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The Effectiveness and Acceptability of Six-Month Isoniazid Preventive Therapy amongst People Living with HIV in KwaZulu-Natal, South Africa

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The Effectiveness and Acceptability of Six-Month Isoniazid Preventive Therapy amongst People

Living with HIV in KwaZulu-Natal, South Africa

by

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ABSTRACT

Tuberculosis (TB) preventive therapy is an integral part of global strategies to end TB. Isoniazid preventive therapy (IPT) is currently the only regimen recommended globally for low-resource settings with high burdens of TB and TB-HIV. In South Africa, where the incidence of TB and TB-HIV are among the highest in the world, health districts were quick to facilitate access to six-month IPT in the absence of active TB symptoms for all people living with HIV, amid numerous unknowns. My doctoral thesis responds to some of these unknowns; specifically, the effectiveness of IPT to reduce TB incidence and its acceptability in communities where latent TB infection was previously unfamiliar.

The research occurred within a community-based participatory research framework including regular meetings with grassroots community advisory teams in three communities of uMgungundlovu District, KwaZulu-Natal. IPT effectiveness was evaluated utilising a retrospective cohort design, comparing TB incidence across two years among people receiving IPT alone, antiretroviral therapy (ART) alone, or IPT+ART to those without intervention. Acceptability was evaluated utilising the ethnographic method, including extensive field work, eight group interviews to learn about perspectives of TB infection, disease and IPT, and nine individual interviews with people accepting, discontinuing or declining IPT to learn about IPT experiences and decision making.

Among those who completed the regimen, IPT significantly reduced the two-year TB incidence by 100% among women (97.5%CI=78-100%), with a less certain effect among men: IR=0.46, 95%CI=0-85%. IPT also appeared to provide additional prevention for people on ART. Nevertheless, IPT was interpreted by some as dangerous when the costs related to pill collection or consumption exacerbated poverty, the stigma associated with HIV and ART were conflated with its use, or it was seen as toxic. Clinical expectations of IPT initiation and adherence may also conflict with expectations of women in Zulu culture. Some women may initiate IPT to please the healthcare provider, rather than from a belief in preventive benefits. Taken together, findings suggest that IPT can reduce the risk of TB among people living with HIV, but may not be a high priority when economic and social needs compete.

PREFACE

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Figure 7 in Chapter 6 is from Pai M, Behr MA, Dowdy D, Dheda K, Divangahi M, Boehme CC, et al. Tuberculosis. Nat Rev Dis Primers. 2016; 2: 16076, used with permission from Springer Nature.

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to all of those we did not reach:
your voices will be heard
be it in this life or through the ancestors

i hope we say it well

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AIDS	Acquired Immunodeficiency Syndrome
ART	Anti-Retroviral Therapy
CR	Case Reduction
CCG	Community Care Giver
CBPR	Community-Based Participatory Research
CI	Confidence Interval
DOT	Directly Observed Therapy
XDR-TB	Extremely Drug Resistant Tuberculosis
GRAT	Grassroots Research Advisory Teams
GI	Group Interview
HIV	Human Immunodeficiency Virus
IRR	Incidence Rate Ratios
II	Individual Interview
IGRA	Interferon Gamma Release Assay
INH	isoniazid
IPT	Isoniazid Preventive Therapy
KZN	KwaZulu-Natal province
MDR-TB	Multi-Drug Resistant Tuberculosis
NGO	Non-Governmental Organisation
P	Participant
PLWH	People Living With HIV
3HP	Rifapentine + Isoniazid
TST	Tuberculin Skin Test
TB	Tuberculosis
UN	United Nations
US$	United States Dollar
WHO	World Health Organisation

CHAPTER 1

Introduction and Literature Review

To me, arriving as an *outsider,* it's like watching a movie from the olden days. I'm met by a land still undeniably divided on colour lines, nowhere close to rebalancing its glaring inequalities. It is a country of have and have-nots, rich, poor and poorest, and, mostly still black and white.

Sarah-Jayne King
Killing Caroline

Introduction

Tuberculosis (TB) is an infectious disease dispersed into the air when a person with active TB in the respiratory system coughs. A person who breathes in minute TB particles known as droplet nuclei may then become infected by the bacterium. About 90% of healthy people who become infected with TB in this manner will neither progress to TB disease nor transmit the bacterium to others, containing the disease in its dormant form, known as latent TB infection. People with immunosuppressive conditions are more likely to be infected with TB [1] and more likely to develop disease once infected [2]. People living with HIV (PLWH) are especially vulnerable to TB infection and disease, and thus South Africa has one of the highest burdens of TB. South Africa has the third highest TB incidence and highest incidence of TB-HIV co-infection globally (860 and 520 per 100 000 population, respectively [3,4]). The World Health Organisation (WHO) has identified three priority targets for reducing the burden of TB in high-incidence settings, namely, intensified case finding, shorter treatment regimens, and TB preventive therapy [5]. In order to boldly counter climbing incidence among PLWH, TB preventive therapy was introduced at no cost by the South Africa government in 2010 [6], amidst a number of unanswered questions. My doctoral thesis responds to some of the unknowns regarding TB preventive therapy in a resource-constrained setting of KwaZulu-Natal (KZN) province. Specifically, I investigate the effectiveness of a six-month regimen of isoniazid to prevent TB disease and explore its acceptability in communities where latent TB infection was previously unfamiliar.

Setting

uMgungundlovu District is located in central KZN. With a population of approximately one million people, the District reports 40% unemployment [7] with 112 000 people living on less than US$1 per day [8]. The District has an ante-natal HIV prevalence of 41% [7], and a TB incidence of 894 per 100 000 population [9,10]. Tuberculosis is the leading cause of death and of years of life lost in the District [7]. Eighty-four percent of the population does not have private healthcare insurance [7]. During the period of study, approximately 30% of the District was under 15 years of age, 65% were between the ages of 15 and 65 years of age, and there were 92

males for every 100 females [10]. Eight-five percent of the District is of African descent, among whom 76% report isiZulu as their home language [8].

What is Isoniazid?

Isoniazid is a medication used in combination with three other drugs to treat TB disease. Due to its low cost [11,12] tolerability [13], efficacy [14,15], and ability to sterilise dormant bacteria [16], isoniazid has also been used to prevent TB among people with latent TB infection. As a prophylactic, it is commonly known as isoniazid preventive therapy (IPT) and is taken as a daily tablet for a series of six to 36 months. While data from low-incidence settings suggests that IPT provides long-term protection from TB [9], the same was unclear in high TB and TB-HIV burden settings due to greater TB exposure and risk of reinfection [10].

Changes to Guidelines

To date there is no definitive diagnostic test for latent TB infection; rather its presence is determined on the basis of a positive skin or blood test which demonstrates cell-mediated immunity to *Mycobacterium tuberculosis* antigens. In health systems unconstrained by resources, such tests are normally followed by a chest x-ray to exclude active TB disease, as monotherapy with isoniazid is often insufficient to treat TB disease and increases the risk of TB strain mutation causing drug resistance [17]. Although IPT use has been recommended by the WHO as part of an integrated TB-HIV prevention strategy since 1998 [18], the cumbersome and costly process of ruling out active TB hindered the use of IPT in resource-constrained settings [19,20]. To encourage the use of IPT in this context, the WHO published special guidelines for low-income settings in 2011, replacing the need for chest x-ray with a symptoms-based approach to exclusion, whereby PLWH who did not currently report cough, fever, drenching night sweats, or unexplained weight-loss would be eligible for IPT [21]. Those reporting any of these would be ineligible to receive IPT until resolution of symptoms or diagnosis and treatment of TB [7]. South African researchers were instrumental in the development of these guidelines, and in 2010, South Africa became the first high-burden country to implement a community-wide IPT programme.

Based on the South African and WHO guidelines, at least in theory, all symptom-free PLWH without a high risk of liver toxicity were to be offered IPT at no cost through the public

healthcare system [6,21]. Although a large efficacy study in Southern Africa suggested that only PLWH with a positive tuberculin skin test (TST) would benefit from IPT [22], the updated guidelines indicated that TST – a two-step process requiring a time-sensitive follow-up visit and a skilled reading of the result – was no longer required to initiate patients on IPT where inclusion proved prohibitive to implementation [6,21]. In South Africa, poverty and disparity, health system challenges [23], and a global shortage of TST [24] have precluded the use of TST to target IPT in most public healthcare settings. While some doubt remained amongst health professionals as to its usefulness [25], community-wide six-month (short-course) 'untargeted' IPT was widely implemented across uMgungundlovu District of KZN in 2011. The timing presented me with the opportunity to evaluate the acceptability of isoniazid as a form of TB prevention during its early implementation, while collecting data on the effectiveness of presumptive treatment of latent infection on the basis of symptom-screen alone in a high TB-HIV burden setting.

Tuberculosis Infection versus Disease

About 30% of otherwise healthy people with prolonged and repeated indoor exposure to someone with symptomatic (coughing) TB disease of the lungs will become infected through the inhalation of minute infectious particles called bacilli [26]. Once inhaled, TB bacilli typically enter the bronchial alveoli of the lungs where they enter macrophages and begin to replicate [27,28]. If an adequate immune response is mounted, the bacilli can be contained within macrophages, and latent TB infection – a non-infectious state – is established in the host [27,28]. The first occurrence of infection in a non-sensitised host is known as primary infection, and often occurs in childhood in high-burden settings [29]. The process of infection usually occurs over two to four weeks [27]. Of those infected, over half will remain latently infected over their lifetime, and may never know they have been exposed; another 2-23% of those infected will experience reactivation of infection later in life as a result of changes to immune system response [27,28].

If an immune response is insufficient to contain the bacilli upon initial inhalation, a non-infectious bacteremia may result with dissemination of bacilli throughout the body [26]. A second immune response is then mounted by macrophages and T-cells, and for most, the infection is again contained [27]. For those with reduced immune function, containment is

unsuccessful, and primary (or recently-transmitted) progressive TB disease results. About 5% of otherwise healthy people with recent infection will develop primary TB [27]. Factors well known to increase the likelihood of developing TB disease following infection include: diabetes, malnutrition, injection drug use, and cancers of the head and neck [26,28]; however, immune suppression from HIV is the single strongest determinant for developing TB disease [21,30]. Among this sub-group, rapid progression to primary disease is common – at about six times the rate of those without HIV in non-industrialized countries [29], and the annual risk of developing TB disease increases to an average of 7-10% per year [31,32].

Isoniazid to Treat TB Disease

Tuberculosis disease that is not resistant to standard antibiotics (*i.e.* drug-susceptible TB) is treated with a standard four-drug regimen taken for six months. The first two months of treatment are known as the 'intensive phase' in which all four drugs (isoniazid, rifampin, ethambutol, and pyrazinamide) are taken daily. The remaining four months of treatment are known as the 'continuation phase,' at which time isoniazid and rifampin are typically continued daily to ensure the sterilisation of dormant bacteria [33,34]. Individuals who show no evidence of TB bacteria upon smear or culture in the last month of first-line treatment are considered cured [29]. Once cured, it is possible for a person to become re-infected with TB and again progress to disease [35]. It is also possible for TB survivors to relapse to disease due to insufficient sterilisation of dormant bacilli [29]. People treated for TB who have resistance to the two strongest bactericidal drugs in the regimen, isoniazid and rifampin, are considered to have multi-drug resistant (MDR) TB and are placed on a second-line regimen, if available, which at the time of study consisted of a daily dose of seven medications (up to 23 pills) for two years, and a daily injection for the first six months [33]. Side effects to this regimen can include permanent hearing loss, liver failure, and depreciation of sight. In 2016 the WHO recommended a new second-line regimen that included a more recently developed anti-TB medication, eliminating the injectable, reducing toxicity, and halving the time on treatment to one year [34]. Nonetheless, first-line treatment remains the best option for drug-susceptible TB, as it is better tolerated, shorter in duration, less expensive, and more widely available in low-income settings.

Isoniazid to Treat TB Infection

Drugs that sterilise dormant bacilli have also been used to prevent TB among the latently infected. Isoniazid has been the most frequently utilised prophylactic, given on its own or in combination with a rifampin derivative. On its own, isoniazid is generally given as a self-administered daily tablet for six, nine, 12 or 36-months at a standard dose of 300mg or at 5mg/kg (up to 300mg) [18,22,34,36,37]. As per guidelines, IPT in South Africa is commonly given as 300mg per day, regardless of weight [6]. IPT has been shown to reduce the risk of developing active TB disease by 81% and reduce TB-related mortality by over 70% when at least 80% of a six-month regimen is completed [38]. The first recorded use of IPT was among children in North America in the 1950s, although its utilisation was reduced in the early 1970s due to a decrease in global TB and a growing concern for hepatotoxic responses, including death, particularly amongst those over 35 years of age [38]. With the resurgence of TB accompanying the HIV pandemic, IPT has been reconsidered, and its use is routine in many industrialized countries amongst the latently infected who show evidence of recent transmission or are at a high risk of reactivation. Resultant protection from TB disease in these low-incidence countries has been estimated at 19 years [38].

The Growing Impetus for IPT

Performance

The WHO guidelines for IPT use in low-resource settings were based on early studies in both low and high-burden settings [34]. More recently, two systematic reviews have been completed on the use of IPT amongst PLWH. The first, by Briggs *et al.*, looked at all comparative studies where IPT was given for six months or longer to PLWH in low or middle-income countries [39]. They found good evidence to support an initial benefit of IPT, although duration of effect and benefits of prolonged therapy varied by population, and little data was available on people who were also on ART [39]. Additionally, the authors reported more evidence supporting the benefit of TST-targeted compared to untargeted IPT, reiterating the WHO guideline that TST should guide testing where possible, but should not hinder the use of IPT as long as active TB symptoms are absent [39]. A second systematic review by Ayele *et al.* looked at the efficacy of IPT among PLWH in randomised controlled trials in two low and eight

high-burden settings [40]. The authors reported a pooled relative risk (RR) of 0.48 (95% CI=0.29 to 0.82) among PLWH with a positive TST and RR = 0.79 (95% CI=0.58 to 1.08) among PLWH with a negative TST compared to placebo or no intervention, both indicating a protective effect against TB [40]. In both reviews, there was little evidence to support an impact on mortality, although authors of both reviews suggested that included studies may not have considered large enough datasets or had patients followed for long enough to adequately evaluate differences in mortality [39,40]. Ayele *et al.* concluded that IPT use among PLWH with a positive TST appears to be a strong indicator for the potential benefit of IPT in both high and low-burden TB settings, but cautioned that given heterogeneity between studies, further research is needed to explore whether IPT is beneficial in all populations [40].

TB elimination targets

Scaling up TB preventive therapy is thought to be an integral stratagem for TB elimination in an effort to reduce transmission and decrease incidence [41]. In the wake of the Millennium Development Goals which set global targets until 2015 [42], the United Nations (UN) and WHO have developed targets to all but eliminate TB [43,44]. Under goal three of the 17 new Sustainable Development Goals, the UN endeavours to eliminate TB by 2030 [43]. The WHO's End TB Strategy sets five-year global targets to ultimately reduce TB incidence by 90%, TB deaths by 95%, and the number of TB-affected families facing catastrophic costs due to TB by 100% by 2035 [44]. The first of the WHO's three-pillar strategy identifies the need for an expansion of preventive therapy for PLWH and refers to the management of latent TB infection among people with a high risk of developing active TB as an "essential component of TB elimination" [44]. The Stop TB Partnership has developed the Global Plan to End TB as the implementation plan to achieve UN and WHO targets for the first five years (2016-2020), introducing the 90-90-90 targets: reach 90% of all people who need TB treatment, including 90% of people in key populations, and achieve at least 90% treatment success [41]. In addition to appropriate treatment of TB disease, the first target aims to place 90% of all PLWH and people who have been in close contact with individuals with TB disease on preventive therapy [41]. Since 2011, six-month IPT is the only preventive regimen with existing global guidelines for use in low-resource settings [21], and is therefore the focus of my study.

Factors Complicating the Use of IPT in South Africa

HIV

Treatment of TB disease appears to be equally effective amongst PLWH compared to people without HIV, although TB mortality in this population is higher due to faster progression of disease and delayed diagnosis as a result of abnormal presentations [30]. Unlike many other HIV co-infections, latent TB infection is known to progress to disease even while the immune system is reasonably intact [27,30]. Following successful treatment of TB disease, the risk of reinfection is much higher amongst PLWH than people without HIV in endemic regions [45]. One study found TB disease with a different strain to be 18.7 times higher amongst miners with HIV compared to miners without HIV [46]. Presentation of TB at lower CD4 cell counts (<250 μm/L) is also an issue [47], especially due to its abnormal presentation, often lacking the classic symptomology such as persistent cough [28], and its confusion with a number of other pulmonary syndromes that occur commonly at lower immune function, such as *Pneumoscystis pneumonia*, cryptoccocus, and Kaposi's sarcoma [48]. More extensive forms of TB outside the pulmonary system are also common amongst PLWH, and pulmonary disease is less likely to be detected with use of sputum smear microscopy [45]. At lower immunity, about 10% of HIV-related active TB cases display normal chest x-rays, further complicating diagnosis [28,48].

As immune function decreases, so too does reliability of TST. At severe levels of immune suppression, PLWH with TB infection or disease may fail to mount an adequate cell-mediated immune response to mycobacterial antigens. In a person with HIV and a relatively high immune function (≥250 μm/L), a non-reactive TST would more than likely indicate a lack of infection [48]. In a person with a CD4 count <250 μm/L, a negative TST does not exclude infection or active TB disease, although recent evidence suggests that TST may be less useful for targeting IPT amongst those already on ART due to rebounding immune function [49,50].

Drug resistance

Given the complications of diagnosing TB amongst the immune-compromised, the use of isoniazid as both prevention and treatment can potentially lead to drug resistance. This can occur through multiple mechanisms. Firstly, using monotherapy for treating infection without definitively ruling out TB disease can result in acquired isoniazid drug resistance. Despite

recently published data suggesting that isoniazid resistance has not risen in KZN since community-wide IPT implementation [51], the biological actions of IPT in anergic immune-compromised adults are still unclear [49]. For some it may mean unnecessary treatment, while for others it may sterilise recently or distantly acquired latent TB infection. Of key concern is the potential for inadequate and inappropriate treatment of preclinical or undiagnosed TB [49], which may go undetected for years.

Isoniazid-resistant TB can also be transmitted from person to person. Review of 2014 data from uMgungundlovu's MDR-TB hospital identified 60% of cases as new MDR-TB cases with no evidence of previous treatment, suggesting the majority of cases resulted from direct transmission of a drug-resistant strain [52]. IPT resistance has been proven to occur mainly due to mutations in the *katG* gene or the *inhA* regulatory region [53,54]. While *inhA* mutations result in low-level isoniazid resistant strains that can successfully be treated in diseased patients using high-dose isoniazid (1000-1500mg per day in adults), *katG* mutations result in high-level isoniazid resistance, which is unlikely to be overcome [55]. Recent research in KZN reported that 83% of MDR and extremely drug-resistant (XDR) TB isolates in the province have the *inhA* mutation, among which, 30% also have the *katG* mutation [56]. Presently, the role of IPT in preventing TB disease among those infected with mutated strains is unclear.

Drug resistance due to selected pressure is also a possibility. If IPT confers at least some protection against activation of isoniazid-susceptible TB strains – and potentially *inhA*-mutant strains – there is risk of indirect selection for highly-resistant mutant strains at the population-level (57). To date there is insufficient evidence to support a conclusion on the long-term implications of drug resistance with untargeted community-wide IPT use [58]. Given the limited resources in this setting, routine drug-susceptibility testing among IPT users and the follow-up of people who do not return for monthly IPT collection is not standard care.

Operational limitations

In addition to disease-related challenges, IPT was also introduced within a resource-constrained health system. Decentralisation of HIV and TB care from district hospitals in urban settings to community health centres and primary care clinics occurred after Aaron Moetsoaledi took over the health portfolio for South Africa in 2009 [23,59]. This shift resulted in a much-needed growth in infrastructure and required additional training and staffing to provide these

services [23,60]. While the process of decentralised care improved physical access for millions of rural KZN residents [23,61-63], the process was not without problems. Primary care clinics were predominantly staffed with low-level nurses and lay health workers without the mentorship of more experienced staff to assist at times of uncertainty [48,60]. Barriers to health provision included low staff morale [63] and a high rate of burn out [48]. Operational barriers to IPT initiation also included health workers who did not discuss the regimen with eligible patients due to their own concerns about patient pill burden and the fear of inducing drug resistance [25].

Biomedical vs cultural models of health

Explanatory models of health and wellness can also affect a person's acceptance of and willingness to complete chemotherapeutics. The biomedical model is a framework on which most Western healthcare services are predicated. As its name implies, this explanatory model focuses on the biological aspects of disease and factors associated with identifying and eliminating the biological pathogen from the human body, such as diagnostic tests, drug regimens, and health indicators like morbidity, mortality, and cure rates [64]. As Ortblad and colleagues pointed out, this model also emphasises service delivery and supply chains related to testing and treatment in favour of social approaches that consider patient demands and the broader social context in which TB programmes are implemented [64]. The formal health system in South Africa is based on the biomedical model, despite the cultural heterogeneity of the population. Many of the healthcare workers that service rural and peri-urban clinics in KZN were raised within African explanatory models, and at times feel in conflict with their biomedical training (personal communication with Tsholofelo Mhlaba, MBChB/PhD candidate, UKZN July 13, 2017; unreferenced). African explanatory models of health often focus on choices that support functioning social relationships in favour of the risk-based approach characterised in the biomedical model, where self-preservation is considered the rational determinant to healthcare decision making [65,66].

A vast literature exists examining acceptability of IPT from a biomedical perspective, the majority of which concentrates on issues of adherence or compliance. In a sense, looking at adherence or compliance already presumes that taking IPT is the desired end, despite the existing complexities. Some researchers betrayed their bias toward its use in the way they chose to report findings on acceptability. For example, two studies reported 'perceived' barriers (in quotations)

to IPT adherence [25,67], implying that the experience reported by participants was invalid or incorrect. One reported 'perceived' side effects, noting that the side effects may have had an alternate cause [67]. The other, which looked at barriers to the prescribing of IPT amongst physicians, reported that physicians who less often prescribed IPT thought that treatment of active symptoms was a safer option. Researchers in both studies concluded that if the study population were better informed, IPT would be better accepted. What these research teams missed in their analyses is that the study of acceptability seeks to learn about why an intervention did not work for participants rather than why the participants did not work for the intervention.

These conclusions lack the depth of some others which included the investigation of barriers to IPT outside of participants' locus of control. Two South African studies reported system-oriented challenges, which included sporadic isoniazid stock outs through IPT collection at peripheral pharmacies [68], poor communication with healthcare workers, and system inefficiencies [69]. Poverty-related factors were also reported in a number of studies. These included the financial burden of food to accompany the regimen [70], travel to the clinic [70,71], and lost wages [69, 70,72]. In one Tanzanian study, 58% of patients who discontinued IPT reported that stigma was the primary factor contributing to this decision [70]. Perhaps related to stigma, two other studies reported "denial of HIV status" [67] or "belief that HIV is incurable" as primary factors given for discontinuation [71]. Among those reporting factors that contributed to IPT acceptability, categories primarily pertained to belief in the biomedical model. These included: acceptance of HIV status [67], viewing IPT as similar to ART [70], belief in IPT safety [69], good relationships with healthcare workers [67,69,70], "knowledge" [69,70], trust in the health system [70], and desire for health preservation [69]. Two of these studies listed social factors contributing to IPT adherence: concern about kids or family members [67] and social support from the community [69]. While these studies often considered patient's perspectives, their conclusions are still entrenched in the biomedical model which presupposes that eliminating latent bacteria through the use of consistent chemoprophylaxis is always the best course of action.

Conversely, research on locally-based explanatory models of health considers a variety of healing systems and paths to wellness as well as the intersection of differing explanatory models [73]. For example, in a study of traditional health practitioners and their patients in KZN and Gauteng provinces, Pascoe *et al.* described that while participants acknowledged risk-based

factors and biological modes of transmission, HIV and other sexually transmitted infections were explained as "pollution" or "dirt in the blood" that arose when ancestral practices were not respected [74]. Modern ethnographies seek to go beyond classification of disease aetiologies, but also explain how people working within cultural explanatory models experience and engage with illness [75]. Despite a number of studies published on IPT adherence in the past decade, few have described the experience through the lens of the participants' explanatory models and none have considered how knowledge about cultural explanatory models related to TB infection and disease can inform healthcare policies and practices to more appropriately address preventive efforts in the South African context.

Gender distinctions

Healthcare experiences and cultural expectations also differ substantially between genders in KZN, which may affect beliefs and decision making around IPT. For example, women from traditional rural backgrounds are typically revered for their docility and ability to care for the family [76,77], while men are thought to embody warrior-like qualities like strength and prowess [78]. Leclerc-Madlala described conflicts between modern and traditional gender expectations for women and girls in peri-urban environments of KZN in response to the AIDS epidemic [75]. In particular, she described the resurgence of the virginity-testing ceremony, a somewhat dated traditional practice, as a method to protect young women from "[actively] pursuing their sexual interests in a manner traditionally associated with men" [75]. The conflict between what is often dubbed "modern" and "traditional" may more appropriately be described as Western/liberal/individualist versus African/collective ideals, in order to underscore the dynamic nature of both cultures, which intersect with one another more frequently in urban settings.

The conflict that women confront between African and Western ideologies is illustrated through contrasting views of leadership in research from KZN. Denis noted from his research with HIV support groups in Pietermaritzburg that women often assumed leadership roles in this domain [78]. He suggested that women's increased assertiveness in matters of gender relations demonstrated in part by their willingness to openly discuss their HIV status had contributed to a decline in overall HIV stigma in recent years [78]. In contrast, Magwaza described the internal conflict for women belonging to the Shembe faith in Inanda, a township of Durban [79]. Shembe

is an African Indigenous religion that brings together the tradition of ancestor worship with elements of Christianity. Religion and healing are closely aligned in African Indigenous churches, as leaders often play a role in healing practices. Magwaza described the patriarchal organisation of the church, which excluded women from leadership positons [79]. Through interview excerpts with women who were lifelong members of the Shembe faith, Magwaza illustrated that even among women who felt that females were unfairly sidelined by the church, modesty and obedience to men were described as a personal and active choice demonstrating commitment to Zulu culture and the Shembe teachings [79]. Gender and cultural identities thus become an important part of understanding how healthcare decisions are made.

Historical and political context

Permeating all aspects of IPT implementation is historical mistrust and exclusion. In 2000, six years after the first democratically elected government in South Africa, patent laws held by big pharma prevented access to ART [80,81] at a time when AIDS was rapidly reducing the average life expectancy of Africans in the country [82]. During the same period, Thabo Mbeki, the South African president at the time, publicly questioned the relationship between HIV and acquired immunodeficiency syndrome (AIDS) [83]. While the Western world was shocked by what appeared from the outside as ignorance of the science, South Africans were only emerging from decades of Apartheid legislation. In addition to policies which fostered racial segregation and forbid miscegenation, the National Party encouraged immigration and fertility among white minorities while hampering rates of fertility among Africans during Apartheid in an effort to retain political domination [84]. As South Africans entered a new post-colonial era, suddenly the world's attention turned to a virus which one could neither feel nor see, and the best methods of protection were to abstain from sex or routinely use condoms – the similarity to population control methods suggested under Apartheid were likely not missed.

A decade later, a similar discourse emerged around TB preventive therapy. What had heretofore been described as a symptomatic disease that was diagnosed when already likely to be infectious via sputum smear microscopy was now repackaged and discussed as a two-staged disease that was relatively simple to treat with a six-month course of IPT, based solely on an absence of symptoms. The idea of taking a pill for a pre-clinical condition for which it is difficult to test brought to mind the debate around so-called 'AIDS denialism.' I wondered if the

transition from treating TB disease to treating TB infection may meet with similar confusion or scepticism.

When I introduced the purposes of my study at the initial stages of enquiry, community stakeholders commonly responded: "prevention is better than cure." It was an interesting choice of words which mimicked a popular radio advertisement at the time. Although I had been unclear about which disease the audience of the advertisement was being asked to prevent and by what means, perhaps the message was clearer to community members. Yet I suspected that the common response might be better explained as what Chavez *et al.* referred to as a "public transcript," *i.e.* a socially desirable response to a given circumstance [85]. Another example of a public transcript might be a client responding that he regularly flosses when asked by his dentist, despite less habitual practices. What I wanted to understand with regard to IPT implementation was what Chavez and colleagues referred to as "hidden transcripts": what did people think, say, and do when health professionals or non-governmental organisation (NGO) workers were not prompting [85]. By characterising hidden transcripts, I aimed to go further than simply reporting the effectiveness of IPT, but to help policymakers, programme implementers, and clinicians understand the complexities of the introduction of IPT in this place and time.

Manuscript Details

My doctoral research is essentially a story told in three parts. The first manuscript, entitled, "When prevention is dangerous: Perceptions of isoniazid preventive therapy in KwaZulu-Natal, South Africa," introduces the reader to the context of IPT implementation in Zulu communities of uMgungundlovu District. This piece familiarises the reader with some of the local explanatory models of TB infection and disease and examines problematic perceptions in relation to TB preventive therapy among people who were offered IPT and in the community at large. Through this ethnographic exploration, I also describe cultural practices that seemingly conflict with notions of chemoprophylaxis to identify potential challenges to IPT implementation that could undermine effectiveness.

In this first manuscript, I contributed to research concept and design, conducted field work, collected and analysed data, and drafted the article; MM contributed to research concept and design, provided supervisory support, contributed to acquisition, analysis, and interpretation of data, and critically reviewed the article; SN contributed to research concept and design, data

collection, analysis, and validation; SS contributed to validation of data, provided clinical perspectives in the South African context, and critically reviewed the article; DF contributed to research concept and design, provided supervisory support, contributed to data acquisition, provided clinical perspectives, and critically reviewed the article; RS contributed to research concept and design, provided supervisory support, and critically reviewed the article; TW provided supervisory support and critically reviewed the article.

Manuscript two is entitled, "The effectiveness of untargeted six-month isoniazid preventive therapy to reduce tuberculosis incidence among people living with HIV with and without antiretroviral therapy in KwaZulu-Natal, South Africa." In this paper, I evaluate whether or not IPT works under everyday programme conditions in a complex setting, and to what degree the simultaneous scale up of ART may mask or bolster potential effects. This retrospective cohort study focussed upon those who could regularly access monthly IPT refills, comparing the proportion of TB disease that developed over two years among people who completed IPT to those for whom no evidence of IPT consumption was recorded. I present this comparison in order to test Churchyard and Corbett's theory that studies of effectiveness would show stronger preventive effects of IPT compared to efficacy studies, as the latter are ethically required to treat participants in control groups with care in excess of resource-constrained community programmes in low-income settings [49].

For this manuscript, I contributed to research concept and design, collected and entered data from paper IPT registers at catchment-area clinics, extracted TB outcome and ART data from electronic health records accessed with permission from the KZN Department of Health and uMgungundlovu Health District, cleaned and analysed data, and drafted the article; DF contributed to research concept and design, provided supervisory support, provided clinical perspectives, and critically reviewed the article; RS contributed to research concept and design, provided supervisory support, and critically reviewed the article; MM provided supervisory support and critically reviewed the article; TW provided supervisory support, provided guidance on data analysis, and critically reviewed the article.

Finally, in manuscript three, entitled, "The role of agency in the implementation of Isoniazid Preventive Therapy (IPT): Lessons from *oMakoti* in uMgungundlovu District, South Africa," I explore some of the incongruities between cultural and biomedical expectations among women in rural uMgungundlovu. Women were both more likely to attend clinic and to accept

IPT compared to men, and yet a look into their stories suggests that accepting IPT may not always indicate confidence in the regimen. In this final paper, I consider theories that may assist healthcare workers to engage Zulu women to better determine if IPT initiation is right for them at a given time.

For the third manuscript, I contributed to research concept and design, conducted field work, collected and analysed data, and drafted the article; MM contributed to research concept and design, provided supervisory support, contributed to acquisition, analysis, and interpretation of data, and critically reviewed the article; SN contributed to research concept and design, provided insight into community protocols, facilitated group interviews and provided interpretation for individual interviews, and assisted with validation of findings; TM reviewed the manuscript for the orthographic accuracy of isiZulu words, provided clinical perspectives in the South African context, and critically reviewed the article; DF contributed to research concept and design, provided supervisory support, contributed to data acquisition, provided clinical perspectives, and critically reviewed the article; RS contributed to research concept and design, provided supervisory support, and critically reviewed the article; TW provided supervisory support and critically reviewed the article.

In the following chapter I describe the mixed methods with which I approached the enquiry as well as the key role of community members whose leadership and guidance enabled me to gain insight into the lived experience of people in this setting. Following the manuscripts (Chapters three to five), I consider the interpretation of the findings collectively, highlight ways in which research is helping to reduce the complexities of TB infection and disease, and describe how commitment to knowledge exchange can help further TB elimination efforts.

References

1. Menzies D, Doherty TM. Diagnosis of latent tuberculosis infection. In Raviglione, editor. Reichman & Hershfield's Tuberculosis: A Comprehensive, International Approach. 3rd ed. Geneva: WHO; 2006.

2. World Health Organisation. Tuberculosis Fact Sheet (2017). Available from http://www.afro.who.int/health-topics/tuberculosis-tb. [Accessed 08th Dec 2017].

3. UNAIDS. South Africa HIV and AIDS Estimates (2015). Available from http://www.unaids.org/en/regionscountries/countries/southafrica. [Accessed 11th Sep 2017].

4. World Health Organisation. Global tuberculosis report 2016. Geneva: The Organisation; 2016.

5. World Health Organisation. WHO three I's Meeting: intensified case finding, isoniazid preventive therapy and TB infection control for people living with HIV. Geneva: The Organisation; 2008.

6. South Africa Department of Health. Guidelines for tuberculosis preventive therapy among HIV infected individuals in South Africa, 2010.

7. uMgungundlovu District Health Office. District Health Plan 2015/16. KwaZulu-Natal Department of Health: 2015. Available at: http://www.kznhealth.gov.za/Strategic/DHP/2015-16/Umgungundlovu.pdf [Accessed on 13 Sep 17].

8. Statistics South Africa. Statistics by place (Census 2011 data). Available at: http://www.statssa.gov.za/?page_id=964 [Accessed 13 Sep 2017].

9. Ngozo J. Overview of the Department of Health Tuberculosis Control Programme in KwaZulu-Natal. [Presentation] Faith Leaders Symposium. 18 July 2016.

10. Municipalities of South Africa. uMgungundlovu District Municipality: Demographic information. Available at: https://municipalities.co.za/demographic/120/umgungundlovu-district-municipality. [Accessed on 08th Dec 17].

11. International Union Against Tuberculosis Committee on Prophylaxis. Efficacy of various durations of isoniazid preventive therapy for tuberculosis: five years of follow-up in the IUAT trial. Bull World Health Organ. 1982; 60(4): 555–564.

12. Bell JC, Rose DN, Sacks HS. Tuberculosis preventive therapy for HIV- infected people in sub-Saharan Africa is cost-effective. AIDS. 1999;13: 1549–1556.

13. Sterling T. New approaches to the treatment of latent tuberculosis. Semin Respir Crit Care Med 2008; 29(5): 532-541.

14. Akolo C, Adetifa I, Shepperd S, Volmink J: Treatment of latent tuberculosis infection in HIV infected persons. Cochrane Database Syst Rev. 2010; (1): CD000171.

15. Golub JE, Paul P, Mohapi L, Thsabangu N, Moshabela M, Struthers H, et al: Isoniazid preventive therapy, HAART and tuberculosis risk in HIV-infected adults in South Africa: a prospective cohort. AIDS. 2009; 23(5): 631-636.

16. Yamori S, Ichiyama S, Shimokata K, Tsukamura M. Bacteriostatic and bactericidal activity of antituberculosis drugs against Mycobacterium tuberculosis, Mycobacterium avium-Mycobacterium intracellulare complex and Mycobacterium kansasii in different growth phases. Microbiol Immunol. 1992;36(4):361-8.

17. Gillespie SH. Evolution of drug resistance in Mycobacterium tuberculosis: clinical and molecular perspective. Antimicrobial agents and chemotherapy. 2002; 46(2):267-74.

18. World Health Organisation and UNAIDS. Policy statement on preventive therapy against tuberculosis in people living with HIV. Geneva: The Organisation; 1998 [cited 2018 April 25]. Available from: http://apps.who.int/iris/bitstream/handle/10665/64509/WHO_TB_98.255.pdf?sequence=1.

19. Samandari T, Bishai D, Luteijn M, Mosimaneotsile B, Motsamai O, Postma M, et al. Costs and consequences of additional chest x-ray in a tuberculosis prevention program in Botswana. Am J Respir Crit Care Med. 2011;183(8):1103-11.

20. Nardell E, Churchyard G. What is thwarting tuberculosis prevention in high-burden settings? N Engl J Med 2011;365(1):79-81.

21. World Health Organisation. Guidelines for intensified tuberculosis case-finding and isoniazid preventive therapy for people living with HIV in resource-constrained settings. Geneva: The Organisation; 2011.

22. Samandari T, Agizew TB, Nyirenda S, Tedla Z, Sibanda T, Shang N, et al. 6-month versus 36-month isoniazid preventive treatment for tuberculosis in adults with HIV infection in Botswana: a randomised, double-blind, placebo-controlled trial. Lancet. 2011; 377(9777):1588-98.

23. Coovadia H Jewkes R, Barron P, Sanders D, McIntyre D. The health and health system of South Africa: historical roots of current public health challenges. Lancet 2009; 374: 817–34.

24. Tebruegge M, Bohyi M, Soriano-Arandes A, Kampmann B. Shortage of purified protein derivative for tuberculosis testing. Lancet 2014; 384(9959): 2026.

25. Lester R, Hamilton R, Charalambous S, Dwadwa T, Chandler C, Churchyard GJ, Grant AD. Barriers to implementation of Isoniazid preventive therapy in HIV clinics: a qualitative study. AIDS. 2010;24(Suppl 5):S45-S48.

26. Long R, Schwartzmann K. Transmission and pathogenesis of tuberculosis. In: Long R, Ellis E, editors. Canadian Tuberculosis Standards. 6th ed. Ottawa: Minster of Health; 2007. pp.37-52.

27. Parish NM, Dick JD, Bishai WR. Mechanisms of latency in *Mycobacterium tuberculosis*. Trends Microbiol. 1998 ;6(3):107-12.

28. Page KR, Godfrey-Faussett P, Chaisson RE. Tuberculosis-HIV co-infection: Epidemiology, clinical aspects, and interventions. In Raviglione, editor. Reichman & Hershfield's Tuberculosis: A Comprehensive, International Approach. 3rd ed. Geneva: WHO; 2006.

29. South Africa Department of Health. National Tuberculosis Programme Guidelines. Pretoria: The Department; 2014.

30. Lawn SD, Bekker SG. Co-pathogenesis of tuberculosis and HIV. In Schaaf HS, Zumla AI, editors. Tuberculosis: A Comprehensive Clinical Reference. London: Elsevier;2009. p. 96-106.

31. Guelar A, Gatell JM, Verdejo J, et al. A prospective study of the risk of tuberculosis among HIV-infected patients. AIDS. 1993;7(10):1345–9.

32. Selwyn PA, Hartel D, Lewis VA, et al. A prospective study of the risk of tuberculosis among intravenous drug users with human immunodeficiency virus infection. N Engl J Med. 1989; 320(9): 545–50.

33. World Health Organisation. Stop TB Initiative. Treatment of tuberculosis: Guidelines. Geneva: The Organisation; 2010.

34. World Health Organisation. WHO treatment guidelines for drug-resistant tuberculosis. 2016 update. WHO/HTM/TB/2016.04. 2016. Available at: http://www.who.int/tb/MDRTBguidelines2016.pdf. Accessed 10 June 2016.

35. van Rie A, Warren R, Richardson M, Victor TC, Gie RP, Enarson DA, et al. Exogenous reinfection as a cause of recurrent tuberculosis after curative treatment. N Engl J Med. 1999; 341(16): 1174-9.

36. Date AA, Vitoria M, Granich R, Banda M, Youssef M, Gilks C. Implementation of co-trimoxazole prophylaxis and isoniazid preventive therapy for people living with HIV. Bull World Health Organ. 2010; 88: 253-259.

37. Comstock G. How much isoniazid is needed for prevention of tuberculosis among immunocompetent adults? Int J Tuberc Lung Dis. 1999; 3(10): 847-850.

38. Apers L, Robert C, Nachega JB. Prophylaxis with antituberculosis drugs in special situations. In Schaaf HS, Zumla AI, editors. Tuberculosis: A Comprehensive Clinical Reference. London: Elsevier; 2009. p. 780-85.

39. Briggs MA, Emerson C, Modi S, Taylor NK, Date A. Use of isoniazid preventive therapy for tuberculosis prophylaxis among people living with HIV/AIDS: a review of the literature. JAIDS. 2015; 68: S297-305.

40. Ayele HT, van Mourik MS, Debray TP, Bonten MJ. Isoniazid prophylactic therapy for the prevention of tuberculosis in HIV infected adults: a systematic review and meta-analysis of randomized trials. PLOS One. 2015; 10(11): e0142290.

41. Stop TB Partnership. The Paradigm Shift: Global Plan to End TB 2016-2020. Geneva: UNOFP; 2015.

42. World Health Organisation. Health and the Millennium Development Goals. Geneva: The Organisation; 2014.

43. United Nations. Resolution adopted by the General Assembly on 25 September 2015. Available at: http://www.un.org/ga/search/view_doc.asp?symbol=A/RES/70/1&Lang=E. Accessed on 19 Dec 2017.

44. World Health Organisation. The End TB Strategy: Global strategy and targets for tuberculosis prevention, care and control after 2015. Geneva: The Organisation; 2014.

45. Churchyard G, Corbett E. Tuberculosis and HIV. In Abdool Karim SS, Abdool Karim Q, editors. HIV/AIDS in South Africa. 2nd ed. Cambridge: Cambridge; 2010. p. 457-78.

46. Sonnenburg P, Murray J, Glynn JR, Shearer S, Kambashi B, Godfrey-Faussett P. HIV-1 and reoccurrence, relapse, and reinfection of tuberculosis after cure: A cohort study in South African mineworkers. Lancet 2001; 358: 1687-93.

47. Cohen MS, Chen YQ, McCauley M, Gamble T, Hosseinpour MC, et al. Prevention of HIV-1 with early anti-retroviral therapy. N Engl J Med. 2011; 365(6):493-505.

48. Wilson D, Fairall L. Challenges in managing AIDS in South Africa. In Abdool Karim SS, Abdool Karim Q, editors. HIV/AIDS in South Africa. 2nd ed. Cambridge: Cambridge; 2010. p. 503-28.

49. Wood R, Bekker, LG. Isoniazid preventive therapy for tuberculosis in South Africa: An assessment of the local evidence base. South African Med J 2014; 104(3): 174-177.

50. Rangaka MX, Wilkinson RJ, Boulle A, Glynn JR, Fielding K, van Cutsem G, et al. Isoniazid plus antiretroviral therapy to prevent tuberculosis: A randomised double-blind placebo-controlled trial. The Lancet 2014; 384(9944): 682 – 690.

51. National Institute for Communicable Diseases. South African Tuberculosis Drug Resistance Survey 2012–14. Johannesburg: The Institute; 2016.

52. District Health Information System. Doris Goodwin MDR-TB Hospital [dataset]; Pietermaritzburg: uMgungundlovu District of Health; 2014.

53. T Zhang Y, Yew WW. Mechanisms of drug resistance in *Mycobacterium tuberculosis*. Int J Tuberc Lung Dis. 2009;13: 1320–1330.

54. Müller B, Streicher EM, Hoek KG, et al. *inh*A promoter mutations: a gateway to extensively drug-resistant tuberculosis in South Africa? Int J Tuberc Lung Dis. 2011; 15: 344–351.

55. Bollela VR, Namburete EI, Feliciano CS, Macheque D, Harrison LH, Caminero JA. Detection of *kat*G and *inh*A mutations to guide isoniazid and ethionamide use for drug-resistant tuberculosis. Int J Tuberc Lung Dis. 2016; 20(8): 1099-1104.

56. Niehaus AJ, Mlisana K, Gandhi NR, Mathema B, Brust JCM (2015) High Prevalence of *inh*A Promoter Mutations among Patients with Drug-Resistant Tuberculosis in KwaZulu-Natal, South Africa. PLOS ONE 10(9): e0135003.

57. Wilson D, Fisher D, Geffen N, Cohen T. Implementing Isoniazid Prophylactic Therapy in High HIV-Prevalence Settings: Need for Nuance. [unpublished draft]

58. Balcells ME, Thomas SL, Godfrey-Faussett P, Grant AD. Isoniazid Preventive Therapy and Risk for Resistant Tuberculosis. Emerging Infect Dis. 2006; 12(5): 744-751.

59. Bateman C. Evidence of doctors' health minister at last. S Afr Med J 2010; 100:76–9.

60. Wilson D, Howell V, Toppozini C, Dong K, Clark M, Hurtado R. Against all odds: diagnosing tuberculosis in South Africa. J Infect Dis. 2011; 204(Suppl 4):S1102-9.

61. Mutevedzi PC, Lessells RJ, Heller T, Bärnighausen T, Cooke GS, Newell ML. Scale-up of a decentralized HIV treatment programme in rural KwaZulu-Natal, South Africa: does rapid expansion affect patient outcomes?. Bulletin of the World Health Organization. 2010 Aug;88(8):593-600.

62. Harris B, Goudge J, Ataguba J, McIntyre D, Nxumalo N, Jikwana S, et al. Inequities in access to health care in South Africa. J Public Health Pol. 2011; 32(Suppl 1): S102.

63. McIntyre D, Klugman B. The human face of decentralisation and integration of health services: experience from South Africa. Reproductive health matters. 2003; 11(21):108-19.

64. Ortblad KF, Salomon JA, Bärnighausen T, Atun R. Stopping tuberculosis: a biosocial model for sustainable development. The Lancet. 2015; 386(10010):2354-62.

65. Beckmann N. Responding to medical crises: AIDS treatment, responsibilisation and the logic of choice. Anthropology & medicine. 2013; 20(2): 160-174.

66. Kielmann K, Cataldo F. Tracking the rise of the "expert patient" in evolving paradigms of HIV care. AIDS Care. 2010; 22(sup1): 21-28.

67. Ngamvithayapong J, Uthaivoravit W, Yanai H, Akarasewi P, Sawanpanyalert P. Adherence to tuberculosis preventive therapy among HIV-infected persons in Chiang Rai, Thailand. AIDS. 1997; 11: 107–112.

68. Szakacs T, Wilson D, Cameron DW, Clark M, Kocheleff P, Muller FJ, et al. Adherence with isoniazid for prevention of tuberculosis among HIV-infected adults in South Africa. BMC Infect Dis. 2006; 6: 97.

69. Jacobson KB, Niccolai L, Mtungwa M, Moll AP, Shenoi SV. "It's about my life": Facilitators of and barriers to isoniazid preventive therapy completion among people living with HIV in rural South Africa. AIDS Care. 2017; 29(7): 936–942.

70. Munseri PJ, Talbot EA, Mtei L, Fordham von Reyn C. Completion of isoniazid preventive therapy among HIV-infected patients in Tanzania. Int J Tuberc Lung Dis. 2008; 12(9): 1037–1041.

71. Rowe KA, Makhubele B, Hargreaves JR, Porter JD, Hausler HP, Pronyk PM. Adherence to TB preventive therapy for HIV-positive patients in rural South Africa: implications for antiretroviral delivery in resource-poor settings? Int J Tuberc Lung Dis. 2005; 9(3): 263–269.

72. Gust DA, Mosimaneotsile B, Mathebula U, Chingapane B, Gaul Z, Pals SL, et al. Risk factors for non-adherence and loss to follow-up in a three-year clinical trial in Botswana. PLOS ONE. 2011; 6(4): e18435.

73. Parle J, Noble M. New Directions and challenges in histories of health, healing and medicine in South Africa. Med Hist. 2014; 68(2): 147-165.

74. Pascoe SJS, Moolla A, Tabane R, Mbele-Khama S, Dlamini N, Darkoh E. Traditional explanatory models of disease and messaging around HIV and STI risk and prevention: Findings from an exploratory study with traditional health practitioners in South Africa [abstract]. BMJ. 2013; 89(Supp1): O12.5.

75. Leclerc-Madlala S. AIDS in Zulu Idiom: Etiological configurations of women, pollution and modernity. In: Zulu Identities: Being Zulu Past and Present. Carton B, Laband J, Sithole J, editors. Durban: University of Natal, 2009; pp 554-565.

76. Rudwick S, Shange M. Hlonipha and the rural Zulu woman. Agenda. 2009; 23(82): 66-75.

77. Bhana D. Masculinities, Femininities and the Burden of Culture Among Rural South African Teenagers in the Context of HIV. In P Liamputtong, editor. Children and young people living with HIV/AIDS. Basel: Springer; 2016. p. 127-145.

78. Denis P. New patterns of disclosure: How HIV-positive support group members from KwaZulu-Natal speak of their status in oral narratives. Med Hist. 2014; 58(2): 278–297.

79. Magwaza T. Conversations with women from the Shembe church. Agenda. 2004; 60: 137-144.

80. Mbali M. The Treatment Action Campaign and the history of rights-based, patient-driven HIV/AIDS activism in South Africa. In Jones P, and Stokke K, eds. Democratising Development: The Politics of Socio-economic Rights in South Africa. Martinus Nijhoff, 2005: 213-244.

81. 't Hoen EFM. TRIPS, pharmaceutical patents and access to essential medicines: Seattle, Doha and beyond. Chic J Int Law. 2002; 3(1): 27-46.

82. Bor J, Herbst AJ, Newell M-L, and Bärnighausen T. Increases in adult life expectancy in rural South Africa: Valuing the scale-up of HIV treatment. Science, 339. 2013; 961-965.

83. Fassin, D. & Schneider, H. The politics of AIDS in South Africa: Beyond the controversies. BMJ. 2003; 326(7387): 495.

84. Chimere-Dan O. Population policy in South Africa. Studies in Family Planning. 1993; 1:31-39.

85. Chavez V, Duran B, Baker QE, Avila MM, Wallerstein N. The dance of race and privilege in CBPR. In Minkler E, Wallerstein N, editors. Community-Based Participatory Research for Health: From Process to Outcomes (2nd ed). San Francisco: Jossey-Bass; 2008: 91-106.

CHAPTER 2

Methods

Wisdom… is the comprehension of context.

Thomas H Cook
Sandrine's Case

Research Questions and Objectives

Question 1

What is the acceptability of presumptive treatment for latent TB infection among people living with HIV (PLWH) in Zulu communities of uMgungundlovu District?

1. Objectives:
1.1 To describe the lived experiences of members of three Zulu communities in uMgungundlovu District relevant to isoniazid preventive therapy (IPT)
    1.1.1 to develop Grassroots Research Advisory Teams (GRATs) in each of the three communities, with whom to routinely engage
    1.1.2 to participate in the cultural events and everyday experiences of community members
    1.1.3 to identify community assets and challenges that may influence IPT uptake and completion
1.2 To identify and describe community perceptions regarding TB disease, TB infection, and IPT
    1.2.1 To identify divergent groups within the community by which to divide group interviews
    1.2.2 To undertake group interviews on TB perspectives
1.3 To describe the experiences and decisions of PLWH offered IPT in these communities
    1.3.1 to undertake individual interviews with PLWH declining, discontinuing, or completing IPT

Question 2

Does six-month TST-untargeted IPT effectively reduce the incidence of TB over two years compared to no intervention in a high-burden TB-HIV setting, such as uMgungundlovu District?

2. Objective:
2.1 To determine the effectiveness of six-month TST-untargeted IPT to reduce TB incidence
    2.1.1 to collect individual-level clinic data on patient demographics, IPT uptake and completion, and TB-outcome data from six clinics in uMgungundlovu District
    2.1.2 to compare the difference in two-year TB incidence rates between PLWH who completed IPT versus PLWH who had never used IPT

Figure 1: Overview of data sources

| Research Question | Objective | Data sources by objective |

Legend
____ primary data source
------ secondary data source

- IPT Acceptability
  - Lived Experiences
    - Observation
    - Key informants
    - GRATs
  - Community Perceptions
    - Group Interviews
  - IPT Experiences & Decisions
    - Individual Interviews

Structured Interviews

- IPT Effectiveness
  - TB by IPT & ART status
    - Clinic IPT registers
    - District TB register
    - NGO ART registers

Acronyms: IPT=Isoniazid Preventive Therapy, GRATs=Grassroots Research Advisory Teams, TB=Tuberculosis ART=Antiretroviral Therapy, NGO=Non-Governmental Organisation

Community-Based Participatory Research and Ethnography

This study was informed by both community-based participatory research (CBPR) and ethnography. CBPR is a guided research approach for engaging with communities [1]. In most contexts, this means collaborating with members of marginalised populations who are more likely to recognise and be critical of the ideas that members of the dominant society consider to be 'the norm' [2]. Utilising the CBPR approach prioritises the participation of community stakeholders in the development, collection, interpretation, and dissemination of research, with an emphasis on multi-directional knowledge exchange and actionable outcomes [3-5]. Community stakeholders are defined as people who are directly affected by the phenomena under study and the advocates and activists who represent them [4].

Ethnography is a qualitative methodology rooted in anthropology. Ethnographic practice is characterised by extensive time in the field participating in local activities, acquiring language proficiency, and working with key informants to understand the local context and lived experiences related to a given phenomenon [6,7]. Ethnography is also characterised by "textwork," which involves documentation of cultural immersion and key informant interactions [8] as well as the constant reflection of the ethnographer to consider how their participation and worldview may have shaped or altered the exchange [5]. Following in-depth consideration of these documents, ethnographers then draw upon existing theory in order to translate culture-bound experiences into something more familiar to the intended audience [8]. In healthcare, ethnography is especially well-suited to understanding behaviours related to health and disease, demonstrating for example how cultural beliefs and practices can influence the effectiveness of interventions and how hegemonic assumptions can undermine intervention efforts [7].

Ethics

Community approvals for all aspects of the research were obtained from tribal authorities and ward councils. Institutional approval for patient data was received from the uMgungundlovu District Manager and the Health Research and Knowledge sub-component of the KZN Department of Health. Ethics approval for community engagement and group discussions was received from the University of Alberta's Research Ethics Office, and approval for patient interviews and the collection and analysis of patient data was received from the University of

Calgary's Conjoint Health Research Ethics Board. Additionally, the University of KZN's Biomedical Research Ethics Board granted ethics approval for all components of the study.

Acceptability

Sampling

1. Community Selection

To begin my interaction with communities in the Edendale catchment area, I sought the assistance of a local community member who was both knowledgeable and respected in the community. An early collaborator connected me to the head of a non-governmental organisation (NGO) operating out of Edendale Hospital. The NGO called iTEACH employed a number of community members to assist with community-based projects. After some consideration, the head of iTEACH connected me with Ms Sithembile (Sthe) Ndlovu, an underemployed and well-respected resident of Edendale township who had previously worked with iTEACH to provide TB and HIV counselling to hospital patients. Ms Ndlovu became a dedicated cultural liaison, whose many roles included isiZulu interpreter, cultural advisor, meeting coordinator, group interview facilitator, and a community consultant on IPT and TB treatment. Ms Ndlovu began the community engagement process by accompanying me on visits to selected communities and undertaking a community mapping exercise, described below.

When I had gained a degree of familiarity with Edendale township through Ms Ndlovu's assistance, we then identified six of 18 communities in the Edendale Hospital catchment area in which to begin formal engagement and other qualitative aspects of the project. Based on previous experience in working with indigenous communities on the Canadian prairies, I expected that perceptions and knowledge about TB and IPT may differ depending on the level of isolation of the community. To begin with, communities were divided into peri-urban and rural – called "townships" and "homelands" in the South African context, the former falling under municipal ward guidelines and the latter organised by tribal authority structures at the community level. On the Canadian prairies, it was common for indigenous communities outside of cities to be further stratified as rural and remote, remote indicating a lack of direct road access for at least part of the year [9]. Although "rural" and "remote" communities were not a routine classification in KwaZulu-Natal, access to clinic by clay road was a difficulty identified by key

informants which also limited access to clinics and urban centres. As such, homelands were further divided into those accessible by tar versus clay roads.

Once the distance categories had been defined, I then randomly selected two clinics and their associated communities from each of the three distance categories. Following a research visit from committee members in 2012, I further reduced the selection to one community per distance category to ensure close relationships and feasibility of the project. Grassroots Research Advisory Teams (GRATs) were then struck in these three communities: Caluza (peri-urban), Songonzima (rural), and Embo (remote). Although distinctions from structured interviews (*i.e.*, individual and group interviews) were largely overlapping and thus transcripts analysed collectively, socioeconomic and educational differences were more clearly observed in those with regular access to urban environments. Communities also differed in geography and employment.

Figure 2: Location of study communities

Although interview data were analysed collectively – rather than by distance strata – due to overlapping codes, community dissemination occurred differently between townships, rural, and remote homeland communities. With increasing proximity to cities, advisory team members appeared more confident in terms of research and TB literacy, and were better able to integrate findings into a variety of community-developed and initiated dissemination products.

2. Community Descriptions

Embo is a remote homeland community embedded in the hills of uMbumbulu, surrounded by large, commercially-owned sugar plantations. Residents live on the steep inclines

of hillsides and travel long distances by foot on informal paths and clay roads to reach the nearest services. During the period of study, water services were provided weekly by truck, and many houses were limited to pit latrines for sanitation purposes. Songonzima is a rural homeland community 30 km from the nearest hospital. It is mainly a farming community with some inhabitants owning subsistence plots. Horses are also commonly found on some of the wealthier plots, providing a form of local transport for some residents. Caluza is a peri-urban 'area' or community located within the boundaries of Edendale township. Townships are communities in or near urban centres which house primarily people of African-descent as a result of race-based exclusionist policies from the Apartheid era. Many townships still exist today and present unique assets and challenges resulting from a tight-knit and often economically disadvantaged population. Edendale township is located adjacent to Pietermaritzburg, the provincial capital. With a population of 500 000, Pietermaritzburg is considerably smaller than nearby Durban, with a metropolitan area of nearly four million people. In the Caluza area, socio-economic status is quite varied between inhabitants.

3. Community Mapping

I initiated community mapping exercises, as described by Rifkin and Pridmore, at the beginning of community engagement to learn more about the communities in which Ms Ndlovu and I focused our qualitative enquiry [10]. Community mapping exercises included institutional mapping and guided walkabouts in the greater Edendale area and the three selected communities. Institutional mapping is a practice whereby key informants draw a map of their community, identifying key places, people, and assets that best represent their communities [10]. The maps are then discussed in-depth with the researcher, allowing for informants to reflect on the importance of details they choose to include. Area walkabouts are then led by the same key informants, who walk the researcher through the physical spaces depicted in maps. Guided walkabouts familiarise the researcher to the lay of the land and help to normalise their presence in everyday spaces [10]. Moreover, they are an opportunity to query and clarify the meaning and use of physical spaces, enable interactions with additional stakeholders, and help key informants to appreciate the depth of information required to introduce the lived experiences of community members [10]. For my study, the information gleaned from community mapping exercises helped to identify community assets and challenges, as well as sub-populations to include in

routine community engagement and group interviews (described in participant selection and recruitment below).

4. Justification of Numbers

Sample selection in qualitative research is not predicated on statistical generalisability, but rather theoretical generalisability [11]. Sample numbers are therefore not based on calculations, but rather on the groups to which the researcher aims to generalise and the resources (human, time, and monetary) available for the study [15]. As previously mentioned, I had originally intended to sample from a greater number of communities (six versus three), with the intent to investigate differences related to proximity to the District hospital. As I became familiar with the original six communities selected, it soon became apparent that engaging meaningfully in all six communities within study timelines and budget would be infeasible. Rather, I narrowed the scope and collected fewer interviews. While this limited my ability to consider distance factors between communities, common patterns across the data were apparent. A strong sense of collective cultural and linguistic identity among the Zulu population, who are largely situated in KZN – the home of the Zulu monarchy, likely contributed to the homogeneity between communities [12].

Following the selection of communities, the primary sampling unit of interest was individual participants, although for observation, the sampling units were places and events within the community to which I was invited. In terms of individual participants, sub-populations were identified to include a broad representation in groups as GRAT members or individually as key informants. GRATs were appointed community representatives, as described in CBPR best practices [3-5], who met with Ms Ndlovu and me quarterly to review the research process; whereas key informants, commonly described in ethnography, were trusted and knowledgeable members of the community who were interested and willing to reflect on their own experiences and perspectives of life in the community with a less regimented schedule [5].

I utilised a pro-poor approach [13] when requesting GRAT membership recommendations, with an emphasis on recruiting individuals who were concerned about the health of their community and had diverse community networks, but no formal clinical training or advanced degree. I had a modest budget to offer as a stipend to those participating in meetings, but the positions were introduced as voluntary to attract people who were motivated primarily by the potential benefit to the community. Each GRAT was made up of eight or nine

community members to encourage depth of interaction and active involvement from all participants [14]. There was no *a priori* limit to the number of key informants with whom I engaged during the project, and informants were added throughout the process as new dimensions of community life became apparent [15].

Structured interviews were also sampled at the level of the individual. To strike a balance between depth of enquiry and feasibility in terms of the number of structured interviews I was able to collect and analyse, I aimed to collect three individual and three group interviews in each community according to sub-groups defined below. Group interviews included 4-10 people in line with standard practices [14,16].

Participant selection and recruitment

1. Grassroots Research Advisory Teams

Working within the CBPR framework, I prioritised the creation of GRATs in each community early in the process as a mechanism to routinely engage with community representatives. Ms Ndlovu guided me through local protocols to meet with community leaders and seek advice on GRAT membership. In Caluza and Songonzima, Ms Ndlovu knew of respected members who we initially approached to learn about local customs for negotiating work relationships within the community. In Caluza we were directed to the local ward councillor to introduce the project and discuss recruitment to the GRAT. In Songonzima we were introduced to local *iziNduna* (community liaisons to the traditional leader; plural form) to begin the engagement process. In Embo, a community in which Ms Ndlovu and I had little familiarity, we drove along the main path until we encountered a group of *oGogo* (grandmothers or female elders) in the street who directed us to the local *iNduna* (singular of *iziNduna*). We were then invited to meet with *iNkosi* (the traditional leader; singular) and to present at a meeting of the tribal authority, a member of which helped us to connect to potential representatives.

To recruit members, Ms Ndlovu and I held gatherings or made personal visits to the homes of potential members to discuss the project. Prospective members were then invited to join the team, with responsibilities to include the review and revision of research questions and tools, expertise in cultural competency, and critical consideration of research processes and findings from the perspective of their community networks. At initial GRAT meetings, terms of agreement were developed collaboratively with the community representatives (see example in

Appendix 1). Discussions during these sessions included selection of future members, decision-making processes, recognition of GRAT members, responsibilities in the community, and the consultative process prior to sharing findings to differing audiences. GRAT meetings then occurred at least quarterly in each community between 2013-2016.

2. Key Informants

Selecting key informants was also an intentional process. As Tremblay described, key informants are selectively sampled for their specialised knowledge about particular aspects of culture [17]. GRAT meetings provided an opportunity for regular and coordinated key informant interaction, and some GRAT members also contributed as individual key informants outside of the context of meetings to help provide deeper insight into patterns, contradictions, or theories that resulted from consideration of the data. These interactions occurred during community events, before or after GRAT meetings, during visits to informants' homes, and occasionally over the telephone. Additional key informants were identified iteratively throughout the project, providing a variety of perspectives through formal and informal dialogue, discussions, and meetings. While it is impossible to list all of the community members whose willingness to engage helped inform this work, Appendix 2 describes an assortment of key informants with whom I had many discussions during my research.

3. Group Interview Participants

At the beginning of the project, I suspected that in general, community members with whom we had not regularly interacted may be more inclined to provide "public transcripts" in individual interviews, providing medically acceptable responses rather than reflecting on the unique perspectives and practices in the community [18]. As such, to get at community perspectives, Ms Ndlovu and I facilitated group interviews, which can elicit deeper discussion on a topic specified by the researcher through the dialogue between participants [18]. To promote open discussion, I identified sub-populations from which to sample within communities based upon research objective 2.1, community mapping, and discussions with key informants.

A set of group interviews (one in each community) occurred among PLWH. Given IPT eligibility and a higher risk for developing TB, this was an important sub-population from whom to learn; yet, participants with HIV may have been unwilling to discuss their perspectives among people without HIV, for fear of the stigma that may result from discussion that discloses their HIV status [5]. To contrast the perspectives of PLWH, Ms Ndlovu and I also recruited groups of

people who identified as HIV negative or who were unaware of their HIV status. Through community mapping and conversations with key informants, we also identified a third group with whom we orchestrated group interviews, minibus drivers. People who drive minibuses, the main mode of public transportation in and between communities, were identified as an important group with whom to speak because of their routine interaction with daily commuters. I refer to this group hereafter by the colloquial title of "taxi driver." While the taxi drivers we interviewed could not recall conversations about IPT with or amongst their passengers, the inclusion of data from this group provided insight into the experiences, practices, and beliefs of a group often missing from clinic rosters: working men between the ages of 20 and 35.

To recruit participants for group interviews, we utilised a combination of purposive and convenience sampling, with the process differing somewhat between sub-populations and communities. To select taxi drivers, for example, Ms Ndlovu and I visited taxi ranks and liaised with rank managers and taxi associations to determine mutually agreeable interview times. In one instance, after Ms Ndlovu and I went through the informed consent process with a group of taxi drivers at a central rank in Caluza, we arranged to meet with the drivers over the following weekend to undertake the interview. When no one returned for the interview, we revised our approach for future group interviews, undertaking interviews immediately following the consent process, despite the increased time commitment. For the purposes of the Caluza group interview, Ms Ndlovu and I utilised snowball sampling after identifying a first taxi driver willing to participate. In Embo, a taxi driver who sat on the GRAT arranged for a group of his colleagues to attend the discussion at a particular date and time. In Songonzima, we were unable to convene taxi drivers because we did not receive approval from the community taxi association, whose members continually delayed meetings or bumped us from agendas. After many attempts, Ms Ndlovu and I decided to forego this group interview, as we suspected there was mistrust of our intentions.

For group interviews with people living with and without HIV, community care givers (CCGs) identified potential participants through convenience sampling at the clinic or through home visits. CCGs are local community members employed by the government or NGOs to provide outreach support to patients. They were thus aware of the HIV status of many community members in the catchment areas in which they worked, and therefore able to approach people with or without HIV to enquire about their willingness to meet with Ms Ndlovu

and me to learn more about the project. We encouraged CCGs to seek potential participants who varied in both age and sex so as to gain a broader representation of these demographics in group interviews.

4. Individual Interviews with People Eligible for IPT

To learn about patient experiences on IPT, I aimed to interview one participant who accepted, one who discontinued, and one who declined IPT in each community. Interviews with one participant are usually referred to as one-on-one interviews in qualitative literature [19]; however, I refer to these throughout as 'individual' interviews since a third person (the community liaison/interpreter) was present in all interviews. With the intent to capture potentially divergent information, I sought out male and female participants of varying ages living in different sections of each community. Although participants varied in age and location, all individual interview participants were female, which was a function of who was easily reached and available to meet during the day.

Participant recruitment for these interviews varied slightly between communities. In Songonzima, I utilised a combination of patient records and registers to identify people who had taken or discontinued IPT. A staff nurse made initial enquiries by phone to determine if patients were willing to learn more about the project and to arrange a convenient place and time to meet with Ms Ndlovu and me to enter into the informed consent process. In Embo and Caluza, where individual patient records were not kept or made accessible, participants were selected with the assistance of CCGs.

Patients who declined IPT proved to be difficult to identify, since IPT was offered through nurses (not CCGs) at clinic, and no record was kept when eligible patients declined. Ms Ndlovu and I managed to recruit one participant who declined IPT directly from a group interview because she shared her IPT decision during the discussion. A second was identified by a CCG, but upon interview we determined that the participant had initiated IPT and discontinued within the first month. Another participant who was listed as discontinuing had actually completed the regimen, which was validated on her personal patient card. As lived experiences overlapped in many accounts, I included all of these data in the analysis, but report the participant composition based upon corrected patient categories.

Data collection

1. Observation

In the context of ethnography, observation refers to much more than documenting visual stimuli, but also participation in social interaction so as to gain the perspective of what it is like to be part of a given experience [5,13,20,21]. As a middle-class, white Canadian woman, for example, it is impossible to appreciate decisions being made in a rural KZN context without actually experiencing the daily practices of life. As such, observation in modern ethnography might be better characterised as reflective participation.

I began observation with a mind to interacting in a culturally appropriate way, watching hand gestures, eye movements, and general body language with each interaction, asking questions of Ms Ndlovu with regard to situations that seemingly involved tensions or novel reactions, given my lived experience as a Canadian. These are what Musante refers to as "tacit" aspects of culture which are often performative and occur without members being conscious of them [21]. I also observed "explicit" aspects of culture, observing everyday work and life practices or taking part in particular events or rituals [21]. One of the first events in which I participated was the funeral of a community member. I noted that many women were gathered in a rondavel prepping food for cooking, and, although as a Westerner on a community visit it was expected that I would stand quietly and watch, I began to participate in the preparations with the other women. We wore bright aprons and each took a position in the assembly line: peeling potatoes, carrots, beets, onions and tomatoes into large pots. Others were located behind the rondavel preparing the meat of a cow that had been slaughtered for the occasion. As the day progressed, my novelty as a foreigner waned; although I dressed differently, spoke a different language, and presented evidence of uncertainty in my movements, I soon became another pair of useful hands to complete the preparations. In this space, the women were in their element, undertaking familiar routines while exchanging family updates and community gossip. While my presence at community gatherings was at times exciting and at others humorous, it became increasingly normative. In time, my behaviour also modified; I asked fewer questions and exhibited fewer cultural *faux pas*.

Other events of note included town hall and traditional council meetings and events, engagement ceremonies, weddings, and other religious and coming of age celebrations. I documented my observations from these events in the form of field notes [5], which often

included reflections and questions that developed in light of the other qualitative datasets. Data from group and individual interviews, for example, informed individual-level cultural aspects that may affect decision making around IPT, providing a lens with which to observe relevant group interactions. GRAT meetings and interactions with key informants provided opportunities to further investigate patterns and subtle distinctions between beliefs and practices, promoting a deeper understanding of events through multiple vantage points and perspectives.

2. Grassroots Research Advisory Teams

GRAT meetings were held in isiZulu with Ms Ndlovu providing real-time English and isiZulu translation. Meetings were documented in formal minutes. I maintained field notes of in-depth discussions of data patterns and theories and recorded particularly rich discussions which I later transcribed in English for inclusion in data analysis.

3. Key Informants

Data from key informants were largely collected informally without structured questions or recordings. I kept field notes during or after particularly rich discussions, filling in additional details soon after encounters. During the analysis phase of research, I recorded and transcribed sections of key informant interviews that elucidated particular aspects of enquiry.

4. Structured Interviews

Here I use the term "structured" to refer to group and individual interviews for which planning began at the research proposal stage and which involved specific data collection tools. It is important to note that although the specifics of these data sets were conceptualised *a priori*, the process of collection remained fluid and iterative, with real-time reflections and analysis resulting in modifications and additions to the tools.

I drafted initial group and individual interview guides following articulation of the research question and early feedback from district officials, clinic staff, and other community stakeholders (see Appendices 3 and 4 for Group and Individual Interview Guides). Group interview questions were primarily descriptive with regard to understandings and perceptions of TB disease, latent TB infection, and IPT, e.g. "What do people say about TB?" "Do you know anyone who has taken IPT? What do they say about it?" and "What are other ways to treat 'sleeping TB'?" Individual interviews explored acceptance, access, stigma, and pill taking. Questions were both descriptive, *e.g.* "What does it mean to be sick?" and "What do people say about IPT in your community?"; and structural, *e.g.* "How did you get your medication?" and

"How did you remember to take it?". Prior to undertaking group or individual interviews, I reviewed the guides several times with Ms Ndlovu, and we ran mock interviews to ensure the purpose of questions was clear before working with participants.

Group interviews were held in central meeting spaces such as school classrooms and boardrooms at ward offices. Ms Ndlovu facilitated group interviews in isiZulu, prompting participants to engage in conversation in their home language, unhindered by interruptions for interpretation [19]. In total eight group interviews were held with a total of 54 participants. I observed group dynamics and took notes during these interviews. Ms Ndlovu often brought me into the conversation near the end of each discussion if participants had further questions or if there was a particular line of enquiry upon which I might have wanted to follow up. Since I was not fluent in isiZulu, Ms Ndlovu and I debriefed at length immediately following each of the eight group interviews to review the content of responses and discuss any new directions of enquiry.

Individual interviews took place in the homes of participants. I led individual interviews while Ms Ndlovu provided real-time interpretation from English to isiZulu and isiZulu to English. In all, we undertook interviews with nine participants, among whom, three had completed, three had discontinued, two were currently taking, and one had declined IPT. While I was interested in recruiting a diverse segment of the population in terms of age, sex, and location within each community, all interviewees were female.

All group and individual interviews were digitally recorded with permission from participants. Recordings of group interviews were then transcribed in isiZulu and translated into English by a local research assistant. I reviewed English transcripts and clarified any unfamiliar cultural references with the assistant. For individual interviews, I transcribed the English interpretations directly from the recording. IsiZulu portions of group and individual interview recordings were revisited by an independent translator to explore alternate meanings of words and phrases that were of particular relevance to reported findings [19].

Data analysis

Individual and group transcripts and relevant field notes were analysed using qualitative content analysis as described by Mayan [22]. I uploaded and reviewed data using Nvivo 10 software. Transcripts and field notes were entered into the programme and reviewed

independently before being reviewed again along with previously uploaded data. At each read through, I would create, expand, or merge codes to demarcate sentences or sections that may inform any of the qualitative research objectives. After considering the eight group and nine individual interviews separately, I began to see commonalities between the data, and made the decision to analyse the 17 transcripts collectively.

The process of coding was repeated several times in order to identify coherent patterns that could be brought forth for discussion with GRAT members and other key informants, enabling me to consider alternate lines of enquiry while still collecting and analysing data. Morse *et al.* refer to such feedback as a *constructive* validation strategy, which helps to limit misinterpretations early in the process [23]. Once codes were relatively consistent, I began to consider categories: groups of related codes that could coherently answer particular aspects of research question 1 (*i.e.*, acceptability of presumptive treatment for latent TB infection). Building from the categories reported in analysis, I then worked with existing theories (*e.g.,* Douglas' notion of "dirt" representing "matter out of place" in a given society [24] in manuscript one and Marlatt's harm reduction model [25] in manuscript three) to help situate the findings of my work within frames of reference familiar to the target audience of the journal to which each manuscript was aimed.

Rigour

To ensure scientific rigour, I employed several mechanisms important in CBPR and ethnography. During development, research tools were first piloted with patients at an anti-retroviral therapy (ART) clinic in Edendale, and then vetted through GRAT meetings. Informed consent forms and interview guides were also back-translated from isiZulu to English by an independent translator to improve construct validity [26]. Data collection and analysis were dynamic and concurrent as a means of constructive validation [23]. GRATs and key informants were consulted throughout the process to ensure accurate descriptions of cultural concepts [3,5,27]. Negative or deviant examples were included in the sample [23,28]. Categories were member-checked by a sample of participants and peer-checked with healthcare providers working in South Africa to ensure credibility [27]. Theories were developed in relation to the data and compared to existing theory [23], a process which was also negotiated with and approved by GRATs [3].

Effectiveness

Study design

To assess IPT effectiveness, I utilised a retrospective cohort design. Access to paper (IPT register) and electronic (ART and TB register) datasets was provided by uMgungundlovu Health District Office through the District Health Information System.

Object design

Ole Miettinen describes object design as the operationalisation of theoretical variables into clear and measurable scales, ideally a single index measure for each variable at the outset of data collection, in order to consistently compare variables between groups [29]. In order to evaluate effectiveness, I defined the following variables *a priori*:

I defined the exposed group as PLWH who collected at least five monthly prescriptions of IPT by the eighth month according to IPT registers, as 80% of regimen completion over a nine-month period is considered adequate to achieve protective benefit [30]. Only people who began IPT between January 1, 2011 and December 31, 2012 were included in the IPT exposure group. As not all clinics in the Edendale catchment area routinely collected data on PLWH not yet on ART, determining an equivalent unexposed group was more complicated than originally anticipated. A subset of patients at an HIV clinic in a community health centre catchment in Edendale township were routinely monitored by a local NGO, with data uploaded to the District of Health's electronic ART register during the study period. For the purposes of assessing effectiveness, I therefore limited the scope to PLWH receiving HIV care and/or IPT through one of the three clinics which made up the community health centre catchment for purposes of comparison.

As ART initiation strengthens overall immunity, ART is itself an intervention that can reduce TB incidence [31]. As such, I had originally planned to collect ART data to control for its use at the time of analysis. At the same time as IPT was introduced, ART was also being scaled up across uMgungundlovu District. Since the comparison dataset included people on and off ART, I had the opportunity to evaluate IPT effectiveness with ART as a competing exposure, thus creating three intervention groups (IPT alone, ART alone, and IPT+ART). Each intervention group was then compared to the same intervention-free group in analysis.

ART users were defined as PLWH whose first ART prescription was collected prior to or during study time and whose last prescription was collected after censoring or outcome of TB, with no treatment stoppage recorded in the ART register database. People whose last ART prescription was collected prior to or during the study period were excluded from analysis. IPT+ART users were those who met criteria for both IPT and ART use as defined above. People receiving no intervention were those with no record of ART prior to or during the study period, or who initiated ART only after TB diagnosis, and for whom there was no evidence of IPT use prior to or during the study period according to ART, IPT, or TB case registers. People who took fewer than five months (n=237) or who collected less than 80% of the IPT regimen by the eighth month (n=2) were omitted from analysis.

Among IPT users, I defined IPT start date as the date of first IPT collection according to the IPT register. I defined IPT completion date as the last collection date recorded on the register plus 28 days, assuming completion of pills collected at last pick-up. I defined study time among the exposed as the duration between actual IPT start and completion dates plus 540 days (18 months) of follow-up. Among the unexposed and ART alone groups, study time was set to the mean start date (27 October 2011) and 540 days after the mean end date (23 September 2013) of IPT completers. I defined a TB case as any diagnosis of TB (pulmonary or extra-pulmonary) confirmed by smear, culture, and/or GeneXpert during cohort time according to district-level datasets for drug-susceptible and drug-resistant TB, excluding *a priori* any diagnoses based solely on radiological or other clinical suspicion in an effort to limit false positives. I excluded TB cases listed as "repeat after default" when the initial TB diagnosis occurred before the study period.

Covariates included sex, dichotomous age at cohort start date, dichotomous CD4 cell count at ART baseline, ART duration at IPT completion, and ART regimen. Sex (male or female) was recorded from registers. Age was divided dichotomously according to standard epidemiologic groupings upon which IPT is generally used more judiciously in low-burden settings due to potential increase in hepatotoxic responses (≥35 versus <35 years of age) at cohort start date [28]. CD4 cell count was dichotomised under which ART initiation had been shown to significantly improve TB outcomes (<250 versus ≥250 μm/L) [32]. CD4 cell count was available only for the time of ART initiation in the District dataset, and was therefore considered with and without ART duration to account for CD4 counts rising following ART initiation. ART duration

was dichotomised as ≥1 versus <1 year at IPT completion. In terms of ART regimen, there were more than 20 distinct regimens recorded during study time in the ART database, reflecting both the changing policies of ART regimen as new drugs developed (patients were not switched to updated regimens if current regimens remained acceptable and efficacious), and the updated practice guidelines to tailor ART regimens according to individual drug side effects and/or susceptibility to different classes of drugs [33,34]. To keep contingency tables manageable, I chose to dichotomise ART regimens by the presence or absence of tenofovir in the combination, a drug which was implemented widely during study time and represented a new generation of ART regimens thought to be better tolerated and more efficacious [35]. Although part of my *a priori* covariate decisions, I could not consider previous TB as a potential confounder or effect modifier, as comprehensive TB data was unavailable for the catchment area prior to 2010.

Description of sources

1. IPT Registers

At the time of study, paper IPT registers were provided to clinics by NGOs to assist with IPT implementation. Each clinic reported aggregate-level IPT data to the District and Department of Health electronically, and original paper forms were not submitted or reviewed by the programme; I therefore relied on original paper records to create a cohort of PLWH exposed to IPT. Following a lengthy approval process, I collected exposure data from paper registers in June 2015 and employed two people to assist me with the systematic entry of paper records into an excel form.

The IPT register (see Appendix 5) included basic patient information and demographics, such as name, sex, date of birth, and contact information. Additionally, the paper register was used to record date of IPT initiation, dates of monthly tablet collection, as well as monthly checks for side effects and TB symptoms. No unique patient identifiers such as South African identity number were routinely collected. Contact information such as phone number and address were also not entered routinely. Addresses in the community health centre catchment were largely informally organised with few houses utilising unit numbers, and entries might appear as simply the neighbourhood of residence and/or proximity to local buildings, *e.g.* "near Zondi store" or "next to La Lucia primary school." One of the clinics did not receive new register

registers when old books were filled, and clinic staff developed their own reporting forms for IPT, with some deviations and omissions from the standard register.

2. ART Registers

I utilised data from electronic ART registers to identify the unexposed group with whom to compare IPT users as well as to evaluate ART as a competing intervention. ART records were developed and maintained by two NGOs in the region, Health Systems Trust and Kheth'Impilo. These datasets were accessed with permission from uMgungundlovu District who held these electronic datasets.

During the study period, ART was provided principally at the community health centre level. Within the Edendale Hospital catchment area, there were four community health centres. One of the four, a large peri-urban community health centre called Imbalenhle, provided ART initiation and treatment services to the Edendale township.

3. TB Registers

The TB case register was housed and maintained electronically by the District of Health on the Department of Health Information System. Paper registers were collected at clinics organised by the TB Control Programme and delivered to the District of Health office where four staff members entered the data and managed the dataset in an electronic database. As TB is a notifiable disease, a database known as the Electronic TB Record or "etr.net" was developed specifically for national TB reporting. As such, fields were well maintained and test results were updated regularly directly through the provincial laboratory located in Durban.

For purposes of my thesis, I was approved to access all TB case data from the uMgungundlovu District, including nominal information for the purposes of data linkage to IPT register data. I also received access to a database of information on drug resistant cases maintained at Doris Goodwin MDR-TB Hospital, where I reran the probabilistic linkage processes described in the section below, identifying one additional case. The small increase makes sense, as it would be common for people to first appear in the District database before their results would be recorded as multi-drug resistant and they would be transferred into specialised care.

Combining datasets

To combine datasets, I performed probabilistic linkage using first and last names and

dates of birth with relative likelihoods of a variable match indicating a true match weighted at 8, 10, and 15 out of 20, respectively. To link IPT and ART datasets I began with a probability cut-off of 0.80 and later reduced the cut-off to 0.60 to account for the fact that 4.18% of IPT register data was missing one of the three linkage variables. Match scores <0.99 were reviewed individually to determine match acceptability [36]. Matches above 0.80 were often mistypes of common names or reversal of month and day of birth. Matches between 0.60-0.80 were considered matches only when an identical phone number, address, or South African ID number could be identified using free-text variables in the original datasets. Of the 134 IPT users matched to the ART database, 66 were perfect matches, 42 had match-scores between 0.80-0.99 and 26 had match-scores between 0.60-0.80. An additional 307 IPT users were added to the dataset who lived in the community health centre catchment, but did not appear in the ART database. I assumed that these individuals did not receive ART through private clinics or alternate community health centres during follow-up, which seemed a reasonable assumption, since these individuals routinely accessed IPT to completion through their local public primary care centres. As CD4 cell counts were not collected on IPT registers, CD4 data were missing for these individuals.

To determine TB disease outcome, I then probabilistically linked the above dataset to district-wide electronic drug-susceptible and drug-resistant TB databases using the original 0.80 match score cut-off. Proportionally fewer entries were missing linkage data (0.56%) and consistency of nominal information was greater given the use of drop-down menus in ART and TB case databases. Again, match scores of <0.99 (3.24%) were reviewed on a case-by-case basis.

Data analysis

I utilized Stata/IC for Mac version 13.1 for all analyses. At-risk time was calculated as the total disease-free time each person contributed to the cohort, with censoring occurring at the end of the study period. Due to the complexities of the pathogenesis of TB, drug resistance, and the potential for lasting TB preventive effects following treatment, individuals developing TB during the study period did not return to disease-free status after being diagnosed and treated for TB within the study period. I calculated cumulative incidence, incidence rates, and incidence rate ratios with confidence intervals to evaluate differences between the three interventions

compared to no intervention.

Given the numerous covariates considered in the model, I utilized stratified analysis to allow for the evaluation of effect modification as well as confounding. Since contingency tables were limited by the number of IPT users, I could not run a logistic regression to consider every possible covariate combination through backward elimination. Rather, I considered which configurations of covariates actually occurred together in the dataset to get an impression of which groups could reasonably be compared. I omitted results for strata that had less than 1000 people per group. For example, most patients in the dataset were on a tenofovir-based regimen, so grouping patients by regimen made it impossible to assess other factors, and tenofovir alone was not a significant predictor of disease or suggestive of a confounder in combination with IPT use. In this way (considering univariate analysis along with existing groupings), I also eliminated ART duration from analysis, and was left with binary sex, age, and CD4 cell count to consider as potential modifying or confounding variables. As some contingency tables included zero cell counts, I considered and reported point estimates and confidence intervals on both the additive (risk difference) and multiplicative (incidence rate ratios) scales. Although sex and age also appeared to have a jointly modifying effect on the ART-only group, I chose to report the jointly modifying effects of CD4 count and age in this group for two reasons. Firstly, CD4 count is an indicator for immune function, thus one can expect that people presenting with overly compromised immune systems would be less successful at fighting disease progression, despite the presence of an intervention. Secondly the modifying effect of sex and age combined may be because sex is also a (less direct) proxy for immune function, as males generally present later for treatment compared to females. Although I could not adequately evaluate CD4 cell count among the IPT alone group given the amount of CD4 data that was unavailable for this group, I still present the point estimates by joint age and CD4 cell count strata for all groups in the results section of manuscript two to enable readers to draw their own conclusions based on data trends and precision levels.

To estimate the impact of IPT initiation without the use of TST to target those most likely to benefit, I also compared actual to expected TB outcomes among ART-naïve IPT users after developing assumptions that disproportionately favoured the use of targeted TST. Since there were no available data on TST positivity for this setting, I assumed the proportion of TST positivity in the catchment was equal to the highest documented proportion among PLWH in

under-resourced settings, 32.6% [37], later confirmed as a reasonable over-estimate by colleagues who undertook a school-based TST survey in northern KZN during the study period (e-mail communications with Thomas Yates, MD/PHD and Richard Lessells, MD/PhD LSHTM, May 2, 2017; unreferenced). I estimated expected TB events by multiplying the proportion of people who developed TB over two years in the non-intervention group by sex with the number of people who were estimated to be TST negative by sex. I then assumed that all actual TB events occurred amongst the number of females or males who were estimated to be TST-negative responders, and compared expected with actual TB events using Z-tests.

Limitations

Given the small number of IPT users, I was unable to investigate a potential dose-response relationship among IPT users, and thus limited the analysis to PLWH whose records provided evidence of IPT completion and/or consistent ART use. As such, the findings are limited to adherent patients already seeking regular care at primary care clinics for whom other health, mobility, and economic conditions did not prevent the collection of monthly IPT prescriptions. In short, these analyses speak to the effectiveness of IPT in the best-case scenario.

Another limitation is that the epidemiologic datasets were collected for purposes other than research, which at times required less than ideal data comparisons or the use of assumptions, which, if incorrect could impact the associations drawn between interventions and TB. For example, CD4 counts were recorded consistently only at the time of ART initiation, which did not always align with IPT initiation. This likely means that there is some differential misclassification among the stratified contingency tables involving ART users, as people who were started on ARTs before IPT may have had higher CD4 counts at the time of IPT initiation due to ART-related immune reconstitution.

Most notably, I was unable to access and link all-cause mortality data, which would have enabled me to assess safety of the regimen. All-cause mortality is ideally collected in analytic studies to compare the proportion of deaths occurring among unexposed and exposed groups. If a higher proportion of deaths occur among the exposed, it may indicate that the intervention is responsible for life threatening complications that prevent exposed persons from developing the outcome. If for example people who completed IPT did not develop TB during follow-up because they died due to complications related to IPT use, then the findings would be biased

away from the null, meaning we unwittingly champion an intervention that may actually pose more harm to an already vulnerable population.

Research Questions Revisited

Given the iterative nature of the methodologies described above, research questions were revisited as I became increasingly familiar with the data collected. As such, the research questions that opened this chapter were refined accordingly. Each manuscript that follows responds directly to one of the refined questions:

1. What are community perspectives or "hidden transcripts" related to IPT in three communities of uMgungundlovu District? (manuscript one)

2. Did IPT reduce TB incidence rates in a setting where ART is increasingly available? (manuscript two)

3. Given that females more often initiated and completed IPT, what can we learn from the women of uMgungundlovu to improve IPT implementation in this setting? (manuscript three).

References

1. Brown L, Vega WA. A protocol for community-based research. In Minkler E, Wallerstein N, editors. Community-Based Participatory Research for Health: From Process to Outcomes (2nd ed). San Francisco: Jossey-Bass; 2008. pp 395-397.

2. Haraway D. Situated Knowledges: The Science Question in Feminism and the Privilege of Partial Perspective. *Feminist Studies*, Vol. 14, No. 3. (Autumn, 1988), pp. 575-599.

3. Minkler E, Wallerstein N, editors. Community-Based Participatory Research for Health: From Process to Outcomes (2nd ed). San Francisco: Jossey-Bass; 2008.

4. Critical Path to TB Drug Regimens. Good Participatory Practice Guidelines for TB Drug Trials. 2012. [Internet]. Available from: http://www.cptrinitiative.org/downloads/resources/GPP-TB Oct1 2012 FINAL.pdf. [Accessed 15 Nov 2017].

5. Head BW. Community Engagement: Participation on Whose Terms? Austr J Political Sci, 2007; 42(3): 441-454.

6. de Laine, M. Ethnography: Theory and Application in Health Research. Sydney: MacLennan & Petty, 1997.

7. Savage J. Ethnography and healthcare. BMJ. 2000; 321(7273): 1400–1402.

8. Van Mannen J. Ethnography then and now. Qualitative Research in Organizations and Management: An International Journal 2006; 1(1): 13-21.

9. Larratt-Smith J, Barton L. Bridging culture within nations. In Upvall MJ, Leffers J. editors. Global Health Nursing: Building and Sustaining Partnerships. New York: Springer; 2014. pp 176-185.

10. Rifkin SB, Pridmore P. Partners in planning: Information, participation and empowerment. London, GBR: Macmillan Education: 2001.

11. Guest G. Sampling and selecting participants in field research. in Handbook of Methods in Cultural Anthropology (2nd ed). Russel BH, editor. Lanham, USA: Rowman & Littlefield; 2015. pp. 215-50.

12. Carton B, Laband J, Sithole J, editors. Zulu Identities: Being Zulu Past and Present. Durban: University of KwaZuu-Natal; 2009.

13. Smith D. The Everyday World as Problematic: A Feminist Sociology. Boston: Northeastern University Press; 1987.

14. Dawson S, Manderson L, & Tallo VL. A Manual for the Use of Focus Groups. WHO, 1993.

15. Johnson JC. Selecting ethnographic informants. Newbury Park, Calif: Sage; 1990.

16. Gibbs A. Focus Groups. Social Research Update. 1997;19 [about 4 pages]. Available at: http://sru.soc.surrey.ac.uk/SRU19.html [accessed 23 Oct 2017].

17. Tremblay MA. The key informant technique: A non-ethnographic application. American Anthropologist. 1967: 59(4): 688-701.

18. Chavez V, Duran B, Baker QE, Avila MM, Wallerstein N. The dance of race and privilege in CBPR. In Minkler E, Wallerstein N, editors. Community-Based Participatory Research for Health: From Process to Outcomes (2nd ed). San Francisco: Jossey-Bass; 2008: 91-106.

19. Kvale S, Brinkman S. Interview variations. InterViews: Learning the Craft of Qualitative Research Interviewing. Thousand Oaks: Sage; 2009. pp. 143-58.

20. Fife W. Doing Fieldwork: Ethnographic Methods for Research in Developing Countries and Beyond. New York: Palgrave MacMillon; 2005.

21. Musante K. Participant observation. in Handbook of Methods in Cultural Anthropology (2nd ed). Russel BH, editor. Lanham, USA: Rowman & Littlefield; 2015. pp. 251-92.

22. Mayan M. Essentials of qualitative inquiry. Walnut Creek, CA: Left Coast; 2009.

23. Morse JM, Barret M, Mayan M, Olson K, Spiers J. Verification strategies for establishing reliability and validity in qualitative research. Int J Qual Methods 2002, 1(2): 13-22.

24. Douglas M. Purity and Danger: An analysis of concepts of pollution and taboo. New York: Praeger; 1966.

25. Marlatt GA. Harm reduction: Come as you are. Addictive Behaviors. 1996; 21(6): 779-788.

26. Brislin RW. Back-translation for cross-cultural research. Journal of Cross-Cultural Psychology. 1970;1(3):187–216.

27. Côté L, Turgeon J. Appraising qualitative research articles in medicine and medical education. Med Teach 2005, *27*(1):71-5.

28. Holloway I, Todres L. The status of method: Flexibility, consistency and coherence. Qual Res 2003, *3*(3):345-57.

29. Mietinnen OS. Design of the occurrence relation. Theoretical Epidemiology. New York: Wiley; 1985. pp 25-45.

30. Apers L, Robert C, Nachega JB. Prophylaxis with antituberculosis drugs in special situations. In Schaaf HS, Zumla AI, editors. Tuberculosis: A Comprehensive Clinical Reference. London: Elsevier; 2009. p. 780-85.

31. Lawn SD, Harries AD, Williams BG, Chaisson RE, Losina E, De Cock KM, et al. Antiretroviral therapy and the control of HIV-associated tuberculosis. Will ART do it? [Unresolved issues]. Int J Tubercl Lung Dis. 2011;15(5): 571-81.

32. Cohen MS, Chen YQ, McCauley M, Gamble T, Hosseinpour MC, et al. Prevention of HIV-1 with early anti-retroviral therapy. N Engl J Med. 2011; 365(6):493-505.

33. South Africa Department of Health. The South African antiretroviral treatment guidelines. The Department. Pretoria; 2013.

34. Meintjes G, Maartens G, Boulle A, Conradie F, Goemaere E, Hefer E, et al. Guidelines for antiretroviral therapy in adults. Southern African J HIV Medicine. 2012; 13(3): 114-33.

35. Karim QA, Karim SS, Frohlich JA, Grobler AC, Baxter C, Mansoor LE, Kharsany AB, Sibeko S, Mlisana KP, Omar Z, Gengiah TN. Effectiveness and safety of tenofovir gel, an

antiretroviral microbicide, for the prevention of HIV infection in women. science. 2010; 329(5996):1168-74.

36. Blasnik M. Record Linkage. Stata statistical software: Release 13. College Station, TX: StataCorp; 2013.

37. Kerkoff AD, Kranzer K, Samandari T, Nakiyingi-Miiro J, Whalen CC, Harries AD, et al. Systematic review of TST responses in people living with HIV in under-resourced settings: Implications for isoniazid preventive therapy. PLoS One 2012;7(11):e49928.

CHAPTER 3

When prevention is dangerous: Perceptions of isoniazid preventive therapy in KwaZulu-Natal, South Africa

Satisficing is one of the foundations of productive human behavior; it prevails… when we don't waste time trying to find improvements that are not going to make significant difference in our happiness or satisfaction.

Daniel J Levitan
The Organised Mind

Abstract

Introduction: As a result of changes to global recommendations for initiating isoniazid preventive therapy (IPT) to presumptively treat latent tuberculosis infection in low-resource, high-burden settings, the South African government began to offer IPT free of charge to people living with human immunodeficiency virus in uMgungundlovu District of KwaZulu-Natal in 2011. KwaZulu-Natal province has a tuberculosis notification rate of 808 per 100 000 population with 70% HIV co-infection. We aimed to describe community perceptions and experiences of IPT in three Zulu communities in uMgungundlovu during early implementation.

Design: We utilised a hybrid of community-based participatory research and ethnographic methods. Between October 2014 and May 2015, we undertook eight group interviews with community members and nine individual interviews with people accepting, discontinuing, or declining IPT. We met regularly with grassroots research advisory teams and key informants in each community between March 2012 and December 2016 to ensure the accurate descriptions of cultural concepts.

Results: Participants reported multiple ways in which IPT was perceived or experienced as dangerous. IPT became dangerous when costs related to pill collection or consumption were unsustainable for the household, or when daily pill consumption resulted in stigma or was seen to introduce excess dirt, "ukungcola," to the body. Theorist Mary Douglas explained that 'dirt' can represent 'matter out of place' in society. IPT in this setting was at times perceived as 'matter out of place' when given to people who identified as otherwise healthy, suggesting 'prevention as tablet' does not fit within existing explanatory models of health and disease.

Conclusion: Implementing IPT without understanding the social, cultural, and economic realities of community stakeholders can unintentionally undermine TB preventive efforts and introduce excess burden on people who already encounter a number of daily struggles related to health, access, safety, and basic needs.

Introduction

The use of tuberculosis (TB) preventive therapy is an integral part of global strategies to end TB [1,2]. At present, isoniazid preventive therapy (IPT) is the only regimen recommended globally for low-resource settings with high burdens of TB associated with human immunodeficiency virus (HIV). In 2011, the World Health Organisation released guidelines to expedite access to IPT in such settings [3]. Policymakers in South Africa, where the incidence of TB and TB-HIV are among the highest in the world, were quick to implement local guidelines to facilitate access to IPT [4].

uMgungundlovu District of KwaZulu-Natal province began to offer IPT to people living with HIV in early 2011. KwaZulu-Natal is a high-burden TB-HIV setting with a TB notification rate of 808 per 100 000 population, approximately 70% of which occur among the 1.6 million people (21%) living with HIV [5]. With a population of one million people, uMgungundlovu reports 33% unemployment with more than 25% of people living on <US$1 per day [6,7]. The study population consisted primarily of black South Africans of Zulu heritage accessing peri-urban and rural primary care clinics in a District Hospital catchment.

While evidence from low-incidence settings suggests that IPT is relatively low risk with potential for long-term protection from TB, the same may not be true in high-burden settings. High TB incidence and HIV prevalence result in greater exposure to and risk of reinfection with TB [8]. High-burden settings also experience greater deprivation and poverty compared to Western countries where IPT has been utilised routinely. Poverty-related factors can significantly impact health access and interactions [9,10]. Moreover, differences in lived experience, language, and other cultural aspects can influence the acceptance of health-related interventions [11]. As such, we set out to describe the acceptability of IPT in uMgungudlovu District during early implementation. To do so we utilised a hybrid of ethnographic and community-based participatory methods to learn about general perspectives of TB infection, disease and IPT as well as IPT experiences and decision making among those offered IPT in three communities of uMgungundlovu.

Study Population and Methods

In parallel with a longitudinal study of IPT effectiveness, we interacted regularly with three predominantly Zulu communities at varying degrees of distance from a District Hospital in

uMgungundlovu between 2011-2016. A detailed description of our methods has been published elsewhere [12]. From October 2014 to May 2015, we facilitated eight group interviews with a total of 54 community members to ascertain general perspectives on TB infection, disease, and IPT and undertook nine individual interviews with people who accepted, discontinued, or declined IPT. In addition, a PhD student (JB) and community liaison (SN) undertook ethnographic observation and worked with grassroots research advisory teams and key informants. Ethics approvals were granted from the Universities of Alberta, Calgary and KwaZulu-Natal. We also received administrative and community approvals. Transcripts and field notes were coded in NVivo 10.0 and analysed using qualitative content analysis as described by Mayan [13]. Findings were reviewed by a sub-set of participants and discussed with grassroots research advisory teams for validity. We utilised the International Journal of Tuberculosis and Lung Disease guidelines for qualitative research to ensure the quality of data reporting [14].

Results

IPT may exacerbate issues of poverty

For many participants, each day involved making difficult choices with limited resources. Participants described general feelings of powerlessness about meeting basic needs. One participant described job insecurity and feeling expendable in a farm-based community:

> Participant (P)5: The whites, especially on the farms, are used to [thinking of blacks only in terms of work capacity]. Point at a black and they should work hard.
> P2: Work [comes] first, [the farm owner] doesn't care about life because he knows that when you die he will hire another black person. [To him] a black person doesn't think for himself; even his brain is black. (Group Interview number [GI]8)

Participants described how adding IPT for prevention required additional clinic visits for monthly prescription renewals, an added cost and hardship under already difficult circumstances. One older participant who lived two kilometres from clinic described her commitment to the regimen thus: "If I don't have money I have to walk and ask [my assigned community care giver] if they're going to accompany me. If I have money [US$1.60], I take the transport" (Individual Interview [II]4). For others, public transport was not routinely available: "If I am not well I still have to wake up very early in the morning and go to wait for the transport... when I'm finished at the clinic, I have to wait for the transport which will come from [another town]" (II3).

Another participant explained that she had to miss two days of work each month, once to collect her IPT and a second to collect medication for her son who was sick with TB. When asked how this impacted her job, she indicated, "[my employer] doesn't like it, but I have to force it" (II3).

Some participants described weekday clinic hours as prohibitive for day labourers, citing the need to work. One participant explained that "it's because these days people don't have enough money" (P3, GI1) while another responded, "In our community we go to the doctor only when we are sick" (P4, GI1). A third participant explained that it is difficult for labourers because "we don't have health facilities on weekends" (P1, GI1).

Some also described difficult monetary situations when children may be at risk and eligible for IPT:

> Maybe… the grandmother is sick [with TB] and she is supposed to encourage the kids to [go to clinic]. The kids are at school, they can't go to the clinic; they can't go because there is no money. The money they have is for food and it disappears quickly. (P1, GI8)

A lack of food also complicated adherence to IPT, which is recommended to be taken with food to minimise potential stomach upset or diarrhoea. For some this expectation was difficult: "I am trying to follow the diet, but I'm struggling since I don't have money, as I was only able to find a job recently" (II3). Two participants described an increase in appetite that they associated with the regimen, which they could not accommodate. One explained that she felt she should "eat now and again, now and again, but [in her household] there [was] no one… employed and that was very hard for [her]" (II9). The second described her experience as follows:

> I felt hungry and I'm staying with my mum and my mother is the only… breadwinner, and she has to [pay] rent as well as buy food, pay for funeral [insurance], and sometimes she would complain about the amount of food that we are taking… Eventually I decided to quit [IPT] because I couldn't take that anymore. (II5)

Daily tablet-use leads to disease stigma

Although the IPT regimen was the focus of interviews, many participants entered into discussion of daily tablet-use in relation to TB and HIV as well. Many participants described daily pill-use as an indication of disease. For some, an absence of pills indicated wellness, *e.g.* "Health is feeling happy… [not] taking tablets" (IPT9). Others were exasperated by the thought of taking tablets long-term, "Maybe I find that I have TB, I feel like *Aish [exasperated]*, I'm going to be on treatment for six months, or you find you have HIV and you have to take

treatment for life. This is a problem" (P1, GI3). Others described the discomfort of pill taking: "They are big. If you swallow them, you want to vomit" (P7, GI3).

For many participants, the concept of 'disease' was synonymous with HIV due to its proliferation in the community, referring to HIV as simply "the virus" or "the disease." One participant described sickness as "when you are not feeling well and… you think 'maybe it's HIV'" (P1, GI1). Others described how easily community members might suspect someone of having HIV, for example: "let's say maybe you are limping, you have a knee injury, and you pass people. They will say 'you have the disease'" (P1, GI8). For many participants fears about HIV related to the accompanying stigma: "[people] are afraid of being discriminated… at home and in the community" (P1, GI5). Stigma was related particularly to assumptions about sexual promiscuity, being "dirty," or falling prey to addictions, what one participant summarised as "not living in a correct way" (P2, GI4).

HIV stigma also translated to IPT. Often participants talked about antiretroviral therapy (ART) for HIV treatment and IPT regimens simply as "treatment," and discussed the two interchangeably. One participant who initiated IPT and ART concurrently recalled instructions characteristic of ART adherence counselling when asked what she was told about IPT:

> They told me that I have to take care of myself. I have to take precautions. I have to clean the environment where I am. I have to wash my clothes, don't wear the dirty clothes. I have to open the windows. I have to clean everything, even the bed linen. (II3)

When asked to clarify if this information actually related to ART, she replied, "they said they go along. When there is TB, HIV is there" (II3). Others described TB and HIV as "siblings" or "twin diseases." In one group interview, a participant explained the meaning of "TB Plus," a local idiom:

> If [the neighbours] hear that you have TB, most people here will gossip… once [a person] said to me 'oh, your husband has TB?' I said, 'yes' and she said, 'no mum, go for a check-up for the virus. You will find that you have the virus too.' (P4, GI8)

The implications of this were described by a second participant: "if you are told you have TB, keep it to yourself and take pills and don't tell people, because they will go around talking about you" (P3, GI8). Another participant described some people's preference to "use suppositories of traditional medicine to try to heal themselves" instead of taking tablets to treat TB disease (P4, GI1).

Furthermore, IPT use was identified as a matter to be kept secret, perhaps because of the conflation with ART. In one instance, a participant indicated she did not know of anyone else on the regimen "because people are so secretive" (II9). Another participant, who declined IPT because she had recently been treated for active TB, was surprised to find her sister had started IPT without telling her: "I went to the clinic on Monday to collect my sister's medication. On the medication there was that [isoniazid] and as she kept quiet, I didn't say anything… I just gave it to her and I kept quiet" (II1).

Pills can be toxic

Although some participants described TB and HIV as diseases that "didn't exist in our parents' time" or "coming from nowhere," TB was often described as a result of exposure to "dirt" (*ukungcola*) in the environment or practicing "dirty" habits. Examples of dirty environments included proximity to pigs, living in a shack or unclean home, or the use of coal or wood indoors. Dirty habits included failure to bathe regularly, smoking, or drinking caffeinated beverages. The word *ukungcola* is distinct from the isiZulu word for virus or germ, "*igciwane*." In one group interview, *ukungcola* and *igciwane* were equated when a participant explained how smoking might cause TB: "maybe your chest is dirty where it all started and it's spreading. Then when you cough, you are coughing *ukungcola* [dirt] and you pass it to the next person. Because it's always said that you cough *igciwane* [germs]" (P5, GI8).

Intensive pill regimens were also linked to *ukungcola*. Daily tablets were thought to "[build] up the amount of poison *ukungcola* in the stomach" (P2, GI1). One participant described a foul body odour whilst on IPT, postulating that "the body is releasing *ukungcola*" (P8, GI8). She further explained, "it becomes so bad that even your urine smells unlike before."

Cleansing practices were described to resolve *ukungcola* in the body. Some participants practiced routine vomiting (daily or weekly) as a general bodily cleanse, but when disease or long-term medications were deemed to build up excess *ukungcola*, a regimen of cleansing may be sought with the aid of herbs prescribed by an ancestral healer (*sangoma*) or herbalist (*nyanga*). One participant described the process, "we would take some ground herbs boiled with water and we drink a whole jug of that and then you stick your two fingers in and you vomit it out to clean the immune system" (P6, GI1). Another described an encounter with his brother whilst on TB treatment, "He said he could feel the tablets burning him here [*indicates mid-chest*]

like they were stuck. He wanted to go to the *sangoma* to get herbs to help him vomit them out"
(Key Informant interview 12). Herbal suppositories and water enemas could also be used for
cleansing, especially among members of African Indigenous Churches which combined
traditional African practices with Christianity. One participant described that "if you can see that
the tablet doesn't help, and I can feel that there is a part of me that needs to be healed, then I
would use the traditional herbs as a suppository. Because tablets won't come out" (P2, GI1).

Discussion

Despite the growing global and national impetus for the use of TB preventive therapy in
low-resource settings with a high burden of HIV-related TB, perceptions of six-month IPT
during early implementation in uMgungundlovu District, KwaZulu-Natal suggest that IPT can be
viewed as dangerous. In this context, dangers of IPT included the exacerbation of poverty,
introduction of stigma, and addition of toxins to the body.

Some participants described struggling with the IPT regimen during economic hardship.
These hardships align with barriers to *gaining* health access. Guillford *et al.* explained that a
person can be seen as *having* health access when the infrastructure exists to provide health
services, *e.g.* clinics, staff, and a reliable supply of medicines; however, a person only *gains*
access when the services provided are affordable, accessible, and acceptable given their
circumstances [15]. Participants described barriers in the form of opportunity costs (*e.g.*
transport, unpaid leave, increased food costs) and organisational obstacles (*e.g.* limited clinic
hours, monthly prescription renewals). Acceptability was also a barrier when IPT use introduced
stigma similar to that found with HIV. Participants revealed that IPT and ART were often
thought of interchangeably, and TB and HIV were known to be closely linked, suggesting a
transfer of stigma. Reports of secrecy concerning IPT were consistent with this finding. IPT
uptake may be undermined in resource-constrained settings if care is not taken to mitigate these
barriers to *gaining* access for the most vulnerable.

In general TB infection and disease did not appear to be well-integrated into culturally-
derived explanatory models of health, evidenced by the use of the term *ukungcola*. Mary
Douglas detailed how, across cultures, the term "dirt" – or description as "dirty" – is used to
describe concepts or objects that do not fit with existing understandings of the world [16-18]. A
dichotomy is created between that which fits as "pure" and that which does not as "dangerous"

[17]. Douglas explained that the term "dirt" has inconsistent definitions, but invariably links to "matter" which is interpreted by a subject or society in a particular context as "out of place" [16]. Her theory fits well in the context of uMgungundlovu when HIV and TB resurgence are perceived as diseases that "come from nowhere" and tablet regimens are described as *ukungcola* in the body. IPT in this setting was at times perceived as *matter out of place* when given to people who identified as otherwise healthy, suggesting that under the present aetiologic model for TB in Zulu culture, 'prevention as tablet' does not fit within the existing classification system. Vernooij *et al.* reported similar findings in a Southern African trial that investigated early ART initiation to prevent HIV transmission, noting that the framing of treatment as prevention "did not fit in well with local biomedical knowledge, kinship dynamics and secrecy" [19].

Interestingly Douglas also discussed the role of ritual in resolving matter out of place [17]. Similarities can be drawn to the practice of cleansing when a perceived build-up of medication becomes quite literally a matter to be purged from the body in order to return to a state of equilibrium. Implementing IPT without adapting to localised aetiologies can unintentionally introduce excess burden for people who already encounter a number of daily struggles related to health, access, safety, and basic needs. In this way prevention becomes toxic, and cleansing is the ritual response.

Implications

Our findings suggest that despite the potential of IPT to prevent TB in high-burden settings, community members in KwaZulu-Natal's uMgungundlovu District encountered dangers that can prove challenging to implementation. In particular access barriers persist among those who live in poverty, and stigma related to TB, HIV, and pill taking may deter some from the regimen. Further, it is apparent that TB infection and disease are not adequately integrated into current cultural explanatory models of health, suggesting that more community engagement is needed to distinguish preventive from therapeutic regimens.

Future research is needed to assess and mitigate impediments to gaining health access. Low-cost methods could include linking at-risk patients to existing food programmes, providing free SMS services to alert health workers about transport issues, and developing novel partnerships with taxi associations, private pharmacies, and faith-based institutions to offer

support to those who are hardest to reach. Existing networks of community caregivers can play an important role. It is also critical to understand the mechanisms of stigma and seek local ideas to overcome them. Finally, future research might also seek local equivalents to preventive therapy or treatment of latent diseases. As the implementation of ART treatment as prevention continues *en masse*, there are bigger implications for prevention in general. If few people are willing or able to initiate or sustain ART regimens from the time of HIV diagnosis, test-to-treat policies could fail soon after implementation or lead to increased drug resistance among those who discontinue.

Conclusion

In three Zulu communities with high burdens of TB and TB-HIV, study participants described situations in which IPT was perceived as dangerous. Specifically, IPT can exacerbate poverty when costs related to pill collection or pill taking are too high for a household to sustain, and the consumption of daily tablets can create stigma or be seen to build up toxins in the body, creating a need to purge. These findings suggest that more community engagement is needed to identify and respond to contextual complexities in IPT implementation in high-burden settings.

References

1. Stop TB Partnership. The Paradigm Shift: Global Plan to End TB 2016-2020. Geneva: UNOFP; 2015.
2. World Health Organisation. The End TB Strategy: Global strategy and targets for tuberculosis prevention, care and control after 2015. Geneva: WHO; 2014.
3. World Health Organisation. Guidelines for intensified tuberculosis case-finding and isoniazid preventive therapy for people living with HIV in resource-constrained settings. Geneva: World Health Organisation; 2011.
4. South Africa Department of Health. Guidelines for tuberculosis preventive therapy among HIV infected individuals in South Africa. Pretoria: National Department of Health; 2010.
5. Ngozo J. Overview of the Department of Health Tuberculosis Control Programme in KwaZulu-Natal. [Presentation] Faith Leaders Symposium. 18 July 2016.

6. uMgungundlovu District Health Office. District Health Plan 2015/16. KwaZulu-Natal Department of Health: 2015. Available at: http://www.kznhealth.gov.za/Strategic/DHP/2015-16/Umgungundlovu.pdf [Accessed on 13 Sep 17].

7. Statistics South Africa. Statistics by place (Census 2011 data). Available at: http://www.statssa.gov.za/?page_id=964 [Accessed 13 Sep 2017].

8. Apers L, Robert C, Nachega JB. Prophylaxis with antituberculosis drugs in special situations. In Schaaf HS, Zumla AI, editors. Tuberculosis: A Comprehensive Clinical Reference. London: Elsevier;2009. p. 780-85.

9. Peters DH, Garg A, Bloom G, Walker DG, Brieger WR, Hafizur Rahman M. Poverty and access to health care in developing countries. Ann N Y Acad Sci 2008;1136: 161–171.

10. Mutchler JE, Burr JA. Racial differences in health and health care service utilization in later life: the effect of socioeconomic status. J Health Soc Behav 1991; 32(4): 342-56.

11. Kleinman A, Benson P. Anthropology in the clinic: the problem of cultural competency and how to fix it. PLoS Med. 2006; 3(10): e294.

12. Boffa J, Mayan M, Mhlaba T, Ndlovu S, Williamson T, Fisher D. Why agency is important when implementing IPT: Lessons from *oMakoti* in KwaZulu-Natal, South Africa. PLoS ONE 13(3): e0193571.

13. Mayan M. Essentials of qualitative inquiry. Walnut Creek, CA: Left Coast; 2009.

14. Mitchell EMH, Harper I, Theobald S. Guidelines for preparing manuscripts on qualitative research in the IJTLD.

15. Guillford M, Figueroa-Munoz J, Morgan M, Hughes D, Gibson B, Beech R, et al. What does 'access to healthcare' mean? J Health Services Research & Policy 2002;7(3): 186–88.

16. Douglas M. Purity and Danger: An analysis of concepts of pollution and taboo. New York: Praeger; 1966.

17. Douglas M. Risk and blame: essays in cultural theory. London: Routledge; 1992.

18. Douglas M. Preface. In: Purity and Danger: An analysis of concepts of pollution and taboo. London: Routledge; 2003.

19. Vernooij E, Mehlo M, Hardon A, Reis R. Access for all: contextualising HIV treatment as prevention in Swaziland. AIDS Care 2016; 28(sup3): 1-7.

CHAPTER 4

The effectiveness of untargeted six-month isoniazid preventive therapy to reduce tuberculosis incidence among people living with HIV with and without antiretroviral therapy in KwaZulu-Natal, South Africa

Tuberculosis is a social disease with medical elements.

Sir William Osler qtd. in Grzybowski *et al.*
History of the disease in Canada, *CMAJ*

Abstract

Introduction: Recent global strategies prioritise the scale-up of isoniazid preventive therapy (IPT) and early initiation of antiretroviral therapy (ART) for people living with HIV (PLWH) in high-burden settings to reduce TB incidence. With a substantial burden of TB and TB-HIV, South Africa implemented these interventions swiftly within the public system. We aimed to determine the effectiveness of six-month untargeted IPT to reduce TB incidence among PLWH in the context of ART scale-up in KwaZulu-Natal province, South Africa. We also compared the number of expected versus actual TB events among IPT completers assumed to have negative tuberculin skin test (TST) results.

Methods: The study took place in uMgungundlovu District, which reports an HIV prevalence of 36% and TB notification rate of 894 per 100 000 population. Using a retrospective cohort design, we collected programme data on PLWH who initiated IPT between Jan 1, 2011 and December 31, 2012 at a community health centre. We then compared the incidence rates of bacteriologically-confirmed TB across two years among people receiving IPT alone, ART alone, or IPT+ART to those without intervention.

Findings and Discussion: We followed 12 412 PLWH across 21 473 person years, among whom 441 completed IPT. Among the 408 incidents of TB, 217 occurred among those who were IPT and ART-naive at TB diagnosis, 186 among people using ART alone, and five among people using IPT alone. Zero cases occurred among 59 people on IPT+ART. Incidence rates were 3976, 1226, 674, and 0 per 100 000 person years, respectively. Among an estimated 191 TST-negative females on IPT alone, zero actual versus 11 expected cases of TB developed (p<0.001), while five actual versus seven expected cases developed among an estimated 66 TST-negative males (p=0.35).

Conclusions: Government-funded IPT offered to PLWH appeared to improve two-year TB incidence rates alone and in combination with ART.

Introduction

Although curable, tuberculosis (TB) is the leading cause of AIDS-related morbidity and mortality globally [1]. South Africa has the world's highest burden of human immunodeficiency virus (HIV; 7 million people [2]) and reports 23% of the global TB-HIV burden [3]. After

infection with *Mycobacterium tuberculosis*, TB bacteria can remain dormant (latent TB infection) or develop into active TB disease. Immune suppression from HIV is the strongest determinant for developing active TB [4,5]. Among people living with HIV (PLWH), progression to TB disease is six times faster [6] and, in endemic regions, reinfection is up to 20% higher compared to people without HIV [7]; however, latent TB infection can be successfully treated using isoniazid preventive therapy (IPT).

Isoniazid is a low-cost bactericidal medication that targets TB. It is commonly used in combination with three other drugs to treat drug-susceptible TB disease. Isoniazid can also be prescribed on its own as IPT, a daily tablet regimen for six, 12, or 36 months to treat latent TB infection, preventing its progression to active disease in individuals and averting ongoing transmission [8-11]. Until 2010, routine use of IPT in health systems was limited to high-resourced settings with low TB incidence [12]. Although settings with high burdens of TB and TB-HIV were thought to have greater potential to benefit from IPT [13], identifying latent TB infection and ruling out active TB disease limited broader implementation [12,14].

To date there is no definitive diagnostic test for latent TB infection; rather its presence is determined from a positive skin or blood test suggesting TB infection, followed by a chest x-ray to rule out active TB disease [15]. Blood tests and chest x-rays are prohibitively expensive in high-burden settings like South Africa, and the use of tuberculin skin tests (TST), which involve a time-sensitive follow-up visit and skilled reader, is often impractical. There has also been a global shortage of TST in recent years [16].

To encourage the use of IPT in resource-constrained settings, the World Health Organisation (WHO) published modified guidelines in 2011, replacing the need for chest x-ray with a symptoms-based approach to exclusion, whereby anyone with current cough, fever, drenching night sweats, or unexplained weight-loss would be deemed ineligible for IPT until resolution of symptoms or diagnosis and treatment of TB [4]. The new guidelines recommended that all symptom-free PLWH be offered IPT unless excessive alcohol consumption, hepatitis, or other disorder put them at a higher risk for liver failure [4]. Despite a large efficacy study in Southern Africa that suggested only PLWH with a positive TST benefit from IPT [11], the new guidelines no longer required the test to initiate patients on IPT where its inclusion proved prohibitive to implementation [4]. In accordance with WHO guidelines, community-wide six-month TST-untargeted IPT has been recommended in South Africa since 2010 [17]. In 2011, IPT

began to be offered community-wide to all symptom-free PLWH at no charge through the public health system in uMgungundlovu District of KwaZulu-Natal.

Overlapping with IPT implementation in South Africa, anti-retroviral therapy (ART) was expanded at community-level, with PLWH offered no-cost ART at progressively higher levels of immune function [18-21]. As ART rapidly improves immune function, it also provides protection against TB disease among those with latent infection [22]. The overlap between interventions made it difficult to determine the degree of IPT effectiveness to prevent TB in this setting.

Randomised controlled trials of IPT use in the South African context have shown heterogeneous results in terms of IPT efficacy with and without ART [23]. One large study of nine-month IPT versus placebo among miners in Gauteng province suggested that IPT may only prevent TB for the duration of use [24]. Another study of HIV-exposed or infected neonates on ART in urban centres of South Africa found no difference in TB incidence between those given 24-month IPT or placebo [25], while a study of adults on ART in Western Cape found a 37% decrease in TB incidence after a median 27 months of follow-up of 12-month untargeted IPT compared to placebo, Hazard Ratio=0.63, 95%CI=0.41-0.94 [26].

In contrast with randomised controlled trials, effectiveness studies involve the analysis of observational health system data, enabling researchers to describe how well a medication works under normal programme conditions. In 2010, Corbett and Churchyard posited that effectiveness studies would show clearer benefits of IPT in high-burden settings since real-world comparison groups would not be held to the high standard of patient care under trial conditions [7]. To date, few effectiveness studies have been undertaken in South Africa [27-28] and none have looked at community-wide, untargeted short-course IPT in comparatively homogenous populations such as Zulu communities in KwaZulu-Natal.

With IPT implementation and ART scale-up occurring early in uMgungundlovu District, we investigated the effectiveness of IPT and ART alone and in combination to prevent TB disease across two years compared with no intervention. We hypothesised that IPT alone and ART alone would provide similar levels of protection against TB and greater protection when used together. Since TST was not used to prioritise people receiving IPT in this setting, we also compared the number of expected versus actual TB events among IPT completers assumed to have negative TST results. Based on existing evidence, we hypothesised that the number of actual TB events among people in the IPT-only group would be greater than or equal to the

number of expected events, suggesting that IPT provided benefit only to the proportion of individuals who we would expect to be TST positive [11].

Methods

Setting

An estimated 70% of TB diagnoses in KwaZulu-Natal are HIV-related, the highest percentage of TB-HIV reported in a general population worldwide [29]. UMgungundlovu District has a population of one million people, among whom 74% speak isiZulu as their home language [30]. The average annual household income is US$2100 [30]. Grobler and colleagues reported an HIV prevalence of 44% among females and 28% among males between the ages of 15-49 years based on household prevalence survey data collected in uMgungundlovu District between 2014 and 2015 [31]. The District reports a TB notification rate of 894 per 100 000 population [29]. Multi-drug resistance to first-line bactericidal drugs isoniazid and rifampin is estimated at 7% among all people with TB and 15% among PLWH [32].

Study design

We conducted a retrospective cohort study among PLWH in a large peri-urban community health centre catchment area of uMgungundlovu District between January 1, 2011 and December 31, 2014 to determine the effectiveness of six-month untargeted IPT for the prevention of active TB amongst ART and non-ART users. The study received ethical approval from the University of Calgary Conjoint Health Research Ethics Board and the Biomedical Research Ethics Committee of the University of KwaZulu-Natal. We received administrative approval from the KwaZulu-Natal Department of Health and the uMgungundlovu Health District Office to access District and catchment-level data. We received a waiver of informed consent from research ethics boards to collect personal identifiers to perform register and database linkage. Once datasets were linked, personal identifiers were then removed for the purposes of data analysis.

IPT data were collected from three public clinics that made up the ART catchment covered by the community health centre. Data from clinic-level, paper-based IPT registers were entered into Microsoft Excel spreadsheets and cleaned using Excel 14.6.9 and Stata/IC for Mac version 13.1. We linked IPT data to electronic catchment-level ART data captured by the District to consider the effect of ART on TB incidence and to identify an unexposed comparison group of

PLWH with access to the same public health services over the study period. As no unique identifiers were uniformly shared, we probabilistically linked these datasets.

As has been published elsewhere, IPT completers were defined as people completing at least 80% of the regimen within a period of nine months [33]. We operationalised this definition by including all PLWH who started IPT between January 1, 2011 and December 31, 2012 and collected at least five month-long prescriptions by the eighth month, according to IPT clinic registers. Due to small numbers that prevented the ability to assess a dose-response relationship, we excluded people who took fewer than five months (n=237) from further analysis. We also excluded records of people who collected their last prescription at month nine or later (n=2). ART users were defined as PLWH whose first ART prescription was collected prior to or during study time and whose last prescription was collected after censoring or outcome of TB, with no treatment stoppage recorded in the ART register database. As the focus of our study was on IPT effectiveness, we excluded people whose last ART prescription was collected during the study period to ensure unambiguous ART categories. IPT+ART users were those who met criteria for both IPT and ART use as defined above. People receiving no intervention were those who did not begin ART during the study period or began ART only after TB diagnosis, and for whom there was no evidence of IPT use prior to or during the study period according to ART, IPT, or TB case registers.

Among IPT users, we defined IPT start date as the date of first IPT collection according to IPT registers. We defined IPT completion date as the last collection date recorded on the register plus 28 days, assuming completion of pills collected at last pick-up. We defined study time among the exposed as the duration between actual IPT start and completion dates plus 540 days (18 months) of follow-up. We defined a TB event as any diagnosis of TB (pulmonary or extra-pulmonary) confirmed by smear, culture, and/or GeneXpert during cohort time according to District-level datasets for drug-susceptible and drug-resistant TB, excluding *a priori* any diagnoses based solely on radiological (n=7950) or other clinical suspicion (n=1562). We excluded cases listed as "repeat after default" when the initial TB diagnosis occurred before the study period. Details of study selection are outlined in Figure 3.

Figure 3: Study selection
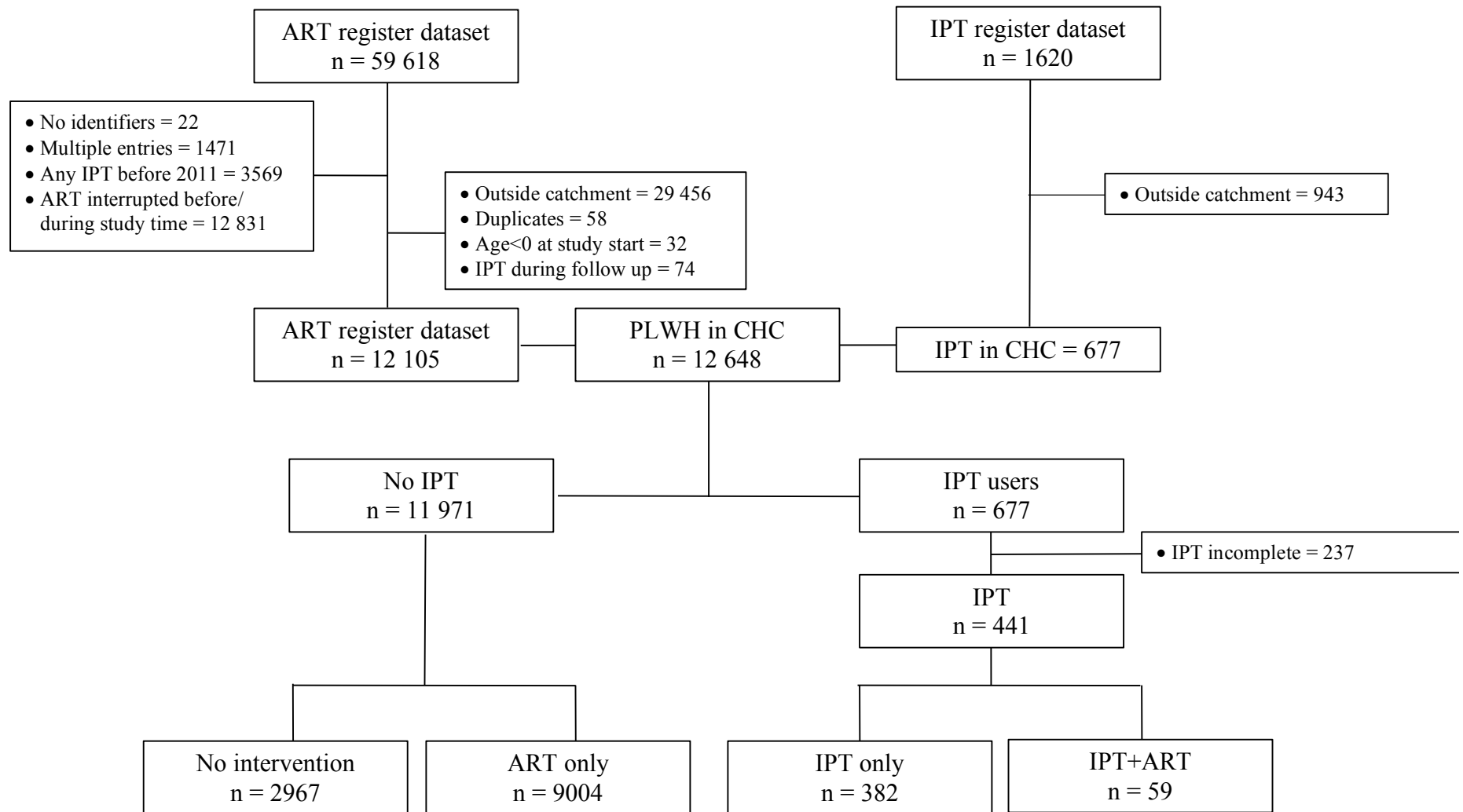
Data analysis

We utilised Stata/IC for Mac version 13.1 for all analyses. As this was a descriptive analysis, we present cohort and event numbers along with person years at risk for each exposure category. As appropriate, proportions were compared using one or two-sample proportion tests. At-risk time was calculated as the total disease-free time each person contributed to the cohort, with censoring occurring at the end of the study period. Due to the complexities of the pathogenesis of TB drug resistance and the potential for lasting TB preventive effects following treatment, individuals developing TB during the study period did not return to disease-free status if they completed treatment during the study period. We calculated cumulative incidence (risk), incidence rates, and incidence rate ratios with confidence intervals to evaluate differences between interventions. Rate differences and associated confidence intervals were also calculated due to zero cell counts in contingency tables. We report rate differences in terms of case reduction (CR) for ease of interpretation. These outcome data were considered collectively to assess stratification.

We utilised stratified analysis to evaluate potential confounders and effect modifiers. Incidence rates and ratios were compared using the Poisson distribution. We considered *a priori* covariates and differences established in the literature, including sex [34], age (<35 versus ≥35 years) at cohort start date [33,35], and CD4 cell count (≥250 versus <250 μm/L) at ART baseline [36]. As ART regimens varied widely during the period of investigation, we considered tenofovir-containing ART regimen (Yes/No) as a proxy for PLWH on next generation ART regimens. Given the rapid improvement of immune function following initiation of ART [22], we also considered ART duration at IPT completion (≥1 versus <1 year). While previous TB is an independent risk factor for recurrent TB [37] and would also involve previous exposure to isoniazid, comprehensive TB data was unavailable for the catchment area prior to 2010. We therefore could not consider the potential confounding or modifying effects of previous TB in our analysis.

To estimate the impact of IPT initiation without the use of TST to target those most likely to benefit, we compared actual to expected TB outcomes among ART-naïve IPT users based on assumptions that disproportionately favoured the use of targeted TST. Since there were no available data on TST positivity for this setting, we assumed that the proportion of TST

positivity in the catchment was equal to the highest documented proportion among PLWH in under-resourced settings, 32.6% [38]. We estimated expected TB events by multiplying the proportion of people who developed TB over two years in the non-intervention group by sex with the number of people who were estimated to be TST negative by sex. We then assumed that all actual TB events occurred amongst the number of females or males who were estimated to be TST negative, and compared expected with actual TB events using Z-tests.

Findings

We followed 12 412 PLWH for a total of 21 473 person years, among whom 441 completed IPT. Table 1 describes the baseline characteristics of PLWH by exposure category. With no intervention, TB incidence rates amongst PLWH appeared to increase with age and decrease with rising immune function. Overall there were 408 incident events of TB amongst the cohort, of which 217 occurred among PLWH who were both ART and IPT-naïve prior to TB diagnosis, 186 occurred among people using ART alone, and five occurred among people using IPT alone. Zero cases occurred amongst 59 PLWH who received both ART and IPT during the study. Incidence rates were 3976, 1226, 674, and 0 per 100 000 person years, respectively. Six TB-related deaths were recorded amongst IPT and ART-naïve PLWH, zero among IPT users, and 27 among ART users, although we were unable to obtain all-cause mortality data for this project. See Table 3 for TB outcomes by intervention.

Table 1: Baseline characteristics by intervention

	No intervention (n=2967)	ART alone (n=9004)		IPT alone (n=382)		IPT+ART (n=59)	
Mean follow-up in days (sd)	671.91 (95.37)	615.48 (162.48)		708.90 (46.89)		626.73 (160.93)	
	n (%)	**n (%)**	**vs None**	**n (%)**	**vs None**	**n (%)**	**vs None**
Sex							
Female	1967 (66.30)	6144 (68.24)	p=0.05	284 (74.35)	p=0.002	42 (71.19)	p=0.43
Male	1000 (33.70)	2860 (31.76)		98 (25.65)		17 (28.81)	
missing	0	0		0		0	
Age							
0-34 years	2036 (68.62)	4298 (47.73)	p<0.001	206 (53.93)	p<0.001	26 (44.07)	p<0.001
≥35 years	931 (31.38)	4706 (52.27)		162 (42.41)		33 (55.93)	
missing	0	0		14 (3.66)		0	
CD4 count at ART initiation							
<250	1311 (44.19)	5499 (61.07)	p<0.001	7 (1.83)	p=0.14	26 (44.07)	p=0.94
≥250	1341 (45.20)	1564 (17.37)		14 (3.66)		26 (44.07)	
missing	315 (10.62)	1941 (21.56)		361 (94.50)		7 (11.86)	
ART duration							**vs ART**
≥1yr at cohort start	-	4403 (48.90)		-		10 (16.95)	p<0.01*
<1yr at cohort start	-	4601 (51.10)		-		10 (16.95)	
Initiated during IPT	-	-		-		39 (66.10)	
missing	-	0		-		0	
ART regimen							
Tenofovir containing	-	5929 (65.85)		-		12 (20.34)	p=0.12
non-Tenofovir	-	2609 (28.98)		-		45 (76.27)	
missing	-	466 (5.18)		-		2 (3.39)	

Abbr: n=number, ART=antiretroviral therapy, IPT=isoniazid preventive therapy, sd=standard deviation, None=No intervention, yr=year

*p-value given for '<1 yr at cohort start combined' with 'initiated ART during IPT' for IPT+ART group

Table 2: Crude and adjusted TB outcomes by intervention

	n	TB events	PYs	Risk (%)	IR	IRR	95% IRR CI	CR	95% CR CI
No intervention	2967	217	5458	7.31	3976	1	-	-	-
ART only	9004	186	15 172	2.07	1226	0.69	0.62-0.75	2750	2192-3307
IPT only	382	5	741	1.31	674	0.17	0.05-0.40	3302	2508-4095
IPT+ART	**59**	**0**	**214**	**0.00**	**0**	**0.00**	**0.00-0.44**	**3976**	**3447-4505**
<35 yoa, CD4≥250									
No intervention	970	39	1812	4.02	2153	1	-	-	-
ART only	**912**	**20**	**1532**	**2.19**	**1305**	**0.61**	**0.33-1.07**	**848**	**38-1 733**
IPT only	8	2	15	25.00	13 677	6.35	0.74-24.54	-11 524	-30 491-7443
IPT+ART	8	0	13	0.00	0	0.00	0.00-13.79	2153	1477-2829
≥35 yoa, CD4≥250									
No intervention	371	20	689	5.39	2903	1	-	-	-
ART only	**652**	**9**	**1126**	**1.38**	**799**	**0.28**	**0.11-0.63**	**2104**	**729-3 480**
IPT only	6	1	10	16.67	9808	3.38	0.08-21.12	-6905	-26 170-12 360
IPT+ART	18	0	34	0.00	0	0.00	0.00-4.09	2903	1631-4176
<35 yoa, CD4<250					IR				
No intervention	837	77	1531	9.20	5031	1	-	-	-
ART only	**2437**	**69**	**4014**	**0.37**	**1719**	**0.34**	**0.24-0.48**	**3312**	**2117-4507**
IPT only	5	0	4	0.00	0	0.00	0.00-7.80	5031	3907-6154
ART+IPT	13	0	23	0.00	0	0.00	0.00-3.22	5031	3907-6154
≥35 yoa, CD4<250									
No intervention	474	65	8434	13.71	7705	1	-	-	-
ART only	**3062**	**55**	**5175**	**1.80**	**1063**	**0.14**	**0.09-0.20**	**6642**	**4748-8537**
IPT only	2	0	10	0.00	0	0.00	0.00-12.63	7705	5832-7705
IPT+ART	13	0	20	0.00	0	0.00	0.00-2.40	7705	5832-9578
Females									
No intervention	1967	111	3645	5.64	3045	1	-		
ART only	6144	111	10 431	1.81	1064	0.35	0.27-0.46	1981	1381-2581
IPT only	**284**	**0**	**554**	**0.00**	**0**	**0.00**	**0.00-0.22**	**3045**	**2478-3611**
IPT+ART	42	0	75	0.00	0	0.00	0.00-1.65	3045	2478-3611
Males									
No intervention	1000	106	1813	10.60	5848	1	-		
ART only	2860	75	4742	2.62	1582	0.27	0.20-0.37	4266	3097-5435
IPT only	**98**	**5**	**187**	**5.10**	**2671**	**0.46**	**0.15-1.10**	**3176**	**584-5 769**
IPT+ART	17	0	27	0.00	0	0.00	0.00-2.40	5848	4734-6961

n=number, PYs=person years, IR=incidence rate per 100 000 person years, IRR=incidence rate ratio, CI=confidence interval, CR=case reduction per 100 000 person years, yoa=years of age, ART=antiretroviral therapy, IPT=isoniazid preventive therapy

IPT alone

Despite a relatively even distribution of TB between sexes in uMgungundlovu District at baseline (females=48.41%), proportionately many more females initiated (71.61%) and completed IPT (73.92%) compared to men (p<0.001 for both comparisons) (see Figure 4). Among PLWH who started IPT, 64.25% of men and 65.59% of women completed IPT (p=0.79).

Figure 4: Baseline TB incidence and IPT uptake proportionally by sex
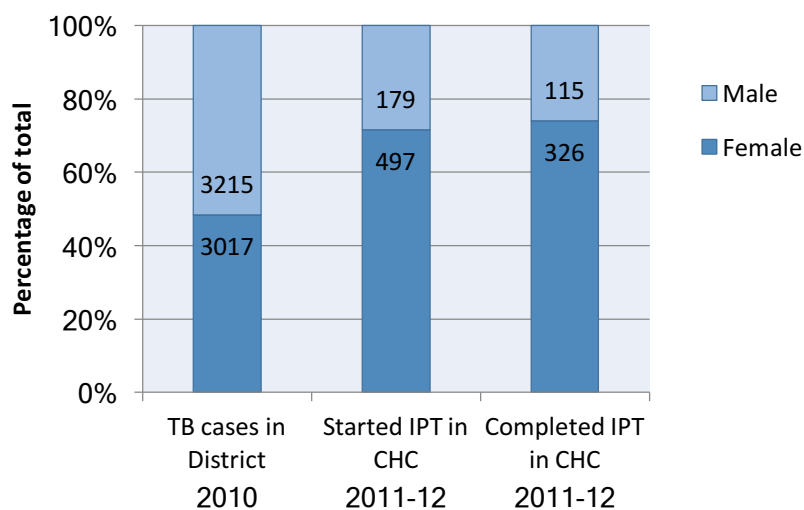
CHC=community health centre, numbers in bars indicate number of people

Overall the use of IPT alone reduced the risk of TB by 83.05% compared to PLWH receiving no intervention (IRR=0.17, 95%CI=0.05-0.40), although this finding appeared to be modified by sex. Zero cases occurred among females (one-sided 97.5%CI$_{IRR}$=0.00-0.22), while TB incidence rates decreased by 54.33% among males (IRR=0.46, 95%CI=0.15-1.10). Stratified results did not appear to vary by age.

Among an estimated 191 TST-negative females, zero actual versus 11 expected cases of TB developed (p<0.001), while five actual versus seven expected cases developed among an estimated 66 TST-negative males (p=0.35).

ART alone

The benefits of ART to prevent TB in follow-up varied by age group and CD4 cell count. Among those receiving ART alone, those at highest risk of TB activation (i.e. older age, low CD4 cell count) received the greatest protection, with the greatest drop in both absolute number

(6642 per 100 000 person years, 95%CI_{RD}=4748-8537) and incidence rate (86.20%) of active TB compared to the same group with no intervention (IRR=0.14, 95%CI_{IRR}=0.09-0.22). ART alone in this group appeared to perform similarly to IPT alone in females and potentially better than IPT alone in males. IPT alone among males and females appeared to perform better than ART among people with high CD4 counts (≥250 μm/L), and people over 35 years of age appeared to receive greater protective benefit from ART alone compared to those under 35 years of age ($IRR_{\geq 35}$=0.27, 95%CI 0.11-0.63 versus $IRR_{<35}$=0.61, 95%CI=0.34-1.07, p=0.11).

ART and IPT

As zero cases of TB developed among IPT users who were also on ART, our data suggest that IPT increased the protective effect of ART (see Figure 5). As the baseline TB incidence rate increased between groups, ART performed more effectively to reduce TB, although there appeared to be a baseline TB incidence rate at around 1000 per 100 000 person years beyond which ART did not provide protection. When IPT and ART are both taken, IPT appears to close the remaining gap in TB incidence rates (Figure 5, plot 1). IPT also appeared to modify the response of ART such that the differences between groups were less pronounced (Figure 5, plot 2).

Figure 5: Changes in TB incidence rates and case reduction with IPT in addition to ART

Plot 1: TB Incidence Rates

Plot 2: TB Case Reduction
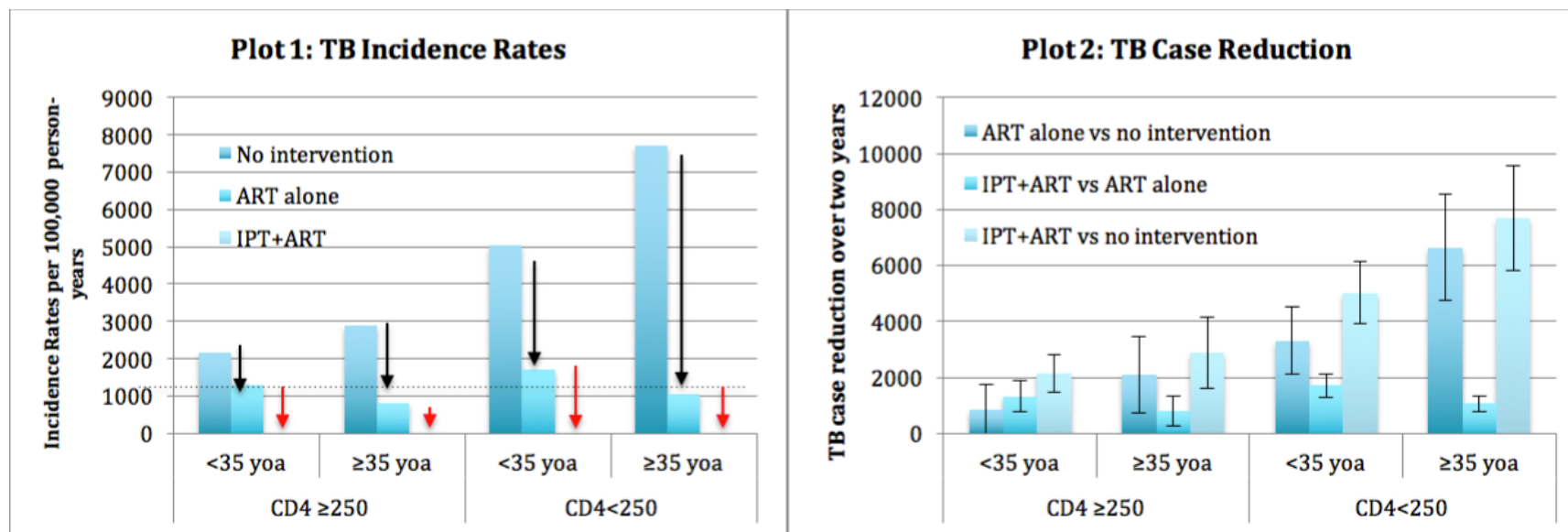
Plot 1: Black arrows represent reduction in TB incidence rates among people receiving ART by age and CD4 stratum; dotted line indicates the theoretical baseline of ART-induced protection against TB; red arrows suggest a closing of the gap in TB incidence rates as a result of adding IPT.

Discussion

Our analysis suggests that among clinic-going PLWH in uMgungundlovu District, KwaZulu-Natal, untargeted six-month IPT works to decrease the incidence of active TB for two-years with and without the use of ART. The ability of ART to prevent TB appears to differ by age and CD4 count, with higher baseline risk showing greater absolute effects in our sample. Together IPT and ART appeared to provide the best protection against TB over two years, with IPT appearing to modify the differing effects of ART between age and CD4 strata.

Our findings also suggest that IPT may be effective at reducing TB incidence rates even amongst individuals who would not mount a response to TST in this setting. Based on our assumptions, which disproportionately favoured the use of targeted IPT, fewer females than expected developed TB (11 expected versus zero actual events, p<0.001). A similar trend was evident among males (seven expected versus five actual events), although the difference was not statistically significant (p=0.35). Although the findings of some efficacy studies in Southern Africa have reported no protective benefit among TST-negative IPT users [11,24,25,39], these studies involved different target populations with varying follow-up periods. Our overall findings are similar to Rangaka and colleagues who undertook a randomised controlled trial of an adult population on or initiating ART in an informal African settlement in Western Cape province [26]. In their study, one-year of untargeted IPT was found to provide 37% better protection against TB compared to placebo over 2.4 years of follow-up, regardless of CD4 cell count [26]. Their study also showed a protective benefit amongst individuals with negative TST, suggesting that TST may be less useful for targeting IPT amongst those already on ART in TB endemic settings [23,26].

Effectiveness studies in other high-burden settings have also found effects of IPT alone and with ART. Golub and colleagues reported adjusted Hazard Ratios (aHR) of 0.47 and 0.36 among ART-only users, 0.32 and 0.73 among users of IPT only, and 0.20 and 0.15 among IPT+ART users who were TST positive in Rio de Janeiro, Brazil and Gauteng province, South Africa, respectively [27,40]. Yirdaw *et al.* reported an aHR of 0.36 for IPT alone (95%CI=0.19-0.16), 0.32 for ART alone (95%CI=0.24-0.43), and aHR of 0.18 when IPT was added to ART (95%CI=0.10-0.42) [41]. Khawcharoenporn *et al.* reported a 4-year incidence rate ratio of 0.45

amongst undifferentiated IPT+ART users (p=0.13), with 0 of 17 TST-positive and 5 of 183 TST-negative PLWH developing pulmonary TB among those whose TST status was known [42].

The strong effect of IPT alone demonstrated in our study, at least among females, is likely related to a combination of a higher HIV prevalence driving TB incidence in KwaZulu-Natal (fast progression to disease) [29], the follow-up of TST untargeted PLWH (large sample with evidence to suggest a reductive effect among individuals with a negative TST), and follow-up limited to 24 months to align with WHO's recommendation to repeat short-course IPT every two years in high TB-HIV burden settings [4]. Given that the one-sided confidence interval indicated a minimum of 77.78% TB reduction among females on IPT alone compared to no intervention (97.5%CI=0.00-0.22), we would also expect that IPT+ART would perform even better, despite a limited sample size in this group. Although the amount of follow-up time among males limited precision of the estimate, potential sex differences in TB prevention due to IPT may relate to higher immune function. Among individuals whose CD4 cell counts were known (n=73), 39.12% of females completing IPT had low CD4 cell counts compared with 59.09% of males (p<0.001). Furthermore, IPT adherence was measured by the number of month-long prescriptions collected, which may not equate to the actual number of pills taken per month by each person. Potential sex differences may therefore also be explained by disproportionate expectations for women to follow instructions in this setting, resulting in better adherence, as we described elsewhere [43]. Nonetheless, in absolute numbers, males in our study demonstrated a similar reduction in the number of TB cases (1-Rate Difference) compared to females, albeit with a wider margin of error (CR_{Male}=3176, 95%CI=584-5769 versus CR_{Female}=3045, 95%CI=2478-3611). Further research is needed to determine a more precise estimate for IPT benefit among males.

Heterogeneous effectiveness findings may also relate to additional epidemiological differences between populations. In Mill *et al.'s* mathematical model of IPT use in HIV-endemic settings, the authors reported a "dramatic heterogeneity" amongst sub-regions with high clustering of TB contacts [44]. A more recent model of non-endemic HIV settings found that IPT would perform best in medium-burden settings (500-900 cases per 100 000 person years) owing to the risk of reinfection over time in high-burden settings [45], but showed that in HIV-endemic areas, the number needed to treat would decrease substantially. The authors demonstrated that the optimal number needed to treat (14 people) was attained in models of HIV-endemic settings

when TB incidence was 3767 per 100 000 person years and HIV prevalence was 26%, similar to communities in our study [44]. Our study population is also at lower epidemiological risk of progressive primary TB compared to neonates in Mahdi *et al.* [25] or reinfection compared to mine workers in Churchyard *et al.* [24], which helps explain the divergence in findings.

Limitations

Given the small number of IPT users, we were not able to investigate a potential dose-response relationship among IPT users, and thus limited our analysis to PLWH whose records provided evidence of IPT completion and/or consistent ART use. As such, our findings are limited to adherent patients already seeking regular care at decentralised clinics for whom other health, mobility, and economic conditions did not prevent the collection of monthly IPT prescriptions. In short, these analyses speak to the effectiveness of IPT in the best-case scenario. Although our findings suggest a longer-term population effect in line with Ragonnet *et al.'s* model [45], factors that preclude adherence and long-term health outcomes have not been considered. We report on broader implications of acceptability of IPT and implications for population-level effectiveness elsewhere [46]. Of particular note is the fact that men are less likely to present to clinic, and thus less likely to benefit from IPT. This trend has also been reported with regard to HIV testing [47]. As Grobler *et al.* reported, among the men that agreed to be tested in a household prevention survey in uMgungundlovu, 48% of males testing positive for HIV did not previously know their HIV status, whereas only 35% of females did not know their HIV status [31]. Again, this means that the generalisability of these findings is limited to people who already interact with the clinic regularly, and findings do not necessarily represent the effectiveness of those at highest risk for developing TB disease. Furthermore, the WHO recommends re-treatment with IPT every two years in high HIV-burden settings due to risk of reinfection and the potential for reduced endemic immunity among those who have taken IPT [4,33]. Current IPT guidelines in South Africa recommend that IPT be offered only once [14], and the degree to which repetition of short-course IPT occurs in this setting is unknown.

Another limitation is that the data were collected for purposes other than research. Considered with the small number of IPT users this could mean a potential for selection bias. Although IPT guidelines recommended that all PLWH be offered IPT unless symptoms of active TB or a high risk for hepatotoxicity were present, the number of people initiated on IPT was

much lower than ART. Part of this is likely explained by the differential push for ART expansion at this time, which was already an established programme with which clinicians were familiar. Nonetheless, it is difficult to know if people offered and initiating IPT differed systematically in some way that would differentially effect IPT outcomes. For example, did some clinicians offer IPT routinely while others not at all, or were seemingly healthier patients more often offered IPT? Since we did not have CD4 cell counts for many of the IPT alone users, it is difficult to gauge the general health of this group at IPT initiation, in which case, if this type of selection bias were present, the strong preventive effects of IPT reported herein could move closer to null values. Future prospective research taking into account measures of immune function at IPT initiation and additional information on clinical decisions for offering IPT would help to clarify the strength of the preventive effect of IPT.

Another limitation of the available data is that of the 382 IPT-only users, 358 did not appear in the ART database by 2015. As such, it is possible that some of these people i) moved out of the District and later developed TB, ii) died from a cause other than TB, but potentially related to IPT use, or iii) accessed ART through the private system. Any of these possibilities could shift the findings about IPT alone toward the null value. As such, we have been particularly cautious about drawing conclusions about this group. However, for the following reasons, these findings still provide compelling evidence for the effectiveness of IPT among people who are already accessing clinic services. In particular, mortality has been of concern for IPT use in this setting after an early efficacy study of 36-month IPT reported an increase in mortality among IPT users in a sub-analysis of actual treatment arms. Yet, the same was not found in the intention-to-treat analysis, as loss to follow-up may differentially bias the results in either arm [11]. A similar increase in mortality has not been reported in other studies [23]. One would also expect that IPT complications would most likely be reported during treatment, when toxicity related to the regimen would be at its highest [48]. Among the 677 IPT users in the community health centre catchment (regardless of completion), zero deaths were reported on IPT registers. Moreover, six-month regimens have been shown to be well-tolerated in similar populations [49]. Finally, the fact that patients accessed IPT regularly through the public system suggests that they would also feel comfortable accessing ARTs through the same channels. Even so, prospectively collected cohort data is needed to confirm these findings. Future research is also needed to help determine the precision of the protective benefits of IPT use in males, IPT

added to ART, and possible dose-response effects of IPT short-course in this population. Further analysis on mortality outcomes in the population must also be investigated.

Implications

Despite recent recommendations to initiate ART at the time of HIV diagnosis regardless of immune function [50,51], the use of ART in high-burden settings is still limited. Even in South Africa, ART availability still varies widely by province and proximity to referral centre. While our data suggest that untargeted IPT would benefit people regardless of TST status, treating immune-compromised PLWH with IPT alone can result in acquired isoniazid drug resistance that may not develop into transmissible disease for years. Despite recently published data suggesting that isoniazid resistance has not risen in KwaZulu-Natal since community-wide IPT implementation [52], the biological actions of IPT in anergic immune-compromised adults are still unclear. IPT use among individuals with negative TST can result in unnecessary treatment, sterilisation of recently or distantly acquired latent tuberculosis, or the potentially inadequate and inappropriate treatment of preclinical or undiagnosed TB [23]. To date there is insufficient evidence to support a conclusion on the long-term implications of drug resistance with untargeted community-wide IPT use, and given the limited resources in settings where ART is not widely available, ability to monitor IPT use consistently is unlikely.

Further considering the complexity of TST use in these settings [11,53] and the prohibitive expense of Interferon Gamma Release Assays or viral load testing, we recommend at minimum that clinical judgements continue to be based upon CD4 cell counts where ART use is limited. Until more data are available or progression to TB disease can be better predicted amongst the immune-compromised, we recommend a cautious approach, providing untargeted short-course IPT to people with high CD4 cell counts and advocating for ART implementation for people with low CD4 cell counts, as ART would provide additional protection against other HIV co-infections. IPT, if available, could then be added to ART regimens to further decrease the risk of progressing to TB disease. In settings where universal HIV test-and-treat policies have been implemented, people would benefit most from concurrent initiation of IPT+ART.

Conclusions

In a peri-urban setting with a high incidence of TB and TB-HIV in the general population, six-month, TST-untargeted IPT offered through the public system appeared to improve two-year TB incidence alone or in combination with ART among PLWH. While the data suggest that untargeted IPT would benefit people regardless of TST result, we recommend that IPT be offered to people with higher CD4 cell counts where ART use is limited until more research is available.

References

1. Stop TB Partnership. The paradigm shift: Global plan to end TB 2016-2020. UNOFP: Geneva, 2015.

2. UNAIDS. South Africa HIV and AIDS Estimates (2015). Available from http://www.unaids.org/en/regionscountries/countries/southafrica. [Accessed 11th Sep 2017].

3. World Health Organisation. Global Tuberculosis Report 2016. Geneva: The Organisation; 2016 Available from: http://www.who.int/tb/publications/global_report/en/ [Accessed 8th Jul 2017].

4. Lawn SD, Bekker SG. Co-pathogenesis of tuberculosis and HIV. In Schaaf HS, Zumla AI, editors. Tuberculosis: A Comprehensive Clinical Reference. London: Elsevier; 2009. p. 96-106.

5. World Health Organisation. Guidelines for intensified tuberculosis case-finding and isoniazid preventive therapy for people living with HIV in resource-constrained settings. Geneva: The Organisation; 2011. Available from: http://www.who.int/tb/challenges/hiv/ICF_IPTguidelines/en/index.html. [Accessed 25th Apr 2017].

6. Menzies D, Doherty TM. Diagnosis of latent tuberculosis infection. In Raviglione, editor. Reichman & Hershfield's Tuberculosis: A Comprehensive, International Approach. 3rd ed. Geneva: WHO; 2006.

7. Churchyard G, Corbett E. Tuberculosis and HIV. In Abdool Karim SS, Abdool Karim Q, editors. HIV/AIDS in South Africa. 2nd ed. Cambridge: Cambridge;2010. pp. 457-78.

8. World Health Organisation. WHO treatment guidelines for drug-resistant tuberculosis. 2016 update. Geneva: The Organisation; 2016. Available at: http://www.who.int/tb/MDRTBguidelines2016.pdf [Accessed 10 June 2016].

9. Date AA, Vitoria M, Granich R, Banda M, Youssef M, Gilks C. Implementation of co-trimoxazole prophylaxis and isoniazid preventive therapy for people living with HIV. Bull World Health Organ. 2010; 88: 253-259.

10. Comstock G. How much isoniazid is needed for prevention of tuberculosis among immunocompetent adults? Int J Tuberc Lung Dis. 1999; 3(10): 847-850.

11. Samandari T, Agizew TB, Nyirenda S, Tedla Z, Sibanda T, Shang N, et al. 6-month versus 36-month isoniazid preventive treatment for tuberculosis in adults with HIV infection in Botswana: a randomised, double-blind, placebo-controlled trial. Lancet. 2011; 377(9777): 1588-98.

12. Nardell E, Churchyard G. What is thwarting tuberculosis prevention in high-burden settings? N Engl J Med 2011;365(1):79-81.

13. World Health Organisation. WHO three I's Meeting: intensified case finding, isoniazid preventive therapy and TB infection control for people living with HIV. Geneva: The Organisation; 2008.

14. Samandari T, Bishai D, Luteijn M, Mosimaneotsile B, Motsamai O, Postma M, et al. Costs and consequences of additional chest x-ray in a tuberculosis prevention program in Botswana. Am J Respir Crit Care Med. 2011;183(8):1103-11.

15. Pai M, Denkinger CM, Kik SV, Rangaka MX, Zwerling A, Oxlade O, et al. Gamma interferon release assays for detection of *Mycobacterium tuberculosis* infection. Clinical Microbiology Reviews. 2014;27(1):3-20. doi:10.1128/CMR.00034-13.

16. Tebruegge M, Bohyi M, Soriano-Arandes A, Kampmann B. Shortage of purified protein derivative for tuberculosis testing. Lancet. 2014; 384(9959): 2026.

17. South Africa Department of Health. Guidelines for tuberculosis preventive therapy among HIV infected individuals in South Africa. Pretoria: The Department; 2010.

18. World Health Organisation. Guideline on when to start antiretroviral therapy and on pre-exposure prophylaxis for HIV. Geneva: The Organisation; 2015. Available from: http://apps.who.int/iris/bitstream/10665/186275/1/9789241509565_eng.pdf [Accessed 25th Apr 2017].

19. Johnson LF. Access to antiretroviral treatment in South Africa, 2004 – 2011. SA J HIV Med. 2012; 13(1). Available from: http://www.sajhivmed.org.za/index.php/hivmed/article/view/156/261 [Accessed 25th Apr 2017].

20. South Africa Department of Health. The South African Antiretroviral Treatment Guidelines 2010. Pretoria: The Department; 2010 Available from: http://apps.who.int/medicinedocs/documents/s19153en/s19153en.pdf. [Accessed 25th Apr 2017].

21. South Africa Department of Health. National Consolidated Guidelines for the prevention of mother-to-child transmission of HIV (PMTCT) and the management of HIV in children, adolescents, and adults. Pretoria: The Department; 2014. Available from: http://www.sahivsoc.org/Files/ART%20Guidelines%2015052015.pdf. [Accessed 25th Apr 2017].

22. Suthar AB, Lawn SD, del Amo J, Getahun H, Dye C, Sculier D, et al. Antiretroviral therapy for prevention of tuberculosis in adults with HIV: a systematic review and meta-analysis. PLoS Med. 2012;9(7):e1001270.

23. Wood R, Becker LG. Isoniazid preventive therapy for tuberculosis in South Africa: An assessment of the local evidence base. South African Med J. 2014; 104(3):147-77.

24. Churchyard GJ, Fielding KL, Lewis JJ, Coetzee L, Corbett EL, Godfrey-Faussett P, et al. A trial of mass Isoniazid Preventive Therapy for tuberculosis Control. N Engl J Med 2014; 370:301-310. DOI: 10.1056/NEJMoa1214289

25. Madhi SA, Nachman S, Violari A, et al. Primary isoniazid prophylaxis against tuberculosis in HIV exposed children. N Engl J Med 2011; 365(1):21-31.

26. Rangaka MX, Wilkinson RJ, Boulle A, Glynn JR, Fielding K, van Cutsem G, et al. Isoniazid plus antiretroviral therapy to prevent tuberculosis: A randomised double-blind placebo-controlled trial. Lancet 2014; 384(9944): 682-90.

27. Golub JE, Saraceni V, Cavalcante SC, Pacheco AG, Moulton LH, King BS, et al. The impact of antiretroviral therapy and isoniazid preventive therapy on tuberculosis incidence in HIV-infected patients in Rio de Janeiro, Brazil. AIDS. 2007; 21(11):1441-8.

28. Charalambous S, Grant AD, Innes C, Hoffmann CJ, Dowdeswell R, Pienaar J, et al. Association of isoniazid preventive therapy with lower early mortality in individuals on antiretroviral therapy in a workplace programme. AIDS 2010;24 (Suppl 5):S5-S13.

29. KwaZulu-Natal Department of Health. IPT indicators [dataset]; Pietermaritzburg: The Department; 2014.

30. Statistics South Africa qtd. in WaziMaps. Statistics by District (Census 2011/2016 data). Available at: https://wazimap.co.za/profiles/district-DC22-umgungundlovu/ [Accessed 06 Apr 2018].

31. Grobler A, Cawood C, Khanyile D, Puren A, Kharsany ABM. Progress of UNAIDS 90-90-90 targets in a district in KwaZulu-Natal, South Africa, with high HIV burden, in the HIPSS study: a household-based complex multilevel community survey. Lancet HIV 2017; 4: e505–13.

32. Moodley P, Shah NS, Tayob N, Connolly C, Zetola N, Gandhi N, et al. Spread of Extensively Drug-Resistant Tuberculosis in KwaZulu-Natal Province, South Africa. PLoS One 2011; 6(5): [about 6 p.]. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3104985/pdf/pone.0017513.pdf. [Accessed 22 Sep 2014].

33. Apers L, Robert C, Nachega JB. Prophylaxis with antituberculosis drugs in special situations. In Schaaf HS, Zumla AI, editors. Tuberculosis: A Comprehensive Clinical Reference. London: Elsevier;2009. p. 780-85.

34. Horton KC, MacPherson P, Houben RM, White RG, Corbett E. Sex Differences in Tuberculosis Burden and Notifications in Low- and Middle-Income Countries: A Systematic Review and Meta-analysis. PLoS Med. 2016 Sep; 13(9): e1002119.

35. Kopanoff DE, Snider DE Jr, Caras GJ. Isoniazid-related hepatitis: A U.S. Public Health Service cooperative surveillance study. Am Rev Respir Dis. 1978 Jun;117(6):991-1001.

36. Cohen MS, Chen YQ, McCauley M, Gamble T, Hosseinpour MC, et al. Prevention of HIV-1 with early anti-retroviral therapy. N Engl J Med. 2011; 365(6):493-505.

37. Panjabi R, Comstock GW, Golub JE. Recurrent tuberculosis and its risk factors: Adequately treated patients are still at high risk. Int J Tuberc Lung Dis. 2007 Aug;11(8):828-37.

38. Kerkoff AD, Kranzer K, Samandari T, Nakiyingi-Miiro J, Whalen CC, Harries AD, et al. Systematic review of TST responses in people living with HIV in under-resourced settings: Implications for isoniazid preventive therapy. PLoS One 2012;7(11):e49928.

39. Mohammed A, Myer L, Ehrlich R, Wood R, Cilliers F, Maartens G. Randomised controlled trial of isoniazid preventive therapy in South African adults with advanced HIV disease. Int J Tuberc Lung Dis 2007;11(10):1114-1120.

40. Golub JE, Pronyk P, Mohapi L, et al. Isoniazid preventive therapy, HAART and tuberculosis in HIV-infected adults in South Africa: A prospective cohort. AIDS 2009; 23:631-636.

41. Yirdaw KD, Jerene D, Gashu Z, Edginton ME, Kumar AM, Letamo Y, et al. Beneficial effect of isoniazid preventive therapy and antiretroviral therapy on the incidence of tuberculosis in people living with HIV in Ethiopia. PLoS One. 2014;9(8):e1045

42. Khawcharoenporn T, Apisarnthanarak A, Manosuthi W, Sungkanuparph S, Mundy LM. Isoniazid preventive therapy and 4-year incidence of pulmonary tuberculosis among HIV-infected Thai patients. Int J Tuberc Lung Dis. 2012;16(3):336-41.

43. Boffa J, Mayan M, Mhlaba T, Ndlovu S, Williamson T, Fisher D. Why agency is important when implementing IPT: Lessons from *oMakoti* in KwaZulu-Natal, South Africa. PLoS ONE 13(3): e0193571.

44. Mills Hl, Cohen T, Colijn C. Community-wide isoniazid therapy drives drug-resistant tuberculosis: A model-based analysis. Sci Transl Med 2013;5(180):180ra49.

45. Ragonnet R, Trauer JM, McBryde ES, Houben RMG, Denholm JT, Handel A, et al. Is IPT more effective in high-burden settings? Modelling the effect of tuberculosis incidence on IPT impact. Int J Tuberc Lung Dis 2017; 21(1):60–66.

46. Boffa J, Mayan M, Ndlovu S, Cowie R, Sauve R, Williamson T, et al. Community-level challenges to tuberculosis preventive therapy provision in KwaZulu-Natal, South Africa. [abstract]. Int J Tuberc Lung Dis 2016;20(12) Supp 1:S109.

47. Camlin CS, Ssemmondo E, Chamie G, El Ayadi AM, Kwarisiima D, Sang N, et al. Men "missing" from population-based HIV testing: insights from qualitative research. AIDS Care 2016; 28(sup3): 67-73.

48. Girling DJ. Adverse effects of antituberculous drugs. Drugs 1982; 23(1-2): 56–74.

49. Tedla Z, Nyirenda S, Peeler C, Agizew T, Sibanda T, Motsamai O, et al. Isoniazid-associated hepatitis and antiretroviral drugs during tuberculosis prophylaxis in HIV-infected adults in Botswana. Am J Resp Crit Care Med 2010; 182(2): 278-85.

50. World Health Organisation. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: Recommendations for a public health approach. 2nd ed. Geneva: The Organisation; 2016. Available from: http://www.who.int/hiv/pub/arv/arv-2016/en/ [Accessed 20th Oct 2017].

51. South Africa Department of Health. Implementation of the universal test and treat strategy for HIV positive patients and differentiated care for stable patients. Pretoria: The Department; 2016. Available from: http://www.sahivsoc.org [Accessed 17 Jul 2017].

52. National Institute for Communicable Diseases. South African Tuberculosis Drug Resistance Survey 2012–14. Johannesburg: The Institute; 2016.

53. Menzies R. Interpretation of repeated tuberculin tests. Boosting, conversion, and reversion. Am J Respir Crit Care Med 1999;159(1):15-21.

54. Blasnik M. Record Linkage. StataCorp. 2013. Stata Statistical Software: Release 13. College Station, TX: StataCorp LP.

CHAPTER 5

The role of agency in the implementation of Isoniazid Preventive Therapy (IPT): Lessons from *oMakoti* in uMgungundlovu District, South Africa

There are two ways of dying from poverty. The first is when you have no food and you slowly waste away. The second is when you have no cattle and your sons cannot marry. They will have children, but the little ones will not be your grandchildren. They are vagrants, human beings with no ancestry. And then you have died because your family has died. You have disgraced everyone who came before you.

'Msani,' an informal tenant on a white-owned farm in KZN, qtd in Jonny Steinberg
Midlands

Abstract

Introduction: In response to revisions in global and national policy in 2011, six-month isoniazid preventive therapy (IPT) became freely available as a preventive measure for people living with HIV in the uMgungundlovu District of KwaZulu-Natal province, South Africa. Given a difference in IPT uptake and completion by sex, we sought to explore the reasons why Zulu women were more likely to accept and complete IPT compared to men in an effort to inform future implementation.

Methods: Utilising a community-based participatory research approach and ethnographic methods, we undertook 17 individual and group interviews, and met regularly with grassroots community advisory teams in three Zulu communities located in uMgungundlovu District between March 2012 – December 2016.

Findings and Discussion: Three categories described women's willingness to initiate IPT: women are caregivers, women are obedient, and appearance is important. The findings suggest that the success of IPT implementation amongst clinic-utilising women of uMgungundlovu is related to the cultural gender norms of *uMakoti*, isiZulu for "the bride" or "the wife." We invoke the cultural concept of *inhlonipho*, meaning "to show respect," to discuss how the cultural values of *uMakoti* may conflict with biomedical expectations of adherence. Such conflict can result in misinterpretations by healthcare providers or patients, and lead some patients to fear the repercussions of asking questions or contemplating discontinuation with the provider, preferring instead to appear obedient. We propose a shift in emphasis from adherence-focussed strategies, characteristic of the current biomedical approach, to practices that promote patient agency in an effort to offer IPT more appropriately.

Implications: Building on existing tools, namely the harm reduction model and the use of mini-ethnography, we provide guidance on how to support women to participate as agents in the decision to initiate or continue IPT, decisions which may also impact the health and choices of the family.

Introduction

Tuberculosis (TB) is now recognised as the deadliest infectious disease globally [1]. Immune suppression from HIV is the single strongest determinant for developing TB disease [2,3]. People living with HIV (PLWH) are 20 to 30 times more likely to develop active TB

disease [4] and progress to TB disease about six times faster [5] than people without HIV. In 2015, 26% of people diagnosed with TB and 71% of people diagnosed with TB-HIV were reported on the African continent [4]. South Africa has the third highest TB incidence rate and highest TB-HIV co-infection rate globally (860 and 520 per 100 000 population, respectively [6,7]). The World Health Organisation (WHO) has identified three priority targets for reducing the burden of TB in high-incidence settings, namely, intensified case finding, shorter treatment regimens, and TB preventive therapy [3,8]. In order to provide TB preventive therapy to those at highest risk of developing TB disease, isoniazid preventative therapy (IPT) was introduced at no cost to PLWH in late 2010 [9].

Isoniazid is a medication used in combination with three other drugs to treat TB disease. Due to its low cost, tolerability, and ability to sterilise dormant bacteria, isoniazid has also been used pre-emptively to prevent TB among the latently infected. As a prophylactic, IPT is generally given as a six, nine, 12 or 36-month regimen dosed as a single 300mg daily tablet. While data from low-incidence settings suggested that IPT provides long-term protection from TB [10], the same was unclear in high TB and TB-HIV burden settings due to greater TB exposure and risk of reinfection [11].

The widespread implementation of IPT followed changes to South African and WHO guidelines in which, for the first time, a negative symptoms screen (lack of current cough, fever, night sweats, and weight loss) could be used in place of a chest radiograph to rule out active TB disease and determine eligibility for IPT [9,12]. Additionally, the use of a Tuberculin Skin Test (TST) to better target IPT was downgraded from requirement to recommendation to encourage initiation of PLWH on IPT in low-income settings where use of TST would prevent implementation – TST is a two-step process requiring a time-sensitive follow-up visit and a skilled reading of the result. These changes enabled IPT to be offered more broadly, and in 2011 uMgungundlovu District of KwaZulu-Natal province implemented the programme, offering TST-untargeted, six-month IPT community-wide to all PLWH based upon a negative symptoms screen. Given the shift from treatment of TB disease to treatment of latent TB infection and early pilot work that found no isiZulu language equivalent for latent TB infection [13], we collected data during early implementation to assess the acceptability of IPT in this setting.

Longitudinal analysis of patient data from a community health centre in peri-urban uMgungundlovu District showed that among those completing IPT in this context, TB incidence

rates declined by roughly 3000 per 100 000 person years compared to those with no intervention, performing better than antiretroviral therapy (ART) alone and increasing the protective effect of ART when provided together [14]. Although males and females appeared to benefit similarly in terms of case reduction, the majority of PLWH who started and completed IPT were female (72 and 74% respectively, p<0.001 for both comparisons) [14]. Given the difference in uptake and completion by sex, we utilised qualitative data to explore the reasons why Zulu women were more likely to accept and complete IPT compared to men, identifying lessons for future implementation of TB preventive therapy in similar settings.

Methods

Study design

1. The INH study

Utilising a community-based participatory research (CBPR) approach, we explored patient experiences and community perceptions around IPT implementation while conducting a parallel cohort study on effectiveness of TST-untargeted six-month IPT for PLWH in uMgungundlovu District. CBPR includes a set of practices for engaging with communities affected by or complicit in the focus of the research, and involves community collaboration in the development, collection, interpretation and dissemination of the research, with an emphasis on multi-directional knowledge exchange and actionable outcomes. Utilising CBPR best practices described in Minkler and Wallerstein, we held quarterly advisory team meetings in communities to develop and undertake the research and to discuss and validate findings [15].

2. The current study

Led by a PhD student (JB) and community liaison (SN), we employed ethnographic methods rooted in the discipline of anthropology to study IPT implementation. Ethnography involves researchers spending extensive time in the field participating in local activities, acquiring language proficiency, and working with key informants to understand the local context and lived experience regarding the given phenomena [16,17]. These practices helped introduce investigators to local cultural norms and normalize their presence in communities. See Figure 6 for a complete list of data sources by method.

Figure 6: Sources of data by method of enquiry
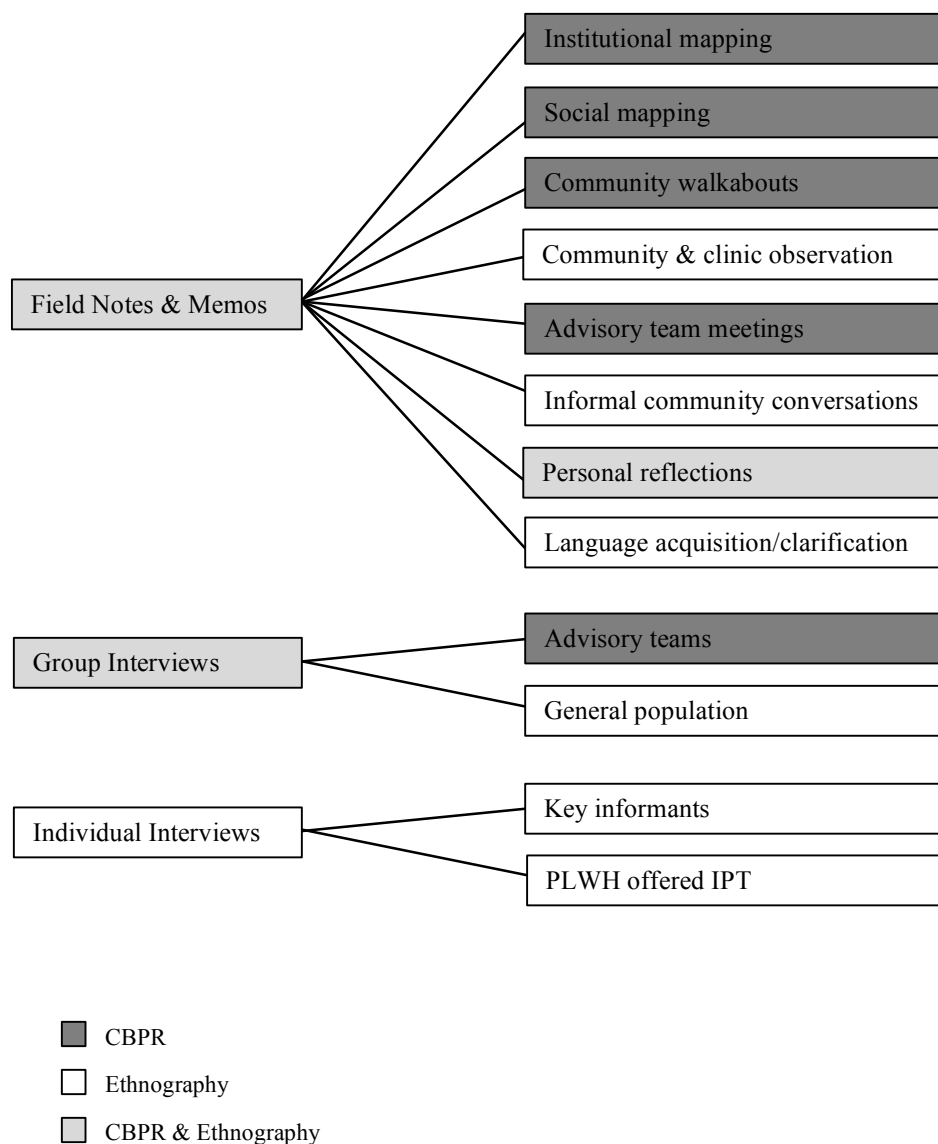
Acronyms: PLWH = people living with HIV; IPT = isoniazid preventive therapy;
CBPR = Community-Based Participatory Methods

Setting

uMgungundlovu District is located in central KwaZulu-Natal province. With a population of approximately one million people, the District reports 40% unemployment [18] with 112 000 people living on less than US$1 per day [19]. The District has an ante-natal HIV prevalence of

41% [18], and a TB incidence of 894 per 100 000 population [20,21]. Tuberculosis is the leading cause of death and of years of life lost in the District [18]. Eighty-four percent of the population does not have private healthcare insurance [18]. During the period of study, approximately 30% of the District was under 15 years of age and 65% were between the ages of 15 and 65 years of age, and there were 92 males for every 100 females [21]. Eight-five percent of the District is of African descent, among which 76% report isiZulu as their home language [19].

Recruitment and sampling

In 2012, we selected three from a total of 18 communities in the Edendale Hospital catchment area in which to begin our community engagement. Prior to selection, communities were divided into groups depending upon the distance of their publically serviced clinics from Edendale Hospital based on the hypothesis that perceptions and experiences may differ between groups due to variations in proximity to health services. Peri-urban communities were defined as those in which the health clinic was ≤25 km from Edendale Hospital, rural communities were >25 km from the hospital and accessible by tar road, and remote communities were >25 km from Edendale Hospital with clinics that lacked tar road access. As we were unfamiliar with the full range of clinics in the catchment, we used a random number table to select one community in each of the three distance categories. To learn about local perspectives on IPT implementation, we interacted regularly with the selected communities between March 2012 – December 2016. We purposively selected key stakeholders and used a mix of purposive and convenience sampling to identify potential group interviewees and individuals who were offered IPT. We utilised CBPR techniques including guided walk-abouts and institutional and social mapping exercises to identify community advisory team members, key informants, and target populations for group interviews [22]. Additional key informants were recruited through ongoing community interactions. Participants for group and individual interviews were recruited via phone by a clinic nurse or at their homes by community caregivers (CCGs). CCGs are government or NGO-employed support workers who come from the communities in which they work. In the KwaZulu-Natal context, CCGs undertook home visits to care for acute or chronically ill patients. If individuals expressed interest in participating, the recruiting nurse or CCG would connect these potential participants to SN and JB to follow up with further explanation of the study and the informed consent process.

Data collection

     Data collection included ethnographic observation at clinics, public meetings, and community ceremonies; formal and informal conversation with key informants; and group and individual interviews.

     From October 2014 to May 2015, we facilitated eight group interviews to learn about community perceptions about TB disease, infection, and IPT, and nine individual interviews to learn about experiences and decision-making strategies of people offered IPT. Field notes and memos from observation and informal interviews helped to articulate and develop categories. The semi-structured group and individual interview tools were reviewed and revised in collaboration with grassroots community advisory teams. Additionally, these tools were pilot tested with volunteer participants from an ART clinic in a non-selected Edendale Hospital catchment community. Individual and group interviews were digitally recorded with permission from participants. CCGs or other health workers were not present during data collection to encourage an open account of perceptions and experience.

1. Group interviews

     With input from grassroots research advisory teams, SN led a series of eight group interviews in the local language (isiZulu) in the three communities, while JB observed and took interview notes. Each group interview included 4-10 participants and followed established practices [24]. Questions were primarily descriptive with regard to understandings and perceptions of TB, latent TB infection, and IPT (See Appendix 3). Recordings were transcribed in isiZulu and then translated into English by a trained transcriber/translator. Unclear translations were reviewed between researcher and translator and interview recordings revisited by an independent translator blinded to the original translation in order to consider alternate meanings where appropriate.

2. Individual interviews

     As a second stage, we investigated the individual-level experiences of PLWH offered IPT in client homes. Individual interviews took place in isiZulu with real-time English translation. English translations were transcribed for analysis and isiZulu recordings revisited by an independent translator to explore alternate meanings of words and phrases relevant to the findings [24]. Questions were primarily descriptive and structural in nature (See Appendix 4).

Analysis

Individual and group transcripts, field notes, and reflections were analysed using qualitative content analysis as described by Mayan [25]. Data were organized, coded, and categorised iteratively by JB utilising Nvivo 10 software for Mac. To ensure scientific rigour, we employed several mechanisms. Data collection and analysis were dynamic and concurrent as a means of constructive validation [26], and grassroots community advisory teams and key informants were consulted throughout the process to ensure accurate descriptions of cultural concepts [27]. Negative or deviant examples were included in the sample [26,28]. Categories were member-checked by a sample of participants and peer-checked with healthcare providers working in South Africa [28]. Theories were developed in relation to the data (*e.g. Makoti* as model) and compared to existing theory (*e.g.* responsibilised patient model) [26], a process which was also negotiated with and approved by grassroots community advisory teams [15].

Ethics

As part of the CBPR process, we developed community partnerships with traditional leaders (*iziNkosi*), their tribal authorities, and community-tribal liaisons (*iziNduna*). Community approvals were obtained from tribal authorities and ward counsels, and institutional approvals were sought from clinic managers. Administrative approvals were granted by the KwaZulu-Natal Department of Health through the National Health Research Database system and by the uMgungundlovu District of Health. We sought and received ethical approvals for observation and group interviews from the University of Alberta's Research Ethics Office and for patient interviews from the University of Calgary's Conjoint Health Research Ethics Board. Additionally, the University of KwaZulu-Natal's Biomedical Research Ethics Board granted ethics approval for both stages of the investigation.

Findings

Data were first considered by location category (peri-urban/rural/remote); however, data codes overlapped substantially, and thus data were analysed collectively.

Category 1: Women are caregivers

Participants overwhelmingly described caregiving as the most important role of women

in the community. Understanding the composition of the typical household is helpful to illustrate this finding. Multi-generational households were common, often arranged along patrilineal lines. Architecturally the household may be made up of a central house or rondavel (round house) where family members come together to eat or socialise, with one or more 'outbuildings' or rondavels separating family units. In these enclaves, it was common for young wives to care for children and older family members. Participants reflected that sisters, mothers, and female in-laws were often the first point of care, especially when household members were sick: "If there is someone sick, most of the time we say maybe it's my sister or mother who usually takes care of them because they are following the way of life that is given" (Participant number [P]6, Group Interview number [GI]4). Another participant, referring to her role said, "here in the family, I was the one who was taking care of [my mother-in-law] and my sister-in-law... and my husband as well... Even if I feel that I can't do it, I have to do it because I am the only [healthy female]" (Individual Interview number [II]6).

Some participants described that it was seen as inappropriate for a man to provide care, for example:

> Let's say you have TB. Sometimes TB gives you swollen feet. They become so swollen that you can't even go to the toilet and you need help to pee. Maybe sometimes you need a foot rub. You can't ask the father; a male figure cannot take you to the toilet or rub your feet. (P3, GI8)

Key informants explained that it is often considered taboo or invasive for a male to help a female with such tasks, even among members of the same household; however, a female helping a male is considered culturally acceptable because women are thought to have more "patience" and be more "hands on" compared to their male counterparts (P6, GI4).

Women also held the overwhelming majority of caregiving positions in the formal healthcare system. Primary care centres were commonly run and staffed by female nurses called "sisters," lay counsellors, and clinic assistants. CCGs were exclusively women. Participants described CCGs as a support system for those who lived alone or in male-only households: "there are people who are hired at hospitals who can give help if I am single and sick and live alone," (P1, GI4). Others described CCGs as mediators between health workers and the sick: "the healthy will sometimes struggle and the doctors will work with the community caregivers to take care of the sick person" (P5, GI1). Some described how CCGs provided more than medical support: "even though I was abandoned by my husband, I did survive. The CCGs brought me some clothes, their own things, even from their own families" (II7).

Category 2: Women are obedient

In study communities, women demonstrated obedience through several mechanisms. Obedience was demonstrated in the home through service to husbands, uncles, elders, and in-laws. For example, when meals were served, women or older female children would dish up first to men and boys and cater to their requests before looking after themselves or other females in the household. Children were often commandeered to run errands for older family members, and girls were guided from a young age to respond to the needs of the household:

> We as females are being taught that we should wake up early, do this and that, and being a female you can't go to bed before everyone. You need to make sure that even your parents are asleep first. Are the windows closed? Is the house clean? …I think not in a negative way, but it is how we've grown up. (Key Informant Interview number 12)

Obedience was also demonstrated through docility. Regardless of personal dispositions, women grew increasingly quiet and submissive in the presence of men and authority figures. For example, one female key informant who regularly provided insightful political context to the female research team fell silent on the subject when similar opinions were elicited in the presence of her son-in-law or other male relatives.

Obedience was also displayed more formally through appearance and body language. In the following field note, one researcher described her introduction to the importance of ritualised body language during a visit to *iNkosi* (the traditional leader; singular) of a community:

> I noted that [SN] wrapped her hair when she learned that we would meet with *iNkosi*. She later explained that women cover their hair as a sign of respect. When he entered [the rondavel] we had to bow our heads slightly, and we (the women) were to remain seated while the men stood up to recognise his entry. SN kept her head slightly bowed and eyes averted as she spoke… She explained to me later that in Zulu culture, a woman must avert her eyes in the presence of authority… She explained that it's not always easy to navigate [what constitutes authority], but that it includes… *iNduna*, *iNkosi*, and elderly in-laws, …[although] it depends on [the personality and one's familiarity with] the person [of authority]. (Field Notes)

During such interactions, it was common for women not to speak until invited, and even then, to keep matters short and eyes averted.

Such displays of obedience were also present in the clinic environment. Silence and submissive body language were commonly observed in clinic consultations, and female participants explained that they had reservations about appearing overly vocal in clinic encounters. One female participant explained that even when she did speak up, she was not provided an explanation and described herself as needing to be "unbearable":

> Some are called on a list and they get [IPT], but me, I don't get it…why don't I ever get it? …I asked and I never did get an explanation for who is given [IPT] …I told myself that maybe it's because I'm already in [an

antiretroviral] treatment programme and maybe those who have started treatment don't get it. …you keep asking about it every time you come for follow-up and you become unbearable. (P3, GI5)

Another participant echoed her sentiment, explaining that one becomes unbearable when "you are asking irritating questions," suggesting that, "you know too much now" (P5, GI5). As the group interview continued, other participants proposed medical reasons that might explain her ineligibility, trying to ease her anxiety. One by one, she discounted their suggestions, indicating that her tests showed she had strong liver and kidney function, for example. Later in the discussion she described another encounter that evoked deeper fears around "knowing too much."

There was this one girl who was taking TB treatment with Nevirapine, and she asked the nurses about it because she knew she wasn't supposed to mix them. I asked her, 'why are you taking these?' because I know that TB pills and Nevirapine don't mix. She said, 'the nurses will not even book a doctor for me.' She became sick and she died. That killed me inside when I found out she died. I had thought about asking about her at the clinic to see if she was doing better, but I worried that [the nurses] would tell me that I know too much, just like that girl. (P3, GI5)

In another encounter, a participant described a comfortable relationship with her regular healthcare provider; however, when her physician offered her a prescription for food parcels to help ensure she had food to take with her IPT, she was unsure of what to do with it. Rather than ask him, she approached the research team to help her navigate the system on her behalf (II4).

For many participants, obedience to healthcare providers was also implied when the decision to initiate IPT was relinquished to the healthcare provider. Several participants reflected that they started IPT "because the nurses told me to" (P5, GI5) or "the results showed that I should be enrolled" (II8). Interestingly, one participant felt unsettled at the end of an interview and asked the interviewer if she ought to have had questions for her healthcare provider when she was initiated on IPT: "The only confusing part now is that maybe I was supposed to ask some questions about this pill" (II8).

Not all participants fit into this category. Although few in number, some participants took noticeable pride when speaking of the open communication they shared with healthcare providers. For example, one participant reflected that she would have probably died if not for the "tough" nurses and dedicated lay counsellors who inspired her to keep living when her husband and his family rejected her following her HIV diagnosis at the time of her first pregnancy. She explained that among clinic staff, "I'm well known. They know about my background, my health background" (II7). She later explained that this close relationship encouraged her to initiate conversations and engage more with community members and clinic staff in matters of health.

Another participant whose experience did not fit with this category openly declined IPT because she had recently completed TB treatment: "I rejected it because I said 'I am already having prevention because I have been on TB treatment, so I'm safe now from TB infection'" (II1). When asked how the healthcare providers responded to her decision, she said they thought she was clever for recognising that isoniazid was also part of her treatment regimen.

Category 3: Appearance is important

A third category commonly reflected in the data was the importance of appearance among Zulu women. Participants spoke about cultural expectations of a woman's outward appearance (*e.g.* freshly bathed, wearing a long skirt or dress), but more often this category was linked to women displaying expected behaviour in the community. For instance, it was considered distasteful for women to drink or smoke in the company of others, and sexual desire or promiscuity was particularly discouraged at a societal and familial level. The latter was reflected in various cultural practices in which virginity among unmarried Zulu women and girls was celebrated. These included *uKuhlolwa kwezintombi* or virginity testing ceremonies; *uMemulo* or coming of age ceremonies; and *iLobolo* or marriage negotiations, all of which have been described in depth by others [29-33].

The desire to present the right appearance also came up in discussions around sickness, as some feared that being unwell would be misinterpreted by others. For example, one participant explained that she would rather get out of bed on days when she felt sick to prevent raising suspicion among neighbours:

> Sometimes the neighbours, if they didn't see me moving around outside, they would come here [and say] 'Oh, we are here to check [on you].' [They think] maybe she is not well cause she is not outside... That is why I'd usually rather [get up]. (II9)

Other participants discussed similar fears about neighbours becoming aware of their health status. As in the next example, concerns often related to disclosure of one's HIV status, suggesting to others that behavioural expectations have not been met:

> You find [a lot of people] saying, 'I would like to get checked [for HIV] once and for all,' and once a person has confirmed that they are sick, you see them in the health facilities. And they do not want community caregivers involved because they will go around telling people who is sick… [The CCG] is like a parent to me. She is like my parent. I am supposed to be able to tell her that I was tested and found that I am like this, and there is no reason for her to tell anyone. (P1, GI8)

One participant expressed her frustration with "Zulu culture" for prioritising the appearance of health in favour of care-seeking, following the recent deaths of her husband and

eldest daughter, both of whom were the breadwinners of the household: "My husband died and I didn't know what was the cause of death. And even my [daughter] died and I didn't know [why] because people don't want to disclose their [health] status, and you do not know what [is] really happening" (II8). For this participant who had recently "beaten" breast cancer and reported a good experience on ART, the answer was to take control of her own health and act as a role model for her other children: "In the days when I am sick, I don't have to go to ask [for help] from my neighbour, from my mother-in-law. I should be the one who needs to take care of my life. I need to know about my life" (II8). While this participant was similar to other participants in that she wished to avoid the prying eyes of neighbours, she was unique in that she also rejected support from her family, preferring instead to look after herself alone. Another participant who felt comfortable sharing her HIV status in the community, described how she encouraged others to overcome concerns with appearance:

> Some people who get well [following ART]… disclose openly their status. Others are afraid to disclose their status to the CCGs [to seek treatment]… I encourage them that they don't have to worry because at the end of the day [they] will be healthy. Many people come to me for help because of my openness. (II7)

For some participants, decisions to interact with healthcare providers in relation to IPT also involved concerns with appearance. For instance, one participant described her response to IPT following symptoms of extreme hunger and tingling in the hands and feet, which she associated with starting the regimen, "I decided that I would rather stop for a week so I could see whether the pills [were] the cause or not, and in a week [the symptoms] disappeared" (II9). When asked if she went back to the clinic to discuss the issues, she giggled and replied, "No, I didn't. No, I won't! It's good to tell the truth. I didn't." When later asked if she would warn others about her IPT experience, she responded:

> It might depend how close I am with that person. But the person whom I'm not close that much, I can't talk about the side effects because I might scare that person… I will encourage that person to take [IPT] for the full six months, unlike myself who defaulted, because I defaulted. (II9)

Discussion

Ultimately what encouraged many women to take IPT was the cultural gender norm of being *uMakoti*, an isiZulu word that directly translates as "the bride" or "the wife" (the prefix 'u' indicating the definite article), but is also a term of endearment afforded to females whose behaviour indicates maturity and high moral standing according to Zulu culture [30]. As Ngwenya explained, *Makoti* (wife, singular) is not merely a title; there are "a whole range of

practices" that construct the identity, including "chores she is expected to carry out" [34]. In a more nuanced way, the title *Makoti* represents the duty to be a good woman, wife, mother, and in-law. Notions of good are demonstrated through docility: the good woman is caring, obedient, and represents herself well in the public domain. The interplay of these expectations is aptly summarised in a traditional Zulu wedding song that is sung to the bride during the wedding ceremony:

> *uMakoti ungowethu* / The bride is ours
> *Uzosiwashela asiphekele* / She will wash and cook for us
> *Sithi helele siyavuma!* / We rejoice!
> - unknown

These findings are consistent with what contemporary Zulu scholars have called *inhlonipho*, meaning 'to show respect.' Rudwick explained that higher status, seniority, age, and "quite often male gender" are common qualifiers for people to whom *inhlonipho* must be directed [35]. *Inhlonipho* can be displayed through the avoidance of particular words or syllables (*isiHlonipho*) that link to the names of male in-laws, lowered gaze or posture whilst speaking to those of higher authority, and right behaviour [30,31,35]. Similar to our findings, Bhana described 'right behaviour' as chastity, shyness, and docility, especially among rural Zulu women who offer little economic value through work outside the home [31].

As with most medicinal interventions, valuations of successful IPT implementation are determined by measures of adherence, such as how many people start and complete therapy [36]. If what is ultimately sought in IPT intervention is adherence, then the qualities of being *Makoti* seem to support a model for achieving IPT adherence – *oMakoti* (plural form) are caregivers, but ultimately not care decision makers. Indeed, our data confirm that among the women using IPT, the majority exhibited *inhlonipho* by ceding IPT decision-making power to the healthcare provider. This may explain why the majority of IPT initiators in our evaluation of IPT effectiveness were women [14].

Participants' experiences highlight several situations in which *uMakoti* may elect to relinquish control. Firstly, she may trust implicitly the expertise of the healthcare provider and her or his interpretation that she is "in the right condition" or "the results said [she] should be on these pills." Secondly, *uMakoti* may opt to reserve questions to appear grateful and "happy that there is help which is coming." Thirdly, *uMakoti* may feel pressured to demonstrate *inhlonipho* for fear she may be singled out and reprimanded through health delay or exclusion for "asking

too many questions" or "knowing too much." The different intentions behind these demonstrations of *inhlonipho* highlight the circumstances in which a good *Makoti* does not necessarily equate to a good patient by Western biomedical standards – sometimes expressions of *inhlonipho* are merely performance. As Rudwick and Shange asserted, "the *hlonipha* (sic) framework is based on the idea that one must, by all means, avoid *appearing* disrespectful" [30] (our emphasis).

In the biomedical paradigm, any deviation from a medical regimen without consulting the healthcare provider is an indication that adherence has been compromised; therefore, instances in which *inhlonipho* is performed out of duty or placation rather than trust in the regimen would not conform to biomedical expectations. The practice of performance is not entirely unfamiliar to healthcare providers. Directly Observed Therapy (DOT), whereby nurses or CCGs physically witness the act of pill taking at least five days per week, was developed by a TB clinician for the purposes of ensuring regimen compliance [37]. Similarly, health initiatives such as adherence training, which are employed in KZN upon entry into the public ART programme, are intended to educate eligible patients on the importance of pill compliance [38].

Yet, our findings do not suggest that *oMakoti* were unaware of reasons to adhere. Decisions around initiation and discontinuation were justified with thoughtful consideration. While it may first seem perplexing that some participants would not seek help from their healthcare provider or other community members following difficulties attributed to IPT, decisions to remain silent were informed by previous experience or collective interpretations about the experience of others. In her 2013 ethnography, Beckmann described what she termed "the logic of choice" among PLWH in Tanzania, referring to the logical processes which precede healthcare decisions that may run counter to healthcare workers' expectations [39]. Beckmann explained that practices such as performance can be "responsible" in terms of life circumstance, "but may not be considered responsible in the eyes of those trying to control [a] pandemic within a strictly biomedical framework" [39]. In essence, *uMakoti* does not feel safe to admit to the healthcare provider or others with whom she is "not that close" what she interprets as 'disobedient' behaviour: Don't be like me: "I defaulted." The very practice of identifying oneself as "defaulter" situates one in the lexicon of the biomedical framework, in which failure to complete according to a predetermined schedule results in internalisation of the decision, regardless of circumstances.

The problem is that adherence in the biomedical framework requires an openness that does not align with identity as *uMakoti*. As Kielmann and Cataldo explained, such expectations are based on a risk-based approach to preventive care in which patients are "rationally motivated to change their behaviours towards self-preservation" [40]. Community life often involves making difficult choices with minimal resources, thus quality of daily life in uMgungundlovu can take precedence to longevity. The biomedical approach fails to take into account situations in which a life worth living is dependent on functioning social relationships [39], requiring at times elements of performance in public spheres. It is not only the fear of biological manifestations of disease that determine *uMakoti*'s course of action, but also local support structures with which she identifies that may be crucial to her wellbeing. The notion of defaulter is therefore filtered through *Makoti* notions of *inhlonipho* and responses based upon more than potential physical health outcomes, but also societal expectations or fallout with ramifications to her or her household.

Not all data were consistent with women as *oMakoti*. Certainly, some women did engage more readily with healthcare providers. These women fit well with what Robins described as a new form of "responsibilised citizenship" that accounts for the ways in which illness experience in collective societies has social implications [41]. Robins described the experience of a "social death" common to South Africans newly diagnosed with HIV, which he identified as a necessary intermediate step toward a "new life" or identity as activist. Similarly, in our study, a few participants described a period in which they felt a loss of social connectedness followed by the realisation that, "I should be the one who needs to take care of my life," in essence, rejecting the societal norm of *uMakoti*. In line with Robins' activist model, these participants created a new life by embracing their HIV status and served as activists or sources of support for others in their community. In doing so, they chose to reinvent themselves as good patients, an identity that more closely aligns with the current biomedical notion of adherence. While we wish not to condemn this position, examples of women who fit the responsibilised citizenship model appeared infrequently in our field experience, suggesting that Robins' theory is unlikely to represent the experience of most women in traditional Zulu communities.

Lessons from oMakoti

Insofar as notions of obedience overlap with the biomedical framework, the success of

IPT implementation amongst clinic-utilising women of uMgungundlovu appears to rest in large part with identity as *oMakoti*. Difficulty arises where the overlap ends: practicing *inhlonipho* at times requires the appearance of obedience, and the concept of adherence at all cost may threaten women's social status or safety. Being *uMakoti* comes from a set of cultural expectations derived from the experiences of those who live within the community; whereas norms of 'good patienthood' come from a largely neoliberal paradigm of self-responsibility and gender neutrality that infiltrates from without [42]. In other words, biomedicine is born from a cultural framework established by and for the West, giving preference to certain forms of knowledge and beliefs above others. For women who identify as *oMakoti,* the practice and responsibility of *ukuHlonipha* (acting respectfully) would be much more familiar, thus explaining the less frequent occurrence of the 'responsibilised citizen' in our fieldwork.

We argue that successful public health interventions are best taken up when they adapt to the local culture rather than expecting the local culture to adapt. While authority may be observed in the formal clinic setting, *uMakoti* can exercise her decision-making power through 'disobedience' in private without disturbing "the way of life that is given." As our data suggest, authority in the Zulu context is a fluid concept to be navigated, depending in part on levels of familiarity and the personality of the authoritarian figure. This suggests an opportunity for healthcare providers to construct less hierarchical environments, inviting *oMakoti* to interact more comfortably.

The first step is a shift from adherence-based thinking to an agency-based focus. What we can learn from *uMakoti* is that women in these settings feel comfortable providing care to those around them, yet based on Zulu notions of respect, feel less comfortable making healthcare decisions - or at least appearing as the healthcare decision maker. The onus then falls to the healthcare provider to elicit information that can help determine the needs of potential *Makoti*, recognising that agreement does not necessarily equate to buy in. To be clear, the term 'agency' is not an invitation to bestow power upon a person in order to 'correct' behaviour, as Shefer cautioned [43]. Rather, it is an acknowledgement that the provider's role is limited until current life complexities are ascertained. For example, what necessities must be in place for someone to be able to adhere to the IPT regimen? It is important to determine if such necessities are available to the patient at each contact, and if not, to be aware of existing support systems to which the healthcare provider can link the patient. If there are remaining barriers, the healthcare

provider can communicate the potential difficulties of the regimen in light of these barriers, providing information that might help the patient to draw her own conclusions. This exercise takes place through active engagement with the patient. To assist with this process, we have included an example from Kleinman and Benson's mini-ethnography tool [44], outlining particular steps that can help healthcare providers gain insight into the lived experience of patients who identify as *oMakoti* and work to identify any of their own pre-conceived notions of what it means to be a good patient (see Appendix 6).

The shift to an agency-based approach would also require healthcare providers to engage in a process of self-reflection on the ways in which their own practices may unwittingly contribute to power differentials that may impact a patient's ability to express their preferences, despite the information provided. The harm reduction model developed by Marlatt can help to guide this process [45]. Marlatt described the harm reduction model as a means to extricate moral and medicalised expectations from care provision [45]. The first step is to recognise that biomedicine is itself a culture, one among many, and as such certain practices are taken as 'correct' without consideration of what is at stake for people with different life experiences – such as extreme poverty [40,42-45]. A woman who presents at clinic has by definition met the requisite of 'patient' in the formal healthcare system; by virtue of showing up she has demonstrated the belief that medical knowledge may benefit her and her family. She is not there to adopt a new value system; she is already working within one. The potential to assist the patient is thus limited until the healthcare provider can gain insight into the patient's current circumstances (any combination of social, economic, political, or otherwise), which may include identification with – or rejection of – societal obligations as *uMakoti*.

Despite the pressure to meet health systems targets, initiation on and adherence to IPT ought not to be the end, but a means toward improved health outcomes in the community. Given that women are revered as caregivers, then active participation to take or not take IPT (i.e. her buy in to whichever decision) may also have ramifications on the practices of others in the household, especially children and the sick. Assessing what may affect a woman's (or other patient's) ability to make choices and act on them may in fact provide better insight as to how more immediate threats to health and wellness can be addressed. In other words, in agency-based practice, the ideal would be that the healthcare provider and patient work together to establish the best plan for her, and what might be altered if her circumstances change. If IPT is among her

options, discuss the consequences of taking IPT, the consequences of starting and stopping IPT, and the consequences of not initiating at this time – not only the physical consequences, but also the social, economic, and emotional implications for her, and her family and community. In this way, the culture-bound moral valuations are left out of the equation, and a woman can coexist as patient and *Makoti* without the additional pressure and expectation of being 'good' at both.

Conclusion

Our ethnography on IPT acceptability among Zulu women in uMgungundlovu District suggests that those who identify with *uMakoti* culture may be more likely to accept IPT on the basis of the authority position of the healthcare provider rather than personal beliefs. Under such circumstances, IPT uptake may not always equate to buy in, and may not meet the expectation of the healthcare provider in terms of adherence. Rather than interpreting such instances as a lack of commitment on the patient's behalf, we suggest that it stems from a misalignment of value systems that may unwittingly encourage deception. Other culture-based approaches to health and wellbeing are not inferior to, and often intersect with, biomedicine. The point where they meet provides an opportunity for deeper engagement. Utilising methods to reduce authoritative influence and engage in active dialogue with patients can encourage *oMakoti* to feel heard and understood, creating a safe and informed environment that promotes patient agency instead of adherence at all cost.

References

1. Stop TB Partnership. The paradigm shift: global plan to end TB 2016-2020. UNOFP: Geneva, 2015.
2. Lawn SD, Bekker SG. Co-pathogenesis of tuberculosis and HIV. In Schaaf HS, Zumla AI, editors. Tuberculosis: A Comprehensive Clinical Reference. London: Elsevier;2009. p. 96-106.
3. World Health Organisation. WHO three I's Meeting: intensified case finding, isoniazid preventive therapy and TB infection control for people living with HIV. Geneva: The Organisation; 2008.
4. World Health Organisation. Tuberculosis Fact Sheet (2017). Available from http://www.afro.who.int/health-topics/tuberculosis-tb. [Accessed 08th Dec 2017].

5. Menzies D, Doherty TM. Diagnosis of latent tuberculosis infection. In Raviglione, editor. Reichman & Hershfield's Tuberculosis: A Comprehensive, International Approach. 3rd ed. Geneva: WHO; 2006.

6. UNAIDS. South Africa HIV and AIDS Estimates (2015). Available from http://www.unaids.org/en/regionscountries/countries/southafrica. [Accessed 11th Sep 2017].

7. World Health Organisation. Global tuberculosis report 2016. Geneva: The Organisation; 2016.

8. World Health Organisation. The End TB Strategy: Global strategy and targets for tuberculosis prevention, care and control after 2015. Geneva: The Organisation; 2014.

9. South Africa Department of Health. Guidelines for tuberculosis preventive therapy among HIV infected individuals in South Africa. Pretoria: The Department; 2010.

10. Apers L, Robert C, Nachega JB. Prophylaxis with antituberculosis drugs in special situations. In Schaaf HS, Zumla AI, editors. Tuberculosis: A Comprehensive Clinical Reference. London: Elsevier; 2009. p. 780-85.

11. Nardell E, Churchyard G. What is thwarting tuberculosis prevention in high-burden settings? N Engl J Med 2011;365(1):79-81.

12. World Health Organisation. Guidelines for intensified tuberculosis case-finding and isoniazid preventive therapy for people living with HIV in resource-constrained settings. Geneva: The Organisation; 2011.

13. Boffa J, Mayan M, Ndlovu S, Cowie R, Sauve R, Wilson D, et al. Understandings of tuberculous infection, TB disease and isoniazid preventive therapy in KwaZulu-Natal, South Africa [abstract]. Int J Tuberc Lung Dis. 2015;19(12) Supp 2:S279.

14. Boffa J, Williamson T, Cowie R, Sauve R, Mayan M, Fisher D. The effectiveness of community-wide, untargeted isoniazid preventive therapy to reduce the incidence rate of tuberculosis among people living with HIV in the context of upscaling anti-retroviral therapy in KwaZulu-Natal, South Africa. (in revision; PLoS One).

15. Minkler E, Wallerstein N, editors. Community-based participatory research for health: from process to outcomes. 2nd ed. San Francisco: Jossey-Bass; 2008.

16. de Laine, M. Ethnography: Theory and Application in Health Research. Sydney: MacLennan & Petty, 1997.

17. Savage J. Ethnography and healthcare. BMJ. 2000; 321(7273): 1400–1402.

18. uMgungundlovu District Health Office. District Health Plan 2015/16. KwaZulu-Natal Department of Health: 2015. Available at: http://www.kznhealth.gov.za/Strategic/DHP/2015-16/Umgungundlovu.pdf [Accessed on 13 Sep 17].

19. Statistics South Africa. Statistics by place (Census 2011 data). Available at: http://www.statssa.gov.za/?page_id=964 [Accessed 13 Sep 2017].

20. Ngozo J. Overview of the Department of Health Tuberculosis Control Programme in KwaZulu-Natal. [Presentation] Faith Leaders Symposium. 18 July 2016.

21. Municipalities of South Africa. uMgungundlovu District Municipality: Demographic information. Available at: https://municipalities.co.za/demographic/120/umgungundlovu-district-municipality. [Accessed on 08th Dec 17].

22. Rifkin SB, Pridmore P. Partners in planning: information, participation and empowerment. London, GBR: Macmillan Education; 2001.

23. Dawson S, Manderson L, & Tallo VL. A Manual for the Use of Focus Groups. WHO, 1993.

24. Kvale S, Brinkman S. Interview variations. In: InterViews: learning the craft of qualitative research interviewing. 2 ed. Thousand Oaks: Sage; 2009. p. 143-58.

25. Mayan M. Essentials of qualitative inquiry. Walnut Creek, CA: Left Coast; 2009.

26. Morse JM, Barret M, Mayan M, Olson K, Spiers J. Verification strategies for establishing reliability and validity in qualitative research. Int J Qual Methods 2002, 1(2): 13-22.

27. Côté L, Turgeon J. Appraising qualitative research articles in medicine and medical education. Med Teach 2005, *27*(1):71-5.

28. Holloway I, Todres L. The status of method: Flexibility, consistency and coherence. Qual Res 2003, *3*(3):345-57.

29. Wickström A. Virginity testing as a local public health initiative: a 'preventive ritual' more than a 'diagnostic measure'. J Royal Anthropological Institute. 2010; 16(3): 532-550.

30. Rudwick S, Shange M. Hlonipha and the rural Zulu woman. Agenda. 2009; 23(82): 66-75.

31. Bhana D. Masculinities, Femininities and the Burden of Culture Among Rural South African Teenagers in the Context of HIV. In P Liamputtong, editor. Children and young people living with HIV/AIDS. Basel: Springer; 2016. p. 127-145.

32. Hunter M. Love in the time of AIDS. Pietermaritzburg: University of KwaZulu-Natal; 2010.

33. Posel D, Rudwick S. . Marriage and ilobolo in contemporary Zulu society. African Studies Review. 2014; 57(2), 51-72.

34. Ngwenya T. Introducing critical language awareness in IsiZulu: the why and the how. Southern African Linguistics and Applied Language Studies. 2006; 24(2): 165–173.

35. Rudwick SI. Shifting norms of linguistic and cultural respect: Hybrid sociolinguistic Zulu identities. Nordic Journal of African Studies. 2008; 17(2): 152-174.

36. KwaZulu-Natal Department of Health. IPT indicators [dataset]; Pietermaritzburg: The Department; 2014.

37. Frieden TR, Sbarbaro JA. Promoting adherence to treatment for tuberculosis: the importance of direct observation. World Hosp Health Serv. 2007; 43(2): 30-33.

38. South Africa Department of Health. Adherence guidelines for HIV, TB and NCDs: policy and service delivery guidelines for linkage to care, adherence to treatment and retention in care. Pretoria: The Department; 2016.

39. Beckmann N. Responding to medical crises: AIDS treatment, responsibilisation and the logic of choice. Anthropology & medicine. 2013; 20(2): 160-174.

40. Kielmann K, Cataldo F. Tracking the rise of the "expert patient" in evolving paradigms of HIV care. AIDS Care. 2010; 22(sup1): 21-28.

41. Robins S. From "rights" to "ritual": AIDS activism in South Africa. American Anthropologist. 2006; 108(2): 312-323.

42. Farmer P. An anthropology of structural violence. Current Anthropology. 2004; 45(3): 305-325.

43. Shefer T. Resisting the binarism of victim and agent: Critical reflections on the 20 years of scholarship pm young women and heterosexual practices in South Africa contexts. Global Public Health. 2016; 11(1-2): 211-223.

44. Kleinman A, Benson P. Anthropology in the clinic: the problem of cultural competency and how to fix it. PLoS Med. 2006; 3(10): e294.

45. Marlatt GA. Harm reduction: Come as you are. Addictive Behaviors. 1996; 21(6): 779-788.

CHAPTER 6

Conclusion

Tradition has it that disputes which break out in a village are worked out in public. By this I mean collective self-criticism with a touch of humor… because in the end we all want the same thing.

Frantz Fanon
The Wretched of the Earth

Summary

My doctoral research investigated the acceptability and effectiveness of government offered six-month untargeted isoniazid preventive therapy (IPT) to prevent tuberculosis (TB) disease among people living with HIV (PLWH) in uMgungundlovu District of KwaZulu-Natal (KZN). In paper one I discussed ways in which IPT could be interpreted as dangerous when: the costs related to pill collection or consumption exacerbated existing poverty, the stigma associated with HIV and antiretrovirals (ART) are conflated with its use, or it is seen as a toxin that builds up in the body. In paper two, I analysed IPT-related data from the catchment area of a community health centre in uMgungundlovu. These data showed that among those who completed the regimen, IPT reduced the two-year TB incidence by 100% among women (97.5%CI=78-100%), but with a less certain effect among men: IR=0.46, 95%CI=0-85%. Findings also suggested that IPT provided additional protection for people already on ART, regardless of sex, age, or CD4 count. Proportionally, women were more likely to start (71.61%) and complete (73.92%) IPT compared to men. In paper three, I described how clinical approaches to IPT initiation and adherence can conflict with expectations of women in Zulu culture. Participants described initiating the regimen because a healthcare provider suggested it, a decision that may relate more to a desire to seem grateful or obedient for some, rather than a belief in the potential of the regimen to prevent TB. This same desire to please prevented some participants from reporting difficulties on IPT and others from demanding an explanation as to why they were not eligible for it. Taken together, this body of work suggests that IPT can reduce the risk of developing TB disease among PLWH, but the regimen may not be a high priority to all in this high-risk population when other economic and social needs compete.

Nonetheless, the idea of TB treatment as prevention is gaining traction among funders, policymakers, NGOs, and government programmes. In this discussion chapter, I review the findings and their implications in light of current research and reflect on how the engagement process with Grassroots Research Advisory Team (GRAT) members provided further evidence to support the lessons for IPT implementation. I also consider the limitations of the findings and ideas for future research.

Implications

As a disease, TB is not straight forward to describe or diagnose. Much of its complexity relates to its various presentations, manifestations, and degrees of infectiousness – alone or in combination with HIV. GRAT members soon grasped this complexity following early TB and research literacy training sessions, and entered into thought-provoking discussions about what constitutes exposure, infection, and disease. Members also questioned why researchers had not yet developed vaccines or shorter and less toxic regimens to prevent and treat TB. Furthermore, they provided advice on problematic messaging that can contribute to some of the barriers outlined in this research (e.g. economic hardship, mistrust of the formal healthcare sector, or misaligned expectations of treatment). Some of these concerns are being addressed through biomedical research and are reflected in new ways of thinking about TB. Persisting barriers will require further commitment to community engagement and knowledge exchange.

Improving preventive regimens

In line with concerns of GRAT members, a high priority for TB prevention and treatment research has been the shortening and simplifying of regimens [1]. Recently there has been movement toward implementing a weekly dose of a combination of rifapentine and high-dose isoniazid (1000mg) for three months to improve adherence. The regimen, known more commonly as 3HP, has been shown to have similar efficacy to six-month IPT [1-3]. The National TB Programme in South Africa recently developed a strategic plan to implement the use of 3HP in the public health system for children under five years of age and PLWH over the next five years [4], although the standard use of 3HP has yet to be implemented in KZN province. In March of 2018, a similar daily regimen of rifapentine and isoniazid for one month was shown to be equivalent to a nine-month regimen of IPT [5].

MDR-TB preventive regimens are also in various stages of testing and use [1], and a combination of isoniazid and delamanid is currently being tested among adults in Africa, South America, and Asia [2]. As delamanid is one of only two new TB-specific treatment drugs developed in the past 60 years [6] and there is already evidence of acquired drug resistance [7], its use as a preventive therapy at the community-level must be carefully considered. Nonetheless, its potential for prophylactic use further underscores the need for prioritizing research related to the acceptability of treatment as prevention. In uMgungundlovu, and settings with cultural

overlap, my research suggests that in particular, members of NGOs and government departments who implement TB interventions must consider if and how prevention models can work without challenging social norms for women or increasing burdens on the extreme poor.

Rethinking TB infection and disease

Recent genomic and radiographic studies have challenged the standard dichotomy of TB as latent or active [8-12], suggesting that medical researchers also struggle with differentiating TB at various stages. Pai and colleagues suggested that thinking of TB as a spectrum more adequately describes the potential stages of TB at which science is presently able to differentiate [12]. Their figure below also depicts the dynamic nature of these stages between which a person might progress or revert depending on innate or acquired immunity and the presence or absence of comorbidities such as HIV [12].

| | Infection eliminated | | Latent TB infection | Subclinical TB disease | Active TB disease |
	With innate immune response*	With acquired immune response			
TST	Negative	Positive	Positive	Positive	Usually positive
IGRA	Negative	Positive	Positive	Positive	Usually positive
Culture	Negative	Negative	Negative	Intermittently positive	Positive
Sputum smear	Negative	Negative	Negative	Usually negative	Positive or negative
Infectious	No	No	No	Sporadically	Yes
Symptoms	None	None	None	Mild or none	Mild to severe
Preferred treatment	None	None	Preventive therapy	Multidrug therapy	Multidrug therapy

Figure 7: The spectrum of TB from Pai *et al*. [12]

The dynamic nature of TB and diagnostic limitations may also contribute to the potential for mistrust of the formal healthcare sector in communities. For example, if a person were to present at clinic with a cough, and a GeneXpert test was unable to detect bacteria in a sputum sample, many healthcare workers would rule out TB. If that person's symptoms persisted or worsened, trust in the clinic system may be compromised, and future care, when sought, may go through alternative means, such as private or informal practitioners, driving up the cost to the

patient and prolonging (potentially transmissible) disease. Mistrust of the system may also occur when typical symptoms are absent or active TB symptoms develop on or following a regimen of IPT.

In an effort to more appropriately target preventive therapy, a group of researchers launched the correlates of risk project in South Africa's Western Cape province which seeks to identify biomarkers that help predict who will develop active TB disease [11,13]. Based on positive TSTs or interferon gamma release assays (IGRA – a blood-based test that detect a person's immune reactivity to *Mycobacterium tuberculosis*), a transcriptomic signature score has significantly lowered the number of people needed to treat with preventive therapy in order to prevent one individual from developing active TB [13]. The researchers theorise that the 16-gene signature added on to TST or IGRA detects incipient or sub-clinical TB disease, as depicted in Pai *et al.*'s figure [12], rather than latent infection [13]. Further studies are currently underway to test the use of these biomarkers to inform targeted preventive therapy. If the trend holds, such a test would alleviate at least some of the confusion resulting from poor diagnostic performance, altering what we currently consider "TB." If disease is detected sooner, then the sub-clinical stage depicted in Pai *et al.'s* figure [12] would shift or disappear altogether, making a simple dichotomy such as latent (or potentially benign) TB infection versus TB disease a less problematic distinction.

Since affordable and accessible point-of-care tests to diagnosis latent and active TB do not yet exist, the persisting pathogenic and diagnostic uncertainties serve to feed the confusion and potential mistrust among those who are at the greatest risk for developing disease. While biomedical research can respond to some aspects of the problem, treatment alone will not suffice to eliminate TB. We need to understand the human dynamics and address persisting socio-economic barriers that will also be required to achieve the 90-90-90 targets [14-16]. The community-based research components of my project suggest that confusion and mistrust can be mitigated through committed, cross-cultural knowledge exchange.

Sharing between Department of Health and local knowledge systems

Sir William Osler once described TB as "a social disease with medical elements" [17]. While Osler spoke these words in the context of transmissibility of disease, the ethnographic findings from my research suggest that treating TB infection requires equal consideration of the

social issues that might prevent access or informed decision making. Despite the potential for effective preventive treatment and the impact of better diagnostics, the success of TB preventive therapy in a given society will ultimately be determined by its acceptability. In this section I highlight the ways in which a one-directional approach to prevention may unintentionally undermine acceptability, drawing on examples from Department of Health educational materials and GRAT discussions. I close with a description of some successes from the knowledge exchange that occurred within this research, wherein the social complexities of preventing TB through medical intervention continue to come to light, demonstrating the benefits of the process.

One-size-fits-all approaches risk over-simplifying messages, which can in turn create stigma or display ignorance and disrespect toward the local population. A Department of Health brochure that was shared with GRAT members by a visiting nurse in late 2017 provides a useful example of this. The intended learning tool described a handful of measures to prevent TB transmission. These focussed on personal responsibilities including maintaining a clean home and avoiding cigarettes and alcohol. To my knowledge there is no evidence to support that a clean environment prevents exposure to droplet nuclei; and while smoking and excessive alcohol consumption can moderately increase the likelihood of progressing from latent to active TB [18], they also provide accessible short-term relief from struggles associated with economic hardship [19,20]. As highlighted in paper three, in such an environment, the benefits of an action (e.g. self-medicating with an addictive substance) may outweigh any potential decrease in life expectancy. On the other hand, as GRAT members noted, inaccurate messaging such as this can contribute to stigma, as anyone who develops TB disease may be dismissed in society as dirty, an addict, or an "unsavoury character" – perhaps even 'un-*makoti,*' if a woman.

Other TB prevention methods noted in the brochure demonstrated an ignorance of the lived experience of the average community member. Suggestions for preventing TB included sleeping fewer people to a room and eating a healthy diet including "meat, fish, eggs, and beans." As summarized in manuscript one, extreme poverty (lack of adequate housing and food insecurity) is a major concern for many community members. Simply informing people to eat nutritious food and live in a spacious environment does not address the lack of resources that may prevent a person from heeding this advice. It might even contribute to a disconnect between nursing staff and community members, reflecting a disparity in status or economic wellbeing.

Finally, the use of simplistic messaging without investment in cross-cultural exchange can also betray a lack of respect for community members. One of the frequently asked questions answered on the Western Cape province's Department of Health TB website is whether or not traditional medication can be used "to cure TB while on TB treatment." The Department's response read as follows:

> No, you mustn't use traditional medicine together with TB medicine because this may cause other side effects or make the TB treatment not work properly. It is important to take your TB medication every day for six months to be cured. You should NOT stop taking medication you received from the clinic, but you should stop the traditional medicine while taking TB treatment. [21, their emphasis]

Although the response pertains to treating active TB disease, it is not unlike the IPT messaging reported by participants in my research. The response presupposes biomedical buy in to the exclusion of other local knowledge systems without considering what these other practices may include and how they might benefit the health seeker [22-24]. Culture pertains to how we make sense of the world, and when someone challenges our worldview by saying 'no' without taking the time to understand the reasoning, one cannot help but feel patronised [25]. Working with communities to understand local knowledge can help to integrate interventions within existing cultural models [24,26].

In terms of translating the complexities of the biomedical findings on effectiveness, my work with GRATs met with success. In total, GRAT membership consisted of 28 people, among whom only one had a post-secondary degree, many were rural, and all spoke isiZulu as their home language. Following a four-year collaborative journey (2013-2017), GRAT members were able to hypothesise about the effectiveness findings before I presented them. After explaining the comparisons that were made and given their knowledge of the process, members made the same predictions as the findings; they thought that IPT would perform better given that it is meant to target just TB, while ART would also perform well given that it decreases viral load overall. They also hypothesised that the combination would further reduce incidence rates.

Unintentionally, GRAT members also demonstrated the limitations of these findings in practice. When asked to indicate anonymously whether or not each member would take IPT if offered, the response was split somewhere in the middle. Some members disclosed how they came to their decisions. One member indicated he would take IPT because he had lived with family members who were diagnosed and treated for TB disease. He felt his risk of having latent TB was relatively high. Another member declined because she ate fresh foods and felt her

current risk of developing active TB was relatively low. This does not mean that she and others who responded 'no' lacked "a universal willingness to preserve health" [24], or required "more education" in order to comply, as concluded in a number of studies which aimed to understand barriers to IPT uptake or adherence [27-29]. Rather, these mixed responses provide evidence that decisions related to TB prevention include consideration of biomedical aspects and the lived experience of community members. As the harm reduction model presented in manuscript three detailed, it is not up to a person from outside the community to judge whose decision is 'correct,' but it is meaningful to understand the reasons behind these decisions [30]. This information may shape interventions differently, ensuring that effective methods are also acceptable to the local context.

Although at the outset of my research, many community members outwardly welcomed the prospect of IPT because "prevention is better than cure," these feelings were not always reflected in the detailed experiences and perceptions that arose in conversation with participants. As outlined in paper one, IPT was interpreted as dangerous because it was linked to exacerbated poverty (financial costs related to pill collection or consumption), stigma (associated with HIV and ART), and toxicity (pills were considered a toxin that builds up in the body). In paper three, I developed the idea that clinical expectations regarding IPT initiation and adherence may conflict with expectations of women in Zulu culture. These manuscripts detail tangible examples of how knowledge about the lived experience of community members can improve the development and implementation of interventions. For example, understanding existing access barriers and cultural practices can encourage healthcare providers to engage with patients through the use of harm reduction [30] or mini-ethnography [26] techniques, promoting a collective decision about if and when IPT initiation and continuation is a safe option for each patient.

A paradigm shift

The idea of working with different populations to understand explanatory models is by no means new in healthcare, although it is generally recognised that the TB research world moves cautiously toward change, especially compared to HIV [31-34]. This likely relates to the lack of funds made available to a disease that affects primarily poor populations [32]. Initiatives like the Global Fund and the Millennium Development Goals have helped renew interest in TB, and a

new agenda put forth in relation to global TB elimination strategies in the last five years has placed greater emphasis on engaging with community stakeholders prior to implementation to help overcome the shortfalls of conventional prevention efforts [14,35]. Yet there is another reason that approaches to TB prevention and control have shifted little compared to HIV prevention and control efforts. In developing new ideas, people are heavily influenced by existing knowledge [36], and previous experience of TB before its resurgence in the 1990's was based upon outbreaks in Western Europe and North America. The approaches to prevention and control in these settings in the 20th century developed primarily from a paternalistic culture of doctor-knows-best [37-39], which continues to reflect in the TB treatment modalities of today. Conversely, HIV was an entirely new disease affecting a variety of populations due to global mobility. There was no 'existing knowledge' upon which to draw [40]. While public health paradigms of disease control were employed as researchers learned about this new disease, many advances in HIV have been based upon an appreciation of varying aetiologies in different populations [41]. Certain HIV preventive strategies that were once recommended globally, such as the ABCs – Abstain from sex, Be faithful, or use Condoms [42] – and the avoidance of breast feeding [43], were later revised based on the lived experiences of the various cultures in which HIV was spread [42,44,45].

At the 2017 International AIDS Society Conference in Durban, a call was made to shift focus from broad-based programming to location-specific solutions for HIV prevention and treatment in the highest burden settings; as these settings shift to a more rapid decline in incidence, the next highest burden populations would then be prioritised. This call occurred amidst an increased interest in HIV community engagement and a focus on bridging the gap between medical and social sciences. Several documents have been developed on good participatory practices for HIV drug trials [31,46,47], and implementation science, often lead by social scientists, is now a required component by most HIV clinical trial funding organisations.

In the field of TB research, similar changes are also occurring. Good participatory practice guidelines were recently developed for TB drug trials [48], and the TB Alliance – a global TB drug trial consortium – now has a dedicated community engagement team. In an effort to reach ambitious TB elimination targets [14,37], learning from the successes of the HIV research community in terms of community engagement will be important. The addition of my mixed methods enquiry into IPT effectiveness and acceptability will also provide direction for

community engagement in the implementation of TB preventive therapy and other interventions in high-burden settings of sub-Saharan Africa.

Limitations and Future Research

Limitations

In general, my investigation was limited by the sample population, constraints of available data, and a shortage of data specific to men. The sample population was limited both qualitatively and quantitatively. In selecting one community in each of three distance categories on which to focus community observation and engagement (peri-urban, rural, and remote), I did not have enough comparative data from each group to confidently conclude that differences in perspectives and practices were due only to geography. While statistical significance is not used to evaluate differences between groups in qualitative research, a qualitative researcher would seek out more than one instance in each category to reasonably conclude that differences found were not due to other community-level factors, such as political affiliation [49]. Without the ability to consider these geographic differences, important nuances may be missing from my analysis of IPT acceptability. During the dissemination of my work, for example, certain differences between GRATs were more pronounced. In Caluza, the peri-urban site, GRAT members developed the idea to hold a praise poetry competition based upon the findings. The team members took ownership of the project, sharing progress and final output with the larger group. In rural Songonzima, where the idea to develop a script for a radio "soapie" came about, members chose instead to provide health information sessions in a number of group gatherings, similar to those provided by NGOs and clinic-related interventions with which they had become familiar. Finally, in Embo, the remote community, where the team had been very excited to host an *ukuSina* (Zulu dance) competition incorporating the findings, the project never quite materialised despite several additional interactions with me at their request. Team members in Embo seemed less comfortable developing ideas from the findings that resonated with them. This suggested to me that community ownership and an increase in interaction between biomedical and cultural elements may not be as easily achieved as distance to cities – and their resources – increases. The implications for the acceptance of IPT in more distant communities may be affected. Perhaps healthcare decisions based on obedience to authority are more prominent in remote settings, or community members are less likely to know their HIV status

due to access issues and thus less likely to encounter and consider IPT. Had I the time and resources to collect and analyse additional data – i.e. more communities and more interviews in each community – I may have found important differences in the level of acceptability of IPT or treatment as prevention between geographical categories.

While the effectiveness findings are encouraging, they were also limited by the sample included in the analysis. As my data collection was retrospective, I was limited by the availability of comparative data from electronic ART registers, which reduced the number of clinics from which I could draw the sample of IPT users (exposed group). In a cohort study, contingency tables are used to compare the number of exposed and unexposed people (or the exposure time contributed by each group) to the number of people who do or do not develop disease during follow-up; therefore, the contingency cells that limit the estimate are those that represent people who develop disease. Since the occurrence of TB over two years is relatively rare in epidemiologic terms (even among PLWH in KZN), large numbers are needed among both exposed and unexposed groups to statistically compare the relationship to exposure. A prospectively collected dataset would enable the identification of more PLWH who did not take IPT, increasing the sample size in both the exposed and unexposed groups, thus improving precision of the estimates among smaller groups, e.g. among men. A large enough sample would also enable comparison of time to TB diagnosis (survival analysis) between exposure groups, and whether or not the rate of TB shifted amongst the IPT-exposed during and after the regimen. Prospective data collection would also facilitate control of other potential confounding variables, e.g. history of TB disease and health characteristics of PLWH who did and did not receive IPT. Collecting viral load or CD4 cell count at IPT initiation would also help to clarify any potential variation in effectiveness based upon level of immune function in this population. While future prospective research would likely improve the precision and depth of IPT comparisons, the comparison of IPT by ART status would now be difficult to evaluate prospectively, as a universal HIV test-to-treat policy has been instituted in South Africa since mid-2017 [50]. Future research might also consider collection of or linkage to mortality data, where possible, to assess safety of the regimen.

The constraints of working with retrospective clinic data also meant I was unable to improve or troubleshoot data in collaboration with the nurses who routinely recorded data from patient interactions. I faced similar limitations in group interviews, although to a lesser extent.

Although I was present, group interviews were undertaken in isiZulu by a trained facilitator. While I had the ability to add or clarify questions at the discretion of the facilitator, my minimal comprehension of the language during group interviews meant that I was unable to clarify or follow up on any novel responses from participants. Interpretation of data was iterative; however, some group interviews took place before transcriptions and translations were completed and reviewed. I did not encounter the same issue during individual interviews, as Ms Ndlovu provided real-time interpretation between isiZulu and English.

Both effectiveness and ethnographic data were limited in terms of male participation. Fewer men started and completed IPT compared with women, which may relate to men's reduced participation in the formal healthcare system as compared to women. This has also been noted in other recent studies in sub-Saharan Africa [51]. With limited epidemiologic data, the degree to which IPT prevents TB in men with or without ART in this setting is less precise than for women. No women living with HIV who completed IPT and were not yet on ART developed TB disease during follow-up, with a one-tailed confidence interval suggesting that IPT would reduce the TB incidence in this group by at least 77.78% compared to women with HIV who had not yet taken IPT or ART. Data among men suggested a net 54.33% decrease in TB incidence rate on IPT alone, varying between an 85.35% decrease and no difference according to the 95% confidence interval. Additional data on men who completed IPT would have allowed for a more precise estimate of the preventive effects of IPT. As I was unsuccessful at recruiting men for individual interviews, I could also not comment on factors that contributed to their IPT decision making. Participation of men in interviews was constrained by a few factors, including fewer men on IPT registers, inability to reach them through information provided on the register, and the hours during which I collected data – primarily during the day on weekdays, when more men were likely at work. I was also unable to arrange a group interview with taxi drivers in Songonzima due to bureaucratic delays imposed by the taxi association, which may indicate a level of mistrust as to my intentions. Although the two group interviews with taxi drivers provided helpful insight into the challenges of IPT uptake and general clinic usage among men, the small number of interviews and participants meant that I was unable to achieve data saturation and could not adequately speak to differences in this group.

It is also important to note that my qualitative analysis is by no means exhaustive. To paraphrase Haraway, I have attempted to imperfectly stitch together multiple perspectives that

are ultimately understood through my own vantage point, limited by my own cultural referents [52]. As an outsider to the community, I run the risk of mistaking an infrequent occurrence with a cultural norm. However, I sought to minimize misinterpretations through regular dialogue with GRATs and other key informants. Nonetheless, after five years of regular interaction with communities, I continue to encounter new layers of meaning to concepts that I thought I had fully understood.

Implications for future research

The community aspects of the project suggested interest, impetus, and an untapped knowledge base within communities of uMgungundlovu that could be drawn upon in order to optimise the benefits of IPT to reduce TB incidence in this high-burden setting. Additional research is needed to understand if and how the concept of prevention as treatment can fit within existing explanatory models without challenging social norms or exacerbating poverty. Research with additional communities would help elucidate potential geographic differences in acceptability, which would also have implications on effectiveness.

Prospective cohort research is needed to confirm the potential benefit of IPT among PLWH who test negative by TST in this population, as well as safety of the regimen. Research with a larger sample from this population would help to determine the degree to which men in particular may benefit from the regimen and enable an evaluation of the dose-response relationship in this real-world setting. My findings also suggest a need to assess the ways in which men might be better engaged in the formal healthcare system as well as the use of harm reduction and/or ethnographic interviews to encourage patient engagement related to IPT decision making in clinical interactions.

As part of my ongoing collaboration with GRAT members, we have developed a community-driven intervention intended to provide TB information and support through African Indigenous and mainline faith institutions with the hope of reaching more people who experience difficulties accessing clinics. The intervention also involves engagement with nurses at primary health centres and the KZN Department of Health to support the connection of community members to the public health system for the purposes of TB testing and IPT or active TB treatment. This presents an opportunity to introduce harm reduction approaches, reduce IPT

knowledge gaps among junior nursing staff, and for the research team to learn more about the challenges that health workers currently face in rural and peri-urban primary care clinics.

Implications beyond South Africa

Evidence from other IPT studies suggests that efficacy and/or effectiveness varies even within South Africa [53-55]. The degree of protection will depend on many factors, including TB incidence and HIV prevalence in the population, the degree to which IPT is offered and followed-up at the primary care level, the sustained availability of ART, the duration of IPT, whether or not IPT is targeted on the basis of TST results, and the amount and type of isoniazid resistance present in the population. As was suggested in a recent model by Ragonnet *et al.*, the high level of IPT effectiveness reported in this sample was likely influenced by the high TB incidence combined with endemic HIV in the population [56].

Effectiveness will also be influenced by acceptability in the population at risk, which the ethnographic components of my research have helped to elucidate. Because ethnography is situated in a particular place and time, from a particular perspective, it also means that findings on acceptability are not generalisable in the conventional sense, as they are not intended to be representative of the entire population [26,57,58]. Additionally, acceptability of IPT may shift and change over time as new information becomes available or as cultural dynamics shift within the community [26]. That said, lessons on IPT drawn from the ethnographic research may also be applicable to other Southern African cultures with similar belief systems and political and economic conditions, extend to members of the Southern African diaspora outside of the region, and apply to other cultures in response to similar circumstances. An example of more broad applicability is evident in a description of ethnic minority women in rural Vietnam who, much like Zulu women identifying as *oMakoti*, were reluctant to communicate openly with primary care professionals [59]. Policymakers, healthcare practitioners, and NGO and government programme implementers may wish to consider the ways in which seemingly disparate cultures overlap – and in which ways they do not – in order to transfer the lessons learned from one context to another. Suggestions on how to assess and incorporate lessons from differing explanatory models remain relevant to all biomedical healthcare interactions.

In closing, the findings from my thesis suggest that IPT is effective at reducing the incidence rate of TB in uMgungundlovu among those with access, and could be extremely useful

in the effort to end TB. Current research is focussed on less burdensome regimens and diagnostics that will better target these regimens to those who are truly at risk. Considering the current knowledge gaps with respect to host-related factors and the high number of people needed to treat with IPT for the purposes of TB prevention, it is critically important to invest in knowledge exchange to understand cultural complexities to introducing IPT in the global South. Trust in the formal healthcare system is already a challenge given the plurality of cultures and historical injustices found in South Africa and other former colonies. Bidirectional knowledge sharing is one way to combat misinterpretations occurring within communities and among those who attempt to intervene on behalf of communities. The nuances presented in my thesis suggest that our approach to community engagement was successful at drawing out hidden transcripts and may be useful to others who wish to engage in more participatory practices in TB interventions. Lessons from successful HIV community engagement can also provide models for the implementation of TB preventive therapy moving forward. The lessons learned through the process of engagement can help ensure the acceptability of IPT and similar interventions to improve both the quality and quantity of people's lives in high-burden, resource-constrained settings.

References

1. Schaaf S, Seddon JA. Drug-resistant tuberculosis and advances in the treatment of childhood tuberculosis. Pneumonia. 2016; 8(1): 20.
2. Fox DJ, Daubler CC, Marais BJ, Denholm JT. Preventive therapy for latent tuberculosis infection—the promise and the challenges. Int J Infect Dis. 2017; 56:68-76.
3. Martinson NA, Barnes GL, Moulton LH, Msandiwa R, Hausler H, Ram M, et al. New regimens to prevent tuberculosis in adults with HIV infection. New England Journal of Medicine. 2011; 354(1):11-20.
4. South Africa Department of Health. National Tuberculosis Program Strategic Plan 2017-2021. Pretoria: The Department; 2017.

5. Swindells S, Ramvhandani R, Gupta A, Benson CA, Leon-Cruz JT, Omoz-Oarhe A, et al. One month of rifapentine/isoniazid to prevent TB in people with HIV: Brief-TB/A5279 [abstract]. Proceedings of the Conference on Retroviruses and Opportunistic Infections. Boston, USA, 2018: 37LB.

6. Zumla A, Memish ZA, Maeurer M, Bates M, Mwaba P, Al-Tawfiq JA, et al. Emerging novel and antimicrobial-resistant respiratory tract infections: new drug development and therapeutic options. Lancet Infect Dis. 2014; 14(11): 1136-1149.

7. Bloemberg GV, Keller PM, Stucki D, Trauner A, Borrell S, Latshang T, et al. Acquired Resistance to Bedaquiline and Delamanid in Therapy for Tuberculosis. N Engl J Med 2015; 373(20): 1986-1988.

8. Barry CE 3rd, Boshoff HI, Dartois V, et al. The spectrum of latent tuberculosis: rethinking the biology and intervention strategies. Nat Rev Microbiol 2009; 7: 845–855.

9. Esmail H, Barry CE 3rd, Young DB, et al. The ongoing challenge of latent tuberculosis. Philos Trans R Soc Lond B Biol Sci 2014; 369: 20130437.

10. Delogu G, Goletti D. The spectrum of tuberculosis infection: new perspectives in the era of biologics. J Rheumatol Suppl 2014; 91: 11–16.

11. Petruccioli E, Scriba TJ, Petrone L, Hatherill M, Cirillo DM, Joosten SA, et al. Correlates of tuberculosis risk: predictive biomarkers for progression to active tuberculosis. Eur Respir J 2016; 48(6): 1751-1763.

12. Pai M, Behr MA, Dowdy D, Dheda K, Divangahi M, Boehme CC, et al. Tuberculosis. Nat Rev Dis Primers. 2016; 2: 16076.

13. Zak DE, Penn-Nicholson A, Scriba TJ, Thompson E, Suliman S, Amon LM. A blood RNA signature for tuberculosis disease risk: a prospective cohort study. Lancet 2016; 387: 2312–22.

14. World Health Organisation. The End TB Strategy: Global strategy and targets for tuberculosis prevention, care and control after 2015. Geneva: The Organisation; 2014.

15. Ortblad KF, Salomon JA, Bärnighausen T, Atun R. Stopping tuberculosis: a biosocial model for sustainable development. The Lancet. 2015 Dec 5;386(10010):2354-62.

16. Wingfield T, Tovar MA, Huff D, Boccia D, Saunders MJ, Datta S, Montoya R, Ramos E, Lewis JJ, Gilman RH, Evans C. Beyond pills and tests: addressing the social determinants of tuberculosis. Clinical Medicine. 2016 Dec 1;16(Suppl 6):s79-91.

17. Osler W qtd in Grzybowski S, Allen EA. Tuberculosis: 2. History of the disease in Canada. CMAJ. 1999; 160 (7): 1025-1028.

18. Bates MN, Khalakdina A, Pai M, Chang L, Lessa F, Smith KR: Risk of tuberculosis from exposure to tobacco smoke: a systematic review and meta-analysis. Archives of internal medicine. 2007, 167(4): 335-342.

19. Stead M, MacAskill S, MacKintosh AM, Reece J, Eadie D. "It's as if you're locked in": qualitative explanations for area effects on smoking in disadvantaged communities. Health & place. 2001 Dec 1;7(4):333-43.

20. Pearlin LI, Schooler C. The structure of coping. Journal of health and social behavior. 1978 Mar 1:2-1.

21. Western Cape Department of Health. What you need to know about TB (Tuberculosis). 2014. [website]. Available at: https://www.westerncape.gov.za/general-publication/what-you-need-know-about-tb-tuberculosis. Accessed 20 Dec 2017.

22. Bodkin C. Alternative therapies for the holistic care of the HIV/AIDS patient: overview. Health SA Gesondheid. 2003 Sep 1;8(3):37-46.

23. Ntukamazina PM, Malangu N. Use of Traditional, Complementary and Alternative medicines in people receiving antiretroviral therapy in the Village Clinic in Botswana. Pula: Botswana Journal of African Studies. 2017 Jul 5;31(1):108-19.

24. Beckmann N. Responding to medical crises: AIDS treatment, responsibilisation and the logic of choice. Anthropology & medicine. 2013 Aug 1;20(2):160-74.

25. Filc D. The medical text: between biomedicine and hegemony. Social science & medicine. 2004; 59(6):1275-85.

26. Kleinman A, Benson P. Anthropology in the clinic: the problem of cultural competency and how to fix it. PLoS Med. 2006; 3(10): e294.

27. Jacobson KB, Niccolai L, Mtungwa M, Moll AP, Shenoi SV. "It's about my life": Facilitators of and barriers to isoniazid preventive therapy completion among people living with HIV in rural South Africa. AIDS Care. 2017; 29(7): 936–942.

28. Makanjuola T, Taddese HB, Booth A. Factors Associated with Adherence to Treatment with Isoniazid for the Prevention of Tuberculosis amongst People Living with HIV/AIDS: A Systematic Review of Qualitative Data. PLOS One. 2014; 9(2): e87166.

29. Lester R, Hamilton R, Charalambous S, Dwadwa T, Chandler C, Churchyard GJ, Grant AD. Barriers to implementation of Isoniazid preventive therapy in HIV clinics: a qualitative study. AIDS. 2010;24(Suppl 5): S45-48.

30. Marlatt GA. Harm reduction: Come as you are. Addictive Behaviors. 1996; 21(6): 779-788.

31. Boulanger RF1, Seidel S, Lessem E, Pyne-Mercier L, Williams SD, et al. Engaging communities in tuberculosis research. Lancet Infect Dis. 2013 Jun;13(6):540-5.

32. Reichman LB. How to ensure the continued resurgence of tuberculosis. Lancet. 1996 Jan 20;347(8995):175-7.

33. Daftary A, Calzavara L, Padayatchi N. The contrasting cultures of HIV and tuberculosis care. AIDS. 2015; 29(1):1.

34. Frick M, Henry I, Lessem E. Falling short of the rights to health and scientific progress: inadequate TB drug research and access. Health and human rights. 2016 Jun;18(1):9.

35. Stop TB Partnership. The paradigm shift: global plan to end TB 2016-2020. UNOFP: Geneva, 2015.

36. Ward TB. What's old about new ideas. In Smith SM, Ward TB, Fink RA, eds. The Creative Cognitive Approach. 1997. Cambridge, Mass, MIT: p 157-177.

37. Sherwin S. Gender, race, and class in the delivery of health care. Bioethics: An introduction to the history, methods, and practice. 2007:283-92.

38. Gupta R, Cegielski JP, Espinal MA, Henkens M, Kim JY, Lambregts-van Weezenbeek CS, Lee JW, Raviglione MC, Suarez PG, Varaine F. Increasing transparency in partnerships for health–introducing the Green Light Committee. Tropical Medicine & International Health. 2002 Nov 1;7(11):970-6.

39. Frieden TR, Sbarbaro JA. Promoting adherence to treatment for tuberculosis: the importance of direct observation. World Hosp Health Serv. 2007; 43(2): 30-33.

40. Gallo RC, Montagnier L. The discovery of HIV as the cause of AIDS. New England Journal of Medicine. 2003 Dec 11;349(24):2283-5.

41. Grant AD, De Cock KM. ABC of AIDS: HIV infection and AIDS in the developing world. BMJ. 2001; 322(7300):1475.

42. Dworkin SL, Ehrhardt AA. Going beyond "ABC" to include "GEM": critical reflections on progress in the HIV/AIDS epidemic. American journal of public health. 2007 Jan;97(1):13-8.

43. Colebunders R, Kapita B, Nekwei W, Bahwe Y, Lebughe I, Oxtoby M, Ryder R. Breastfeeding and transmission of HIV. The Lancet. 1988 Dec 31;332(8626-8627):1487.

44. Murphy EM, Greene ME, Mihailovic A, Olupot-Olupot P. Was the "ABC" approach (abstinence, being faithful, using condoms) responsible for Uganda's decline in HIV?. PLoS medicine. 2006 Sep 12;3(9):e379.

45. Iliff PJ, Piwoz EG, Tavengwa NV, Zunguza CD, Marinda ET, Nathoo KJ, Moulton LH, Ward BJ, Humphrey JH, ZVITAMBO Study Group. Early exclusive breastfeeding reduces the risk of postnatal HIV-1 transmission and increases HIV-free survival. Aids. 2005 Apr 29;19(7):699-708.

46. AVAC & UNAIDS: Good participatory practice: Guidelines for biomedical HIV prevention trials. New York: UNAIDS, 2011.

47. Hannah S, M Warren M, Bass E. Global implementation of Good Participatory Practice Guidelines for biomedical HIV prevention research: charting progress and setting milestones. Retrovirology. 2012; 9(Suppl 2): P240.

48. Critical Path to TB Drug Regimens. Good Participatory Practice Guidelines for TB Drug Trials. 2012. [Internet]. Available from: http://www.cptrinitiative.org/downloads/resources/GPP-TB Oct1 2012 FINAL.pdf. [Accessed 15 Nov 2017].

49. Bricki N, Green J. A Guide to using Qualitative Methodology. London: Medicins Sans Frontiers; 2007. Available from: http://fieldresearch.msf.org/msf/handle/10144/84230 [Accessed 20 Mar 2017].

50. South Africa Department of Health. Implementation of the universal test and treat strategy for HIV positive patients and differentiated care for stable patients. Pretoria: The Department; 2016. Available from: http://www.sahivsoc.org [Accessed 17 Jul 2017].

51. Camlin CS, Ssemmondo E, Chamie G, El Ayadi AM, Kwarisiima D, Sang N, et al. Men "missing" from population-based HIV testing: insights from qualitative research. AIDS Care 2016; 28(sup3): 67-73.

52. Haraway D. Situated knowledges: The science question in feminism and the privilege of partial perspective. Feminist Studies. 1988; 14(3): 575-599.

53. Churchyard GJ, Fielding KL, Lewis JJ, Coetzee L, Corbett EL, Godfrey-Faussett P, et al. A trial of mass Isoniazid Preventive Therapy for tuberculosis Control. N Engl J Med 2014; 370:301-310. DOI: 10.1056/NEJMoa1214289

54. Madhi SA, Nachman S, Violari A, et al. Primary isoniazid prophylaxis against tuberculosis in HIV exposed children. N Engl J Med 2011; 365(1):21-31.

55. Rangaka MX, Wilkinson RJ, Boulle A, Glynn JR, Fielding K, van Cutsem G, et al. Isoniazid plus antiretroviral therapy to prevent tuberculosis: A randomised double-blind placebo-controlled trial. Lancet 2014; 384(9944): 682-90.

56. Ragonnet R, Trauer JM, McBryde ES, Houben RMG, Denholm JT, Handel A, et al. Is IPT more effective in high-burden settings? Modelling the effect of tuberculosis incidence on IPT impact. Int J Tuberc Lung Dis 2017; 21(1):60–66.

57. Côté L, Turgeon J. Appraising qualitative research articles in medicine and medical education. Med Teach 2005, 27(1):71-5.

58. Savage J. Ethnography and healthcare. BMJ. 2000; 321(7273): 1400–1402.

59. McKinn S, Duong LT, Foster K, McCaffery K. "I do want to ask, but I can't speak": A qualitative study of ethnic minority women's experiences of communicating with primary health care professionals in remote, rural Vietnam. Int J Equity Health (in press).

BIBLIOGRAPHY

1.   't Hoen EFM. TRIPS, pharmaceutical patents and access to essential medicines: Seattle, Doha and beyond. Chic J Int Law. 2002; 3(1): 27-46.

2.   Akolo C, Adetifa I, Shepperd S, Volmink J: Treatment of latent tuberculosis infection in HIV infected persons. Cochrane Database Syst Rev. 2010; (1): CD000171.

3.   Apers L, Robert C, Nachega JB. Prophylaxis with antituberculosis drugs in special situations. In Schaaf HS, Zumla AI, editors. Tuberculosis: A Comprehensive Clinical Reference. London: Elsevier; 2009. p. 780-85.

4.   AVAC & UNAIDS: Good participatory practice: Guidelines for biomedical HIV prevention trials. New York: UNAIDS, 2011.

5.   Ayele HT, van Mourik MS, Debray TP, Bonten MJ. Isoniazid prophylactic therapy for the prevention of tuberculosis in HIV infected adults: a systematic review and meta-analysis of randomized trials. PLOS One. 2015; 10(11): e0142290.

6.   Balcells ME, Thomas SL, Godfrey-Faussett P, Grant AD. Isoniazid Preventive Therapy and Risk for Resistant Tuberculosis. Emerging Infect Dis. 2006; 12(5): 744-751.

7.   Barry CE 3rd, Boshoff HI, Dartois V, et al. The spectrum of latent tuberculosis: rethinking the biology and intervention strategies. Nat Rev Microbiol 2009; 7: 845–855.

8.   Bateman C. Evidence of doctors' health minister at last. S Afr Med J 2010; 100:76–9.

9.   Bates MN, Khalakdina A, Pai M, Chang L, Lessa F, Smith KR: Risk of tuberculosis from exposure to tobacco smoke: a systematic review and meta-analysis. Archives of internal medicine. 2007, 167(4): 335-342.

10.   Beckmann N. Responding to medical crises: AIDS treatment, responsibilisation and the logic of choice. Anthropology & medicine. 2013 Aug 1;20(2):160-74.

11.   Bell JC, Rose DN, Sacks HS. Tuberculosis preventive therapy for HIV- infected people in sub-Saharan Africa is cost-effective. AIDS. 1999;13: 1549–1556.

12. Bhana D. Masculinities, Femininities and the Burden of Culture Among Rural South African Teenagers in the Context of HIV. In P Liamputtong, editor. Children and young people living with HIV/AIDS. Basel: Springer; 2016. p. 127-145.

13. Blasnik M. Record Linkage. Stata statistical software: Release 13. College Station, TX: StataCorp; 2013.

14. Bloemberg GV, Keller PM, Stucki D, Trauner A, Borrell S, Latshang T, et al. Acquired Resistance to Bedaquiline and Delamanid in Therapy for Tuberculosis. N Engl J Med 2015; 373(20): 1986-1988.

15. Bodkin C. Alternative therapies for the holistic care of the HIV/AIDS patient: overview. Health SA Gesondheid. 2003 Sep 1;8(3):37-46.

16. Boffa J, Mayan M, Mhlaba T, Ndlovu S, Williamson T, Fisher D. Why agency is important when implementing IPT: Lessons from *oMakoti* in KwaZulu-Natal, South Africa. PLoS ONE 13(3): e0193571.

17. Boffa J, Mayan M, Ndlovu S, Cowie R, Sauve R, Williamson T, et al. Community-level challenges to tuberculosis preventive therapy provision in KwaZulu-Natal, South Africa. [abstract]. Int J Tuberc Lung Dis 2016;20(12) Supp 1:S109.

18. Boffa J, Mayan M, Ndlovu S, Cowie R, Sauve R, Wilson D, et al. Understandings of tuberculous infection, TB disease and isoniazid preventive therapy in KwaZulu-Natal, South Africa [abstract]. Int J Tuberc Lung Dis. 2015;19(12) Supp 2:S279.

19. Boffa J, Williamson T, Cowie R, Sauve R, Mayan M, Fisher D. The effectiveness of community-wide, untargeted isoniazid preventive therapy to reduce the incidence rate of tuberculosis among people living with HIV in the context of upscaling anti-retroviral therapy in KwaZulu-Natal, South Africa. (in revision; PLoS One).

20. Bollela VR, Namburete EI, Feliciano CS, Macheque D, Harrison LH, Caminero JA. Detection of *kat*G and *inh*A mutations to guide isoniazid and ethionamide use for drug-resistant tuberculosis. Int J Tuberc Lung Dis. 2016; 20(8): 1099-1104.

21. Bor J, Herbst AJ, Newell M-L, and Bärnighausen T. Increases in adult life expectancy in rural South Africa: Valuing the scale-up of HIV treatment. Science, 339. 2013; 961-965.

22. Boulanger RF1, Seidel S, Lessem E, Pyne-Mercier L, Williams SD, et al. Engaging communities in tuberculosis research. Lancet Infect Dis. 2013 Jun;13(6):540-5.

23. Bricki N, Green J. A Guide to using Qualitative Methodology. London: Medicins Sans Frontiers; 2007. Available from: http://fieldresearch.msf.org/msf/handle/10144/84230 [Accessed 20 Mar 2017].

24. Briggs MA, Emerson C, Modi S, Taylor NK, Date A. Use of isoniazid preventive therapy for tuberculosis prophylaxis among people living with HIV/AIDS: a review of the literature. JAIDS. 2015; 68: S297-305.

25. Brislin RW. Back-translation for cross-cultural research. Journal of Cross-Cultural Psychology. 1970;1(3):187–216.

26. Brown L, Vega WA. A protocol for community-based research. In Minkler E, Wallerstein N, editors. Community-Based Participatory Research for Health: From Process to Outcomes (2nd ed). San Francisco: Jossey-Bass; 2008. pp 395-397.

27. Camlin CS, Ssemmondo E, Chamie G, El Ayadi AM, Kwarisiima D, Sang N, et al. Men "missing" from population-based HIV testing: insights from qualitative research. AIDS Care 2016; 28(sup3): 67-73.

28. Carton B, Laband J, Sithole J, editors. Zulu Identities: Being Zulu Past and Present. Durban: University of KwaZuu-Natal; 2009.

29. Charalambous S, Grant AD, Innes C, Hoffmann CJ, Dowdeswell R, Pienaar J, et al. Association of isoniazid preventive therapy with lower early mortality in individuals on antiretroviral therapy in a workplace programme. AIDS 2010;24 (Suppl 5):S5-S13.

30. Chavez V, Duran B, Baker QE, Avila MM, Wallerstein N. The dance of race and privilege in CBPR. In Minkler E, Wallerstein N, editors. Community-Based Participatory Research for Health: From Process to Outcomes (2nd ed). San Francisco: Jossey-Bass; 2008: 91-106.

31. Chimere-Dan O. Population policy in South Africa. Studies in Family Planning. 1993; 1:31-39.

32. Churchyard G, Corbett E. Tuberculosis and HIV. In Abdool Karim SS, Abdool Karim Q, editors. HIV/AIDS in South Africa. 2nd ed. Cambridge: Cambridge; 2010. p. 457-78.

33. Cohen MS, Chen YQ, McCauley M, Gamble T, Hosseinpour MC, et al. Prevention of HIV-1 with early anti-retroviral therapy. N Engl J Med. 2011; 365(6):493-505.

34. Colebunders R, Kapita B, Nekwei W, Bahwe Y, Lebughe I, Oxtoby M, et al. Breastfeeding and transmission of HIV. The Lancet. 1988 Dec 31;332(8626-8627):1487.

35. Comstock G. How much isoniazid is needed for prevention of tuberculosis among immunocompetent adults? Int J Tuberc Lung Dis. 1999; 3(10): 847-850.

36. Coovadia H Jewkes R, Barron P, Sanders D, McIntyre D. The health and health system of South Africa: historical roots of current public health challenges. Lancet 2009; 374: 817–34.

37. Côté L, Turgeon J. Appraising qualitative research articles in medicine and medical education. Med Teach 2005, *27*(1):71-5.

38. Critical Path to TB Drug Regimens. Good Participatory Practice Guidelines for TB Drug Trials. 2012. [Internet]. Available from: http://www.cptrinitiative.org/downloads/resources/GPP-TB Oct1 2012 FINAL.pdf. [Accessed 15 Nov 2017].

39. Daftary A, Calzavara L, Padayatchi N. The contrasting cultures of HIV and tuberculosis care. AIDS. 2015; 29(1):1.

40. Date AA, Vitoria M, Granich R, Banda M, Youssef M, Gilks C. Implementation of co-trimoxazole prophylaxis and isoniazid preventive therapy for people living with HIV. Bull World Health Organ. 2010; 88: 253-259.

41. Dawson S, Manderson L, & Tallo VL. A Manual for the Use of Focus Groups. WHO, 1993.

42. de Laine, M. Ethnography: Theory and Application in Health Research. Sydney: MacLennan & Petty, 1997.

43. Delogu G, Goletti D. The spectrum of tuberculosis infection: new perspectives in the era of biologics. J Rheumatol Suppl 2014; 91: 11–16.

44. Denis P. New patterns of disclosure: How HIV-positive support group members from KwaZulu-Natal speak of their status in oral narratives. Med Hist. 2014; 58(2): 278–297.

45. District Health Information System. Doris Goodwin MDR-TB Hospital [dataset]; Pietermaritzburg: uMgungundlovu District of Health; 2014.

46. Douglas M. Preface. In: Purity and Danger: An analysis of concepts of pollution and taboo. London: Routledge; 2003.

47. Douglas M. Purity and Danger: An analysis of concepts of pollution and taboo. New York: Praeger; 1966.

48. Douglas M. Risk and blame: essays in cultural theory. London: Routledge; 1992.

49. Dworkin SL, Ehrhardt AA. Going beyond "ABC" to include "GEM": critical reflections on progress in the HIV/AIDS epidemic. American journal of public health. 2007 Jan;97(1):13-8.

50. Esmail H, Barry CE 3rd, Young DB, et al. The ongoing challenge of latent tuberculosis. Philos Trans R Soc Lond B Biol Sci 2014; 369: 20130437.

51. Farmer P. An anthropology of structural violence. Current Anthropology. 2004; 45(3): 305-325.

52. Fassin, D. & Schneider, H. The politics of AIDS in South Africa: Beyond the controversies. BMJ. 2003; 326(7387): 495.

53. Churchyard GJ, Fielding KL, Lewis JJ, Coetzee L, Corbett EL, Godfrey-Faussett P, et al. A trial of mass Isoniazid Preventive Therapy for tuberculosis control. N Engl J Med 2014; 370:301-310. DOI: 10.1056/NEJMoa1214289

54. Fife W. Doing Fieldwork: Ethnographic Methods for Research in Developing Countries and Beyond. New York: Palgrave MacMillon; 2005.

55. Filc D. The medical text: between biomedicine and hegemony. Social science & medicine. 2004; 59(6):1275-85.

56. Fox DJ, Daubler CC, Marais BJ, Denholm JT. Preventive therapy for latent tuberculosis infection—the promise and the challenges. Int J Infect Dis. 2017; 56:68-76.

57. Frick M, Henry I, Lessem E. Falling short of the rights to health and scientific progress: inadequate TB drug research and access. Health and human rights. 2016 Jun;18(1):9.

58. Frieden TR, Sbarbaro JA. Promoting adherence to treatment for tuberculosis: the importance of direct observation. World Hosp Health Serv. 2007; 43(2): 30-33.

59. Gallo RC, Montagnier L. The discovery of HIV as the cause of AIDS. New England Journal of Medicine. 2003 Dec 11;349(24):2283-5.

60. Gibbs A. Focus Groups. Social Research Update. 1997;19 [about 4 pages]. Available at: http://sru.soc.surrey.ac.uk/SRU19.html [accessed 23 Oct 2017].

61. Gillespie SH. Evolution of drug resistance in Mycobacterium tuberculosis: clinical and molecular perspective. Antimicrobial agents and chemotherapy. 2002; 46(2):267-74.

62. Girling DJ. Adverse effects of antituberculous drugs. Drugs 1982; 23(1-2): 56–74.

63. Golub JE, Paul P, Mohapi L, Thsabangu N, Moshabela M, Struthers H, et al: Isoniazid preventive therapy, HAART and tuberculosis risk in HIV-infected adults in South Africa: a prospective cohort. AIDS. 2009; 23(5): 631-636.

64. Golub JE, Saraceni V, Cavalcante SC, Pacheco AG, Moulton LH, King BS, et al. The impact of antiretroviral therapy and isoniazid preventive therapy on tuberculosis incidence in HIV-infected patients in Rio de Janeiro, Brazil. AIDS. 2007; 21(11):1441-8.

65. Grant AD, De Cock KM. ABC of AIDS: HIV infection and AIDS in the developing world. BMJ. 2001; 322(7300):1475.

66. Guelar A, Gatell JM, Verdejo J, et al. A prospective study of the risk of tuberculosis among HIV-infected patients. AIDS. 1993;7(10):1345–9.

67. Guest G. Sampling and selecting participants in field research. in Handbook of Methods in Cultural Anthropology (2nd ed). Russel BH, editor. Lanham, USA: Rowman & Littlefield; 2015. pp. 215-50.

68. Guillford M, Figueroa-Munoz J, Morgan M, Hughes D, Gibson B, Beech R, et al. What does 'access to healthcare' mean? J Health Services Research & Policy 2002;7(3): 186–88.

69. Gupta R, Cegielski JP, Espinal MA, Henkens M, Kim JY, Lambregts-van Weezenbeek CS, Lee JW, Raviglione MC, Suarez PG, Varaine F. Increasing transparency in partnerships for health–introducing the Green Light Committee. Tropical Medicine & International Health. 2002 Nov 1;7(11):970-6.

70. Gust DA, Mosimaneotsile B, Mathebula U, Chingapane B, Gaul Z, Pals SL, et al. Risk factors for non-adherence and loss to follow-up in a three-year clinical trial in Botswana. PLOS ONE. 2011; 6(4): e18435.

71.   Hannah S, M Warren M, Bass E. Global implementation of Good Participatory Practice Guidelines for biomedical HIV prevention research: charting progress and setting milestones. Retrovirology. 2012; 9(Suppl 2): P240.

72.   Harris B, Goudge J, Ataguba J, McIntyre D, Nxumalo N, Jikwana S, et al. Inequities in access to health care in South Africa. J Public Health Pol. 2011; 32(Suppl 1): S102.

73.   Head BW. Community Engagement: Participation on Whose Terms?, Austr J Political Sci, 2007; 42(3): 441-454.

74.   Holloway I, Todres L. The status of method: Flexibility, consistency and coherence. Qual Res 2003, *3*(3):345-57.

75.   Horton KC, MacPherson P, Houben RM, White RG, Corbett E. Sex Differences in Tuberculosis Burden and Notifications in Low- and Middle-Income Countries: A Systematic Review and Meta-analysis. PLoS Med. 2016 Sep; 13(9): e1002119.

76.   Hunter M. Love in the time of AIDS. Pietermaritzburg: University of KwaZulu-Natal; 2010.

77.   Iliff PJ, Piwoz EG, Tavengwa NV, Zunguza CD, Marinda ET, Nathoo KJ, Moulton LH, Ward BJ, Humphrey JH, ZVITAMBO Study Group. Early exclusive breastfeeding reduces the risk of postnatal HIV-1 transmission and increases HIV-free survival. Aids. 2005 Apr 29;19(7):699-708.

78.   International Union Against Tuberculosis Committee on Prophylaxis. Efficacy of various durations of isoniazid preventive therapy for tuberculosis: five years of follow-up in the IUAT trial. Bull World Health Organ. 1982; 60(4): 555–564.

79.   Jacobson KB, Niccolai L, Mtungwa M, Moll AP, Shenoi SV. "It's about my life": Facilitators of and barriers to isoniazid preventive therapy completion among people living with HIV in rural South Africa. AIDS Care. 2017; 29(7): 936–942.

80.   Johnson JC. Selecting ethnographic informants. Newbury Park, Calif: Sage; 1990.

81.   Johnson LF. Access to antiretroviral treatment in South Africa, 2004 – 2011. SA J HIV Med. 2012; 13(1). Available from: http://www.sajhivmed.org.za/index.php/hivmed/article/view/156/261 [Accessed 25th Apr 2017].

82. Karim QA, Karim SS, Frohlich JA, Grobler AC, Baxter C, Mansoor LE, Kharsany AB, Sibeko S, Mlisana KP, Omar Z, Gengiah TN. Effectiveness and safety of tenofovir gel, an antiretroviral microbicide, for the prevention of HIV infection in women. science. 2010; 329(5996):1168-74.

83. Kerkoff AD, Kranzer K, Samandari T, et al. Systematic review of TST responses in people living with HIV in under-resourced settings: Implications for isoniazid preventive therapy. PLoS One 2012;7(11): e49928.

84. Khawcharoenporn T, Apisarnthanarak A, Manosuthi W, Sungkanuparph S, Mundy LM. Isoniazid preventive therapy and 4-year incidence of pulmonary tuberculosis among HIV-infected Thai patients. Int J Tuberc Lung Dis. 2012;16(3):336-41.

85. Kielmann K, Cataldo F. Tracking the rise of the "expert patient" in evolving paradigms of HIV care. AIDS Care. 2010; 22(sup1): 21-28.

86. Kleinman A, Benson P. Anthropology in the clinic: the problem of cultural competency and how to fix it. PLoS Med. 2006; 3(10): e294.

87. Kopanoff DE, Snider DE Jr, Caras GJ. Isoniazid-related hepatitis: A U.S. Public Health Service cooperative surveillance study. Am Rev Respir Dis. 1978 Jun;117(6):991-1001.

88. Kvale S, Brinkman S. Interview variations. In: InterViews: learning the craft of qualitative research interviewing. 2 ed. Thousand Oaks: Sage; 2009. p. 143-58.

89. Haraway D. Situated Knowledges: The Science Question in Feminism and the Privilege of Partial Perspective. *Feminist Studies*, Vol. 14, No. 3. (Autumn, 1988), pp. 575-599.

90. KwaZulu-Natal Department of Health. IPT indicators [dataset]; Pietermaritzburg: The Department; 2014.

91. Larratt-Smith J, Barton L. Bridging culture within nations. In Upvall MJ, Leffers J. editors. Global Health Nursing: Building and Sustaining Partnerships. New York: Springer; 2014. pp 176-185.

92. Lawn SD, Bekker SG. Co-pathogenesis of tuberculosis and HIV. In Schaaf HS, Zumla AI, editors. Tuberculosis: A Comprehensive Clinical Reference. London: Elsevier; 2009. p. 96-106.

93. Lawn SD, Harries AD, Williams BG, Chaisson RE, Losina E, De Cock KM, et al. Antiretroviral therapy and the control of HIV-associated tuberculosis. Will ART do it? [Unresolved issues]. Int J Tubercl Lung Dis. 2011;15(5): 571-81.

94. Leclerc-Madlala S. AIDS in Zulu Idiom: Etiological configurations of women, pollution and modernity. In: Zulu Identities: Being Zulu Past and Present. Carton B, Laband J, Sithole J, editors. Durban: University of Natal, 2009; pp 554-565.

95. Lester R, Hamilton R, Charalambous S, Dwadwa T, Chandler C, Churchyard GJ, Grant AD. Barriers to implementation of Isoniazid preventive therapy in HIV clinics: a qualitative study. AIDS. 2010;24(Suppl 5): S45-48.

96. Long R, Schwartzmann K. Transmission and pathogenesis of tuberculosis. In: Long R, Ellis E, editors. Canadian Tuberculosis Standards. 6th ed. Ottawa: Minster of Health; 2007. pp.37-52.

97. Madhi SA, Nachman S, Violari A, et al. Primary isoniazid prophylaxis against tuberculosis in HIV exposed children. N Engl J Med 2011; 365(1):21-31.

98. Magwaza T. Conversations with women from the Shembe church. Agenda. 2004; 60: 137-144.

99. Makanjuola T, Taddese HB, Booth A. Factors Associated with Adherence to Treatment with Isoniazid for the Prevention of Tuberculosis amongst People Living with HIV/AIDS: A Systematic Review of Qualitative Data. PLOS One. 2014; 9(2): e87166.

100. Marlatt GA. Harm reduction: Come as you are. Addictive Behaviors. 1996; 21(6): 779-788.

101. Martinson NA, Barnes GL, Moulton LH, Msandiwa R, Hausler H, Ram M, et al. New regimens to prevent tuberculosis in adults with HIV infection. New England Journal of Medicine. 2011; 354(1):11-20.

102. Mayan M. Essentials of qualitative inquiry. Walnut Creek, CA: Left Coast; 2009.

103. Mbali M. The Treatment Action Campaign and the history of rights-based, patient-driven HIV/AIDS activism in South Africa. In Jones P, and Stokke K, eds. Democratising Development: The Politics of Socio-economic Rights in South Africa. Martinus Nijhoff, 2005: 213-244.

104. McIntyre D, Klugman B. The human face of decentralisation and integration of health services: experience from South Africa. Reproductive health matters. 2003; 11(21):108-19.

105. McKinn S, Duong LT, Foster K, McCaffery K. "I do want to ask, but I can't speak": A qualitative study of ethnic minority women's experiences of communicating with primary health care professionals in remote, rural Vietnam. Int J Equity Health (in press).

106. Meintjes G, Maartens G, Boulle A, Conradie F, Goemaere E, Hefer E, et al. Guidelines for antiretroviral therapy in adults. Southern African J HIV Medicine. 2012; 13(3): 114-33.

107. Menzies D, Doherty TM. Diagnosis of latent tuberculosis infection. In Raviglione, editor. Reichman & Hershfield's Tuberculosis: A Comprehensive, International Approach. 3rd ed. Geneva: WHO; 2006.

108. Menzies R. Interpretation of repeated tuberculin tests. Boosting, conversion, and reversion. Am J Respir Crit Care Med 1999;159(1):15-21.

109. Mietinnen OS. Design of the occurrence relation. Theoretical Epidemiology. New York: Wiley; 1985. pp 25-45.

110. Mills Hl, Cohen T, Colijn C. Community-wide isoniazid therapy drives drug-resistant tuberculosis: A model-based analysis. Sci Transl Med 2013;5(180):180ra49.

111. Minkler E, Wallerstein N, editors. Community-Based Participatory Research for Health: From Process to Outcomes (2nd ed). San Francisco: Jossey-Bass; 2008.

112. Mitchell EMH, Harper I, Theobald S. Guidelines for preparing manuscripts on qualitative research in the IJTLD.

113. Mohammed A, Myer L, Ehrlich R, Wood R, Cilliers F, Maartens G. Randomised controlled trial of isoniazid preventive therapy in South African adults with advanced HIV disease. Int J Tuberc Lung Dis 2007;11(10):1114-1120.

114. Moodley P, Shah NS, Tayob N, Connolly C, Zetola N, Gandhi N, et al. Spread of Extensively Drug-Resistant Tuberculosis in KwaZulu-Natal Province, South Africa. PLoS One 2011; 6(5): [about 6 p.]. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3104985/pdf/pone.0017513.pdf. [Accessed 22 Sep 2014].

115. Morse JM, Barret M, Mayan M, Olson K, Spiers J. Verification strategies for establishing reliability and validity in qualitative research. Int J Qual Methods 2002, 1(2): 13-22.

116. Müller B, Streicher EM, Hoek KG, et al. *inh*A promoter mutations: a gateway to extensively drug-resistant tuberculosis in South Africa? Int J Tuberc Lung Dis. 2011; 15: 344–351.

117. Municipalities of South Africa. uMgungundlovu District Municipality: Demographic information. Available at: https://municipalities.co.za/demographic/120/umgungundlovu-district-municipality. [Accessed on 08th Dec 17].

118. Munseri PJ, Talbot EA, Mtei L, Fordham von Reyn C. Completion of isoniazid preventive therapy among HIV-infected patients in Tanzania. Int J Tuberc Lung Dis. 2008; 12(9): 1037–1041.

119. Murphy EM, Greene ME, Mihailovic A, Olupot-Olupot P. Was the "ABC" approach (abstinence, being faithful, using condoms) responsible for Uganda's decline in HIV?. PLoS medicine. 2006 Sep 12;3(9):e379.

120. Musante K. Participant observation. in Handbook of Methods in Cultural Anthropology (2nd ed**).** Russel BH, editor. Lanham, USA: Rowman & Littlefield; 2015. pp. 251-92.

121. Mutchler JE, Burr JA. Racial differences in health and health care service utilization in later life: the effect of socioeconomic status. J Health Soc Behav 1991; 32(4): 342-

122. Mutevedzi PC, Lessells RJ, Heller T, Bärnighausen T, Cooke GS, Newell ML. Scale-up of a decentralized HIV treatment programme in rural KwaZulu-Natal, South Africa: does rapid expansion affect patient outcomes?. Bulletin of the World Health Organization. 2010 Aug;88(8):593-600.

123. Nardell E, Churchyard G. What is thwarting tuberculosis prevention in high-burden settings? N Engl J Med 2011;365(1):79-81.

124. National Institute for Communicable Diseases. South African Tuberculosis Drug Resistance Survey 2012–14. Johannesburg: The Institute; 2016.

125. Ngamvithayapong J, Uthaivoravit W, Yanai H, Akarasewi P, Sawanpanyalert P. Adherence to tuberculosis preventive therapy among HIV-infected persons in Chiang Rai, Thailand. AIDS. 1997; 11: 107–112.

126. Ngozo J. Overview of the Department of Health Tuberculosis Control Programme in KwaZulu-Natal. [Presentation] Faith Leaders Symposium. 18 July 2016.

127. Ngwenya T. Introducing critical language awareness in IsiZulu: the why and the how. Southern African Linguistics and Applied Language Studies. 2006; 24(2): 165–173.

128. Niehaus AJ, Mlisana K, Gandhi NR, Mathema B, Brust JCM (2015) High Prevalence of *inh*A Promoter Mutations among Patients with Drug-Resistant Tuberculosis in KwaZulu-Natal, South Africa. PLOS ONE 10(9): e0135003.

129. Ntukamazina PM, Malangu N. Use of Traditional, Complementary and Alternative medicines in people receiving antiretroviral therapy in the Village Clinic in Botswana. Pula: Botswana Journal of African Studies. 2017 Jul 5;31(1):108-19.

130. Ortblad KF, Salomon JA, Bärnighausen T, Atun R. Stopping tuberculosis: a biosocial model for sustainable development. The Lancet. 2015 Dec 5;386(10010):2354-62.

131. Osler W qtd in Grzybowski S, Allen EA. Tuberculosis: 2. History of the disease in Canada. CMAJ. 1999; 160 (7): 1025-1028.

132. Page KR, Godfrey-Faussett P, Chaisson RE. Tuberculosis-HIV co-infection: Epidemiology, clinical aspects, and interventions. In Raviglione, editor. Reichman & Hershfield's Tuberculosis: A Comprehensive, International Approach. 3rd ed. Geneva: WHO; 2006.

133. Pai M, Behr MA, Dowdy D, Dheda K, Divangahi M, Boehme CC, et al. Tuberculosis. Nat Rev Dis Primers. 2016; 2: 16076.

134. Pai M, Denkinger CM, Kik SV, Rangaka MX, Zwerling A, Oxlade O, et al. Gamma interferon release assays for detection of *Mycobacterium tuberculosis* infection. Clinical Microbiology Reviews. 2014;27(1):3-20. doi:10.1128/CMR.00034-13.

135. Panjabi R, Comstock GW, Golub JE. Recurrent tuberculosis and its risk factors: Adequately treated patients are still at high risk. Int J Tuberc Lung Dis. 2007 Aug;11(8):828-37.

136. Parish NM, Dick JD, Bishai WR. Mechanisms of latency in *Mycobacterium tuberculosis*. Trends Microbiol. 1998 ;6(3):107-12.

137. Ragonnet R, Trauer JM, McBryde ES, Houben RMG, Denholm JT, Handel A, et al. Is IPT more effective in high-burden settings? Modelling the effect of tuberculosis incidence on IPT impact. Int J Tuberc Lung Dis 2017; 21(1):60–66.

138. Rangaka MX, Wilkinson RJ, Boulle A, Glynn JR, Fielding K, van Cutsem G, et al. Isoniazid plus antiretroviral therapy to prevent tuberculosis: A randomised double-blind placebo-controlled trial. Lancet 2014; 384(9944): 682-90.

139. Reichman LB. How to ensure the continued resurgence of tuberculosis. Lancet. 1996 Jan 20;347(8995):175-7.

140. Rifkin SB, Pridmore P. Partners in planning: information, participation and empowerment. London, GBR: Macmillan Education; 2001.

141. Robins S. From "rights" to "ritual": AIDS activism in South Africa. American Anthropologist. 2006; 108(2): 312-323.

142. Rowe KA, Makhubele B, Hargreaves JR, Porter JD, Hausler HP, Pronyk PM. Adherence to TB preventive therapy for HIV-positive patients in rural South Africa: implications for antiretroviral delivery in resource-poor settings? Int J Tuberc Lung Dis. 2005; 9(3): 263–269.

143. Rudwick S, Shange M. Hlonipha and the rural Zulu woman. Agenda. 2009; 23(82): 66-75.

144. Rudwick SI. Shifting norms of linguistic and cultural respect: Hybrid sociolinguistic Zulu identities. Nordic Journal of African Studies. 2008; 17(2): 152-174.

145. Samandari T, Agizew TB, Nyirenda S, Tedla Z, Sibanda T, Shang N, et al. 6-month versus 36-month isoniazid preventive treatment for tuberculosis in adults with HIV infection in Botswana: a randomised, double-blind, placebo-controlled trial. Lancet. 2011; 377(9777):1588-98.

146. Samandari T, Bishai D, Luteijn M, Mosimaneotsile B, Motsamai O, Postma M, et al. Costs and consequences of additional chest x-ray in a tuberculosis prevention program in Botswana. Am J Respir Crit Care Med. 2011;183(8):1103-11.

147. Savage J. Ethnography and healthcare. BMJ. 2000; 321(7273): 1400–1402.

148. Schaaf S, Seddon JA. Drug-resistant tuberculosis and advances in the treatment of childhood tuberculosis. Pneumonia. 2016; 8(1): 20.

149. Selwyn PA, Hartel D, Lewis VA, et al. A prospective study of the risk of tuberculosis among intravenous drug users with human immunodeficiency virus infection. N Engl J Med. 1989; 320(9): 545–50.

150. Shefer T. Resisting the binarism of victim and agent: Critical reflections on the 20 years of scholarship pm young women and heterosexual practices in South Africa contexts. Global Public Health. 2016; 11(1-2): 211-223.

151. Sherwin S. Gender, race, and class in the delivery of health care. Bioethics: An introduction to the history, methods, and practice. 2007:283-92.

152. Smith D. The Everyday World as Problematic: A Feminist Sociology. Boston: Northeastern University Press; 1987.

153. Sonnenburg P, Murray J, Glynn JR, Shearer S, Kambashi B, Godfrey-Faussett P. HIV-1 and reoccurrence, relapse, and reinfection of tuberculosis after cure: A cohort study in South African mineworkers. Lancet 2001; 358: 1687-93.

154. South Africa Department of Health. Adherence guidelines for HIV, TB and NCDs: policy and service delivery guidelines for linkage to care, adherence to treatment and retention in care. Pretoria: The Department; 2016.

155. South Africa Department of Health. Department of Health. National Tuberculosis Programme Guidelines. Pretoria: The Department; 2014.

156. South Africa Department of Health. Guidelines for tuberculosis preventive therapy among HIV infected individuals in South Africa. Pretoria: The Department; 2010.

157. South Africa Department of Health. Implementation of the universal test and treat strategy for HIV positive patients and differentiated care for stable patients. Pretoria: The Department; 2016. Available from: http://www.sahivsoc.org [Accessed 17 Jul 2017].

158. South Africa Department of Health. National Consolidated Guidelines for the prevention of mother-to-child transmission of HIV (PMTCT) and the management of HIV in children, adolescents, and adults. Pretoria: The Department; 2014. Available from: http://www.sahivsoc.org/Files/ART%20Guidelines%2015052015.pdf. [Accessed 25th Apr 2017].

159. South Africa Department of Health. National Tuberculosis Program Strategic Plan 2017-2021. Pretoria: The Department; 2017.

160. South Africa Department of Health. The South African antiretroviral treatment guidelines. The Department. Pretoria; 2013.

161. Statistics South Africa qtd. in WaziMaps. Statistics by District (Census 2011/2016 data). Available at: https://wazimap.co.za/profiles/district-DC22-umgungundlovu/ [Accessed 06 Apr 2018].

162. Statistics South Africa. Statistics by place (Census 2011 data). Available at: http://www.statssa.gov.za/?page_id=964 [Accessed 13 Sep 2017].

163. Stead M, MacAskill S, MacKintosh AM, Reece J, Eadie D. "It's as if you're locked in": qualitative explanations for area effects on smoking in disadvantaged communities. Health & place. 2001 Dec 1;7(4):333-43.

164. Sterling T. New approaches to the treatment of latent tuberculosis. Semin Respir Crit Care Med 2008; 29(5): 532-541.

165. Stop TB Partnership. The Paradigm Shift: Global Plan to End TB 2016-2020. Geneva: UNOFP; 2015.

166. Suthar AB, Lawn SD, del Amo J, Getahun H, Dye C, Sculier D, et al. Antiretroviral therapy for prevention of tuberculosis in adults with HIV: a systematic review and meta-analysis. PLoS Med. 2012;9(7):e1001270.

167. Swindells S, Ramvhandani R, Gupta A, Benson CA, Leon-Cruz JT, Omoz-Oarhe A, et al. One month of rifapentine/isoniazid to prevent TB in people with HIV: Brief-TB/A5279 [abstract]. Proceedings of the Conference on Retroviruses and Opportunistic Infections. Boston, USA, 2018: 37LB.

168. Szakacs T, Wilson D, Cameron DW, Clark M, Kocheleff P, Muller FJ, et al. Adherence with isoniazid for prevention of tuberculosis among HIV-infected adults in South Africa. BMC Infect Dis. 2006; 6: 97.

169. Tebruegge M, Bohyi M, Soriano-Arandes A, Kampmann B. Shortage of purified protein derivative for tuberculosis testing. Lancet 2014; 384(9959): 2026.

170. Tedla Z, Nyirenda S, Peeler C, Agizew T, Sibanda T, Motsamai O, et al. Isoniazid-associated hepatitis and antiretroviral drugs during tuberculosis prophylaxis in HIV-infected adults in Botswana. Am J Resp Crit Care Med 2010; 182(2): 278-85.

171. Tremblay MA. The key informant technique: A non-ethnographic application. American Anthropologist. 1967: 59(4): 688-701.

172. uMgungundlovu District Health Office. District Health Plan 2015/16. KwaZulu-Natal Department of Health: 2015. Available at: http://www.kznhealth.gov.za/Strategic/DHP/2015-16/Umgungundlovu.pdf [Accessed on 13 Sep 17].

173. UNAIDS. South Africa HIV and AIDS Estimates (2015). Available from http://www.unaids.org/en/regionscountries/countries/southafrica. [Accessed 11th Sep 2017].

174. United Nations. Resolution adopted by the General Assembly on 25 September 2015. Available at: http://www.un.org/ga/search/view_doc.asp?symbol=A/RES/70/1&Lang=E. Accessed on 19 Dec 2017.

175. van Mannen J. Ethnography then and now. Qualitative Research in Organizations and Management: An International Journal 2006; 1(1): 13-21.

176. van Rie A, Warren R, Richardson M, Victor TC, Gie RP, Enarson DA, et al. Exogenous reinfection as a cause of recurrent tuberculosis after curative treatment. N Engl J Med. 1999; 341(16): 1174-9.

177. Vernooij E, Mehlo M, Hardon A, Reis R. Access for all: contextualising HIV treatment as prevention in Swaziland. AIDS Care 2016; 28(sup3): 1-7.

178. Ward TB. What's old about new ideas. In Smith SM, Ward TB, Fink RA, eds. The Creative Cognitive Approach. 1997. Cambridge, Mass, MIT: p 157-177.

179. Western Cape Department of Health. What you need to know about TB (Tuberculosis). 2014. [website]. Available at: https://www.westerncape.gov.za/general-publication/what-you-need-know-about-tb-tuberculosis. Accessed 20 Dec 2017.

180. Wickström A. Virginity testing as a local public health initiative: a 'preventive ritual' more than a 'diagnostic measure'. J Royal Anthropological Institute. 2010; 16(3): 532-550.

181. Wilson D, Fairall L. Challenges in managing AIDS in South Africa. In Abdool Karim SS, Abdool Karim Q, editors. HIV/AIDS in South Africa. 2nd ed. Cambridge: Cambridge; 2010. p. 503-28.

182. Wilson D, Fisher D, Geffen N, Cohen T. Implementing Isoniazid Prophylactic Therapy in High HIV-Prevalence Settings: Need for Nuance. [unpublished draft]

183. Wilson D, Howell V, Toppozini C, Dong K, Clark M, Hurtado R. Against all odds: diagnosing tuberculosis in South Africa. J Infect Dis. 2011; 204(Suppl 4):S1102-9.

184. Wingfield T, Tovar MA, Huff D, Boccia D, Saunders MJ, Datta S, et al. Beyond pills and tests: addressing the social determinants of tuberculosis. Clinical Medicine. 2016 Dec 1;16(Suppl 6):s79-91.

185. Wood R, Becker LG. Isoniazid preventive therapy for tuberculosis in South Africa: An assessment of the local evidence base. South African Med J 2014; 104(3): 174-177.

186. World Health Organisation and UNAIDS. Policy statement on preventive therapy against tuberculosis in people living with HIV. Geneva: The Organisation; 1998 [cited 2018 April 25]. Available from: http://apps.who.int/iris/bitstream/handle/10665/64509/WHO_TB_98.255.pdf?sequence=1

187. World Health Organisation. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: Recommendations for a public health approach. 2nd ed. Geneva: The Organisation; 2016. Available from: http://www.who.int/hiv/pub/arv/arv-2016/en/ [Accessed 20th Oct 2017].

188. World Health Organisation. Global Tuberculosis Report 2016. Geneva: The Organisation; 2016 Available from: http://www.who.int/tb/publications/global_report/en/ [Accessed 8th Jul 2017].

189. World Health Organisation. Guideline on when to start antiretroviral therapy and on pre-exposure prophylaxis for HIV. Geneva: The Organisation; 2015. Available from: http://apps.who.int/iris/bitstream/10665/186275/1/9789241509565_eng.pdf [Accessed 25th Apr 2017].

190. World Health Organisation. Guidelines for intensified tuberculosis case-finding and isoniazid preventive therapy for people living with HIV in resource-constrained settings. Geneva: The Organisation; 2011. Available from: http://www.who.int/tb/challenges/hiv/ICF_IPTguidelines/en/index.html. [Accessed 25th Apr 2017].

191. World Health Organisation. Health and the Millennium Development Goals. Geneva: The Organisation; 2014.

192. World Health Organisation. Stop TB Initiative. Treatment of tuberculosis: Guidelines. Geneva: The Organization; 2010.

193. World Health Organisation. The End TB Strategy: Global strategy and targets for tuberculosis prevention, care and control after 2015. Geneva: The Organisation; 2014.

194. World Health Organisation. Tuberculosis Fact Sheet (2017). Available from http://www.afro.who.int/health-topics/tuberculosis-tb. [Accessed 08th Dec 2017].

195. World Health Organisation. WHO three I's Meeting: intensified case finding, isoniazid preventive therapy and TB infection control for people living with HIV. Geneva: The Organisation; 2008.

196. World Health Organisation. WHO treatment guidelines for drug-resistant tuberculosis. 2016 update. Geneva: The Organisation; 2016. Available at: http://www.who.int/tb/MDRTBguidelines2016.pdf [Accessed 10 June 2016].

197. Yamori S, Ichiyama S, Shimokata K, Tsukamura M. Bacteriostatic and bactericidal activity of antituberculosis drugs against Mycobacterium tuberculosis, Mycobacterium avium-Mycobacterium intracellulare complex and Mycobacterium kansasii in different growth phases. Microbiol Immunol. 1992;36(4):361-8.

198. Yirdaw KD, Jerene D, Gashu Z, Edginton ME, Kumar AM, Letamo Y et al. Beneficial effect of isoniazid preventive therapy and antiretroviral therapy on the incidence of tuberculosis in people living with HIV in Ethiopia. PLoS One. 2014;9(8):e1045

199. Zak DE, Penn-Nicholson A, Scriba TJ, Thompson E, Suliman S, Amon LM. A blood RNA signature for tuberculosis disease risk: a prospective cohort study. Lancet 2016; 387: 2312–22.

200. Zhang Y, Yew WW. Mechanisms of drug resistance in *Mycobacterium tuberculosis*. Int J Tuberc Lung Dis. 2009;13: 1320–1330.

201. Zumla A, Memish ZA, Maeurer M, Bates M, Mwaba P, Al-Tawfiq JA, et al. Emerging novel and antimicrobial-resistant respiratory tract infections: new drug development and therapeutic options. Lancet Infect Dis. 2014; 14(11): 1136-1149.

LIST OF APPENDICES

Appendix 1A GRAT Terms of Agreement (English)

Appendix 1B GRAT Terms of Agreement (isiZulu)

Appendix 2 Summary descriptors of notable key informants

Appendix 3 Group interview guide

Appendix 4 Individual interview guide

Appendix 5 IPT register

Appendix 6 Kleinman and Benson's mini-ethnography tool adapted to the context of *uMakoti*

Appendix 7 Copyright forms

APPENDIX 1A: GRAT Terms of Agreement (English)

Songonzima Advisory Team
Terms of Agreement

Purpose of Terms of Agreement
The following Terms of Agreement describes the negotiated working relationship between research representatives ("research group") and the Songonzima community representatives ("uMphakathi") on the Songonzima INH Advisory Team.

Purpose of INH Project
In 2012 estimated TB incidence in South Africa was 530 000 or 1% of the population, among which 330 000 cases were among people living with HIV and 6 000 were multi-drug resistant. UMgungundlovu District has an HIV prevalence of 15%, a TB incidence rate of 1%, and multi-drug resistance is reported at 7% among TB cases and 15% amongst people living with HIV.

In 2011 the South African government introduced access to free 6-month isoniazid ("INH") preventive therapy for people at a high-risk of developing active tuberculosis (TB). Patients in whom active TB has been reasonably excluded by symptoms screen are eligible for therapy without the necessity of a Tuberculin Skin Test. The INH project was developed to evaluate the effectiveness of INH in KwaZulu-Natal province, where co-infection rates of TB-HIV are the highest. The research involves a mixed-methods approach to determine 1) the impact of preventive therapy on explanatory models of TB in predominantly Zulu communities, 2) the experiences and beliefs of patients completing, discontinuing, or declining IPT, and 3) the longitudinal and comparative TB disease and mortality outcomes amongst those completing IPT. The research involves community-based Advisory Teams in three communities (Embo, Songonzima, and Caluza) to help researchers better understand the impact of culture on implementation and patient experience.

Description of Partners
Research Group
The INH project was developed as a thesis component of Ms. Jody (Nombuso) BOFFA's PhD degree from the University of Calgary, Canada and involves the community expertise of research assistant Ms. Sithembile NDLOVU, Chief Executive Officer of Izimbali Zesizwe, a community feeding scheme in Imbali, uMgungundlovu.

The INH project is supervised by Dr. Dina FISHER and Dr. Bob COWIE at the University of Calgary and community-based research specialist Dr. Maria MAYAN from the University of Alberta in Canada. Dr. Fisher and Dr. Mayan have had the opportunity to visit uMphakathi and meet the members of the Songonzima Advisory Team shortly after the team was struck.

uMphakathi
With the assistance of iNduna and the youth leader of the Ward Office, members were identified that met the following criteria requested by the research group to ensure a broad representation of Songonzimna community members from the grass roots: Members of the community with an interest in health, but no formal clinical training. Current membership includes Ms. Balungile MADLALA, volunteer community care giver; Ms. Hlengiwe NGQULUNGA, community care giver with Songonzima clinic; Mr. Sandile ZACA, youth committee leader for ward counsel; Mr Themba DLUNGWANE, iNduna; Mrs. Zibuyile MNIKATHI, Sangoma; Pastor Bongani MKHIZE; and Ms. Lungile MKHIZE, community educator and activist.

Guiding Principles and Objectives

The guiding principle of Songonzima Advisory Team is to improve health of community members through research-based policy recommendations and information sharing. Objectives of the team include:

- Communicating relevant and correct information to the community on pressing health issues
- Providing policy recommendations to clinic staff and government based on health research carried out in the community
- Ensuring that patient-specific information remains confidential, while also conveying respectful and representative community perspectives and knowledge to stakeholders

Roles and Responsibilities

- to share information that clarifies perspectives, knowledge, and practices within the community to others outside of the community
- to serve as community experts in local health issues, helping to answer questions and dispel myths
- To build capacity among team members and in the community with regard to research and health knowledge
- To identify ongoing research needs in Songonzima
- to aid in the development of local protocols and processes for research carried out under the team's scope
- To provide recommendations to government and health authorities based upon the shared interpretation of research findings
- To approve health messages and presentations for dissemination
- To encourage people in the community to share their health challenges and gain knowledge

Meetings

The advisory team shall meet between 2 and 6 times per year, depending on activities. Members shall be given 2 weeks lead time for the meeting and a two-day reminder call from the meeting organizer (research assistant). If a member misses more than two consecutive meetings without a valid reason, members in attendance shall vote on the continued participation of the absent member.

Decision-Making Processes
The Songonzima Advisory Team will seek for consensus on all decisions by means of tabling down disputes to one shared vision, which incorporates the viewpoints of all members

Conflict Resolution
- Step 1: Conflict will be brought to a roundtable discussion with a moderator which may be a neutral team member or a ward counsellor; if further resolution is needed, move to step 2.
- Step 2: Conflict will be brought to a roundtable discussion with an Nduna as moderator; if further resolution is needed, move to step 3.
- Step 3: Conflict will be brought to a roundtable discussion with iNkosi as moderator.

Process Evaluation
An evaluative questionnaire on the effectiveness of the Advisory Team will be drafted and ratified by all Advisory Team Members to be completed once per year. uMphakathi will undertake a training activity to assess knowledge and proficiencies acquired.

Process for Termination and Timeline
The INH project and dissemination is scheduled to complete on 30 April 2016. At this time the group shall meet to determine that all objectives have been met, otherwise the termination date will be extended. It is also possible that future projects will enable the team to continue to work together beyond the INH project. If and when this occurs, the termination process and timeline will be revised in the terms of agreement.

Signed this _____ day of _____, 2013 at Songonzima
          day   *month*

APPENDIX 1B: GRAT Terms of Agreement (isiZulu)

Ithimba lokuLileka laseSongonzima
Imogomo yeSivumelwane

Injongo yeMigomo yeSivumelwano
Imigomo yeSivumelwano elandelayo ichaza ngobudlelwane bokusebenza ekexoxiswane ngayo phakathi kwabacwaningi (Ithimba locwaningo) nabamele umphakathi waseSngonzima kwithimba lokuLuleka laseSongonzima.

Injongo yeProject yeINH
Ngonyaka ka2012 izingathekiso ezimayelana neTB eNingizimu ye-Afrika yayi530 000 noma i1% labantu, kubantu abawu330 000 ababikiwe phakathi kwabo abaphila nesandulela ngculazi naba 6 000 babe ngasazweli ekulashweni eSifundazweni saseMgungundlovu balinganiselwa kwisibalo esiwu15%, izinga le TB liyi1%, nokuthi eleTB engasazweli kwimshanguzo elibikiwe lingu7% kwabaneTB abaziwayo no 15% wabaphila nesandulela ngculazi.

Ngonyaka ka2011 uhulumeni waseNingizimu ye-Afrika wethula ukunikezelwa mahhala izinyanga 6 kwe-isonaizid ('INH') ukuvikela iTB kubantu abasesimweni esibucayi sokungenwa TB.Kuziguli ekungase kuzona iTB ingatholakali ngokuhlola ngezimpawu bavumelekile ngaphandle kokudingeka kokuhlolwa kwesikhumba (Tubercullin Skin Test).I_INH project yasungulelwa ukubuyekeza ukusebenza kwwe INH eSifundazweni saKwaZulu Natal, lapho ukutheleleka kweSandulela Ngculaza neTB kusezingeni eliphezulu. Ucwaningo lusebenzisa ikuxubana kwezindlela ukunquma 1) umphumela wokulashwa ngokuvikela ngendlela echasisayo ye TB emphakathini onaZulu amaningi,2) amava nezinkolelo kubantu abaqedile ukwelashwa, abangaqhubekanga noma abangakuvumanga ukulashwa ngokuvikela, noma3) ubude nokuqhathaniswa kweSifo sofuba nemiphumela yokushona kulabo abaqede ukulashwa ngokuvikela.Ucwaningo lubandakanya isisekelo somphakathi iThimba lokuLuleka emphakathini emithathu(Embo, Songonzima, neCaluza)ukusiza ukufinyelela ekuqondeni kancono umthelela wesiko ekwenzeni nasemaveni eziguli.

Ukuchazwa kobusebenzisana
Iqembu labaCwaningi
I-INH project yasungulwa njengombono ohlangene wa Nks. Jody (Nombuso) BOFFA'skwimfundo esezingeni eliphakeme leziqu ze PhD eNyuvesi yaseCalgary eCanada ibandakanya okulindeleke emphakathini ngosizo lukaNks. Sithembile NDLOVU, Umphathi weZimbali Zesizwe, Inhlangano ephakela umphakathi eMbali eMgungundlovu.

I-INH projectibhekwe Dr. uDina FISHER kanye noDr. uBob COWIE oseNyuvesi yaseCalgary kanye noDr, Maria MAYAN eNyuvesi yase-Alberta eCanada Dr. Fisher noDr. Mayan babenethuba lokuvakashela umphakathi nokuhlangana neThimba lokuLuleka laseSongonzima ngednkathi iqembu lalisanda kusungulwa.

uMphakathi
Ngosizo lweNduna kanye nomholi weNtsha wehhovisi leWodi, amalungu akhethwa lawo ayefanelekile ukuhlangabezana nezidingo zocwaningo ezilandelayo ezazidingwa iqembu

locwaningo ukuqinisekisa ukumeleleka komphakathi waseSongonzima ngokubanzi emazingeni aphansi: Amalunga omphakathi anezinjongo kwezempilo,kodwa bebe bengenakho ukuqeaeshwa okuhlelekile kwezempilo.Amalunga akhona okwamanje uNk. Balungile MADLALA, ivolontiya elinakekela abagulayo emphakathini, Nk. Hlengiwe NGQULUNGA,onakekela abagulayo emphakathini noMtholampilo waseSongonzimz,uMnu. Sandile ZACA, umholi wentsha wekhansela lewodi, Mnu. Themba DLUNGWANE, induna, uNkz. Zibuyile MNIKATHI, iSangoma, uMfundisi Bongani MKHIZE, kanye noNks. Lungile MKHIZE, umqeqeshi womphakathi nokhuthele emphakathini.

IMITHETHO YEZIQONDISO NEMPHOKOPHELE
Imithetho eqonidisayo yethimba lokwaluleka laseSongonzima ukuthuthukisa kwezempilo kumalunga ompnhakathi ngemithetho yezo cwaningo, izincomo nokwabelana ngolwazi. Izimphokophelo zeqembu zimbandakanya :
- Ukuxhumanisa okuyikona okuphathelene nokulungisa ulwazi emphakathini   ngokugcizelela eziphatheleni nezempilo.
-Ukunikeza imithetho encomekayo kubasebenzi baemthola mpilo nakuhulumeni okuncike ocwaningweni lweze mpilo oluqhubeke emphakathini.
-ukuqinisekisa izighuli ngemithetho eqondene nokugcina isifuba, kube futhi kuqhutswa ngenhlonipho nokumeleleka kwedlela umphakathi obonangayo izinto, nolwazi kwekusetsenziswana nabo.

IMISEBENZI NEZIBOPHO
- Uwabelana ngolwazi olucacisa indlela okubukwa ngayo, ngolwazi, kanye nendlela okuqhutswa ngayo emphakathi ukwabela abakweminye imiphakathi engaphandle.
- Ukusebenza njenga nabavelele kwezemphilo ezindaba ezingaphakathi, ukusiza ukuphendula imibuzo nokuchitha izinkolelelo-ze .
- Ukwakha umthamu phakathi kwamalunga ethimba nasemphakathini ngokuqhondene nocwaningo nolwazi ngezemphilo.
- Nokubona izidingo zocwaningo eSongonzima
- Ukusiza ekuthuthukiseni iziqhumo ngaphakathi kaye nezindlela ekuqhutswa ngazo ucwaningo ngaphansi kwenqhubo yeqembu.
- Ukunikeza izincomo kuhulumeni nemithethe yezempilo encike encazelweni ekuboniswane ngayo ngokutholakele uCwaningo
- Ukunikeza umbiko wezemphilo nokuthulwa okusakazwa kombiko
- Ukukhuthaza abantu emphakathini ngokwabelana ngezinqinamba zempilo nokuzuza ulwazi

IMIHLANGANO
Ithimba lokkubonisana lingahlangana phakathi 2-6 ngonyaka, kuncike emisebenzini. Amallunga ayokwaziswa emasontweni amabili ngaphambi komhlangano nokukhunjuzwa ngocingo kusele izinsuku ezimbili ngaphambi komhlangano, umhleli (umsizi wocwaningo), uma ilunga lingaphumelelanga emihlanganenwini emibili ilandelana ngaphandle kwesizathu esibalulekile, amalunga asemhlanganweni ayovotela ukuqhubeka ngaphandle kokubakhona kwelunga elingekho.

IQUBO YOKUTHATHWA KWEZINQUMO
Ithimba lokwaluleka laseSongonzima liyofuna ukuvmelana ukwenza zonke izinqumo yokubeka phansi etafuleni izixhabano ngombono owodwa, okuyohlanganisa indlela ababonangayo amaphuzu bonke.

UKUXAZULULWA KWEZINGXABANO
- Isinyathelo 1: Igxabano iyobekwa etafuleni lokubonisana kunomungameli ophakathi nendawo noma ikhansela lendawo, umakudlula lapho kuyiwa esinyathelweni 2
- Isinyathelo 2 :Igxabano iyobekwa etafuleni kanye nenduna njengomungameli, umakudingeka kuyothathwa isinyathelo 3
- Isinyathelo 3: Igxabano iyobekwa etafuleni nennkosi njengomungameli.

IQHUBO YOKUHLUZA

Imibuzo yokuhluza ngokusebenza kahle kwethimba lokululeka iyo-pulanwa ngokuvumelana kwamalunga wonke ethimba lokululeka iqedwe kanye ngonyaka. Uphakathi uyongenele ukuqeqeshelwa ukucubungula ulwazi nobuncwati obudingekayo.

INQUBO YOKUVALA NESIKHATHI

iINH project nokwazisa kuhlelelwe ukuqedwa ngomhla zinga 30 kuMbasa ngo2016.Ngalesisikhathi amaqembu ayohlangana ukuknquma ukuthi imighomo/ izimphokophelo zifezekile, okungenani isikhathi sokuvala siyokwengezwa. Kungenzeka ukuthi kkumaProject alandelayo kuyovunyelwa ithimba ukuba liqhubeke lisebenze ndawonye ngale kweINH project. Uma noma lokhu kwenzeka iqhubo yokuvalwa nesikhathi kuyobuyekezwe ngokuvumelana.

Isayinwe _____usuku luka _____, 2013 at Songonzima
                    day   *month*

APPENDIX 2: Notable Key Informants

- Ms Ndlovu Ndlovu, community-based cultural liaison
- Ms Ndlovu's three daughters, each differing in age by five years, and able to share the experiences of younger generations navigating a post-Apartheid space in Edendale township
- A male pastor from a mainstream Christian church
- A female church organiser of an African indigenous church
- A male traditional leader with a remarkable sense of humour
- An urban woman who rejected customary Zulu traditions in adulthood, but recollected years of growing up in the rural north and a year of high school living with a family who had strong ancestral beliefs
- An educated female community member who had suffered many losses and maintained her affinity for traditional life
- Two male youth leaders
- A publicly quiet, yet reflective female *iSangoma* (ancestral healer)
- Two female HIV activists
- Two particularly reflective male taxi drivers in their 30s
- A middle aged male *iNduna* (community liaison to traditional leader)
- Two female members of traditional councils
- A young man who had survived MDR-TB, but lost his sister and livelihood to the disease
- A female TB survivor living with HIV, unwilling to start ART
- A male ward counsellor
- An elderly woman who fostered orphaned youth in her community

APPENDIX 3: Group Interview Guide

1. Kusho ukuthini uku "gula'' (*What does it mean to be "sick"*)?

2. Kusho ukuthini uku "phila" (*What does it mean to be "healthy"*)?

3. Ubani onakekela ogulayo ekhaya lakho? Emphakathini wangakini (*Who looks after the sick in your household? Your community*)?

4. Yini isifo sofuba (TB) (*What is TB*)?

5. Yini efika engqondweni uma ucabanga ngomuntu ophethwe isfiuba (TB) (*What comes to mind when you think of a person sick with TB)*?

6. Kunesikhathi esingakanani iTB iyinkinga emphakathini wakho (*How long has TB been a problem in your community*)?

7. Kungani iTB yande kangaka eNingizimu Africa (South Africa)? Emphakathini wakho (*Why is TB so common in South Africa? Your community*)?

8. Abantu bathi iTB iqhamukaphi (*Where do people say TB comes from*)?

9. Iziphi izindlela zokuvikela iTB (*What are ways to avoid TB*)?

10. Umuntu wazi kanjani ukuthi uneTB (*How would one know that they have TB*)?

11. Imaphi amakhambi asetshenziswa emakhaya okwelapha izimpawu zeTB (*What are home remedies for treatment of TB symptoms*)?

12. Uma amakhambi asekhaya engasasebenzi, umuntu uyaphi ukuthola ukulashwa? Ibe isilapheka kanjani (*If home remedies don't work, where would one go next for treatment? How would it be treated*)?

13. Uma lokho kungabanga impumelelo, umuntu ube eseyaphi ngokulandelayo (*If that were unsuccessful, where would one go next*)?

14. Abantu bathini ngokulashwa kweTB emtholampilo nasezibhedlela (*What do people say about TB treatment in clinic or hospital*)?

15. Ingabe ukuwezwa ngeINH (*Have you heard of INH*)?

16. Wazini ngayo (*What do you know about it*)?

17. Ukhona omaziyo okewaba kuINH? Bathini ngayo? (*Do you know anyone who has been on INH? What do they say about it*)?

18. Ingabe wake wanikezwa i-INH (*Have you ever been offered INH*)?

19. Ingabe wayithatha? Kungani? (*Would you take it? Why/why not*)?

20. Iziphi ezinye izindlela zokwelapha "iTB elele" (*What are other ways to treat "sleeping TB"*)?

APPENDIX 4: Individual Interview Guide

Legend

C=INH completed *(oseqedile iINH)*; DC=INH discontinued *(Ongaqedanga iINH)*; D=INH declined *(Oyenqabile iINH)*; A=All *(Konke)*

1. (A) What does it mean to you to be "sick"? *Kuchaza ukuthini "ukughula"?*

2. (A) What does it mean to you to be "healthy"? *Kuchaza ukuthini "ukuphila"?*

3. (A) What do you normally do when you feel sick? *Yini ovamisile ukuyenza umaughula?*

4. (A) Who looks after the sick in your household? Your community? *Ubani ovamisile ukuthi anakekele oghulayo ekhaya ? emphakathini wenu?*

5. (A) At what point do you see a physician or nurse at the local clinic? Hospital? (Prompt re: izangoma, izinyanga, other local healers) *kufika nini la nibona khona ukuthi sekufanele nibonane noDokotela noma onesi clinic yangakini? isibhedlela sona? (mukhumbuze ngezangoma nezinyanga abaholi bomuphakathi)*

6. (A) Think back to your last visit to the clinic. Can you tell me about it? (probe re: issues of confidentiality) *Awuke ucabange ujule mhlazane ugcina ukuya eclinic.ungangixoxela ngakho? (kuyifinhlo yethu sobabili)*

7. (A) What do you know about INH? (Show INH pill to help remind participant) *Wazini ngokuphathwa iINH? (veza iphilisi lokumukhumbuza)*

8. (A) Thinking back to when you were offered INH, who first offered it to you? What did they say about it? (probe confidentiality) *Uyakhumbula mzukwane unikwa iINH, ubani owakunika kuqala? Wathini kuyena ngayo? (imfihlo yethu sobabili)*

9. (A) Did you have any questions about INH? Did you ask them? Tell me more about that. *Wabane mibuzo ngeINH? Wayibuza? Awungixoxela ngalokho*

10. (A) Why did you decide to use/not use INH? Were there any other reasons? *Yini eyabanga ukuthi usebenzise/ungayisebenzisi iINH? Zazikhona ezinye izizathu?*

    10.1 (C, DC) Do you recall when you first started INH how it made you feel? Did you notice any changes over time? (Prompt with side effect examples if needed) *Uyakhumbula muzukwane uqala ukusebenzisa iINH wazizwa unjani? Kukhona ushentso ulubonayo ekuhambeni kwesikhathi? (mubalele imiphumela engemihle makudingeka)*

    10.2 (C, DC) How did you get your INH? Where did you get your INH from? How did you remember to take it? (Prompt with pillbox/ help from child/family member) *Uyithola kanjani iINH ?Uyitholaphi iINH yakho? Ukhumbula kanjani ukuyithatha iINH yakho? (mukhumbuze ngebhokisi lamaphilisi/usizo enganeni/ilunga lomundeni)*

    10.3 (C, DC) Did you have any unanswered concerns about INH while you were on it? *Unakho ukukhathazeka okungaphenduliwe ngeINH ngesikhathi uyithatha?*

    10.4 (C, DC) Is there anything that you can think of that would have improved your experience on INH? *Kukhona yini into ongayichabanga ebingayi khuphula impilo yakho ngokuthatha iINH?*

10.5 (DC) Why did you stop taking INH? Were there other reasons that made you stop taking INH? *yini eyabanga ukuthi uyeke ukuthatha iINH ?zikhona yini ezinye izizathu ezakwenza uthathe iINH?*

11. (A) Do you know anyone else that has taken INH? What was their experience like? *Kukhona yini obaziyo abake bathatha iINH? Ibaphathe kanjani bina?*

12. (A) What do other people say about INH in your community? (Prompt with chief, sangoma, elders, religious leaders if needed) *Bathini abantu emuphakathini wakho ngeINH? (mubalele Inkosi,Izangoma,Abadala,Abaholi benkolo umakufanele)*

13. (A) What do you think about INH now? Ucabangani ngeINH manje?

14. (A) Would you recommend INH to other people? Why/Why not? Ungayi ungayincoma iINH kubanye abaantu? ngoba/ungeke ngobani?

APPENDIX 5: IPT Register

Year: 2014
Month: MAY

IMB PG 23

Registration		Patient's Details				Initial Visit			Month 2					Month 3					Month 4					Month 5				
Registration Number	Starting Registration Date	Surname	Address (Traceable)	Sex	Date of Birth	TB Screening done	Appointment date	Return date	Adverse event	TB Screening done	TB suspect	Appointment date	Return date	Adverse event	TB Screening done	TB suspect	Appointment date	Return date	Adverse event	TB Screening done	TB suspect	Appointment date	Return date	Adverse event	TB Screening done	TB suspect	Appointment date
Number/mm/yy	dd/mm/yy	Name	Telephone Number	F/M	dd/mm/yy	Tick (✓)	dd/mm/yy	dd/mm/yy	Specify	Tick (✓)	Y/N	dd/mm/yy	dd/mm/yy	Specify	Tick (✓)	Y/N	dd/mm/yy	dd/mm/yy	Specify	Tick (✓)	Y/N	dd/mm/yy	dd/mm/yy	Specify	Tick (✓)	Y/N	dd/mm/yy
100/14	23.05					✓	18.06.20																				
101/14	25.06					✓	23.06.20																				
102/14	30.05					✓	23.06.14																				
~~25~~	07.07									entered in error																	
103/14	18.06.14					✓	16.07.14																				
104/14																											
105/14																											
106/14																											
107/14																											
108/14																											

*Outcomes: End of Treatment (ET), Stop for AE (SAE), Stop for Lack of Adherence (SLA), Stop for Patient's will (SP), Stop for TB disease (TB), Stop for Other reason (O)

P 2023

Month 6				Month 7					Month 8					Month9						Outcome*	Comments
Return date	Adverse event	TB Screening done	TB suspect	Appointment date	Return date	Adverse event	TB Screening done	TB suspect	Appointment date	Return date	Adverse event	TB Screening done	TB suspect	Appointment date	Return date	Adverse event	TB Screening done	TB suspect	Appointment date	Stop Date	
dd/mm/yy	Specify	Tick (✓)	Y/N	dd/mm/yy	dd/mm/yy	Specify	Tick (✓)	Y/N	dd/mm/yy	dd/mm/yy	Specify	Tick (✓)	Y/N	dd/mm/yy	dd/mm/yy	Specify	Tick (✓)	Y/N	dd/mm/yy		
07/12/14	No	✓	No																	dd/mm/yy	
20.10.14	N	✓	No	Completed	Successful															dd/mm/yy	
																				dd/mm/yy	
																				dd/mm/yy	
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																				dd/mm/yy	

APPENDIX 6: Kleinman and Benson's mini-ethnography tool adapted to the context of *uMakoti*

1. Assess her identity as *uMakoti* - Does she identify as *uMakoti*? How does she view and express *inhlonipho*? Observing her dress and body language will be helpful. For example, is she wearing a long skirt? Is her head wrapped? Does she avert her eyes, gaze downward or speak little? These features may prompt questions directly related to her experience as *oMakoti*, which may be important to acknowledge and affirm in relation to health and illness.

2. Determine what is at stake for her – Is she responsible for the care of others at home (e.g. children, in-laws, visitors)? Who does she consult in relation to healthcare decisions (e.g. in-laws, husband, family herbalist)? What is at stake for her and her loved ones by introducing or not introducing IPT?

3. Illness narrative – How does HIV affect her or her household in the everyday? What are other daily pressures that exist for her around illness and wellbeing? Does TB factor into her list of worries/stressors? How does the threat of TB compare to other health concerns? This exercise is not about correcting or interjecting with medical information, but rather gaining insight into her lived experience and perceptions.

4. Psycho social stresses – Building upon what is at stake, what may be the psychosocial consequences of initiating IPT, collecting IPT, responding poorly to IPT, stopping IPT, or declining IPT? Can she, in her capacity of caregiver, safely reach out to those with whom she feels close to help her take decisions on how to proceed if problems arise? How might the healthcare provider's expectations around IPT initiation create a tension for the patient, and how might these tensions be mitigated?

5. Influence on clinical relationships – This step is about critical self-reflection. How do a healthcare provider's relationships (with patients, care networks, institutions, and biomedical training) affect interactions with *oMakoti*? To what degree do the providers own biases and stereotypes affect the interactions and options offered to patients? How does the provision of care in a formal clinic setting affect perceptions of authority in a provider-patient relationship? How might gestures, eye contact, personal space, and physical positioning affect power differentials? How might your comfort level differ from hers in this regard? Can the provider challenge herself or himself to make adjustments to decrease perceived imbalance?

6. Recognise your limitations. The degree to which patients relinquish decision-making power will depend on a combination of the above factors and will differ between interactions. While these steps may help to open the conversation, they will not guarantee a patient's forthrightness. Patience is required as rapport builds, and in many scenarios, especially among traditional rural women who are closely tied to identity as *uMakoti*, it may not even be possible to elicit open discussion at first. This may just be too far from patients' levels of comfort. However, consistently asking more open-ended questions, using culturally appropriate terms, and remaining open to alternate explanatory models can help to shift power dynamics.

APPENDIX 7: Copyright Forms

The role of agency in the implementation of Isoniazid Preventive Therapy (IPT): Lessons from *oMakoti* in uMgungundlovu District, South Africa

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Abstract

Introduction

In response to revisions in global and national policy in 2011, six-month isoniazid preventive therapy (IPT) became freely available as a preventive measure for people living with HIV in the uMgungundlovu District of KwaZulu-Natal province, South Africa. Given a difference in uptake and completion by sex, we sought to explore the reasons why Zulu women were more likely to accept and complete IPT compared to men in an effort to inform future implementation.

Methods

Utilising a community-based participatory research approach and ethnographic methods, we undertook 17 individual and group interviews, and met regularly with grassroots community advisory teams in three Zulu communities located in uMgungundlovu District between March 2012–December 2016.

Findings & discussion

Three categories described women's willingness to initiate IPT: women are caregivers, women are obedient, and appearance is important. The findings suggest that the success of IPT implementation amongst clinic-utilising women of uMgungundlovu is related to the cultural gender norms of *uMakoti*, isiZulu for "the bride" or "the wife." We invoke the cultural concept of *inhlonipho*, meaning "to show respect," to discuss how the cultural values of *uMakoti* may conflict with biomedical expectations of adherence. Such conflict can result in misinterpretations by healthcare providers or patients, and lead some patients to fear the repercussions of asking questions or contemplating discontinuation with the provider, preferring instead to appear obedient. We propose a shift in emphasis from adherence-

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Institution name	University of Calgary
Expected presentation date	May 2018
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