

Implementing antiretroviral therapy in resource-constrained settings: opportunities and challenges in integrating HIV and tuberculosis care

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Introduction

Highly active antiretroviral therapy (HAART) can transform the natural course of HIV infection by reducing morbidity and mortality as has been observed in many industrialized countries [1]. The increasing availability of antiretroviral therapy through resources from, among others, the Global Fund to fight AIDS, tuberculosis (TB) and malaria is a major step forward in the global effort to make HAART available in the developing world. There is therefore an urgent need to develop simple and sustainable strategies for initiation and delivery of HIV care and therapy to large numbers of patients in the context of the existing under-developed health care delivery systems. Among the various models of HIV care provision [2–4], one proposed strategy is to integrate this care, including HAART provision, into the existing TB directly observed therapy (DOT) programs. This would allow for the opportunity to initiate HIV care and HAART for patients identified as HIV infected during TB treatment as well as to be able to continue such management for those who develop TB during HIV treatment.

Rationale for integrating TB and HIV care

Efficient mechanism for identifying those in need of care

In a resource-constrained setting, such as South Africa, it is estimated that less than 10% of HIV-infected individuals are aware of their HIV status, despite the availability of voluntary counseling and testing (VCT) centres [5]. This presents a challenge to identifying those who require HAART. Further, most developing countries do not have the resources to test large numbers of people for HIV infection, and thereafter perform laboratory markers relevant for initiation and follow-up of antiretroviral treatment on all HIV-positive participants. TB is a familiar, commonly diagnosed, and treated, clinical disease in sub-Saharan Africa. TB is also the most common serious infectious complication associated with HIV infection in sub-Saharan Africa [6]. In South Africa, up to 60% of TB patients are co-infected with HIV [7]. The high rates of HIV among those with active tuberculosis provide one efficient approach for identifying individuals with HIV who are likely to benefit from antiretroviral therapy. HIV test-

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ing of TB patients is cost-effective and efficient since about one-third are HIV positive with advancing HIV disease (World Health Organization Stage III/IV) and are thus appropriate for HAART initiation [8]. Thus in countries where TB is a common presentation of AIDS, the existing TB program provides an efficient opportunity for identifying those patients who are HIV-infected and those eligible for HAART and for initiating therapy in these patients.

Established TB infrastructure that can be utilized for HIV care

The introduction of antiretroviral therapy in resource-constrained settings requires the efficient and effective use of available health care infrastructure as far as possible since the necessary resources for new buildings, staff and health care infrastructure are not readily available. The existing, established infrastructure that is available in many developing countries to provide treatment for patients with TB, provide an existing clinical infrastructure to incorporate HIV care. While not universally well developed or well managed, TB treatment services may also have laboratory and radiological support services, clinical services, systems for procurement of TB medications, and an infrastructure for DOT for TB treatment adherence. Staff at these health facilities are trained to identify TB, to appropriately clinically manage the patients and to provide the appropriate linkages and supports to encourage adherence to treatment. In addition, these programs participate in surveillance activities which include linkages to local and national TB control organizations that guide and monitor TB incidence, prevalence, its management and treatment outcomes.

An opportunity to decrease TB case fatality rates

An integrated treatment system may also have the additional advantage of reducing the case fatality rate of patients co-infected with HIV and TB. Despite the availability of appropriate TB chemotherapy, HIV-related TB is associated with higher case fatality rates and HAART may have a substantial beneficial impact on HIV-related TB [9]. With high rates of HIV co-infection among TB patients, as high as 60%, the impact of HIV on outcomes of these patients is substantial. The use of HAART among patients with TB has been associated with improvement in outcomes in terms of decrease in morbidity and dramatic decrease in mortality [10]. Thus, the integration of HIV and TB care can result in a reduction in the TB case fatality rate, improvement in patient outcomes in these programs and in the large populations co-infected with HIV and TB.

Adherence and availability of DOT programs for TB treatment to be utilized for HAART

DOT is used as a means of enhancing adherence to TB treatment and improving TB outcomes. The impor-

tance of adherence to TB medications is fundamental to treatment success. Poor adherence impacts on both the individual and public health, resulting in an increased morbidity and mortality, further transmission to others and the emergence of multi-drug resistant (MDR) tuberculosis. DOT has been effective in tuberculosis treatment [11,12] in many settings, although not all, and is a component of the TB treatment strategy that has been adopted by WHO as the standard of care for management of TB globally [13]. Similarly, adherence to antiretroviral regimens is essential for therapeutic success [14] and strategies to assure adherence to therapy are required.

Although studies using DOT to treat HIV are limited and some question its applicability [15], some studies indicate that DOT for HIV medication may be useful [16,17]. Studies in institutional settings have shown the most impressive results. In one prison-based study, a significantly greater proportion of prisoners in the DOT group achieved and sustained non-detectable HIV RNA viral loads compared with the self-administered community-based group [16,18]. Prison population data may not be generalizable, hence studies, especially randomized controlled trials are required in general population settings. A pilot project to administer antiretrovirals at home or community sites, in a physician referred poorly adherent patient population has reported favourable preliminary data [19].

The use of DOT alone may not be uniformly successful [20] and programs may need more resources in order to enhance the services to provide DOT for both TB and HAART. The integration of TB and HIV care and utilizing DOT for HIV medication may generate more resources for enhancing those DOT programs that need to be improved, thereby potentially improving the outcome of treatment for both diseases. Moreover, the DOT strategy may not be the best or most appropriate way to implement HAART in all settings but it certainly increases the options and possibilities for HIV care provision in resource-constrained settings.

Concerns about the provision of HAART in TB services include the potential for nosocomial transmission of TB to a high-risk population of AIDS patients and the potential of TB services becoming overwhelmed by the ever-increasing number of patients on lifelong HAART. This is a particular concern if patients with AIDS are managed in the long-term in the TB services; an alternative is to initiate HAART during TB therapy to benefit from the DOT and upon completion of TB therapy, to provide the ongoing long-term AIDS care at ambulatory and hospital services closer the patients' homes.

In the past, HAART regimens were too complex and drug half-lives too short to realistically employ the

DOT strategy for HIV disease. A major step forward for the provision of HAART in resource-constrained settings has been the increasing availability of simpler regimens such as once daily dosing regimens, and newer HAART formulations that allow triple drug combinations in a single tablet taken twice daily. The combination of once-a-day antiretroviral regimens with the mechanism of DOT may provide an important method to obtain sufficiently high levels of adherence to achieve individual therapeutic success, population-based reduction in morbidity associated with HIV and TB and public health benefit of lower levels of antiretroviral drug resistance.

DOT for TB and HIV disease have important differences and similarities. Therapy for TB is simpler, less frequent and time limited, whereas antiretroviral regimens can be more complicated and are likely to be lifelong. Current DOT strategies for TB are based on providing medication three to five times a week – the use of DOT infrastructure for HAART will require it to be extended to accommodate a daily treatment regime. Both address the central issue of adherence to therapy and require monitoring for side effects and toxicities as well as efficacy.

Thus, there is a logical synergy in linking both treatments to a supportive medication adherence system. The benefits and disadvantages of such a strategy need to be compared in a formal and rigorous study. The simplification of antiretroviral regimens, coupled with existing DOT programs for TB treatment, and the growing need and demand to begin administration of antiretroviral drugs in the public sector in sub-Saharan Africa offers an opportunity to test the hypothesis that antiretroviral drugs can be successfully administered through the existing TB DOT programs as one strategy to increasing access and adherence to antiretroviral therapy.

Challenges of integrating TB and AIDS care

Notwithstanding the advantages of the co-administration of TB and HIV medication, this strategy is not without challenges and possible complications. The treatment of HIV in those co-infected with HIV and TB has conventionally been deferred because of concern for drug interactions, which may affect the blood levels of agents administered, immune reconstitution events, fear of increased side effects and toxicities and programmatic concerns.

Drug interactions

Among the existing classes of antiretrovirals, protease inhibitors and non-nucleoside reverse transcriptase inhibitors have pharmacologic interactions with the

rifamycins (rifampin, rifabutin and rifapentin) used to treat mycobacterial infections [21]. Rifamycins induce CYP450 and may decrease blood levels of these antiretroviral drugs, which are metabolized by this system, resulting in potential therapeutic failure and promoting the development of drug resistance. However, the current and recently revised CDC guidelines indicate that rifampin can be used for the treatment of TB in patients whose antiretroviral regimen includes the non-nucleoside reverse transcriptase inhibitor, efavirenz and two nucleoside reverse transcriptase inhibitors and do not recommend dose adjustment for efavirenz when used together with rifampin despite an average 25% decrease in efavirenz level [22]. Others recommend an increase in efavirenz dose to 800 mg daily, but this may be associated with increased rates of side effects and toxicity [23]. Another possibility is the use of a triple nucleoside regime. It is hoped that new antiretroviral drugs may allow their co-administration with rifampin-containing TB treatment regimens. The introduction of HAART through the TB DOTS infrastructure will need to be co-ordinated with TB programs so that the success of treatment in established TB programs is not diminished. In addition, monitoring of side effects and toxicities will need to be part of all integrated systems.

Immune reconstitution events

In addition to potential drug interactions, the initiation of HAART during TB treatment has been linked to the development of immune reconstitution events. A transient worsening of TB symptomatology or appearance of new lesions following HAART may occur [24,25]. One study showed that immune reconstitution events started at a median time from the start of antiretroviral therapy of 22.5 days [26]. All participants with immune reconstitution events had initiated HAART within the first 2 months of anti-TB treatment. These events were more likely to occur in patients with larger reductions in HIV RNA and higher increases in CD4+ cell count. In 1998, Narita and colleagues reported that immune reconstitution events occur in 36% of patients dually treated [27]. An event rate of 30–40% has also been estimated in patients who start treatment with a low (i.e. $< 100 \times 10^6$ cells/l) CD4+ counts [28]. The occurrence of these events can complicate that management of patients as it is often difficult to differentiate them from adverse events due to medications, failure of TB treatment or occurrence of another HIV-related complication.

Side effects and toxicity of drugs

The treatment of TB requires intake of two to four medications daily whereas the treatment of HIV requires intake of three medications on a daily basis. Each of these regimens may be associated with adverse events. These include gastro-intestinal intolerance, hepatitis, hypersensitivity reactions, peripheral neuro-

pathy, rash and neuro-psychiatric symptoms. The combination of both regimens may result in additive toxicity and side effects. Some studies suggest that HIV-infected patients have a higher rate of adverse events whereas other studies do not support these findings [29]. The extent of additive side effects and toxicities as well as tolerability of the combined therapy approach are not known and needs to be assessed.

Stigma and non-disclosure of HIV status

The integration of HIV care in TB settings will require the provision of HIV counseling and testing by care providers. In addition, the integration of HIV care in the TB setting requires HIV testing to distinguish patients with and without HIV co-infection. The availability of HAART for eligible HIV infected patients, may serve as potent encouragement for TB patients to come forward for HIV testing. Although HIV testing is an additional burden on TB services, the added benefits of HIV testing for HIV prevention are likely to outweigh the effort to conduct the HIV testing. Indeed, HIV testing in health services has additional benefits such as the opportunity to undertake risk reduction counseling.

In addition, because exclusive reliance on stand-alone VCT sites is unlikely to generate the testing levels needed for an effective response to the epidemic, settings such as TB programs could be used to supplement routine testing of volunteers seeking to know their HIV status. By encouraging HIV testing in TB treatment services, the number of at-risk individuals who know their HIV status may increase substantially. Indeed, health care services dealing with large numbers of at-risk patients, are increasingly choosing the opt-out approach where patients are informed that an HIV test will be performed unless they refuse [30].

Disclosure of HIV status continues to be an obstacle to care and prevention. In a pilot study, conducted in a primary care TB clinic in KwaZulu-Natal, South Africa, approximately two-thirds of the participants interviewed reported that they had disclosed their HIV status to one other person, primarily friends and family, with hope of receiving support from them. However, of those who did disclose their HIV status, few disclosed it to their primary sexual partner [31].

The main reason offered by participants for non-disclosure of their HIV status was that they felt people around them would not respond positively or that they did not want to worry family members. This was particularly noted in participants who had families that had recently experienced an AIDS related death. Non-disclosure of HIV status is linked with issues of stigma. One participant did not disclose his HIV status because he said that, 'people point at you. I don't want to be a bad example. Until there is a cure people will continue

to stigmatize' [31]. It is anticipated that the availability of HAART may enhance the uptake of voluntary counseling and testing at TB care sites, a key entry point for prevention, care and efforts to fight stigma.

Overwhelming already overstretched TB programs

The integration of TB and HIV care may put additional pressure on an already overstretched TB treatment delivery system. In South Africa, since 1991, TB case rates have been increasing steadily primarily as a result of co-infection with HIV. In one rural hospital in South Africa TB cases have increased from 450 in 1990 to 2600 in 2001 [32]. Resources to treat TB have not matched this exponential increase. TB care centres that are already understaffed and have inadequate infrastructure would find it more challenging to integrate HIV care into their existing services. This potential stumbling block should not be underestimated and the increases in resources necessary to make HAART a success using this approach could be immense. However, while there will be an increase in the number of HIV patients at established TB clinics, once HIV-infected patients are stable and adherent they could be referred to their local public health facilities or local hospitals for continued treatment and monitoring thus reducing the impact on existing TB clinics.

Conclusion

For many years, the TB and HIV epidemics have been viewed separately. On account of the overlapping epidemiology of TB and HIV and the mutual benefits of addressing both conditions simultaneously, there is growing recognition of the need for increased collaboration between TB and HIV programs to provide a coherent health service response to the dual TB/HIV epidemics. Integrating management strategies for both conditions to allow for initiation of treatment for both in one setting can result in substantial benefits to the individual patients and their communities. However, for an integrated strategy to work, existing services in the TB clinics will require upgrading and supplementation with additional resources. Furthermore, the success of this strategy will be dependant on the establishment of clinical services that will provide ongoing HIV care upon completion of TB treatment.

Despite the many challenges of providing HAART in resource-constrained settings, the provision of HIV care to those who urgently need it should not be delayed. The integration of TB and HIV care and treatment provides one possible model to start scaling up access in resource-constrained settings. It is necessary to explore the feasibility of this strategy while randomized controlled trials are needed to provide definitive scientific

data on benefits and risks of this strategy compared to present separate approaches for each disease.

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Appendix

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