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Adverse Events Occurrence in Multidrug Resistant Tuberculosis and Human Immunodeficiency Virus in KwaZulu-Natal, South Africa

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Abstract

Adverse Events Occurrence in Multidrug Resistant Tuberculosis and Human Immunodeficiency Virus in KwaZulu-Natal, South Africa

By Sarah Shier

Multidrug resistant tuberculosis (MDR TB) and HIV epidemics have converged geographically in South Africa leading to current guidelines to treat both diseases concurrently. In this study the affect of concurrent treatment on laboratory adverse events (AEs) was examined, with the hypothesis that concurrent treatment would lead to increased adverse events in coinfected populations compared to MDR TB only groups. Frequency and severity of MDR TB symptoms, laboratory AEs and MDR TB adverse events was compared across HIV-positive (n=250) and HIV-negative (n=99) groups with both groups demonstrating similar AE distribution and severity over the first 14 clinic visits. Bivariate and multivariate logistic analysis was then conducted to determine association between patient baseline characteristics (N=349) and experiencing a laboratory AE scoring at least a 2 on the DAIDS scale. Baseline age and sputum smear result were included in the final multivariate logistic model, but neither were significant at $P<0.05$. The lack of difference in AE frequency or severity in coinfected and non-coinfected populations indicates that current guidelines for concurrent treatment should be supported. All findings are interim and are subject to change as data continues to be collected.

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Epidemiology of Tuberculosis

In the modern era, the tuberculosis epidemic continues to evolve with an estimated 8.7 million new cases of TB and 1.4 million deaths in 2011 (1). In 2000, the World Health Organization (WHO) included the fight against tuberculosis in the Millennium Development Goals (MDGs). As the deadline for the MDGs approaches, the WHO claims that, "The Millennium Development Goal target of halting and reversing TB incidence has been achieved…and the world is on track to reach the global target of a 50% reduction by 2015" (1). While this statement may be true on a global level and global tuberculosis incidence may have been reversed, the decrease in tuberculosis prevalence lacks global uniformity. Certain regions have excelled in the control of new cases, while others, such as Eastern Europe and Africa, are struggling to respond to the expanding epidemic.

Africa and Asia, the two regions with the highest tuberculosis prevalence, represent the dichotomy of the epidemic. In Asia, China and India represent 40% of the global tuberculosis burden, and yet both are expected to meet their 2015 goals. Meanwhile, Africa as a whole represents 26% of the global tuberculosis burden, but few, if any, Sub-Saharan countries are expected to meet the 2015 targets (2). On a global scale tuberculosis incidence and mortality may be declining, but at the region and country level the decline clearly lacks uniformity.

The regional variability in meeting the MDG targets has been attributed to regional differences in comorbidity and funding gaps in tuberculosis programming (3, 4). Comorbidity with either communicable or non-communicable diseases affects tuberculosis treatment success rates, leaving regions like sub-Saharan Africa struggling to

respond to concurrent HIV/AIDS and tuberculosis epidemics. The funding gap also adds another layer of complexity to large-scale tuberculosis programming (5). Within the African continent, the 25 lowest-income countries receive 60% of the international funding, regardless of the tuberculosis burden (1). This leaves high-burden and middle-income countries such as South Africa left to largely self-finance explosive tuberculosis epidemics.

South Africa is currently ranked as one of the top five countries for tuberculosis incidence with 400,000-600,000 cases in 2011 and is not expected to meet the 2015 Millennium Development Goal targets (1). While global tuberculosis incidence trends downward, South Africa's incidence rates have consistently increased. In just over a decade the tuberculosis incidence has increased from 576 per 100,000 (2000) to 993 per 100,000 (2011), almost double what it had been a decade earlier (6). Of the 22 countries labeled as high-tuberculosis burden by the WHO, South Africa is one of only two experiencing an increase in incidence. The WHO has attributed the rising incidence to the exceptionally high rates of comorbidity with HIV/AIDS (55% of TB patients also test positive for HIV) (7). With an adult HIV prevalence of 17.9% in 2012, South Africa presents an optimal environment for tuberculosis infection (8).

Drug Susceptible Tuberculosis with HIV Coinfection

Human Immunodeficiency Virus (HIV) has long been known to cause severe immunosuppression, leading to a rise in opportunistic infections, including tuberculosis. The increased risk of tuberculosis in HIV-positive populations is caused by immunosuppression that impairs their ability to mount an effective immunologic

response to tuberculosis infection. In HIV-negative individuals the lifetime risk of tuberculosis infection is 10%, while in HIV-positive individuals the risk is 7-12% per year (9, 10).

The increased risk of tuberculosis in HIV-positive individuals calls for amendments to the WHO standard tuberculosis control and treatment protocols (11-13). The risks of progressing directly to active tuberculosis following initial infection, or from latent tuberculosis are increased in HIV-positive patients, but standard WHO protocol advises treatment in active tuberculosis only—a potential shortfall as latent infections are not addressed (12-13). In high HIV prevalence settings the methods used to control the epidemic must adapt to changing needs and priorities (9). Preemptive action is required to reduce disease rates in highly immunocompromised populations.

Immunosuppression increases the risk of progressing to active tuberculosis while also making accurate diagnosis more challenging. Typical initial tuberculosis symptoms such as night sweats, weight loss and fatigue can be attributed to HIV itself with the possibility of tuberculosis overlooked (11). Diagnostic tests vary in reliability as well. Sputum smear microscopy is the standard and more readily available diagnostic tool in resource-limited areas, but in the event of a negative result is not conclusive in HIV-positive patients. Sputum culture, on the other hand, while scarce in resource-poor regions, is reliable (12). Additionally, HIV-positive patients are also more likely to present with extra-pulmonary tuberculosis than HIV-negative patients.

WHO guidelines acknowledge the challenge of tuberculosis diagnosis in HIV-positive patients and provide alternative tools to sputum smear microscopy. Where

referral to another more specialized facility is not possible the recommendation is to use chest radiograph and clinical assessment to augment smear-microscopy (12). For extrapulmonary tuberculosis either a sample from the site is cultured or clinical evidence is used to determine tuberculosis status (12).

Beyond diagnostic challenges, limited laboratory capacity and access to care are bottlenecks to accurate tuberculosis diagnosis. In 2011 it was estimated that only 66% of global tuberculosis cases were diagnosed (2). To be sure that MDG targets are actually met, diagnostic capacity and accuracy must be increased. However, even if scaled up, diagnostic challenges in HIV/TB coinfection must still address immunosuppression.

Immunosuppression, as measured by CD4+ T-cell count and viral load, does more than just impact diagnostic ability—it is directly linked to the risk of contracting tuberculosis. When CD4+ cell counts fall below 100 cells/mL the risk of contracting tuberculosis is nine times that of an individual with CD4+ cell count greater than 700 cells /mL (14). Risk is also contingent on viral load, with incidence three times higher when viral load is greater than 1000 cells/mL than when less that 1000 cells/mL (14). These results indicate that in order to decrease risk of incident tuberculosis maintaining high CD4+ T-cell count and low viral load is imperative.

Antiretroviral therapy (ART) is the primary tool for improving CD4+ T-cell count and reducing viral load, so high ART adherence over time reduces the risk of incident tuberculosis by improving host immune response. After 5 years of ART the risk of a tuberculosis disease is estimated to be 60% lower than during the first year of ART (14).

However, the risk of HIV-positive patients will always be higher than that of HIV-negative patients, regardless of adherence to ART.

When active drug-susceptible tuberculosis disease does occur in HIV-positive patients, early concurrent tuberculosis and ART either reduces or delays morbidity and mortality. When CD4+ count is low (less than 50 per mm^3) ART should be initiated within two weeks of TB treatment start. However, when CD4+ count is above 50 per mm^3ART can be delayed 4-12 weeks after TB treatment initiation to reduce the risk of IRIS or other AEs (15-17). Other early studies used a higher CD4+ cutoff point (200 per mm^3), but showed similar findings: patients below 200 CD4+ cells per mm^3 should start ART within two weeks of TB initiation to improve survival and patients above the cutoff should delay treatment to the first four weeks of the continuation phase of tuberculosis treatment to reduce the risk of IRIS and other AEs (17). By adapting treatment timelines to the immune status of the patient it is possible to increase both quality of life and survival time. Currently, similar practices are used in MDR TB/HIV infection as no studies have shown benefits from altering the drug-susceptible TB/HIV timeline

By incorporating CD4+ count into treatment timeline decisions, it is possible to limit the risk of immune reconstitution inflammatory syndrome (IRIS). In TB/HIV coinfected individuals there are two sub-categories of IRIS: paradoxical tuberculosis-associated IRIS and unmasking tuberculosis-associated IRIS. Paradoxical tuberculosis-associated IRIS requires diagnosis of tuberculosis before ART initiation along with initial improvement on appropriate tuberculosis treatment. IRIS will then present as "recurrent, new or worsening symptoms of tuberculosis, such as fever, return of cough, or lymph node enlargement, or recurrent, new or deteriorating radiological manifestations" (18).

Overall, the risk of paradoxical TB IRIS is highest within the first month of tuberculosis treatment (18). The case definition for unmasking tuberculosis-associated IRIS is still provisional. Cases of unmasking tuberculosis-associated IRIS are identified when the patient is receiving ART, but there is preexisting undiagnosed tuberculosis and an extreme inflammatory clinical reaction or complication of treatment due to a paradoxical reaction occurs (18).

IRIS ranges in severity, but can usually be treated without ART discontinuation or interruption. The majority of mild IRIS cases will benefit from non-steroidal anti-inflammatory drugs (NSAIDS), while moderate-severe cases may require corticosteroids (13). When used in randomized placebo-controlled trials, prednisone was proven to reduce hospitalizations or therapeutic interventions while simultaneously reducing IRIS symptoms and improving overall quality of life (15). Like many adverse events, simple solutions like NSAIDS are extremely beneficial as they permit patients to continue tuberculosis and HIV treatment while also managing the symptoms of debilitating illnesses.

Tuberculosis Drug-resistance

The bacterium responsible for tuberculosis, *Mycobacterium tuberculosis*, has undergone a series of mutations leading to the current MDR TB epidemic. The mutation from drug-susceptible to drug-resistant tuberculosis occurs naturally in patients with active tuberculosis, but it can also be accelerated by misuse of antimicrobials. Misuse can prompt selection for resistance then allow the drug-resistant strain to proliferate,

changing the nature of the disease and its treatment (19). Mycobacterium resistance therefore occurs in stages, with less resistant strains losing traction—transforming from drug-susceptible to MDR TB over time. Once antimicrobial resistance has developed, treatment is more expensive, less effective and often comes with a host of negative side effects (20).

Drug-resistant tuberculosis can range in severity from resistance to one drug to resistance to all available drugs. Three clinical definitions are commonly used to describe stages of tuberculosis resistance: drug-susceptible tuberculosis, multidrug-resistant tuberculosis (MDR TB), and extensively drug-resistant tuberculosis (XDR TB). MDR TB is defined as resistance to at least isoniazid and rifampin, while extensively drug-resistant tuberculosis demonstrates resistant to fluoroquinolones and one second-line injectable agent (amikacin, capreomycin, kanamycin) in addition to isoniazid and rifampin (1, 20).

Overall MDR TB has risen globally, but is distributed and reported disproportionately. The South-East Asian region has the highest estimated case load, while the highest proportion of MDR TB cases (of all reported TB cases) is in Eastern Europe. The most recent WHO reports state that of the estimated 450,000 cases of MDR TB, only 94,000 (21%) were actually reported (2). One alarming trend in the spread of MDR TB is that it is often linked to previous TB treatment. In 2013 only 3.6% of new TB cases were drug-resistant, but many had previously been treated for drug-susceptible TB (2). The same year, of patients who had previously been treated for TB, 20.2% had resistance profiles consistent with MDR (2). The link between drug-susceptible TB and

drug-resistant TB is inexorable, requiring proper treatment and control of the former to stop the spread of the later.

Once drug-resistance has developed its transmission patterns and fitness are similar to drug-susceptible tuberculosis--droplet nuclei carry the bacterium from host to contact (23). In the early days of MDR TB many thought that increased resistance resulted in lower fitness, but this may not be true (24). Comparable fitness in drug-susceptible and MDR TB mean congregate wards, like those used in many resource-poor areas, provide optimal settings for transmission (1). Poor ventilation and immunocompromised patients are the perfect backdrop for transmission so current WHO guidelines advise the use of ambulatory treatment for MDR TB. Ambulatory treatment in either secondary or tertiary facilities has the potential to reduce transmission risk, particularly in high HIV settings like South Africa (1).

Limiting transmission also depends on accurate and timely diagnosis. Starting effective therapy early reduces the time to sputum smear conversion, a vital public health endeavor to control the spread of MDR TB (25). MDR TB diagnosis begins with a positive sputum culture, similar to drug-susceptible tuberculosis. Then, drug-susceptibility testing takes place, although it is often not completed due to insufficient laboratory capacity. DST, using either sputum culture or genotyping, allows clinicians to identify drugs with high efficacy against a particular strain of tuberculosis and is necessary to create a successful treatment plan (19).

That limited access to drug-susceptibility testing (DST) and culture compounds the challenge of identifying cases. In 2013 there were an estimated 450,000 new cases of

MDR TB with an additional backlog of cases waiting for drug-susceptibility confirmation, limiting the ability to confirm drug-resistance (2). Moreover, of the cases that did undergo DST only 50% of first-line DST results were shared with the WHO and only 23% of confirmed cases underwent DST for second-line injectables and fluoroquinolones. Countries like South Africa, that have strong DST result rates (72% of cases treated for MDR TB in 2013) are by far the exception, but need to become the norm to fully gauge the scope of the MDR TB epidemic (2). The increased DST rate could be responsible for South Africa's ability to report more MDR TB cases than were estimated by the WHO in 2013. Unfortunately, high DST rates did not translate to treatment initiation with only 42% of confirmed cases started on appropriate MDR TB drugs (globally 25% are started on MDR TB therapy) (2).

Scaling up DST in conjunction with treatment depends on expanding laboratory capacity. Resource-limited settings often have finite laboratory capacity, commonly resulting in delays of smear microscopy and often have no access to culture methods (25). In many cases proper DST is never completed, or even requested, directly reducing case reporting to the WHO and reducing treatment success rates. DST via any of the laboratory methods currently available, needs to be scaled up to meet the current demand.

There are a number of DST tools available, with varying ability to detect particular resistance patterns. Sputum culture is the standard diagnostic tool for tuberculosis, which includes MGIT or BacTec. Other forms of culture also include microscopic drug-susceptibility assay, colorimetric redox indicator assay, and thin-layer agar (thin-layer agar is not endorsed by the WHO for MDR TB diagnosis) (19). Genotypic analysis methods use nucleic acid amplification, such as a line-probe assay or

Xpert MTB/RIF (rifampin resistance only). Genotypic analysis can also be done using high-resolution melt assay (19). Despite the multiple methods for determining drug susceptibility, laboratory capacity remains a significant bottleneck in the DST process. Among the high burden countries, only 14 of the 22 have one microscopy center for every 100,000 people (2). Even fewer have quality control measures in place. The advent and adoption of Xpert MTB/RIF to diagnose rifampin resistance is just one of many steps that can be taken to improve the speed of resistance testing. However, until significant investments are made in laboratory capacity, drug-susceptibility testing rates will not meet the current demand and too few patients will receive effective therapy. Detecting drug resistance is key to developing MDR TB treatment plans that are effective.

Effective treatment regimens are key to limiting the development of further drug resistance by reducing the risk of selection pressure. Because drug resistance arises from spontaneous mutations in the *Mycobacertium tuberculosis* genome, using effective therapy (at least three drugs with demonstrated effect against a particular strain of *Mycobacertium tuberculosis*) decreases the risk of selection-pressure (19, 26). Drug combinations that only include one or two effective drugs and low adherence, both increase the risk of acquired resistance, further limiting treatment options (26).

MDR TB patients require much longer drug therapy than their drug-susceptible tuberculosis counterparts. MDR TB treatment duration is increased from six months for drug-susceptible tuberculosis to an average of 20 months for MDR TB. Treatment consists of an initial phase (7-8 months) and a continuation phase (18-20 months) (12). Early evidence suggests that treatment success has been greatest when the initial phase

includes at least four effective drugs and the continuation phase at least three effective drugs (21, 27). Success is also increased when total treatment duration is greater than 18 months and directly observed therapy (DOT) is employed the entire time. Other WHO recommendations, while not timeline specific, include using a later generation fluoroquinolone, even when DST indicates resistance to a representative fluoroquinolones. Using a later generation fluoroquinolone is just one of the treatment measures shown to increase survival (22, 27). Unfortunately, many of these recommendations are based on expert opinion rather than actual data, indicating a need for further investigation to improve treatment success.

Treatment success for MDR TB has been consistently lower than that of drug-susceptible tuberculosis. In 2011 the global drug-susceptible tuberculosis treatment success proportion was 87%, much higher than the MDR TB success of 48% (2). Even among global HIV coinfected populations, tuberculosis was treated successfully in 73% of cases (2). In the same year in South Africa's treatment success for drug-susceptible tuberculosis was 79%, significantly higher than global MDR TB treatment success (2). The second- or third-line drugs required, resulting side effects and toxicity, and the extended timeline required for MDR TB treatment all contribute to overall lower successful treatment.

Impact of Drug Resistance on HIV Patients

As mentioned previously, due to their immunocompromised status, patients with HIV are at increased risk of tuberculosis, including MDR TB. In regions such as sub-

Saharan Africa the increased risk is particularly noteworthy as high HIV prevalence and insufficient tuberculosis control programs offer the perfect setting for the burgeoning MDR TB/HIV epidemic. The convergent epidemics are fueled by both initial tuberculosis treatment failure and low adherence.

Moving forward, preventing MDR TB development in high-HIV prevalence settings will necessitate successful drug-susceptible tuberculosis treatment. When initial tuberculosis treatment does fail, it is followed by a well-documented increase in MDR TB incidence (28). To prevent treatment failure and the subsequent rise in MDR TB, high-medication adherence throughout all phases of treatment is essential. That same adherence can also reduce the selection for drug-resistant mutations, another essential element to controlling the spread of MDR TB.

Controlling MDR TB transmission remains a vital public health initiative, especially in high HIV-prevalence populations. When exposed to MDR TB, patients with HIV are more likely to progress to active tuberculosis compared to their HIV-negative counterparts (10). Because HIV-positive patients are more likely to progress to active tuberculosis the size of the tuberculosis patient pool is larger than in HIV-negative cohorts. A larger risk-pool may in turn increase the number of spontaneous mutation conferring drug resistance, further evidence that prompt and effective treatment is necessary to controlling the spread of MDR TB in HIV-positive populations (29). To reduce the size of the risk pool, effective treatment that reduces the time to sputum culture conversion, and therefore reduces infectious patient-time, is necessary.

Preventing transmission in treatment facilities, particularly in nosocomial settings with limited resources, is a challenge that can be partially addressed with ventilation (30, 31). Both natural and artificial ventilation, when used properly can limit tuberculosis transmission in congregate wards like those used in South Africa. In resource-poor areas natural ventilation is an excellent tool to reduce transmission of drug-susceptible tuberculosis. In some cases it is even more effective than mechanical ventilation used in many colder or resource-rich regions (30). Where permitted by climate, open doors and windows are low-cost options to maximize ventilation, particularly in traditional clinics with high ceilings and large windows (30). Transmission of MDR TB cannot be completely eliminated, but creative use of available resources will slow the spread of the MDR TB/HIV epidemic. Increasing ventilation in treatment facilities can reduce risk of transmission, but patient infectivity remains the same.

From patient to patient tuberculosis infectiousness is highly variable, particularly in HIV co-infected patients, making it challenging to predict who will transmit disease and who will not (31). This variability in infectivity paired with the immunosuppression of HIV-patients makes identifying those at greatest risk of MDR TB transmission particularly challenging. Again, congregate wards like those used in South Africa, are especially high-risk for HIV-positive patients (20). As there is no way to predict a patient's infectiousness beyond active verses latent or treated disease, proper ventilation is essential to limiting transmission.

Risk factors for MDR TB infection cannot be completely eliminated, but strong infection control measures and community involvement can help both slow transmission and provide support to patients. Strong infection control practices in the hospital, clinic

and home play a pivotal role in halting the spread of tuberculosis, as well as other opportunistic infections known to occur in HIV positive patients (19). By utilizing both hospital-based and community-based infection control measures such as proper ventilation, facemasks, or outpatient-based treatment, the spread of MDR TB could be dramatically reduced (32). For patients with MDR TB, social support networks are key to maintaining both nutritional and emotional well being, particularly in resource poor areas (33). Strong patient care programs and initiatives can be employed even in resource-poor areas to limit the spread of MDR TB and prevent continued expansion of the MDR TB/HIV concurrent epidemic.

Despite the clear need for effective treatment, tuberculosis programs are strained to provide for increasing number of MDR TB/HIV coinfected patients. These programs struggle to provide accurate surveillance, laboratory, diagnostic and treatment capacity at a level that will address the current epidemic, let alone control it. For instance, many patients still lack appropriate treatment due to insufficient diagnostic capacity, particularly incomplete culture (2). Without proper treatment patients remain infectious, increasing the risk of MDR TB transmission in both nosocomial and community settings (32). Any progress in controlling the spread of MDR TB in high HIV prevalence regions depends on scaling up testing and treatment facilities simultaneously.

Scaling up will require a global investment in tuberculosis treatment infrastructure, particularly in high HIV burden countries. Proven methods such as proper ventilation and prompt DST are just two of many tools that will need to be employed to fully address the spread of MDR TB within HIV-positive population, but are good steps

in the right direction. With a concurrent scale-up of treatment capacity, effective treatment can start earlier and be more effectively sustained (33).

MDR TB Treatment in HIV Patients

As the concurrent epidemic continues to spread, the WHO has responded with provisional guidelines to address patient and health system needs, albeit many of the guidelines are based on expert advice rather than scientific evidence. The basic principles of concurrent MDR TB and HIV infection treatment are early drug therapy initiation, drug-susceptibility testing, and close monitoring for drug toxicity or adverse events. Extrapolating evidence from drug-susceptible TB studies suggests that patients have a twofold benefit from these practices—similar MDR TB treatment success and decreased AIDS-defining illness (35-36).

One effective method to improve patient outcomes is to determine the nature of their illness. Once HIV-status is known, the next step is to determine drug-susceptibility for both HIV and MDR TB. Drug resistance profiles can depend on previous history of tuberculosis and the original strain with which the patient was infected. Drug-susceptibility testing allows clinicians to establish effective treatment plans that incorporate both MDR TB and ART medications, preferably reducing the risk of interaction or overlapping toxicity.

MDR TB medications vary according to drug-susceptibility testing. However, the WHO recommends a series of medications to be used for all MDR TB and MDR TB/HIV drug regimens. Currently these recommendations are based on expert opinion due to

insufficient data (37). Recommendations apply to both MDR TB and MDR TB/HIV patients, as data do not suggest a benefit in deviating from the standard therapy. During the initial phase combinations of drugs are used, one of which is a fluoroquinolone (37). Fluroquinolones, including levofloxacin, moxifloxacin, gatifloxacin and ofloxacin, are strongly recommended for all patients with MDR TB, with preference given to later-generation fluoroquinolones (38). The initial intensive phase also includes an injectable parenteral agent (kanamycin, amikacin or capreomycin) (38). Ethionamide or prothionamide should also be used in the intensive phase. Later, during the continuation phase of treatment, at least four drugs that are likely to be effective should be used, one of which should be a pyrazinamide (38). According to these recommendations all regimens should include a pyrazinamide, a fluoroquinolone, a parenteral agent, ethionamide or prothionamide and either cycloserine or *p*-aminosalicylic acid (PAS) (38). Each of these recommendations comes directly from the WHO, but the evidence base is still weak.

Just as the evidence for MDR TB medications in coinfected populations needs strengthening so too does the evidence for treatment timelines. Regardless, the *WHO 2011 Update to the Guidelines for the programmatic management of drug-resistant tuberculosis* outlines each phase of treatment and the corresponding timelines for coinfected individuals, with the caveat that recommendations will change as research continues. Currently the recommendations include two phases of treatment for patients who have not previously been treated for tuberculosis: the intensive phase and the continuation phase. The intensive phase lasts eight months for the majority of patients, while the continuation phase lasts another 12-14 months (12). Overall treatment in

coinfected individuals should last a minimum of 20 months, with modifications as needed in respect to individual patient response to therapy (38). These timelines apply to both MDR TB and MDR TB/HIV coinfected individuals, although the data to support similar timelines across patient groups is lacking.

MDR TB treatment can therefore be adapted to patient needs, particularly if adverse events are overly frequent or severe. Close monitoring of potential side effects due to drug interaction or toxicities may help prevent life-threatening adverse events. Avoiding known interactions when developing treatment plans is also key to preventing life threatening adverse events. In the event that known drug interactions or toxicities cannot be avoided (typically due to resistance patterns or medication tolerance), increased monitoring is required to assess patient well-being.

Patient well-being is directly affected by the type and number of drugs prescribed to treat concurrent MDR TB/HIV infections. The pill-burden required for simultaneous MDR TB and HIV treatment requires 6-10 drugs per day and often results in overlapping toxicity, drug malabsorption, or drug-drug interaction (29). Overlapping toxicity is often identified when the patient experiences adverse events such as peripheral neuropathy, gastrointestinal intolerance or rash, all of which can be caused by multiple medications in the MDR TB/HIV regimens. Experiencing adverse events can reduce adherence, thereby increasing the likelihood of developing resistance (29, 35). Malabsoprtion and drug interaction can also work to increase resistance, although the mechanism is different. Malabsorption and drug interaction may lower anti-tuberculosis drug concentrations to subtherapeutic levels, creating an opportunity for selection pressure (29). To decrease the potential for toxicity, malabsoprtion or interaction all MDR TB/HIV treatment plans

require intensive monitoring. However, like so many other necessities for tuberculosis treatment and testing the resources for patient monitoring and care are limited.

HIV treatment in MDR TB patients & Drug-drug Interactions

The expanding MDR TB/HIV epidemic requires aggressive treatment protocols, which are only just beginning to be developed. For patients who have contracted both HIV and TB, early diagnosis and treatment is key (39). Medications are modified as needed due to the potential for overlapping toxicities, but combination antiretroviral therapy (ART) usually remains unchanged for coinfected individuals. Standard ART uses two nucleoside analogue reverse transcriptase inhibitors (NRTIs) and one nonnucleoside analogue RTI (NNRTI), one protease inhibitor or, rarely, a third NRTI (34). Like ART, formalized MDR TB medication protocols have been established. When the two diseases occur concurrently, WHO guidelines advocate for early ART and MDR TB treatment initiation (37). As with drug-susceptible TB, ART initiation is dependent on CD4+ count, but further evidence is needed before WHO MDR TB guidelines are revised.

Treatment guidelines have also been adapted to account for drug-drug interaction between ART and first line anti-TB medications in the hopes of improving treatment outcomes and reducing resistance-conferring mutations. Interaction can result in sub- or supra-therapeutic levels that negatively impact patient outcomes by either increasing the potential for resistance or increasing the risk of toxicity. Compounding the issue of toxicity, early evidence indicates that coinfected patients may have a decreased intestinal absorptive area, which could reduce the potential serum concentration of anti-

tuberculosis drugs (40). Common drug-drug interactions among first line drugs like rifabutin, which is known to reduce serum levels of HIV protease and reverse transcriptase inhibitors up to 80%, and also reduce levels of moxifloxacin, limiting efficacy in comorbid treatment regimens (35, 41). Other drug interactions of note are rifampin reduction of moxifloxacin exposure, para-aminosalicylate reduction of rifampin and increase of isoniazid, and clarithromycin inhibition of rifabutin (41).

In drug-resistant tuberculosis drug-drug interaction in second-line TB and ART medications is a strong possibility, but early evidence does provide some direction. This early evidence states that the ideal therapy profile would preferably eliminate the NNRTI category due to increased risk of toxicity and interaction with cytochrome P450 isoforms (CYP450) (41). When a NNRTI does need to be included in the regimen, Efavirenz is recommended as a first choice (42). Protease inhibitors can also inhibit CYP450, with ritonavir acting as the strongest inhibitor (42). While the understanding of drug-drug interaction is limited, current knowledge can help shape treatment options that will optimize outcomes.

Second-line anti-TB drugs also negatively interact with ART, impacting toxicity. One such interaction occurs when macrolides increase exposure of protease and reverse transcriptase inhibitors (41). Other interactions lead to serious adverse events, which can then result in treatment disruption or discontinuation. Interactions with the potential for toxicity include quinolones with didanosine, ethionamide/protionamide with ART, and clarithromycin with protease inhibitors and NNRTIS (1). The natural relationship between toxicity and adverse events requires close monitoring for the duration of

treatment (43). Close monitoring is necessary to detect toxicity-related and other adverse events early, before they escalate.

Other adverse events are independent of toxicity or drug-drug interaction. One such adverse event is immune reconstitution inflammatory syndrome (IRIS), found in HIV cases and further complicated by TB coinfection (45). IRIS manifestation in MDR TB and HIV coinfection is not well understood and needs further investigation to determine risk factors or preventative and treatment measures.

MDR TB associated Adverse Events

Patients undergoing MDR TB treatment are required to take a number of anti-tuberculosis drugs, many of which can contribute to adverse events (AEs). Adverse events can take a variety of forms, ranging from mild to life threatening and can be graded using scales, such as the National Institute of Health DAIDS toxicity table. These events can impact treatment outcomes, adherence, negatively impact quality of life and can impact drug absorption.

MDR TB patients experience more adverse events than drug-susceptible tuberculosis patients, with nausea/vomiting, diarrhea, arthralgia, dizziness, and hearing disturbance being the most common (36, 45). Other, more severe, AEs include central nervous system impairments, leukopaenia, peripheral neuropathy, renal toxicity, and hypothyroidism (46). Severe AEs can require hospitalization, drug regimen alteration or discontinuation, and may impact treatment success. Severity of the adverse event varies depending on a variety of factors, including baseline health, co-infection, and the type of

adverse event. For instance, low starting BMI and low hematocrit may be associated with experiencing an AE during the course of treatment (47).

Global studies of adverse events for drug-resistant tuberculosis have uncovered a number of antituberculosis agent toxicities. Those toxicities can lead to peripheral neuropathy, depression, headache, nausea/vomiting, abdominal pain, pancreatitis, diarrhea, hepatotoxicity, skin rash, renal toxicity, electrolyte disturbances, optic neuritis, and hypothyroidism just to name a few (45-47). Many of the same adverse events can occur with ART use, increasing the likelihood that drug-resistant TB patients co-infected with HIV will experience an adverse event over the course of treatment (43).

As with drug-susceptible tuberculosis and HIV coinfection, multi-drug resistant tuberculosis and HIV coinfection can increase the likelihood of experiencing an adverse event (29). The body of literature exploring AEs in this subpopulation is still relatively small in comparison, but has pinpointed a number of common treatment side effects. To date, the most common AEs in the MDR TB and HIV coinfected population include gastrointestinal symptoms, peripheral neuropathy, hypothyroidism, psychiatric symptoms, and hypokalemia (48). In some studies, up to 70% of treated individuals experienced at least one adverse event (4). The high rates of complication are potentially linked to underlying disease or may be exacerbated by disease (4).

As more data linking MDR TB medications to specific adverse events becomes available, the ability to predict adverse events may increase. That data will then be incorporated into developing treatment plans, particularly for those at highest risk—the coinfected patients.

HIV associated Adverse Events

Effective HIV treatment requires a combination of highly active antiretroviral medications, many of which can contribute to adverse events via toxicity, or when used with MDR TB, overlapping toxicity or drug-drug interaction. There are currently six major categories of antiretroviral medications (ARTs), three of which are readily available in resource-limited settings. These three categories are nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), and protease inhibitors (PIs).

Proper ART incorporates a number of drugs, creating a cocktail that will prolong life as well as improve quality of life. Common ART combinations include two NRTIs with a PI or NNRTI. Patients receiving a mix of two NRTIS and a PI do have a higher risk of withdrawing from treatment, due to an increase in adverse events (49). However, for those that maintain high adherence, the risk of death is significantly decreased (50). The dilemma for patients and providers is to balance quality of life or increased side effects with decreased mortality. Each of these drug classes, whether used individually or in conjunction with another drug class, carries inherent risk of side effects and each drug class has a unique risk profile.

The risk profile of nucleoside reverse transcriptase inhibitors (NRTIs) ranges from lactic acidosis to hepatic steatosis to body fat redistrubtion (49). The adverse events common to NRTIs fall into two categories—those attributed to the drug class and those attributed to specific drugs within the class. For instance, peripheral lipoatrophy can be

attributed to NRTIs in general, while pancreatitis is directly linked to didanosine (49). Other adverse events generally attributed to the overall NRTIs class are neuropathy, lactic acidosis and hepatic steatosis (of which pancreatitis and lactic acidosis are the most severe) (34, 51). When AEs common to the NRTI drug class do appear, they often have a slow onset and a slow resolution. Some, like peripheral neuropathy and renal tubular acidosis may even increase in severity after drug cessation. Despite the likelihood of adverse events likened to NRTIs the alternative, leaving HIV untreated, is out of the question.

The second class of ARTs in resource-poor regions is non-nucleoside reverse transcriptase inhibitors (NNRTIs), which can individually cause adverse events as well as interact with other drugs to further complicate therapy. NNRTIs are known to produce a range of central nervous system adverse events, including dizziness insomnia, somnolence, impaired concentration, vivid dreams, nightmare and mania. Of all of these AEs, the majority are directly linked to Efavirenz, previously mentioned in reference to interaction with cytochrome P450 isoforms (51). This interaction presents as either an increase or decrease concentrations of various protease inhibitors – increasing the challenge of obtaining proper serum concentrations (51). The risks associated with NNRTIs are therefore twofold in that they can produce both AEs and decreased therapy efficacy.

Just like NNRTIs, protease inhibitors (PI) can induce adverse events, the most common events being nausea and diarrhea (34). While not the most common adverse event overall, gastrointestinal intolerance, abnormal fat distribution and metabolic disorders are the primary effects of PIs (50). Perioral paraesthesiae, which is linked to

both Ritonavir and Amprenavir, is another fairly common adverse event (49). Each of these adverse events presents a unique challenge to treatment success. When ART needs to be administered concurrently with MDR TB treatment those challenges are only amplified.

Antituberculosis agents, further increasing the risk of adverse events, exacerbate many of the toxicities linked to ART. With co-therapy the risk of nephrotoxicity, QT prolongation on the electrocardiogram, psychiatric side effects, and gastrointestinal intolerance can limit the ability to successfully complete treatment (42). A few of the MDR TB and ART medication overlapping toxicities have been identified and include peripheral neuropathy from stavudine, didanosine and ethambutol, hepatotoxicity from nevirapine, efavirenz and pyrazinamide, rash from abacavir, amprenavir, nevirapine, efavirenz, fosamprenavir, and pyrazinamide and ocular impairment from didanosine and ethambutol (28). Beyond drug toxicities, interactions can also result in adverse events or treatment failure.

When planning treatment the goal is always to provide effective therapy, but that planning must also account for the potential side effects of the life-saving treatment.

To circumvent overlapping toxicities the initial drug regimens should be closely evaluated at the start of treatment, with the goal of minimizing risk. When adverse events do occur dose reduction is generally not advised as it could lead to further drug resistance. Instead, the recommendation is to switch to a drug with a different toxicity profile or even stop all treatment for a period of time if the reaction is severe enough and then switch to a new therapy. After an adverse reaction any change in treatment should

be closely supervised as should any rechallenge. Desensitization is usually not recommended as it could lead to further resistance (34).

Overall the benefit of treating HIV with ART far outweighs the risk of adverse events. While adverse events are far from pleasant, they are very rarely fatal. If treatment plans are developed in accordance with current guidelines and the patient is closely monitored, it may be possible to avert or reduce the severity of adverse events, while also improving treatment outcomes.

MDR TB/HIV Adverse Events

The frequency and timing of adverse event varies in MDR TB and MDR TB/HIV populations. The variation may stem from the increased stress of two concurrent drug regimens or from the stress of comorbidity. Both MDR TB and HIV treatment are associated with adverse events, but tuberculosis cure rates can be improved by treating both MDR TB and HIV concurrently (29, 43). In South Africa and India, cohorts of MDR TB/HIV found that the most common adverse events in coinfected individuals include peripheral neuropathy, ototoxicity, anemia, depression and psychosis (52-53). When both diseases occur concomitantly AEs occur throughout MDR TB/HIV treatment, with evidence that highest AE rates are in the early phase of treatment (4).

However, studies focusing on the frequency of adverse events (rather than deaths) in concomitant treatment compared to anti-tuberculosis therapy are inconclusive. Some indicate that patients undergoing concurrent treatment experience more adverse events early in treatment compared to patients receiving only anti-tuberculosis therapy (54).

Those early adverse events include fever, worsening chest infiltrates, and peripheral lymphadenopathy (54). Other studies indicate that concurrent therapy does not affect the frequency of adverse events or therapy default (43).

Beyond concurrent MDR TB and ART, some studies have focused on factors that can be used to predict the rate or severity of adverse events. These investigations have shown the relationship between low BMI and low hematocrit at the start of MDR TB treatment and the probability of experiencing a serious adverse event (55). Knowledge of AE predictors could be used to establish monitoring protocols when patients begin treatment, with patients who have either low BMI or low hematocrit receiving the most intensive monitoring.

As the understanding of adverse events and their precursors grows, the ability to minimize those risks will grow as well. For instance, patients with risk factors at the beginning of treatment could be identified. ART initiation could be timed optimally and MDR TB medications could be chosen to minimize interaction with ART. The current limited scope of understanding of adverse events highlight the need for further investigation to determine a more complete profile of AE risk factors as well as potential solutions.

Adherence

Adherence to ART regimens strongly correlates with treatment outcomes, with higher adherence linked to better outcomes. Poor ART adherence correlates to increased morbidity and mortality, while poor TB or MDR TB adherence is linked to longer times

to sputum culture conversion or treatment failure (21, 33). That longer time to transmission can have severe public health implications continued transmission or conversion to multidrug resistance (10). To avoid these negative consequences adherence should be maintained for both ART and tuberculosis treatment.

Proper treatment requires two forms of adherence, adherence to prescribed medication as well as necessary follow-up visits. Both factors are incorporated into successful treatment, with medication adherence often depending on follow-up visit adherence (if the visits are not completed, the drugs are not obtained). However, despite the relationship between high adherence to improved treatment outcomes, in sub-Saharan Africa adherence is low. Average two-year retention in sub-Saharan Africa was just over 60%, the low rates due primarily to loss-to-follow-up and then death (56).

Low treatment retention can present as reduced mediation adherence or insufficient follow-up visit retention rates. Many factors can influence low adherence, although drug cost, distance to treatment facilities and sporadic drug availability are major barriers to treatment in resource-poor regions (56). In the five highest MDR TB burden countries, the majority of first-line drugs are sold privately and the percentage of second line drugs sold privately is even higher, limiting the ability of the poor to obtain medication (57). For the majority of patients high medication adherence is contingent upon high follow-up visit adherence as it is during the follow-up visits that medication is dispensed and regimens are altered to prevent or remedy toxicities resulting in adverse events. However, the opportunity cost for coinfected individuals is also higher than for those with only HIV or only TB as the number of follow-up visits is higher (43). The

identified barriers to adherence are powerful, but can be addressed with targeted programming and new methods.

There is some evidence that new methods, aimed at increasing medication and follow-up visit adherence, such as mobile-phone text messaging, education and counseling, food supplements and treatment support personnel can be successful (33). Improved adherence has the highest impact in the early stages of ART, while later on in treatment the correlation between high ART adherence and improved outcomes is diminished. This means that while adherence may vary over time, initially high adherence bodes well for the patient in the long term (33). Early ART initiation is also linked to higher retention in tuberculosis treatment plans, enforcing the need for high early adherence. However, the high rate of adverse events due to overlapping toxicities or underlying disease early in concomitant treatment is an immense barrier to high early adherence.

Besides improving patient-level outcomes, high adherence also prevents the development of further drug resistance. Incomplete treatment, either treatment with too few drugs in the regimen or treatment terminated prior to completion, negatively selects for drug-resistant strains. Those strains are both harder to treat and have fitness levels similar to drug-susceptible strains—a combination that is especially damaging to the immunocompromised HIV+ patient population (29). Following the WHO guidelines for TB treatment by completing directly observed therapy has long been the standard approach to preventing the development of further resistance.

Directly observed therapy (DOT) has been the gold standard in tuberculosis care worldwide. With the focus on case finding, quick initiation of effective treatment, direct observation of drug ingestion, monitoring, evaluation and reporting, DOT focusing solely on active cases. However, this focus is insufficient to control the tuberculosis epidemic in the poorest populations where latent infections need to be investigated as well (42).

The value of adherence cannot be understated as the combination of drug resistance, adverse effects and socioeconomic pressures create an optimal scenario for low adherence. That low adherence, if ongoing can lead to treatment failure and future increased drug-resistance. Close monitoring of adherence through medication counts and ongoing counseling is a key aspect of successful treatment.

Current Gaps in the Literature

A dearth of information on MDR TB/HIV co-treatment exists, creating a dilemma for the current epidemic. In South Africa MDR TB/HIV co-infection have created a need for novel treatment delivery structures, leading to the implementation of community-based treatment. Now, the next step consists of determining the most effective treatment plan for co-infected patients, while also minimizing their potential for AEs throughout the treatment period. Deeper understanding of how concurrent MDR TB/HIV treatment affects AEs or what risk factors indicate higher probability of AEs remains elusive. This study seeks to help elucidate how MDR TB/HIV co-treatment affects the timing of AE and the severity of AEs compared to MDR TB treatment without HIV.

Study Aims

As a part of the ongoing *Impact of HIV, Antiretroviral Therapy, and TB Genotype on Survival in Multi-Drug Resistant TB* study in South Africa my aim focuses on the frequency and severity of AEs in the treatment of MDR TB and HIV co-infection. For all study analysis MDR TB/HIV patients are the target population while MDR TB/non-HIV patients serve as the referent group.

The first aim is to analyze the frequency of AEs over time in all patients (MDR TB/HIV and MDR TB/non-HIV) to determine when the frequency of AEs is the highest, during early treatment, mid-treatment or toward the end of treatment. With that analysis, the timeline of MDR TB only patient will be compared to those with both MDR TB and HIV to determine if the timelines are the same between groups.

The second aim is to compare the severity of AEs (using the DAIDS scale) between MDR TB/HIV and MDR TB/non-HIV patients to determine if certain AEs are more common in one group than the other or if AEs are more severe in one group than the other.

Adverse Events Occurrence in Multidrug Resistant Tuberculosis and Human Immunodeficiency Virus in KwaZulu-Natal, South Africa

By Sarah Shier

Abstract

Multidrug resistant tuberculosis (MDR TB) and HIV epidemics have converged geographically in South Africa leading to current guidelines to treat both diseases concurrently. Here, the affect of concurrent treatment on laboratory adverse events (AEs) was examined, with the hypothesis that concurrent treatment would lead to increased adverse events in coinfected populations compared to MDR TB only groups. Frequency and severity of MDR TB symptoms, laboratory AEs and MDR TB adverse events was compared across HIV-positive (n=250) and HIV-negative (n=99) groups with both groups demonstrating similar AE distribution and severity over the first 14 clinic visits. Bivariate and multivariate analysis was then conducted to determine association with experiencing a laboratory AEs scoring at least a 2 on the DAIDS scale on patient baseline characteristics (N=349). Baseline age and sputum smear result were included in the final multivariate model, but neither were significant at $P<0.05$. The lack of difference in AE frequency or severity in coinfected and non-coinfected populations indicates that current guidelines for concurrent treatment should be supported. All findings are interim and are subject to change as data continues to be collected.

Introduction

For decades the HIV epidemic has been concentrated in resource-poor regions such as Sub-Saharan Africa, while the multidrug resistant tuberculosis (MDR TB) epidemic has been concentrated in Eastern Europe (1, 2, 20). More recently, the two epidemics have converged in high HIV prevalence countries, creating new cohorts of coinfected patients (20). MDR TB requires treatment with second-line drug regimens, which are more expensive, less effective, more toxic, and longer than that used to treat drug-susceptible TB. Moreover, the current co-epidemic requires concurrent treatment, increasing the risk of overlapping drug toxicity, adverse events, immune reconstitution inflammatory syndrome (IRIS) and death.

Adverse events are known to occur during both MDR TB and HIV treatment, however the frequency, timing and impact on patients during concomitant drug therapy is not well understood. Some adverse events (AEs) that occur are linked to MDR TB treatment (hypothyroidism, loss of hearing, and seizures) while other AEs are related to anti-retroviral therapy, such as pancreatitis or peripheral lipoatrophy (36, 45-48). Either MDR TB or ART can cause other adverse events, such as peripheral neuropathy or hepatitis (36). Despite the potential risk of increased adverse events, literature currently identifies higher early mortality in HIV-positive patients as a strong incentive for early ART initiation in co-infected populations (15-17). Early concurrent treatment has proven successful in reducing mortality and some AEs in drug-susceptible TB and HIV coinfection (16, 17). Early concurrent treatment is also believed to decrease morbidity and mortality in MDR TB and HIV coinfection, but empirical evidence remains weak.

The timeline of adverse events, and whether events are linked to drug toxicity or underlying disease, remains in question.

This prospective case-control study focuses on adverse events in MDR TB/HIV and MDR TB populations in KwaZulu-Natal, South Africa. The primary objective to determine when in the course of treatment the proportion of AEs is the highest for the MDR TB/HIV and MDR TB only group, as well as whether all AEs show the same trends or if specific AEs act differently. The secondary objective is to compare the severity of AEs (using the DAIDS scale) between the MDR TB/HIV and MDR TB only groups.

Methods

Setting

KwaZulu-Natal is a resource-limited province in South Africa with an HIV prevalence of 37.4% among antenatal clinic attendees in 2011 (58). In the same year, the TB incidence was 889 cases per 100,000 people and the MDR TB incidence was 45 cases per 100,000. When patients are diagnosed with MDR TB they are also tested for HIV. If positive, HIV positive-patients are started on ART, regardless of CD4 count. Both ART and MDR TB treatment are provided free of charge to all South Africans.

Study Participants

This is a prospective, observational study examined two groups of participants: MDR TB/HIV co-infected patients and MDR TB patients without HIV. Regardless of study group, participants were followed monthly (28 day intervals) for the duration of treatment (24 months). Eligible participants were at least 18 years of age, had culture-confirmed MDR TB, a documented HIV status and less than 14 days of second-line TB treatment.

Study participants had to provide informed consent and have received standard MDR TB and HIV treatment with drug susceptibility to fluoroquinolones and all injectable agents. Exclusion criteria included creatinine greater than two times the upper limit of normal or serum ALT five times the upper limit of normal at enrollment. Any women who were pregnant, or planning to become pregnant, were also excluded.

Data Collection

During the initial visit patient demographics, medical history, TB and HIV exposure history, and current medication information were collected. At the initial visit, and all follow-up visits, both clinical and laboratory data was collected. The clinical data consisted of a review of systems, physical exam, adverse event assessment and grading according to the DAIDS scale, vital signs, potential IRIS evaluation, opportunistic infection evaluation, and chest x-ray description and interpretation. Data concerning current medication, current TB and HIV diagnosis, and TB and HIV treatment plans was also collected. Laboratory data included complete blood count, chemistries, liver function tests, urine pregnancy test, sputum, CD4 count and viral load testing. Other tests conducted at regular intervals were thyroid stimulating hormone, color vision and audiology. In the event an in-person follow-up visit was missed, researchers attempted to reschedule the visit or follow-up via phone.

Analysis

Adverse event analysis utilized the NIH Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events[i] to categorize severity for all laboratory tests. The monthly review of systems questionnaire and tuberculosis symptoms used binary responses of yes or no. AEs were analyzed individually, as well as pooled across categories (review of systems, laboratory, and tuberculosis related symptoms) to determine the proportion of patients who experienced AEs over the course of treatment. These values were then stratified by HIV status to compare AE frequency between HIV co-infected and HIV negative participants.

After initial analysis, data was regrouped into two categories—patients who experienced a potassium, creatinine, alkaline phosphatase or ALT AE of grade 2 or greater, and those that did not, to determine factors associated with the development of these AEs. The baseline factors examined were CD4+ count, viral load, gender, age, receiving ART or not, duration on ART, HIV status, TB sputum smear result, previous hospitalization, previous smoking, alcohol use, and previous history of TB. Associations between each baseline factor and the AE outcomes were assessed for statistical significance using Fischer's exact test for categorical variables and Wilcoxon rank-sum test for continuous variables (age and weight). Any factors associated with the outcome with a P value less than 0.2 were included in the multivariate logistic model and then selectively removed using backward elimination. Two-sided hypotheses and tests were used for all statistics. All analysis was conducted using SAS v. 9.1.

The International Review Boards of Emory University, the University of KwaZulu-Natal, Albert Einstein College of Medicine and the South African Medical Research Council granted ethics approval prior to study initiation and analysis. Informed content was obtained prior to screening potential participants and patient confidentiality was maintained throughout the entire study and data analysis process.

Results

Demographics

A total of 349 participants were enrolled, 170 (49%) of which were female, 273 (70%) of which were black, and 250 (72%) of which were HIV positive. The majority, 191 (55%), had previously been treated for tuberculosis. Within the HIV-positive population the median CD4+ count was 259 cells/mm^3 (IQR 154-429), while the median viral load was 40 copies/ml (IQR 39-70) (Table 1).

AE Frequency

Overall, the frequency of adverse events (AEs) was highest in the first five months of treatment, after which there was a sharp drop in AE frequency. Two of the AE categories, tuberculosis symptoms and tuberculosis related, had highest AE frequencies at visit 1 (baseline. Laboratory AEs (including both chemistries and complete blood count) were more consistent over the course of treatment.

At baseline, 88% of study participants presented with at least 1 tuberculosis symptom. Those symptoms diminished over time so that by visit 7 only 34% of patients presented with at least 1 AE and only 29% by visit 14. The decrease in frequency for AEs reported on the review of systems questionnaire was slower, but did decrease from 20% of patients experiencing 1 AE at baseline to 6% experiencing an AE at visit 14. For laboratory-related AEs there was no decrease over time, 83% of patients had at least 1 AE at visit 1, compared to 73% at visit 7, and 83% at visit 14 when grades 1-4 were included in analysis.

Overall, the most common AEs were fatigue or weakness (n=57, 46% at visit 1) and abnormal albumin (n=116, 73% at visit 1). When organized by HIV status the most common AEs in HIV-positive patients also included fatigue or weakness. Other AEs of note in the HIV-positive group were abnormal bicarbonate and albumin. In the HIV-negative group the most common AEs were bicarbonate, albumin, and again, fatigue or weakness.

Also, when organized by HIV status, the frequency of adverse events was higher in the HIV-positive group throughout treatment (Figure 2). For both groups, tuberculosis symptoms, tuberculosis related AE, and laboratory AE frequencies were highest in early visits, and both groups experienced a decreased in AE frequency over time.

AE Severity

Over time the severity of adverse events decreased in both study arms for all laboratory AEs (Figures 1 & 2). Overall, at visit 1, 9% of patients had a laboratory AE grade 2 or higher, but by visit 7 that number had decreased to 4%. Beyond visit 7 the occurrence of AEs of grade 2 or higher was sporadic, with only the occasional presentation of an AE greater or equal to 2.

AE Predictors

A number of tuberculosis covariates were significantly associated with having a grade 2 or greater AE (Table 2). In bivariate analysis, the following baseline factors were associated with a grade 2 or greater AE: negative TB smear status (p=0.04), currently on ARTs (p=0.04), and taking medications other than TB or ART therapy (p=0.002).

Surprisingly, neither HIV, nor previous alcohol use, nor smoking, nor hospitalizations were significantly associated with increased AE severity.

In multivariate analysis two factors increased the patient odds of experiencing a laboratory adverse event greater or equal to two. Increased age and negative sputum smear results were associated with experiencing a severe adverse event, although not significantly (Table 3). The odds of a patient with a negative sputum smear experiencing a serious adverse event was 1.84 times that of a patient who had positive sputum smear at baseline. However, the confidence interval for sputum smear was non-significant, potentially due to limited sample size. The effect measure for age was extremely slight, only 1.01 (95% CI 0.98-1.04).

Discussion

This study presents analysis of the frequency, severity and factors contributing to the occurrence of serious adverse events in MDR TB and MDR TB/HIV coinfected patients in KwaZulu-Natal, South Africa. Adverse events were common to both MDR TB and MDR TB/HIV patients, with the highest frequency of events occurring early in treatment. Proportionally, both groups had similar adverse event distribution, indicating that current recommendations to treat MDR TB and HIV concurrently are supported. Similar to the frequency of adverse events, the severity decreased over time in both HIV-positive and HIV-negative groups. When considered independently of all confounders a number of tuberculosis covariates, including negative tuberculosis smear, taking ARTs and taking other medications, were significantly associated with experiencing a laboratory adverse event scoring at least a two on the DAIDS scale, although in multivariate analysis none were significantly associated.

The frequency of adverse events remained high for the first 4-5 visits, across both groups. There was a slight increase in frequency from the baseline visit (Visit 1) to the first treatment follow-up visit (Visit 2) indicating that treatment may contribute to some adverse events. However, the distribution of these events was similar across the MDR TB-only and the MDR TB/HIV coinfected groups. In this study common AEs in both the MDR TB and MDR TB/HIV groups included fatigue and weakness, abnormal albumin and abnormal bicarbonate, while prior studies of MDR TB populations found the most common adverse events to be nausea/vomiting (32.8%), diarrhea (21.1%) and arthralgia (16.4%) (36). While many of these adverse events were also present in this study, they were not as prevalent. By visit and AE, vomiting peaked at visit 2 (12%), diarrhea at visit

3 (7%), and arthralgia at visit 2 (29%). Overall, the frequency of adverse events were similar in both HIV-positive and HIV-negative groups indicating that concurrent therapy is advisable, as it has previously been shown to increase AIDS-free survival time (15-17).

The severity of adverse events was also similar across groups, without any statistical association base on HIV-positive status and experiencing more severe laboratory adverse events. Other early studies of MDR TB in high-HIV prevalence settings have found that the risk of certain adverse events, such as neuropathy or ototoxicity, is higher among HIV-coinfected patients (4). However, no other studies of MDR TB or MDR TB/HIV coinfection have focused primarily on laboratory AEs, making it probable that this is a novel finding. Further study is required to determine if the decrease in AE severity over time is significant or if the rate at which severity decreases is linked to HIV infection.

When considered independently, a number of patient baseline characteristics were considered significant at an alpha of 0.05. However, when assessed in a multivariate logistic model, the characteristics included in the final iteration were limited to increased age and negative sputum smear. The effect estimate of age was minimal, but the odds ratio associated with negative sputum smear (1.84) was of greater magnitude, although not significant (95% CI 0.83-4.1). With an increased sample size, the precision may have increased and the results might have been significant.

Unlike this study most, if not all, other studies of adverse event risk factors have focused on drug-susceptible tuberculosis or in patients without HIV coinfection and found that low hematocrit or baseline BMI were the primary risk factors (36). While

deeper investigation of serious adverse event risk factors in MDR TB and MDR TB/HIV coinfection are needed in order to minimize treatment risk and identify early indicators of said adverse events, this study has identified a number of potential risk factors.

Of all of the findings, the similar risk patterns across HIV-positive and HIV-negative groups, is of particular import as it provides further evidence of the benefit of concurrent therapy for coinfected patients. Very few previous studies of MDR TB adverse events have had a HIV coinfected group, so the comparisons across groups found in this study offer an initial glimpse into determinants of serious adverse events as well as adverse event frequency and overall severity (14, 21, 30). As MDR TB continues to spread, particularly in high-HIV prevalence settings, the findings of this study can help guide practitioners treating co-infected patients.

Strengths and Limitations

There are several limitations of this study. First, patients with the most severe adverse events were also the most likely to discontinue treatment and therefore be lost to follow-up. The study is ongoing, so as more data is collected this potential bias may or may not present itself clearly. The research protocols dictate that when patients miss an in-person follow-up visit questionnaire will be administered via phone, meaning that some data will still be available. Laboratory values will not be available, but it may be possible to determine why patients discontinue study participation or have lapses in treatment. A second key limitation to this analysis is that only the laboratory adverse events were graded on the DAIDS scale, with all other adverse events reported as binary outcomes (Yes/No). To fully grasp the extent to which AEs impact patient quality of life

a more nuanced grading system for tuberculosis symptoms and other tuberculosis related adverse events is necessary. For non-laboratory adverse events standardization across the grading system can be problematic as grading is dependent on clinician observations. Therefore, the potential for categorization bias would need to be taken into account. Finally, this analysis is interim and data will continue to be collected. The full study will continue until visit 24, while this analysis focused only on visits 1 through 14. As new data is incorporated the findings of this analysis may change, leading to alternate conclusions and recommendations.

Overall, this study found that adverse events occurred most frequently early in treatment, possibly pointing to underlying disease as the culprit. The severity of adverse events also decreased over time, with the majority of adverse events scoring a 2 or higher on the DAIDS scale occurring in the first five visits. These findings were similar across both the HIV-positive and the HIV-negative group, supporting the current recommendation that treatment should be given concurrently. Being one of the first studies to assess the frequency and severity of laboratory adverse events in MDR TB/HIV coinfected populations, the findings of this study can be used to shape future investigation as well as offer evidence to a field in dire need of empirical data.

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Tables

Table 1. Baseline Patient Characteristics for HIV and non-HIV Groups

Patient Characteristic	N=349	HIV+ n=250	HIV- n=99
Gender (Female) — no. (%)	170 (49)	129 (76)	41 (24)
Race — no. (%)			
Black	273 (70)	189 (69)	84 (31)
Other	2 (0.7)	1 (0.4)	1 (0.4)
Age — no. (%)			
Median (IQR)	31	24	32
Interquartile Range	21-40	20-40	22-40
18-30	104 (37)	54 (28)	50 (58)
31-40	92 (33)	80 (41)	12 (14)
41-50	57 (20)	44 (23)	13 (15)
61+	26 (9)	15 (8)	11 (13)
Weight in Kg* — no. (%)			
Median	57	57	57.4
Interquartile Range	50.5-65.2	50-65	51-66
30-40 kg	18 (7)	14 (8)	4 (5)
41-50 kg	69 (26)	53 (29)	16 (20)
51-60 kg	94 (35)	62 (34)	32 (40)
61-70 kg	54 (20)	37 (20)	17 (21)
71-80 kg	18 (7)	12 (7)	6 (7)
80+ kg	13 (5)	7 (4)	6 (7)
Negative TB Smear* — no. (%)	278 (80)	193 (69)	85 (31)
Previous History of TB — no. (%)	191 (55)	148 (75)	43 (23)
CD4+ Count** — no. (%)			
Median	259	259	--
Interquartile Range	154-429	154-429	--
0-50***	9 (8.5)	9 (8.5)	--
51-200***	31 (29)	31 (29)	--
201-350***	27 (25)	27 (25)	--
350+***	39 (38)	39 (38)	--
Available Viral Load* — no. (%)			
Median	40	40	
Interquartile Range	39-70	39-70	
<400***	79 (78)	79 (78)	--
401-1000***	4 (4.0)	4 (4.0)	--
1001-10,000***	2 (1.9)	2 (1.9)	--
10,001-100,000***	6 (5.9)	6 (5.9)	--
100,000+***	10 (9.9)	10 (9.9)	--
Currently on ART — no. (%)	147 (42)	147 (59)	0 (0)
ART duration — no. (%)			
1-2 years	53 (78)	53 (78)	--

3-4 years	9 (13)	9 (13)	--
5-6 years	2 (3)	2 (3)	--
7-8 years	3 (4)	3 (4)	--
9+ years	1 (1)	1 (1)	--
Alcohol — no. (%)	83 (24)	63 (76)	20 (24)
Smoking — no. (%)	63 (18)	47 (75)	16 (25)
Previously Hospitalized — no. (%)	56 (16)	46 (82)	10 (18)
Taking Herbal or Traditional Treatment — no. (%)	18 (5.2)	12 (67)	6 (33)
Seeing a Traditional Healer — no. (%)	6 (1.7)	3 (50)	3 (50)
Other medications	150 (43)	116 (77)	34 (23)

*At Baseline (Visit 1)

**Most recent available

***Percentage of total available CD4+ or Viral Load

Table 2. Odds of Experiencing a Laboratory Adverse Event Greater or Equal to DAIDS=2

Covariate	All Patients N=349	Grade 0-1 n=318	Grade 2+ n=31	Fischer's Exact P-value	Odds Ratio (95% CI)
HIV Positive — no. (%)	250	225 (90)	25 10)	0.30	1.72 (0.68-4.34)
Race — no. (%)				1.00	
Total	275	245(89)	30 (11)		
Black		243 (99)	30 (100)		1.00
Other		2 (1)	0 (0)		--
Gender (Female) — no. (%)	170	150 (88)	20 (12)	0.09	2.04 (0.94-4.39)
Age — no. (%)	278	251 (90)	27 (10)	0.66	1.00 (0.97-1.04
Negative TB Smear* — no. (%)	278	258 (93)	20 (7)	0.04	2.37 (1.08-5.20)
Prior TB — no. (%)	191	169 (89)	22 (11)	0.06	2.16 (0.96-4.83)
Available CD4+ count	102	86(84)	16 (16)	0.68	
0-50***		7 (8)	2 (13)		2.00 (0.32-12.46)
51-200***		22 (26)	7 (44)		1.68 (0.46-6.12)
201-350***		24 (28)	3 (19)		0.88 (0.19-4.01)
350+***		33 (38)	4 (25)		1.00
Available Viral Load* — no. (%)	94	81 (86)	13 (14)	0.48	
<400***		61 (75)	11 (85)		1.00
401-1000***		4 (5)	0 (0)		--
1001-10,000***		1 (1)	1 (8)		5.67 (0.33-96.89)
10,001-100,000***		6 (7)	0 (0)		--
100,000+***		9 (11)	1 (8)		0.63 (0.07-5.43)
Currently on ART — no. (%)	147	128 (87)	19 (13)	0.04	2.35 (1.10-5.01)
ART duration — no. (%)	69	56 (81)	13 (19)	0.22	
1-2 years		46 (82)	8 (62)		1.00
3-4 years		6 (9)	3 (23)		2.88 (0.59-13.91)
5-6 years		1 (2)	1 (8)		5.75 (0.33-101.59)
7-8 years		2 (4)	1 (8)		2.88 (0.23-35.56)
9+ years		1 (2)	0 (0)		--
Alcohol — no. (%)	83	73 (88)	10 (12)	0.27	1.69 (0.72-3.55)
Smoking — no. (%)	63	58 (92)	5 (8)	1.00	0.86 (0.32-2.34)
Previously Hospitalized — no. (%)	56	52 (93)	4 (7)	0.80	0.76 (0.25-2.25)
Taking Herbal or Traditional Treatment — no. (%)	18	17 (94)	1 (6)	1.00	0.59 (0.08-4.59)
Seeing a Traditional Healer — no. (%)	6	5 (83)	1 (17)	0.43	2.09 (0.24-18.45)
Taking other medications — no. (%)	150	135 (90)	15 (10)	0.00	0.14 (0.05-0.44)
Weight* — no. (%)				0.079**	

Total	266	238 (89)	28 (11)	
30-40 kg	18 (7)	13 (5)	5 (18)	4.81 (1.13-20.49)
41-50 kg	69 (26)	58 (24)	11 (39)	2.37 (0.71-7.91)
51-60 kg	94 (35)	89 (37)	5 (18)	0.70 (0.18-2.74)
61-70 kg	54 (20)	50 (21)	4 (14)	1
71-80 kg	18 (7)	16 (7)	2 (7)	1.56 (0.26-9.34)
80+ kg	13 (5)	12 (5)	1 (4)	1.04 (0.11-10.19)

*Indicates values from Visit 1 only

**Wilcoxon-Rank-Sum of Continuous Variable

***Percentage of total available CD4+ or viral load

Table 3. Predictors of Laboratory Adverse Events Greater than DAIDS=2

Predictor	Crude Odds Ratio (95% CI)	P-Value	Adjusted Odds Ratio on Multivariate Analysis (95% CI)	P-Value
Age	1.00 (0.97-1.04)	0.66	1.01 (0.98-1.04)	0.62
Negative TB Smear*	2.37 (1.08-5.20)	0.036	1.84 (0.83-4.1)	0.14
Gender (Female) — no. (%)	2.04 (0.94-4.39)	0.089	--	--
Currently on ART — no. (%)	2.35 (1.10-5.01)	0.035	--	--
Prior TB — no. (%)	2.16 (0.96-4.83)	0.061	--	--
Taking other medications — no. (%)	0.14 (0.05-0.44)	0.0015	--	--
Baseline Weight— no. (%)		0.079**	--	--
30-40 kg	4.81 (1.13-20.49)		--	--
41-50 kg	2.37 (0.71-7.91)		--	--
51-60 kg	0.70 (0.18-2.74)		--	--
61-70 kg	1.00		--	--
71-80 kg	1.56 (0.26-9.34)		--	--
80+ kg	1.04 (0.11-10.19)		--	--

**Wilcoxon-Rank Sum Test

Figures

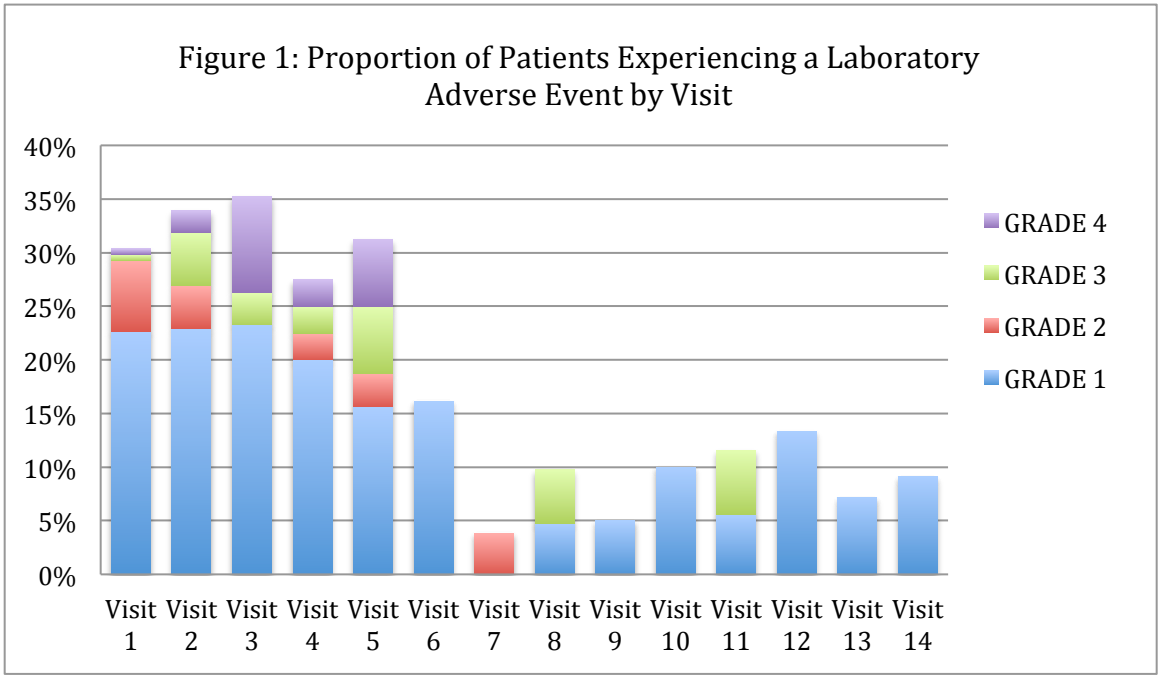
Figure 1: Proportion of Patients Experiencing a Laboratory Adverse Event by Visit
40%
35%
30%
25%
20%
15%
10%
5%
0%
Visit 1
Visit 2
Visit 3
Visit 4
Visit 5
Visit 6
Visit 7
Visit 8
Visit 9
Visit 10
Visit 11
Visit 12
Visit 13
Visit 14
GRADE 4
GRADE 3
GRADE 2
GRADE 1

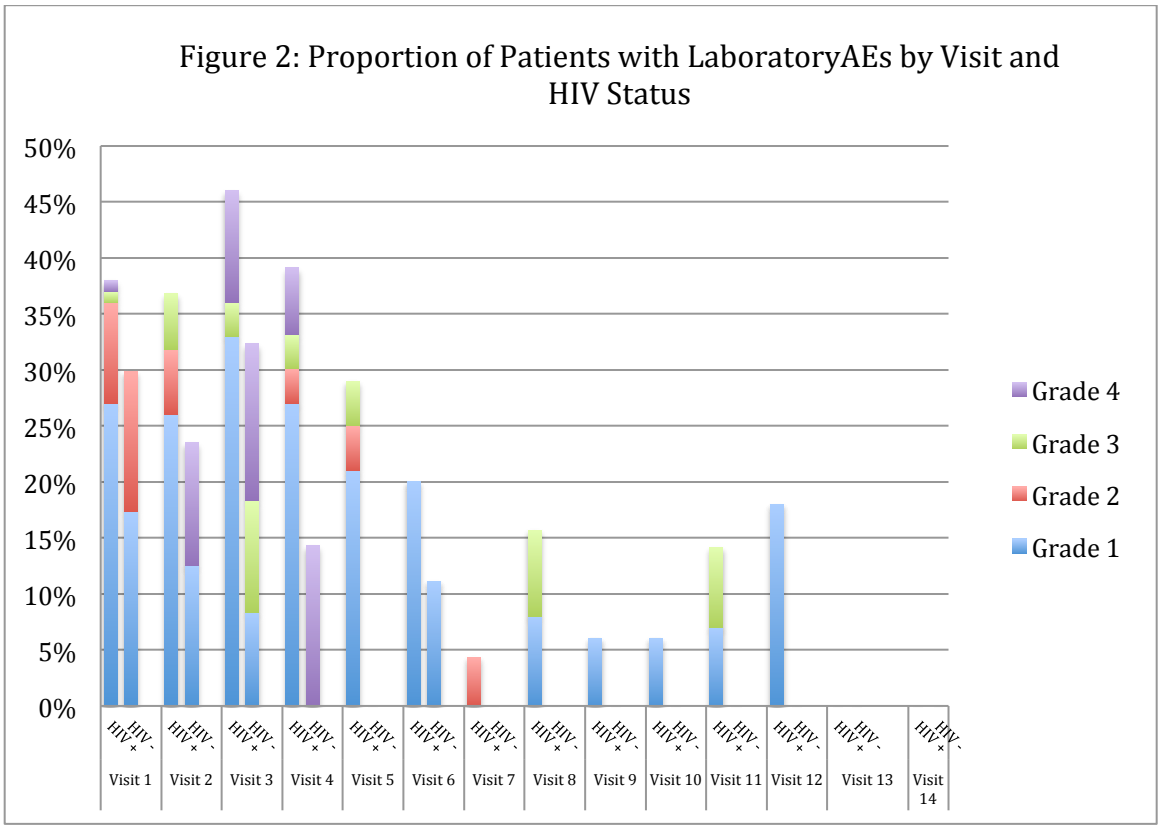
Figure 2: Proportion of Patients with LaboratoryAEs by Visit and HIV Status
50%
45%
40%
35%
30%
25%
20%
15%
10%
5%
0%
Visit 1
Visit 2
Visit 3
Visit 4
Visit 5
Visit 6
Visit 7
Visit 8
Visit 9
Visit 10
Visit 11
Visit 12
Visit 13
Visit 14
Grade 4
Grade 3
Grade 2
Grade 1

Public Health Implications and Possible Future Directions

The global MDR TB and HIV epidemics have converged in South Africa creating a dire need for effective treatment protocols. This prospective observational study is one of the first to compare the impact of concurrent MDR TB/HIV therapy on laboratory adverse event frequency and severity. Moreover, this study included a control population of patients who were MDR TB-positive, but HIV-negative, giving valuable insight into potential differences between the groups. Overall, the differences were minimal, validating the current recommendation that MDR TB and ART be administered concurrently.

Moving forward more research is needed to determine specific factors that impact the occurrence of adverse events and their severity. Patient baseline factors such as weight, age, or HIV status all have the potential to impact the occurrence of adverse events. This study only identified age and sputum smear results as predictors of laboratory adverse events, but as more data is collected it is probable that these indicators could change. With increased follow-up time comes greater potential to determine if these initial predictors are valid or whether there are other factors that could be used to predict adverse event outcomes.

Other than extended follow-up time, increasing analysis to include other categories of adverse events is critical to a full understanding of the impact of concurrent treatment. For instance, ototoxicity is an adverse event with the potential to impact patients for the rest of their lives. Other adverse events like hypothyroidism, pancreatitis or color blindness also need to be included in any comprehensive analysis of adverse

events. With more time, these adverse events could have been addressed. However, as this was an interim study, full assessment of adverse events remains to be completed.

Expanding the list of adverse events to be considered means that the potential for reoccurring adverse events, whether or the same type of different types, is greater. If there are predictors of adverse events, or severe adverse events, there may also be identifiable risk factors for experiencing multiple adverse events. Assessing whether certain events occur multiple times over the course of treatment, how severe they are, and what precedes those events can help care providers identify at risk patients.

While this study gave an initial outline of adverse event timelines, the timeline was condensed compared to average MDR TB treatment duration. As the study continues, data about later stages and even treatment success or failure will be collected. That information is vital to determining how adverse events impact overall treatment, both in regards to treatment outcomes and therapy adherence (which can in turn impact outcomes). A complete understanding of the frequency and severity of adverse events over the full course of MDR TB treatment is also necessary before current guidelines are revised.

The continued analysis proposed here could impact how care providers treat MDR TB/HIV coinfected populations, providing much needed data for a field currently based on expert opinion. As MDR TB continues to spread, particularly in high-HIV prevalence settings like South Africa, the need for in-depth investigation and understanding of adverse events is crucial to providing optimal care. If it is possible to identify risk factors for adverse events, from ototoxicity, to abnormal potassium, to

arthralgia, it may be possible to avoid lapses in treatment or treatment failure. Increasing the rates of successful treatment for MDR TB is necessary to controlling the MDR TB/HIV epidemic.