

INITIATION OF ART/TB THERAPY: TRANSLATING RESEARCH INTO PRACTICE

Concurrent Session 1G – Summary

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PRESENTATION OVERVIEW

In a review of relevant new clinical trial data exploring the sequencing of TB treatment and HIV antiretroviral therapy (ART) in patients co-infected with tuberculosis and HIV, Diane Havlir, MD, noted that there are still 9.27 million cases of tuberculosis (TB) globally every year and nearly 2 million deaths. One point four million of these cases are HIV-associated TB, and there are 500,000 HIV-associated TB deaths – a disproportionately high number. ART is not currently effectively deployed in these co-infected patients. WHO guidelines and the early results of the SAPIt trial make it crystal clear that it is imperative to start ART during the course of TB treatment. Three new studies address the issue of optimal timing of ART during TB treatment:

- CAMELIA Study: Conducted in Cambodia, this study enrolled 661 smear-positive patients with CD4<200 (median CD4 count: 25) and randomized them to start ART two weeks after commencing TB therapy or eight weeks after ART start. The primary end-point was death. The trial found that those with CD4<50 had a 34 percent better chance of survival when ART was initiated two weeks after beginning treatment for TB, as compared with initiating ART eight weeks after beginning TB treatment.
- STRIDE Study: This multi-national study enrolled 800 patients with clinical TB, with CD4<250 (median CD4: 77) and randomized patients to either immediate ART (within two weeks of starting TB treatment) or to early ART (within eight weeks of initiating TB treatment). The primary end points were AIDS and death. There were 42 percent fewer cases of AIDS and death in the immediate ART arm as compared to early ART for those patients with CD4≤50. Immediate ART did not reduce AIDS and death for patients with CD4>50.
- SAPIt Study: Conducted in South Africa, this study enrolled 600 smear-positive patients with CD4<500 (median CD4: 150) and randomized them to start ART within the first two months of TB therapy, at the beginning of the continuation phase of TB therapy, or by the end of TB therapy. The primary end-point was AIDS or death. The study found that initiation of ART during TB treatment reduced mortality by 55 percent compared to ART initiation upon TB treatment completion. Co-infected patients with CD4<50 who received ART initiation within four weeks of starting TB treatment experienced 68 percent better AIDS-free survival, although there was increased risk of immune reconstitution inflammatory syndrome (IRIS). There was not a significant difference in AIDS-free survival between the immediate versus the early arm for those patients with CD4>50.

The studies show that for those with CD4<50, ART should be started immediately – within two weeks of TB treatment initiation. In all three of these studies, immediate ART reduced AIDS or mortality in those with CD4<50, and there was no effect from timing of ART on viral suppression at the end of TB treatment. TB immune reconstitution disease (IRD), however, was higher in the immediate arm in all studies, and higher in frequency at lower CD4 cell counts. For those with CD4>50, ART should be initiated early – eight weeks after the start of TB treatment.

Havlir noted some key points about the current environment that pose challenges to ensuring that TB/HIV patients receive ART and TB treatment. According to the World Health Organization (WHO), only 53 percent of TB patients know their HIV status, and only 37 percent of identified co-infected patients were reported to receive ART. HIV and TB programs are often not coordinated, and inpatient and outpatient HIV and TB programs are often fragmented. However HIV testing of TB patients is expanding; there are point of care CD4 diagnostics on the horizon; there are models for HIV/TB integration; and new rapid TB diagnostics have arrived.

She concluded her presentation by proposing some essential follow-up activities to these scientific findings:

- Disseminate this information to policymakers, program leaders, clinicians, other health care providers and funding agencies.
- Design, evaluate and monitor programmatic approaches.
- Integrate TB diagnostics into new treatment approaches.

Andrea Howard, MD, then gave a perspective from the field given her work with ICAP, which currently supports TB/HIV integration at the site level in 676 HIV clinics and 480 TB clinics throughout various countries in sub-Saharan Africa. ICAP followed up the release of these study data by alerting ICAP clinical advisors on the ground who support these sites. Feedback from these clinical advisors included acknowledgement that the studies were highly relevant, particularly given that most patients at supported sites are identified quite late in their TB and HIV disease and have lower CD4 counts.

Many challenges were identified by these advisors in implementing these treatment changes. From the patients' perspective, many are only interested in TB treatment as there is still a lot of stigma surrounding an HIV diagnosis. Health care workers are also not eager to start ART quickly, due to the increased workload, absence of nurses, the lack of knowledge about how to manage TB patients on ART, and fear of IRD. On the operational front, there are insufficient quantities of antiretroviral drugs in some settings; an absence of TB/HIV integration so that referrals are required for HIV care and treatment; a shortage of counselors to assess ART readiness and adherence; no policy for nurse-initiated ART in some places with resulting clinician shortages; and a lack of on-site CD4 count capability.

There is also a lack of capacity to manage IRD. Not only do clinicians lack the skill and experience to recognize and manage IRD, but health centers and some district hospitals do not have the radiology and laboratory services to evaluate patients with suspected IRD. Patients also lack resources to pay for tests and medication to diagnose and treat IRD. There are also challenges to starting ART so rapidly within this population, as it takes time for patients to stabilize on TB treatment; it takes time until cotrimoxizole preventive therapy is initiated and tolerated; it takes time until additional opportunistic infections are treated and for CD4 counts to come in.

Dr. Howard stressed the need for changes in country ART guidelines to reflect the research findings to promote changes in practice.

Dr. Richard Chaisson discussed the research opportunities for implementation of ART in the setting of TB treatment. In order to control HIV-related TB, there is a need to deploy new technologies to identify cases early and promote preventive therapy among those without active disease. In the treatment realm, we must improve treatment completion, successfully treat multidrug-resistant and extensively drug-resistant TB, and provide ART to all patients with CD4<500. In the prevention arena, isoniazid or other preventive therapy must be more widely used, as global uptake of this recommended intervention is scandalously low. Infection control is also essential, as both patients and health care

workers are endangered by institutional transmission of TB. Finally, we must work to reduce susceptibility to TB through earlier use of antiretrovirals.

While evidence is often slow to influence guidelines and guidelines often are slow to influence practice, research can promote dissemination and implementation. Research opportunities include:

- Impact of training strategies for health care workers (HCW)
- Task-shifting from doctors to nurses, including allowing nurses to initiate ART in TB clinics
- Integrated versus vertical care
- Community-based versus clinic-based care
- Enablers and incentives (for patients, for providers)
- CD4-based versus clinically-based treatment
- Technologies for performance of CD4 counts

Dr. Chaisson discussed his involvement in the study, "Impact of Widespread Use of TB Preventive Therapy for Patients with Access to ART in Rio de Janeiro, Brazil: A Phased Implementation Trial of Training HCWs to Implement TB/HIV Guidelines." The goal was to increase TB/TST screening and IPT in 29 public HIV clinics managed by the city's health department. The intervention, which included provider incentives, worked. Prior to intervention, a small number of patients were getting the skin test and IPT, after the intervention the majority of patients did. It took a median time of one year to achieve, and uptake has greatly improved with the training intervention. Study authors hope to report on the study outcome in Rome at the 2011 International AIDS Society meeting.

Dr. Chaisson stressed the importance of ART for patients with TB and HIV, an intervention that will save many lives, although enormous challenges to scaling up co-treatment remain. Research can both guide the way to and promote uptake of implementation research findings.

DISCUSSION SUMMARY POINTS

Building Research and Clinical Capacity

The Fogarty International Program at the NIH builds research capacity in developing countries. A partnership between the Fogarty program and the President's Emergency Plan for AIDS Relief (PEPFAR) program will assist in developing the clinicians, researchers and policymakers of tomorrow and will contribute to the integration of implementation research with the delivery of clinical care.

Many factors influence clinical practice and health care outcomes. In many cases, health care workers may understand the value of a given intervention, but more didactic education about the research findings and accompanying outcomes might not be the solution. For example, leadership at the clinic or facility level may be a more important factor. There is a gap in training of personnel for management of health services in Africa. Management or leadership training for senior management might change outcomes since often individuals with clinical backgrounds and few management or leadership skills become leaders. Utilizing well-trained managers that can, for instance, reduce drug stock-outs, has been shown to make a big difference in the management of health centers in small studies.

Know Your Setting

Any discussion about implementing research findings and translating them into clinical practice must include an analysis of the very different conditions that exist among developing countries in Africa and even among different regions of the United States.

It is critical to engage in formative research before designing a study—to talk with patients, health care workers, implementers, community leaders and others, and to build the research study on the foundation of those findings. Formative research assists in identifying the real barriers, as opposed to making tacit assumptions that lack of knowledge about the efficacy of the intervention is the main barrier.

Structural and contextual issues must also be considered and should also be the focus of implementation science. For example, chronic drug stock-outs pose a real impediment to ensuring earlier access to ART for TB patients and, in some cases, the immediate administration of TB treatment. Poor supply chain management and other systemic barriers must be acknowledged and research should also explore creative ways to respond.

Integration cuts across all research challenges that involve co-morbidities. Focusing on health systems challenges is essential and one must analyze the multiple levels of the health system infrastructure.

Community Engagement and Impact

Engaging the broader community and not simply health care workers and patients is essential. A community-centered assessment should be done, identifying local barriers to implementation and addressing them, as well as assessing the impact of the intervention on the community. This may require building capacity to garner information from the community.

Support and Incentives for Health Care Workers and Governments

Formative research can also be used to identify possible incentives for health care workers and patients that can then be tested to see if they improve uptake of the intervention.

Health care reporting requirements can drive clinical practice and also ensure that there are defined and measurable outcomes from a given intervention. For example, in South Africa there is no required reporting for the administration of isoniazid preventive therapy (IPT), and there is resistance to adding additional requirements to the registry. It is critical, however, to analyze and harmonize reporting requirements at all levels (including indicators that countries report to the WHO), to ensure that they are truly linked to improved health care outcomes, are user friendly, and do not overwhelm health care providers. The global compilation of these data is also important to encourage country leadership. Utilizing some form of incentive might be useful in improving data reporting. For example in Brazil the government changed its policy to require reporting of TB skin test results and whether or not IPT has occurred as a prerequisite to acquiring ARV drugs. Brazil reports none of that information to the WHO, however.

Moreover, partnering with ministries of health and other stake holders to support/influence their priorities by sharing scientific evidence can be useful: for example, working within the government system to integrate a TB screening questionnaire into the HIV clinical record.

Impact Analysis Must Continue After the Intervention Reaches the Patient

A focus on linkage and retention in care and adherence to care are essential if we are to measure and properly evaluate the impact of an intervention on health outcomes.

Cost-Effectiveness Is a Meaningful Outcome for Programs, Donors and Countries

Cost-effectiveness of an intervention can be a very important outcome given scarce resources and so becomes an additional important research question.