

ISSUES IN RESEARCH

The SAPIT trial provides essential evidence on risks and benefits of integrated and sequential treatment of HIV and tuberculosis

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Bouille *et al.*¹ queried whether a clinical trial was needed to provide the evidence for the mortality benefits of antiretroviral therapy (ART) initiation during tuberculosis (TB) treatment. While several experts, including foremost TB-HIV scientists from South Africa² and the USA,³ senior World Health Organization (WHO)⁴ and UNAIDS⁵ officials at the time the study was initiated, the 2003 WHO AIDS Treatment Guidelines Committee Chair³, the Chair of the Ethics Committee⁶ and the researchers,⁷ have previously addressed the points raised, the SAPIT (Starting Antiretroviral Therapy at Three Points in Tuberculosis) research team welcomes the opportunity also to address the comments. We hold Bouille and his colleagues in high regard and appreciate their contributions to the field of HIV and tuberculosis co-infection. More importantly, we share with them the common goal of rigorously and relentlessly seeking answers to critically important research questions as we confront the devastating dual AIDS and tuberculosis epidemics.

The SAPIT trial,⁸ which was developed in 2004, set out to assess whether integrating tuberculosis and AIDS treatment would lead to improved outcomes compared with the widely practised approach of treating them sequentially. The trial's Safety Monitoring Committee halted the sequential treatment arm in September 2008 because of a 56% lower mortality rate in the integrated treatment arm. We systematically address the queries on equipoise and standard of care.

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Did the SAPIT study have clinical equipoise?

Yes, the optimal timing of ART initiation in patients with tuberculosis was not known at the time the trial was planned and conducted.

Availability of, and experience in providing, ART in developing countries, including South Africa, was limited before 2004, and even less was known about the timing of ART initiation in tuberculosis-HIV co-infected patients. Treatment guidelines were either silent on this issue or contained tentative and provisional guidance largely based on expert opinion, due to the lack of reliable and compelling evidence. The 2003 WHO guidelines specifically mention this limitation and that their recommendations are 'Pending ongoing studies ...'⁹

The SAPIT trial had clinical equipoise because the balance between the potential increase in morbidity and mortality due to combined antiretroviral-tuberculosis drug intolerance, drug-drug interactions and immune reconstitution inflammatory syndrome (IRIS) on the one hand and the potential improved morbidity and mortality from early antiretroviral initiation on the other were unknown.⁹ Published data on IRIS-associated morbidity and mortality at the time were limited, not least owing to substantial under-reporting resulting from the lack of a consistent case definition of what constituted IRIS. A WHO consultation¹⁰ in 2005 highlighted the problem of inadequate data on IRIS and recommended that 'validating the definition of IRIS' be regarded as a research priority. When the standardised case definition of IRIS was published in 2008, the authors pointed out that this definition will help clinicians by providing insight into the incidence, clinical manifestations and impact of TB-associated IRIS.¹¹

Bouille *et al.* cite two retrospective chart review studies¹²⁻¹³ undertaken in the UK to support their argument that the beneficial effect of ART during TB therapy was already known. The first included 159 patients with TB and HIV who were not on ART at presentation, 45% of whom were subsequently initiated on ART by the treating clinicians.¹² Just over a third of the latter patients had either TB or HIV treatment discontinued because of adverse events, making interpretations of safety and effectiveness difficult. The second compared outcomes in 36 patients with TB and HIV in a pre-antiretroviral era with 60 patients in the antiretroviral era.¹³ Both studies provide useful initial descriptive information on experiences in co-treatment, but do not provide the quality of evidence essential for the development of clinical guidelines and treatment policy. Some co-treatment challenges are epitomised in the statement: 'More doubts than certainties are available on which basing the decision on how to cope therapeutically with active tuberculosis developing in a patient also requiring antiretroviral treatment.'¹⁴

The existence of equipoise was confirmed by several levels of scientific, regulatory and ethical review, including independent approval from the Medicines Control Council and the Biomedical Research Ethics Committee of the University of KwaZulu-Natal (a US Office for Human Research Protections-accredited ethics committee), which also oversees research conducted by several of

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the co-authors of the critique.¹ The SAPIT trial was undertaken after widespread consultation in scientific and community forums, including presentations and dedicated sessions at the South African AIDS conferences in 2003 and 2005. Importantly, a rationale for the trial was published in the peer-reviewed literature before its initiation.¹⁵

Were the patients in the SAPIT trial provided the best standard of care?

Yes, the SAPIT trial provided the prevailing best standard of care for antiretroviral initiation, viz. clinician judgement. Clinicians with prior experience in treating TB-HIV co-infected patients were in a position throughout the study to initiate patients (who were seen daily during the week in the directly observed treatment programme) on ART at any time, based on their clinical judgement.

On their point of adequacy of the standard of care provided to patients in the SAPIT trial, Boule *et al.*¹ quote from the World Medical Association's Declaration of Helsinki:¹⁶ '... "the best current" intervention should be provided as the standard of care to patients in studies ...'. In doing so, they omit the crucial word '*proven*'; paragraph 32 of the current Declaration (quoted and referenced in their article) stated in full is: 'The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best current *proven* intervention ...' (our italics).

While it was well recognised that HIV and TB co-infected patients with low CD4+ counts had a higher mortality, it was *not* proven that early antiretroviral initiation in TB co-infected patients improved morbidity and mortality. The 2003 WHO AIDS treatment guidelines, which informed the 2004 South African AIDS treatment guidelines, stated clearly that recommendations on the initiation of ART in TB co-infected patients were 'provisional', since the 'optimal time to initiate [antiretroviral agents] in patients with [tuberculosis] is not known'.¹⁷ Such tentative guidance cannot be considered a proven intervention. To further confirm that that this was not proven, a WHO consultation in 2005 on management of patients with HIV and TB concluded that the optimal time for initiating ART in HIV and TB co-infected patients is 'the major research priority'.¹⁰

Was this trial needed for tuberculosis and HIV treatment?

Yes, the SAPIT trial informed the new WHO treatment guidelines.

Retrospective chart reviews, such as cited by Boule *et al.* in support of initiation of ART during TB treatment, are seldom regarded as

sufficient evidence for authoritative treatment guidelines, as they are prone to many biases and are rarely effective in influencing clinician practices. In 2009, the WHO guidelines¹⁸ were updated to provide definitive advice on the timing of antiretroviral initiation in patients with TB and HIV, drawing upon the results of the SAPIT trial. On World AIDS Day in 2009, the South African government also announced¹⁹ a change in TB-HIV co-treatment guidelines, drawing on the SAPIT trial results.

The SAPIT trial provided the essential evidence on the risks and benefits on integrated HIV and TB treatment to guide clinicians and inform both global and local policy on HIV and TB treatment. We now have the collective opportunity and the responsibility to ensure that patients with TB and HIV are rapidly diagnosed and are initiated on ART during TB treatment.

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