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Non-compliance and associated factors leading to the prevalence of multi-drug resistant tuberculosis in Uganda

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Abstract
The study was done to identify the factors that lead to poor anti-tuberculosis drug compliance and to draw practical, cost-effective interventions to combat multi-drug resistant tuberculosis. Literature of peer reviewed journals, authoritative publications and relevant textbooks was done. Databases such as EBSCOHOST and HINARI were used to retrieve journal articles where only articles published from 2010-2017 were used. The articles were narrowed down to those that provided relevant information on factors affecting compliance to anti-TB drugs leading to MDR-TB in Uganda. The study showed that non-compliance was due to social/economic, health system/healthcare team, patient and therapy related factors. Three approaches to combat MDR-TB were drawn: community empowerment, strategic community education and promotion of research to develop enhanced therapeutic regimens. All factors linked with non-compliance are man-made and none is genetic linked. Approaches to combat MDR-TB should be geared toward increasing knowledge and change of attitudes, beliefs and practices relating to compliance at individual and institutional levels. Research is needed to assess whether there are pharmacokinetic variations among Ugandans, leading to antibiotic resistance. Assessment of knowledge level and attitude toward antibiotic resistance among Ugandan communities is also needed.

Keywords: mycobacterium tuberculosis, tuberculosis, multi-drug resistant

Introduction
Multi-Drug Resistant Tuberculosis (MDR-TB) is defined as tuberculosis (TB) showing resistance to at least isoniazid and rifampicin, which are the two most potent first line drugs in the treatment of TB [1, 2]. MDR-TB remains a global health threat to progress made in TB care and control [3, 4, 5]. Uganda is one of the high TB burdened countries in the world with an estimated 179 cases per 100,000 population [6, 7, 8]. The first national survey showed a MDR-TB prevalence of 1.4% and 12.1% among new and previously treated sputum smear-positive TB patients respectively and Uganda still has unknown rates of anti-TB drug resistance [9]. Further to this, the exact magnitude of DR-TB is not known [2]. Patients who develop MDR-TB can still be treated with second line drugs but this is always the last option and costs the government 30-40 times higher than treating a patient with drug susceptible TB [9, 10]. In addition, this extensive chemotherapy (18-24 months) can produce severe adverse drug reactions in patients. High incidence of developing MDR-TB has been linked with drug non-compliance. Clients who do not comply with the treatment remain highly infectious and increase the chances of developing resistance and the resultant spread of resistant strains [11]. The authors therefore made a review of existing current literature to expose non-compliance pro-factors leading to the prevalence of MDR-TB with the aim of identifying cost-effective, yet practical interventions to combat this global health and security threat. The objective of this study were to identify the factors that lead to poor anti-TB drug compliance and draw practical, cost-effective interventions to combat MDR-TB

Methodology
Peer reviewed journal articles were consulted. The main databases for retrieving journals were EBSCOHOST and HINARI, and search engines such as Google, Google Scholar were also used. Only journal articles published from 2010-2017 were used. Journal articles were retrieved using search terms. This narrative review also employed systematic review methods such as the PRISMA flow diagram to narrow down the generated articles to those of relevancy. Relevant textbooks were also consulted. Textbooks with year of publication dating beyond six years ago were excluded. Official government and other authoritative publications and newspaper articles on Drug Resistant Tuberculosis (DR-TB) were also used. Studies included were those addressing factors affecting compliance to anti-TB drugs in Uganda. However, general studies addressing the same issue in sub-Saharan countries, and not a specific sub-Saharan country were also included. Studies were excluded if addressing a specific age group e.g. pediatric, refugees, etc., was specific for a country other than Uganda or whose year of publication dated earlier than 2016. Several key themes emerged which led us to categorize factors affecting noncompliance as: social-economic factors, health system/healthcare team factors, therapy related factors and patient-related factors. From this information, other authoritative sources were consulted to synthesize logical, practical and cost effective interventions to combat MDR-TB and antibiotic resistance in general.

Results and Discussion

Factors associated with non-compliance to anti-TB drugs

1112 articles were generated using EBSCOHOST, 90 from HINARI and 415 from Google Scholar. 4 articles met our inclusion criteria in the analysis of factors associated with non-compliance to anti-TB drugs. These were arrived to as shown in figure 1 and the findings listed in Table 1.

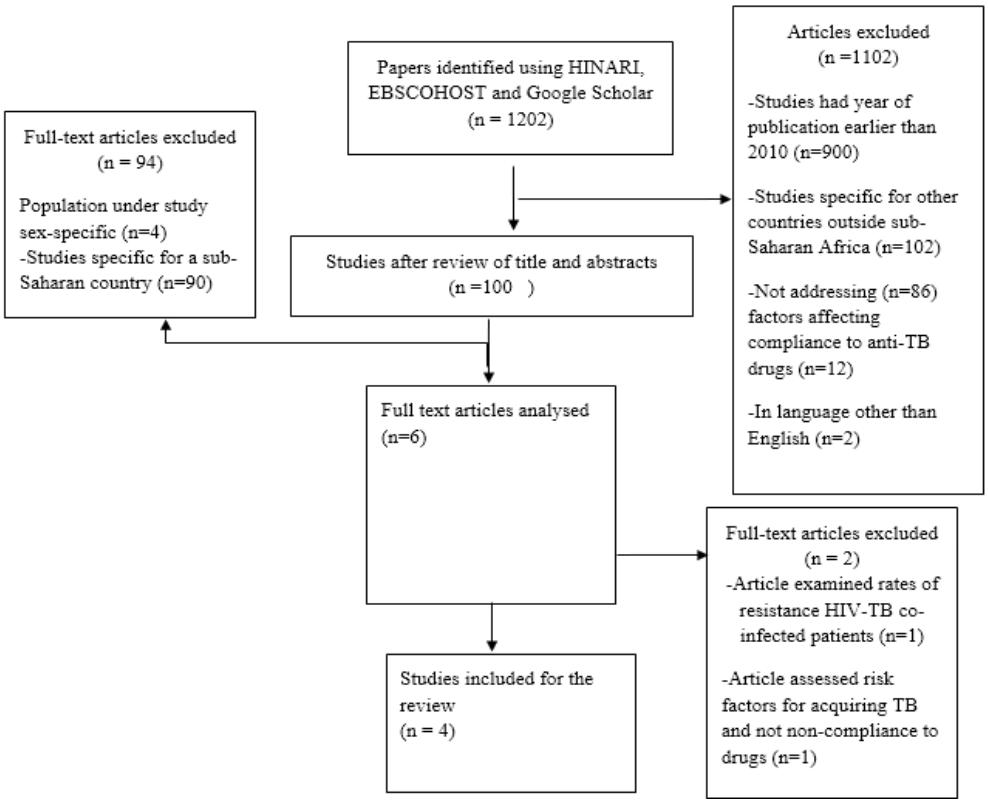

Fig 1: Process of narrowing consulted articles

Table 1: Findings of the factors associated with Anti-TB non-compliance

Article Author(s)	Year of publication	Region/Country	Study design	Factors pointed out
Castelnuovo B	2010	Sub-Saharan Africa	Systematic review	1. Distance from the hospital 2. Not being on the first course of TB medications. 3. Lack of repeated smears. 4. Unit transfer after the intensive phase. 5. Experiencing side Effects. 6. Having no family support 7. Poor knowledge about TB treatment. 8. Being more than 25 years old. 9. Use of public transport.
Lukoye, *et al*.	2013	Uganda (first national survey)	Cohort study	1. Being previously exposed to anti-TB drugs. 2. Urban residence 3. Being above 35 years.
Wynne, A. *et al*.	2014	Western Uganda	Mixed methods study	1. Financial burden 2. Insufficient nutrition 3. 3. Lack of health care worker training Lack of resources to support directly observed therapy (DOTS) 4. Drug stock-outs
Elbireer, *et al*.	2011	Urban Uganda	Unmatched retrospective case control study	1. Distance from home to clinic. 2. Long waiting time at the clinic 3. Poor drug availability 4. Conduct of staff. 5. lack of opportunity to express feelings 6. Lack of health education, i.e. not being aware of the duration of treatment or the risk of discontinuing it. 7. Not knowing that TB can be cured 8. Length of TB treatment 9. Side effects of treatment.

The factors retrieved from the studies (table 1) were categorized into social-economic, Health system/health care team, therapy related and patient factors as summarized in Table 2 below.

Table 2: Summary of factors associated with non-compliance

Category	Factors
Social-economic	▪ Distance from the hospital ▪ Having no family support ▪ Financial burden ▪ Insufficient nutrition
Health system/healthcare team	▪ Lack of repeated smears ▪ Drug stock outs ▪ Long waiting time at the clinic
Therapy-related factors	▪ Side effects ▪ Length of TB treatment
Patient factors	▪ Unit transfer after the intensive phase ▪ Poor knowledge about TB treatment ▪ Being more than 35 years old ▪ Urban residence. ▪ HIV/TB co-infection

Social-economic factors

The main social economic concern is poverty. This might be the explanation for risk factors such as distance from the hospital. The frequent visits to health facilities by TB patients exert high financial pressure on them. This pressure increase as the distance from the health facility also increases. The limited financial resources limit accessibility to life basic needs such as food. Insufficient nutrition worsens drug side effects. This whole milieu of inadequacies compromises compliance [8].

Social support is an important dimension that has been highlighted to affect health outcomes and behaviors [12]. In the case of TB, poor social support leads to poor quality Directly Observed Treatment (DOT), thus non-compliance. The HIV pandemic can also explain why TB patients find themselves lacking social support as their significant social network around them might be affected with similar needs.

Health system/ healthcare team factors

The Health Sector Strategic Investment Plan III 2010/2011-2014/2015 devised the following standard structures for delivery of health services [13]. This gives a snapshot into the state of the Ugandan health system and subsequently the explanation of many health system-associated factors (Table 3).

Table 3: The Health System of Uganda

Type of Facility	Indicator	Current Situation
	Health Facility Population Ratio Standard	
National Referral Hospital	1:10,000,000	1:30,000,000
Regional Referral Hospital	1:3,000,000 or 1 per region	1:2,307,692
District Hospital	1:500,000 or 1 per district	1:263,157
Health Center IV	1:100,000 or 1 per county	1:187,500
Health Center III	1:20,000 or 1 per Sub-county	1:84507
Health Center II	1:5000 or 1 per parish	1:14,940
Health Center I/VHT	1:1000 or 1 per village	Still being piloted

As can be seen from table 3, the first contact for someone living in a rural area would be a community medicine distributor or a member of a village health team (VHT). Each village is supposed to have these volunteers but in many cases they are not well facilitated leading to poor outcome [14]. With poorly functioning village health teams without proper supplies and training, under reporting and poor referral of TB cases result. Lack of Health Center I cover per village leads to a high burden of patients at Health Center II and other levels of healthcare above in the system structure. This leads to inadequate, overworked health care providers, inadequate relationships between health care providers and patients, poor supervision and poor implementation of TB infection control measures [15]. This can be the explanation for actors such as lack of repeated smears and long waiting time at health facilities.

Studies have also pointed out interrupted drug supply and poor quality DOT as crucial determinants of adherence in particular to patients on anti-TB drugs [6, 8, 11]. Stakeholders such as the Ministry of Health (MOH) and National Drug Authority (NDA) should therefore devise strategies to prevent drug stock-outs in the country.

Therapy-related factors

Most notable therapy related factors are those related to the complexity of the medical regimen in the treatment of tuberculosis. Prolonged therapy duration increases the chances of defaulting [16]. One study found out that length of treatment was also a determinant in compliance [17]. Research should therefore be intensified toward shorter duration regimens. Education on the use of medications, their adverse effects, adherence education and use of fixed dose combination preparations to improve drug compliance and prevent resistance is also crucial [18].

Patient-related factors

HIV-TB co-endemicity. It is estimated that about 60% of the TB patients are co-infected with HIV/AIDS [19]. The American lung association, in addition, identified that MDR TB has been a particular concern among HIV-infected persons [16]. HIV-TB co-infected individuals most likely to default TB treatment as a result of polypharmacy.

It is also evident that individuals lack knowledge about TB treatment and implications of non-compliance [17]. Individuals cannot therefore make informed choice regarding compliance while on treatment. Research to assess the exact magnitude of this gap in Uganda is needed. Based on the above assessment, factors affecting compliance to anti-TB drugs are all as a result of human choices and none is of genetic origin. Approaches to combat MDR-TB should therefore strongly aim at spearheading behavior change among individuals and

the concerned institutions. Research, however is needed to find out whether there are pharmacokinetic variations among individual Ugandans that could account for the noted resistance other than non-compliance.

Practical, Cost Effective Interventions to Combat MDR-Tb

In order to achieve the new global TB targets that have been set within the context of Sustainable Development Goals (SDGs), and the End TB Strategy from the Stop TB Strategy, aggressive, practical yet cost-effective methods have to be applied [7]. Four of these were synthesized from the previous objective.

1. Community empowerment

Communities can be empowered against Anti-TB and general antibiotic resistance through training and facilitation of community health teams. This involves giving community health teams anti-TBs so that DOTs can be carried out directly by selected, trained, motivated community health team members, for members who are affected by the disease in their own communities. Community-based support in DOT can be very effective especially if provided by former patients acting as treatment supporters for daily DOT [2]. Therefore TB ambassadors (former TB patients who have recovered from the disease) can also be utilized to carry out DOT. Patients can therefore have quality DOT at home without necessarily travelling health facilities as there is increasing evidence that home-based care is preferable to hospital based type [20].

2. Strategic community education

We also suggest educating communities and individuals, from where they are. The "From where the people are" phenomenon ensures that educative messages about antibiotic resistance reach the people anywhere as they carry out their daily activities. Traditionally, health education is mostly done at health facilities. The MOH can liaise with relevant authorities to ensure all public service vehicles have stickers with messages that teach the public on prevention of antibiotic resistance.

Fig 1: A sticker in a Ugandan public vehicle with a message in both English and Luganda (the local dialect) to increase awareness about reckless driving. Such a tool can also be used to increase public knowledge on antibiotic resistance.

The other approach is that of tax incentives. Many countries are already using this means to promote green energy [21]. Government can offer tax incentives to companies whose products (e.g. food beverages) bear messages on prevention of antibiotic resistance. This can be extended to mass media channels e.g. radios, TVs where messages to teach the public on prevention of MDR-TB and antibiotic resistance in general are aired. Therefore when people travel or go shopping, or sit in the comfort of their homes, they can still learn about how to combat antibiotic resistance without necessarily going to the hospitals. This is in agreement with a 2014 study which found out that home based treatment and care was preferable to hospital based care [20].

3. Research towards shorter duration, potent drugs and effective diagnostics

TB Treatment success does not only depend on patient accessibility to the right drugs but also how well the patient will comply with the accessed treatment. Current MDR-TB treatment is lengthy (up to 2 years) and often poorly tolerated treatment [22]. Prolonged duration of therapy increases chances of defaulting [16]. Promoting research to come up with more potent first line drugs with TB therapeutic effect in shorter duration of time. Currently, the total duration of time for TB treatment in Uganda is 8 months. The shorter the treatment period, the higher the likelihood of the patient to comply with the treatment regimen.

There are still gaps in TB diagnostic coverage in the East African region [23]. Development and adequate distribution of effective diagnostic services is necessary in the elimination of MDR-TB and the TB epidemic as a whole. Without strengthening this approach, WHO's post 2015 End TB Strategy might never be realized.

Conclusion and Recommendations

MDR-TB remains a global threat to progress ade in TB contol with increasing prevalence among previously treated smear-positive TB patients in Uganda.. Non compliance to anti-TB drugs is the major cause of MDR. Non compliance is due to social/economic, Health system/Healthcare team, patient and

therapy related factors. This article points out some strategies for combating MDR-TB including community empowerment through Village Health Teams, mobilization and facilitation of tuberculosis ambassadors to encourage compiance and change of community attitudes towards TB; Tax incentives to agencies that promote community awareness about MDR-TB prevention, educating communities to reduce stigma through media channels and promotion of research to develop enhanced therapeutic regimens. The political and stakeholders' will is therefore urgently required to effect these approaches. All factors linked with non-compliance are man-made and none is genetic linked. Research is needed to assess whether there are pharmacokinetic variations among Ugandans, leading to antibiotic resistance. Research to assess the knowledge level and attitude toward antibiotic resistance among Ugandan communities is also urgently needed. Researchers recommend that

1. Communities should be empowered against MDR-TB through VHTs to improve reporting, DOT and referral of TB cases
2. Health education should be given to both patients and the general public to help in reducing the stigma associated with TB
3. TB ambassadors (patients who recovered from TB) should be identified and facilitated to encourage TB cases along pro-compliance behavior.
4. Research programmes to develop shorter duration regimens, diagnostics and vaccines should be facilitated.

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