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Integrated, Home-based Treatment for MDR-TB and HIV in Rural South Africa: An Alternate Model of Care

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SUMMARY

Treatment outcomes for multidrug-resistant tuberculosis (MDR-TB) in South Africa have suffered as centralized, inpatient treatment programs struggle to cope with rising prevalence and HIV co-infection rates. A new treatment model is needed to expand treatment capacity and improve MDR-TB and HIV outcomes. We describe the design and preliminary results of an integrated, home-based MDR-TB/HIV treatment program created in rural KwaZulu-Natal. In 2008, a decentralized center was established to provide outpatient MDR-TB and HIV treatment. Nurses, community health workers, and family supporters have been trained to administer injections, provide adherence support, and monitor adverse reactions in patients' homes. Physicians assess clinical response, adherence, and adverse reaction severity to MDR-TB and HIV therapy at monthly follow-up visits. Treatment outcomes are assessed by monthly cultures and CD4 and viral load every 6 months. Eighty patients initiated MDR-TB therapy from 2/2008–4/2010; 66 were HIV co-infected. Retention has been high (only 5% defaults, 93% of visits attended) and preliminary outcomes have been favorable (77% cured/still on treatment, 82% undetectable viral load). Few patients have required escalation of care (9%), had severe adverse events (8%), or died (6%). Integrated, home-based treatment for MDR-TB and HIV is a promising treatment model to expand capacity and achieve improved outcomes in rural, resource-poor, and high-HIV prevalent settings.

Keywords

HIV/AIDS; Multidrug-resistant tuberculosis; Community-based treatment; Program development; AIDS

THE PROBLEM

The MDR-TB Epidemic

Multidrug-resistant TB (MDR-TB), defined as TB resistant to at least isoniazid and rifampin, has emerged as a global epidemic. In 2008, there were an estimated 440,000 global cases of MDR-TB,¹ but fewer than 10% of these cases were identified and treated.¹ Treatment scale-up has grown in the past five years, but remains below the capacity needed,² due in part to the complexity of MDR-TB treatment. Treatment for MDR-TB is less potent, more toxic and more expensive than that for drug-susceptible TB. MDR-TB treatment programs must provide daily injections, monitor and manage adverse events, and ensure high levels of adherence throughout a 24-month period to prevent amplification of resistance and treatment failure. The convergence of the HIV and drug-resistant TB epidemics has made MDR-TB treatment an urgent priority, given the high and rapid rates of mortality seen in co-infected patients.^{3,4}

Challenges of Centralized, Inpatient Treatment

Given the complexity of MDR-TB treatment, many countries have employed hospital-based, centralized MDR-TB treatment at regional referral centers.^{5,6} Most programs hospitalize patients for the initial 6 months (intensive phase) to facilitate daily injections and to allow close monitoring of adverse events and adherence. In low prevalence settings, centralized programs can be advantageous because they concentrate MDR-TB cases from larger regions and allow for management by trained experts. While this model may be appropriate in settings with a low MDR-TB prevalence, high-burden settings face additional challenges, including insufficient bed capacity to hospitalize all new MDR-TB patients, difficulty retaining patients if they are far from their families, and difficulty monitoring and tracing patients upon discharge at the end of the intensive phase. As an alternative, community-based treatment models have been developed and shown to be effective in low HIV prevalence settings.⁷

Until recently, KwaZulu-Natal province has had a single, centralized MDR-TB treatment center for the province (population 10 million, 92,000 sq km). All patients were admitted for the intensive phase, after which they were discharged with a one month supply of medications and monthly follow-up for the remaining 18 months of treatment. Although this approach may have been adequate when case rates were low, in 2003, the treatment success rate for MDR-TB was only 44%.⁸ Since then, the MDR-TB caseload in KZN province nearly doubled from 1854 cases in 2003, to 3040 cases in 2007, placing further strain on the hospital-based model of MDR-TB treatment. Newly diagnosed MDR-TB patients were placed on 60–120 day waiting lists for an inpatient bed,⁹ during which time they remained without treatment, continued to transmit disease, and clinically deteriorated. Moreover, while the rate of HIV co-infection continued to rise, TB and HIV programs remained separate, despite the known effectiveness of integrating HIV and drug-susceptible TB care in improving outcomes for both diseases.^{10–14}

Paradoxically, therefore, the centralized, inpatient treatment model may be contributing to poor MDR-TB treatment outcomes and rising drug-resistance rates in high-burden settings. To address these challenges, we implemented an integrated, home-based MDR-TB and HIV treatment program in a rural district of KwaZulu-Natal province as a demonstration project.

In this paper, we describe the program components and present preliminary data supporting its feasibility and effectiveness.

A POTENTIAL SOLUTION

Program Objectives

The objectives of the integrated, home-based program were to: (1) treat all patients diagnosed with MDR-TB, with or without HIV co-infection; (2) provide home-based treatment for both MDR-TB and HIV; (3) ensure high-levels of treatment adherence with modified DOT and adherence support; (4) provide intensive adverse event monitoring; and (5) shorten the length of hospitalization for patients in need of inpatient care.

Setting

The Tugela Ferry area is approximately 2000 km² with a population of 200,000 traditional Zulu people. There is one tar road running through the district with many gravel roads leading off. The majority of the population lives in mud and thatched roof homes without running water or electricity.

The Church of Scotland Hospital is the only public hospital serving the Tugela Ferry area. All TB patients are offered HIV testing, and nearly 80% are HIV co-infected. Free antiretroviral (ARV) therapy has been available since 2004, and since 2005,¹⁵ mycobacterial culture and drug-susceptibility testing (DST) for first- and second-line TB drugs have been routinely available for all TB suspects. Prior to the creation of the new program, all patients with MDR-TB were referred to the TB specialty hospital in Durban, three hours away.

Integrated, Home-based MDR-TB/HIV Treatment Program

The home-based treatment program includes nurses and community health workers (CHWs) who travel to patients' homes daily to provide injections and adherence support, monitor adverse events, and educate patients and family members in infection control practices. For patients who are MDR-TB/HIV co-infected, all services integrate MDR-TB and HIV care (e.g., ARV treatment administration, ARV adverse event monitoring, and physician evaluation for opportunistic infections and response to ARVs).

To increase sustainability and generalizability, the program was designed through a partnership between the KZN Department of Health (DOH), Albert Einstein College of Medicine, Yale University, and *Philanjalo*, a South African non-governmental organization (NGO). The costs of staffing the program (e.g., medical officers, nurses, program assistants, counselors) are shared by the DOH and the academic partners. The DOH supplies all MDR-TB medications, ARVs, laboratory testing, sputum culture and DST, x-rays, inpatient care and referrals for specialist services. The academic partners provide protocol development, technical assistance and training, additional funding, and tools for program monitoring and evaluation.

Program Components

Decentralized MDR-TB Clinic—In February 2008, we established an outpatient clinic for MDR-TB patients in the Tugela Ferry district ("Decentralized MDR-TB Clinic"), enabling treatment for MDR-TB without referral to the provincial TB specialty hospital. Patients newly diagnosed with MDR-TB are traced and evaluated at the decentralized MDR-TB clinic within one week. All patients receive a baseline history; physical exam; chest x-ray; audiometry; blood work for hematology, chemistry and liver function tests; repeat sputum culture and drug-susceptibility testing; HIV testing; and if HIV co-infected, CD4 count and viral load (Figure 1). In accordance with South African national treatment

guidelines, all patients receive a standardized MDR-TB regimen (kanamycin, ofloxacin, cycloserine, ethionamide, pyrazinamide and ethambutol [if known to be ethambutol-sensitive]), and if HIV co-infected, a first-line ARV regimen (efavirenz, lamivudine, and stavudine [tenofovir replaced stavudine as of April 2010]). Most patients are briefly admitted to an adjacent, 32-bed MDR-TB inpatient unit to ensure that they tolerate the MDR-TB medications. The duration of hospital admission varies based on the acuity of illness, with a goal of keeping the length of stay at around 2 weeks.

Soon after initiating therapy, patients complete treatment literacy sessions for both MDR-TB and HIV (see Patient Training, below), either as inpatients or outpatients. Similarly, if patients are HIV co-infected and not already taking ARVs, they are started within the first 6 weeks, irrespective of baseline CD4 count. All pregnant women, patients with XDR-TB, and patients with severe adverse events are referred to the provincial TB specialty hospital for management.

Home visits—During the intensive phase, mobile injection teams consisting of a driver and nurse provide daily injections of kanamycin, observe administration of oral medications, and monitor for any new adverse events. Each team visits 8–15 patients per day, depending on geography and accessibility of the patients' homes.

After the intensive phase, injections are discontinued and community health workers (CHWs) replace the nurses in making home-visits, observing one dose of oral medications, and monitoring for adverse events. CHWs travel on foot, so are assigned only one or two patients. A monthly stipend for CHWs is paid on a per-patient basis.

Monthly follow-up visits—Patients return to the decentralized MDR-TB clinic monthly, where they are evaluated by a physician and have routine labs, sputum culture, and an evaluation of adherence and adverse events (see below). Audiometry is performed every two months and chest x-ray is repeated at least every six months. HIV co-infected patients are monitored monthly for opportunistic infections and immune reconstitution inflammatory syndrome (IRIS), and every six months, CD4 counts and viral loads are measured. All management decisions for both MDR-TB and HIV are made by the same physicians, nurses and counselors. Patients are given a new monthly supply of MDR-TB medications, and if applicable, ARVs, with an appointment to return the following month.

Adverse Event Monitoring—Each week, injection nurses and CHWs use a standardized questionnaire to monitor for common side effects of MDR-TB and HIV medications. These questionnaires are reviewed by a physician each week and minor side effects are addressed. When patients report more serious side effects, the nurses or CHWs bring the patient to the clinic for immediate medical evaluation.

At each monthly visit, a clinic assistant screens patients for medication side effects using a standardized questionnaire. When patients are seen by the clinic physician, these questionnaires are reviewed and any adjustments in therapy are prescribed. Laboratory and audiometry results are also reviewed to assess for any renal, hepatic, thyroid or ototoxicity.

Adherence Support—Several layers of adherence support and monitoring have been built into the program. Because involvement of family members has been shown to improve adherence to treatment for drug-susceptible TB,¹⁶ patients are asked to identify a family member or friend who will serve as a “treatment supporter” from the outset of MDR-TB treatment. Along with the patient, this treatment supporter receives education about both MDR-TB and HIV treatment, and assists the patient with medication adherence at home.

Patients, thus, receive daily adherence support from the nurses/CHWs and from their family treatment supporters, as well as monthly reinforcement by the clinic staff.

Because travel expenses are frequently cited as a reason for treatment default,¹⁷ patients and family members are reimbursed for travel to and from appointments, and for unscheduled clinic visits.

Education of Patient and Family Treatment Supporters—To encourage active patient and family member involvement in treatment, we designed a 3-part educational curriculum which covers information about MDR-TB signs and symptoms, treatment, possible side effects, HIV co-infection, and the importance of adherence. The sessions also teach basic infection control practices in the home, including cough hygiene, and urging patients to sleep alone and to remain outdoors whenever possible. Education sessions are held weekly and led by a clinic assistant and a nurse who use cartoon flip-charts to engage patients and families in the learning process (Figure 2).

Staff Training—In addition to training patients and family members, we developed an educational curriculum for the MDR-TB program nursing and physician staff. Prior to this, nursing staff in Tugela Ferry had not received specific training in MDR-TB or ARV management and most were not familiar with potential adverse effects of treatment. Doctors were also not trained or experienced in MDR-TB management. Nurses and doctors attended educational sessions covering MDR-TB treatment, including identifying and managing medication-related adverse effects. In addition, several of these providers received on-site training both at the provincial referral hospital and at a regional center of excellence in Maseru, Lesotho.¹⁸

Data Collection and Preliminary Analysis

To assess the program's initial performance, we reviewed the medical records of patients with culture-confirmed MDR-TB who initiated treatment in the integrated, home-based program. We identified patients' HIV status, ART history, laboratory results, sputum culture and DST results, and reviewed their adverse events. Severity of adverse events was graded by the treating clinician, using the Division of AIDS toxicity table.¹⁹ Descriptive statistics were used to generate median values and interquartile ranges. This analysis was approved by the institutional review boards at Albert Einstein College of Medicine, Yale University, the University of KwaZulu-Natal and by the KwaZulu-Natal Department of Health.

EARLY EVIDENCE OF FEASIBILITY AND EFFECTIVENESS

The integrated, home-based treatment program commenced in February 2008 and by April 1, 2010, 80 patients with culture-confirmed MDR-TB had initiated treatment. Fifty (63%) patients were female and the median age was 34 years old (IQR 27.5–39.5; Table 1). Patients attended a median of 92.5% of scheduled outpatient clinic appointments.

MDR-TB Outcomes

Sixty patients (75%) were hospitalized to initiate MDR-TB therapy while 20 (25%) started treatment as outpatients. Of the 52 hospitalized patients who survived to hospital discharge and/or had not been transferred to another hospital, the median length of stay was 80 days (IQR 35–111).

Treatment outcomes were analyzed through December 2010. At that point, 59 (77%) were cured or still on treatment (Table 1). Only four (5%) patients defaulted and five (6%) died (range: 1–448 days on treatment). Seven (9%) patients were transferred to the provincial TB

referral hospital for escalation of care. Two (2.5%) patients were considered to have failed treatment after initially converting their sputum culture and remaining culture-negative for several months before reverting and remaining culture-positive thereafter. Data regarding treatment status was not available for 3 patients who requested relocation to a hospital closer to their home.

Among the 67 (84%) patients who completed the intensive phase of treatment, all (100%) converted their sputum culture to negative in a median of 55 days (IQR 34–86).

Integration of HIV Care and Treatment

All 80 MDR-TB patients were tested for HIV and 66 (83%) were HIV co-infected. Of these, 48 (73%) were already receiving ARVs at the time of MDR-TB treatment initiation. Twelve (18%) patients initiated ARVs after starting MDR-TB treatment (median 54.5 days [IQR 19–116]). The remaining six (9%) patients either died or were transferred to another hospital before initiating ARVs.

Of the 48 (73%) patients with a CD4 cell count available around the time of MDR treatment initiation, the median was 170 (IQR 80–294) cells/mm³. Median CD4 count at 6 months (n=47) was 222 (IQR 171–365) cells/mm³ and median CD4 count at 12 months (n=41) was 260 (IQR 180–422) cells/mm³. Among patients with an available HIV viral load at 12 months (n=34), 28 (82%) had an undetectable viral load (<400 copies/mL).

Adverse Events

Seventy-one (89%) patients had outpatient adverse event monitoring performed and 70 (99%) reported at least one clinical adverse event during the course of treatment. Most of these events were mild and did not require any modification of MDR-TB or HIV therapy. Six (8%) patients experienced a severe clinical adverse event (SAE), of which the most common were hearing loss (n=3) and peripheral neuropathy (n=3). Severe laboratory adverse events were uncommon, with the exception of hypothyroidism. Thirty patients (38%) had a thyroid stimulating hormone level >8 µu/mL and most of these required thyroid hormone replacement therapy.

COMMENT

The model of centralized, inpatient treatment for MDR-TB was intended to ensure the highest quality of care for what was initially a low-incidence disease. In South Africa, however, the rapidly expanding caseload—fueled by the HIV epidemic—has exposed the limitations of this model. In response, we implemented an integrated, home-based treatment program for MDR-TB and HIV in a rural area of South Africa, at the epicenter of the TB, HIV and drug-resistant TB epidemics (Table 2). Our preliminary results suggest that home-based MDR-TB/HIV treatment in rural, resource-limited areas is feasible, safe and may lead to successful treatment outcomes for both MDR-TB and HIV.

Our program specifically addresses several of the limitations in the centralized, inpatient program. By allowing patients to remain at home and providing a local outpatient facility for follow-up visits, our retention rates have been very high. Further, without the need to admit every patient, the program's treatment capacity is expandable. Because maintaining high levels of medication adherence is the key to treatment success, we believe that the involvement of family members, close monitoring of patients at home, and empowerment of patients by providing intensive treatment literacy education are critical to improving treatment outcomes. If patients are at home and supported by family, we hypothesized that they would be less likely to default from treatment. Although this program does not have a contemporaneous or randomized "control arm," when compared to historical outcomes for

the inpatient, centralized MDR-TB treatment program – where default rates in 2003 were 21% – our preliminary findings support this hypothesis.⁸

As we have implemented this treatment program, we have encountered several challenges. Among these, patients remained admitted to the hospital longer than we had planned (80 days vs. 2 weeks). This illustrates the difficulty in changing a long-standing practice in MDR-TB treatment, wherein the hospital staff were reluctant to discharge patients who were still culture-positive with the concern that they could transmit their disease to family and/or friends in the community. Several studies, however, have demonstrated low transmission rates once patients with MDR-TB initiate therapy—even before they culture-convert.²⁰ These results and additional education sessions / meetings have been provided to the hospital physicians and the length of hospitalizations in our program have been getting shorter over time (data not shown).

Another challenge has been the use of injection teams as treatment observers of oral medications. Given the rural landscape, poor roads and large distances between family compounds, injections teams arrive at patients' homes at different times each day—often after the patients' morning dose of oral medications. We have therefore relied on the patients' family treatment supporters to observe both morning and evening doses, even while the patient is in the intensive phase.

Much work remains in demonstrating the additional benefits of the program. Future plans include evaluating the long-term program performance, including continued measurement of HIV and MDR-TB treatment outcomes. In addition, because costs will, in large part, determine whether or not other TB programs adopt this treatment model, a comparison of program costs and cost effectiveness to the centralized inpatient model is warranted. A cursory examination in KZN, however, has shown that the operational costs of the home-based treatment model are approximately 25% that of the centralized inpatient model (B. Margot, personal communication), suggesting that the home-based program is both effective and less expensive. Finally, we have not yet investigated community or household transmission in our program. Although some studies have suggested that MDR-TB patients are much less infectious once they begin treatment,²¹ MDR-TB programs which implement a home-based treatment model should closely monitor the incidence of secondary cases in household contacts. Nonetheless, given the early success of the program and the ongoing challenges with the inpatient treatment model, together with similar data from other low HIV prevalence settings, we believe that this program could serve as a model for other rural, resource-limited settings battling the MDR-TB and HIV epidemics throughout the world.

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Figure 1. Flow chart of patient care in the new MDR-TB Program

MDR-TB: multidrug-resistant tuberculosis; CXR: chest x-ray; DST: drug-susceptibility testing; ART: antiretroviral therapy; CHW: community health worker; DOT: directly-observed therapy; AE: adverse event.

*If HIV-infected, CD4 and HIV viral load are checked every 6 months.

†Thyroid stimulating hormone is checked every 6 months; chest x-ray is performed every 6 months, or more often as clinically indicated; audiometry is performed every 1–2 months while patient is receiving injectable agent.

Figure 2. Excerpt from patient educational flip chart. (Design by Jacob Creswell)

Table 1**Baseline Characteristics and Treatment Outcomes of MDR-TB Patients**

Characteristic/Outcome	MDR-TB Patients (n=80)
Female, n (%)	50 (63)
Age, median years (IQR)	34 (27.5–39.5)
Hospitalized to initiate MDR-TB treatment, n (%)	60 (75)
Survived to discharge [*] , n (% of hospitalized patients)	52 (87)
Duration of hospitalization, days (range)	80 (13–217)
Attendance to scheduled clinic appointments, median	92.5%
MDR-TB Outcomes	
Cured or still in active follow-up ^{**} , n (%)	59 (77)
Defaulted treatment, n (%)	4 (5)
Died, n (%)	5 (6)
Time to death, median days (range)	139 (1–448)
Required escalation of care, n (%)	7 (9)
Failed treatment, n (%)	2 (2.5)
Completed Intensive of treatment ^{**} , n (%)	66 (82.5)
Converted culture to negative, n (% completing 6 mos of treatment)	66 (100%)
Time to culture conversion, median days (IQR)	55 (34–83)
HIV Outcomes	
Tested for HIV, n (%)	80 (100)
HIV-positive	66 (83)
Receiving ART prior to MDR TB treatment, n (% of HIV-positive)	48 (73)
Initiated on ART after MDR TB treatment, n (% HIV-positive)	12 (18)
Time to initiation of ART, median days (IQR) (n=12)	54.5 (19–116)
Baseline CD4, cells/mm ³ (IQR) (n=48)	170 (80–294)
6-month CD4 count, cells/mm ³ , median (IQR) (n=47)	222 (171–365)
12-month CD4 count, cells/mm ³ , median (IQR) (n=41)	260 (180–422)
Available HIV viral load at 12 months, n (% HIV-positive)	34 (52)
12-month HIV viral load <400 copies/mL, n (% of available results)	28 (82)

* Excludes patients who died or were transferred to another facility during hospitalization

** As of December 1, 2010, among 77 patients with data on treatment status available

Table 2

Comparison of centralized inpatient treatment model and integrated, home-based treatment model.

Centralized, Inpatient Model	Integrated, Home-based Treatment Model
<ul style="list-style-type: none"> • Insufficient hospital beds 	<ul style="list-style-type: none"> • Home-based treatment
<ul style="list-style-type: none"> • Long distances between patients' homes and referral hospital 	<ul style="list-style-type: none"> • Satellite MDR-TB clinic closer to patients' homes • Treatment and care at home
<ul style="list-style-type: none"> • Separation of TB and HIV care and treatment. Need for multiple appointments/providers to receive MDR-TB and HIV care 	<ul style="list-style-type: none"> • Integrated MDR-TB and HIV care by one provider in single clinic and home care setting
<ul style="list-style-type: none"> • High risk of elopement and default as patients wish to return home 	<ul style="list-style-type: none"> • Low risk of default as patients live at home for duration of therapy
<ul style="list-style-type: none"> • No adverse event monitoring or adherence support during continuation phase of MDR-TB therapy 	<ul style="list-style-type: none"> • Daily home visits by nurse during intensive phase and community health worker throughout continuation phase
<ul style="list-style-type: none"> • No involvement of family members in patients' care 	<ul style="list-style-type: none"> • Family members are identified and trained to serve as treatment supporters