a CD4 count of 350, giving TB and ARV treatment as soon as possible for CD4 counts under 50 and for CD4 counts of 50 - 200, starting ARVs after 2 months of TB treatment. It also says that patients with CD4 counts over 200 should first complete TB treatment.

The Durban trial has virtually pulled the carpet on these guidelines. Said Mvusi: 'What we now need to decide is what the ideal CD4 count level is to start ARVs in TB patients. It's still out for debate for us. Should we raise the bar to 500 and if so, what are the implications in terms of costs, numbers, staffing, etc.? Or should we look at the more conservative WHO level, or should we remain where we are?' She added: 'Some people are saying that if you are co-infected and you treat the TB (at high CD4 cell count levels), the CD4 count needs to improve.'

She and her senior staff would be meeting with Karim's research team as soon as possible 'to get clarification on the issues I'm raising and to chart the way forward'.

Asked about MDR and XDR TB, she said this was 'a different story; we need to start them on ARVs at a much higher CD4 cell count because of the higher mortality'.

Asked how he reached his '10 000 lives' saved per year, Karim said the calculation was based on the national health department's figure of 350 000 TB cases last year, of which an estimated 70% were HIV positive.

Of these resulting quarter of a million co-infected patients, some 20 - 25%

would have CD4 cell counts higher than 500. 'That leaves you with about 200 000 people, of whom I estimated that about 50 000 would reasonably already be on ARVs. That leaves you with about 150 000 who last year were HIV positive, had TB and did not get ARVs'. If their study finding was implemented, these 150 000 people would receive ARVs.

The difference in the mortality rate between the control arm and the study arm of their study was 6.5%, translating into the 10 000 lives saved. Karim said the study 'went against all my expectations'.

Venter said the study had begun to answer one of the most important questions for the HIV field – when we can start ARVs safely in people with TB'.

Anomalies resolved with time

'I thought it would be at the most a slight advantage because of immune reconstitution syndrome, which can be a real problem.'

What the trial does show, is that while the mortality rate in the integrated treatment arm is actually higher than in the sequential arm over the first 3 months, it reverses over the following 3 months. The mortality curve lines track one another before diverging sharply at about 6 months. 'If you wait until you finish the TB treatment, it's too little, too late, so the only way is to start ART with TB treatment,' Karim concluded.

He emphasised that the 55% mortality difference was measured on 'all-cause mortality'. If they were able to separate out the actual AIDS/TB deaths (a virtually impossible task given the lack of autopsies and dismal record

keeping), the difference would have almost certainly been bigger.

Mvusi emphasised that the decision on when to start ARVs 'remains with the clinician and the individual patient'. She wants to thoroughly interrogate with Karim's team the relative merits of earlier ART (i.e. helping to deal with undiagnosed opportunistic infections), and the combined effects of opportunistic infections and antagonistic drug use. 'If very low CD4 cell counts are not properly monitored you may kill instead of save people,' she cautioned.

Acting national HIV/AIDS chief, Dr Frew Benson (Dr Nomonde Xundu was in New York, once again dealing with unresolved UNAIDS funding issues), told *Izindaba* he had yet to study the Durban trial. However, he was certain it 'warrants closer study from our side'.

'We obviously must look at it objectively and develop a policy decision based on these findings. We welcome any research that can assist us to better manage the pandemic,' he added.

The Treatment Action Campaign called on the WHO and the South African Department of Health to integrate the findings into their TB/HIV treatment guidelines. It asked that ARVs be provided to patients not more than 2 months after they have started TB treatment, if their CD4 count is less than 500. 'The Department of Health must put measures in place to prepare for the increased demand in ARVs that would arise from TB patients needing to start ARV treatment earlier,' the TAC added.

Chris Bateman