Operational aspects of diagnosing and treating tuberculosis and HIV infection in Ugandan urban areas
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Chapter 8

General Discussion
The main aim of this thesis was to evaluate the operational issues of diagnosing and treating TB and HIV infection in urban areas in Uganda, East Africa. This chapter first summarizes the findings from the studies, secondly discusses in more detail some of the overriding risk factors found in the studies and then provides some possible solutions and recommendations for interventions to improve the diagnosis and treatment of these two diseases in urban areas. Finally the chapter provides conclusions for the thesis.

**General findings**

Chapter 2 was about diagnostic delay among smear-positive pulmonary tuberculosis patients in Kampala, Uganda. We found a total delay of 8 weeks, with a quarter of the patients having a total delay of more than 14 weeks. Although this total delay is comparable to the varying levels found in other studies sub-Saharan Africa, these studies were conducted earlier than ours and in different study settings. The different health systems and different cultural contexts in which the studies were conducted could possibly explain the differing levels of diagnostic delays. One would expect a reduction in the diagnostic delays across these and other settings in line with improved tuberculosis control indicators globally; the World Health Organization reported that Millennium Development Goal 6 (MDG-6), target 6c of halting and reversing the TB epidemic by 2015 was achieved. Diagnostic delays seem not have significantly improved during the course of time. A recent survey carried out between 2006 and 2007 in an urban area in Guinea Bissau also found the diagnostic delay to be around 2 months. The finding that the total delays in our study were comparable to the total delays found in an earlier study in the same city may suggest that the situation has not improved much except for the reduction of the contribution of the health service delay to total diagnostic delay from 75% to now 50%. Whether the health service delays had declined (as the proportion out of the total delays) also depends on patient delay. The comparable total delays and the comparable contribution of health service delay may be a result of the different definitions used for health service delay by different studies or the differences between study populations. Nevertheless, these findings show that a big proportion of patients remain infectious and could potentially continue spreading *M. tuberculosis* over long periods of time.

Our study identified several missed opportunities for TB diagnosis. A sizeable proportion of the patients (40%) had visited a drug shop or pharmacy prior to achieving a diagnosis of TB. The study also showed that the time interval between visiting the care provider and diagnosis
(in the last step before a diagnosis of TB was finally made) was shortest if that care provider was a private doctor or a city clinic. These findings are similar to those found in a Tanzanian study where the risk for delay was low among patients who first presented to a government health facility. It is reassuring that patients who visited city clinics as the last step before a TB diagnosis was made had shorter diagnostic delays because city clinics are designated TB Diagnostic and treatment centres (DTUs). Diagnostic delays could be reduced even further if private doctor’s clinics could also become designated DTUs, instead of these clinics referring TB suspects to government clinics all the time. At the time of the study there were only 38 DTUs for a big city like Kampala with a resident population of 1.7 million people.

Chapter 3 was about HIV test uptake among smear-positive pulmonary TB patients at the KCC clinics. We found low testing levels of 40% among patients on TB treatment in urban primary care centres. Even a smaller proportion (29%) actually received their HIV test results. This is worrying as between 30% and 50% of TB patients will also have HIV infection. This low test uptake means that many HIV-infected TB patients are not being enrolled into HIV care. The study showed that the low test uptake was a result of the opt-in approach used mainly by the city clinics as opposed to the Provider Initiated Testing and Counseling (PITC) recommended by the WHO. Not having been offered HIV testing by a health care provider was also observed in a study carried out in four rural districts and one peri-urban district in Uganda and this was significantly associated with low HIV test uptake.

Chapter 4 examined the prevalence and factors associated with late a start of cART. We found that many HIV patients start cART late: among patients registered at the HIV services, 83% patients started cART at CD4 counts < 200 cells/μL and 38% started cART at CD4 counts < 100 cells/μL. Our findings are comparable to those found in earlier studies where an estimated 52-73% of HIV-positive patients in Uganda were reported to present at HIV clinics or initiate cART with severe immune suppression defined as CD4 counts < 200 cells/μL. The delay in starting cART could reflect patient delay, or a health system failure to identify those eligible to start cART among those already registered with the HIV services. Our study findings date from the time when the cART eligibility guidelines recommended starting cART at CD4 count <200cells/μL. The current WHO guidelines now recommend starting cART at a CD4 count ≤350cells/μL. There is an urgent need therefore, to identify patients whose CD4 counts decline to below that CD4 count cut-off.
Chapter 5 examined defaulting from TB treatment under the DOT system in which community volunteers act as treatment supporters in an urban setting. This study found that the defaulting levels as reported by the national program were high and may mask deaths and patients continuing treatment elsewhere. The defaulting level of 20% found in our study was similar to what the NTLP reports and to a study carried out recently at the national referral hospital in the city.\textsuperscript{16} However, after updating the data with information from follow-up visits at patients’ homes, the proportion of defaulting was lower: between 14% and 17%. Relying on programme data overestimates the true proportion of defaulting; a key problem is the absence of a reliable patient tracking and follow-up mechanism. A defaulting level of around 14%, although similar to the national average,\textsuperscript{17} is still high compared to the reported defaulting levels from other cities in East Africa, e.g. 5% in Dar-es-Salaam.\textsuperscript{18}

Chapter 6 examined adherence to TB treatment under the DOT strategy using community volunteers as treatment supporters. The study found low levels of poor adherence to treatment; 6% of patients and 3% of measured episodes. These results are comparable to those reported by an earlier study in Malawi, that found low levels of poor adherence, of 4% among PTB patients during the intensive phase of treatment.\textsuperscript{19} However, the 6% poor adherence level is much lower than the 25% poor adherence found in an urban tertiary hospital, in Mbarara, Uganda.\textsuperscript{20} The difference could have resulted from the different study populations and methods used to measure adherence. Our study was carried out in primary healthcare centres where patients are expected to have a less complicated disease and fewer co-morbidities which may possibly result in better adherence to treatment. Not having been in contact with the treatment supporter during the preceding week was associated with poor adherence.

Chapter 7 assessed adherence to cART under routine programme conditions. Poor adherence was defined as having taken <90% of the medicines. Poor adherence was recorded in 7% of the patients on cART. Similar levels of low poor adherence were reported among Ugandan urban HIV patients taking cART in earlier studies although they used different cut-offs for poor adherence.\textsuperscript{21,22} However, the level of poor adherence found in our study was much lower than the 22% found among patients receiving care in a large urban centre operated by The AIDS Support Organization (TASO), a national non-governmental organization with a long tradition of HIV care and support.\textsuperscript{23} As already noted in the studies above, the findings from
this study also confirm the findings from the TB studies, that as long as patients do not abandon treatment they exhibit high levels of adherence to their treatment regimens.

The risk factors identified in all these studies had overriding issues as discussed here below. The overriding risk factors by themselves are not easily amenable to intervention, but they can show at which subgroups of patients the interventions for improving TB and HIV control in Kampala should be targeted. For example, a risk factor such as gender is not amenable to intervention, but interventions can be specifically targeted to either men or women.

**Alcohol consumption**

Several studies have showed heavy alcohol consumption to be associated with diagnostic delay. Of surprise in our study was the finding that alcohol consumption was not associated with diagnostic delay (chapter 2). This contrasts the findings of an earlier study carried out in a tertiary hospital in the same urban area. The difference could possibly be explained by difference in accessibility of the health facilities. It may be possible that those patients with heavy alcohol consumption 1) do not seek early healthcare; 2) when they choose to do so, they do not seek healthcare from the primary health facilities where the study was conducted and 3) they present with severe disease that would often be managed in a tertiary hospital. On the other hand, it may also be true that this is a genuine phenomenon that in urban areas alcohol consumption does not play an important role in diagnostic delay. Patients with TB and/or HIV infection who exhibit signs of heavy alcohol consumption may be more quickly identified by the primary care health services, thereby reducing delay in this sub-population. This view is potentially supported by the study we conducted among patients starting cART (chapter 4). This study also showed that patients who showed signs of alcohol dependence were less likely to start cART late compared to those who did not have signs of alcohol dependence. A study carried out in the developed world did not find a significant association between heavy alcohol consumption and delay in starting ART. However, a recent study carried out in Ethiopia reported heavy alcohol consumption to be significantly associated with late presentation.

When it comes to maintaining patients on treatment, alcohol consumption appears to play a key role. Our studies showed heavy alcohol consumption to be associated with defaulting from treatment (chapter 5) and adherence to cART (chapter 7). Studies carried out in Nairobi,
Kenya and other parts of the world yielded similar association between heavy alcohol consumption and defaulting from TB treatment.\textsuperscript{28,29,30,31} Our findings suggest that heavy alcohol consumption is an impediment for maintaining patients on their TB treatment and adherence to cART. Recent studies carried out in Kampala, Uganda and elsewhere in Nepal have also shown alcohol consumption to be associated with adherence to cART.\textsuperscript{32,33} Heavy alcohol consumption in our study setting could also point to underlying factors such as poor socio-economic conditions and personality issues.

**Sex**

Sex appears to be a major factor in the diagnosis and treatment of TB and HIV infection in the urban setting where our studies were carried out. Our studies show that men tend to do worse when it comes to HIV diagnosis, initiating cART and retention in TB treatment programmes. Male sex was significantly associated with a lower likelihood of HIV test uptake, with increased likelihood of late start of cART, and increased likelihood of defaulting from TB treatment in urban primary care centres (chapters 3-5). Other studies carried out in Uganda and elsewhere in Africa have also found male sex to be associated with either late presentation at HIV clinic or late start of cART.\textsuperscript{34,35,36} A cross-sectional analysis of a large data set from Latin America and the Caribbean also showed that male gender was associated with late start of cART.\textsuperscript{37} These findings can be explained by the fact that male patients do not have opportunities like their female counterparts such as Prevention of Mother to Child Transmission of HIV (PMTCT) programmes which facilitate earlier entry into HIV care services. It may in addition be that male patients do not seek healthcare early as a result of other demands such as often being the head of the family. Possibly a choice has to be made between seeking healthcare and economic demands, often resulting in personal healthcare needs coming at bottom of the priorities.

Although male sex was not associated with total diagnostic delay, patient delay or health service delay, being female was associated with long health service delay (chapter 2). Studies done elsewhere reported similar findings.\textsuperscript{38,39} In contrast, a recent study conducted in Ethiopia found female sex not to be associated with long health service delay.\textsuperscript{40} Most of the gender differences such as a lower socio-economic status and the dependence on husbands in developing countries would be more plausible explanations for long patient delays than for long health service delays. The reasons for female sex being associated with long health
service delay are still unclear and need further elucidation. A possible explanation would be that physicians are more inclined to request for diagnostic investigations among male patients than female patients as has been shown by a study conducted among patients discharged from hospital in which male sex was associated with having been offered an HIV test during admission.41 This may mean health care workers suspect TB less in women than in men. Although this is still debated, women tend to have lower risk of TB as appears from disease notification data in most countries42,43,44 but also from TB prevalence surveys.45

Social Instability

Communities that have strong social capital (where residents relate to and interact with each other to solve problems for the common good) also have a very desirable quality of life, good health outcomes and great economic growth potential. Social support has been shown to inversely predict barriers to health care in the west.46 In Africa this has not been well studied. However, in one study carried out in South Africa, social capital positively correlated with health.47 Building or maintaining social cohesion in urban areas as opposed to rural areas is a key challenge because of the diverse racial, ethnic and cultural backgrounds of urban dwellers. People who lack social support or social capital are most often the ones who end up socially marginalized, homeless and with alcohol use disorders; eventually they fail to get or maintain a job. It is this sub-population that is also likely to delay in seeking health care, initiate treatment late or default from treatment.

The findings from the adherence to TB treatment study showed high adherence levels. In spite of this, the findings also showed that not having been in contact with a treatment supporter during the past week predicted poor adherence to their treatment. Whereas the lack of contact with the treatment supporter may suggest inefficient treatment support, lack of contact with the treatment supporter may point to social instability surrounding the patient, such as patient moving around from one place to another or heavy alcohol consumption resulting in inability to maintain social relations with relatives or neighbours.

Our study on defaulting from TB treatment showed change of residence to be associated with defaulting in an urban setting. This change of residence could be pointing to an unfavorable economic situation. In a study carried out in northern Ethiopia unemployment was associated with unsuccessful treatment outcome (defined as treatment failure, default and death) among
smear-positive PTB patients both in the rural and urban districts. This social instability seems to play a role in poor treatment outcomes such as defaulting.

Findings from our study on HIV test uptake among TB patients showed that younger patients (26-33 years) were less likely to be tested for HIV (chapter 3); the study on late start of cART showed that married and older patients (≥ 40 years) were less likely to start cART late (chapter 4). The older patients are likely to have a stable environment with possible support from spouses, other family members, friends or neighbours. Lack of family support or social support seems to be an underlying factor in the late start of cART as already shown in the study by Muhamadi et al.35

Although it is still a subject of debate, there seems to be an association between socioeconomic status and adherence to cART.49 Unemployment has been shown to be associated with mortality and HIV morbidity among patients on cART in the developed world.50 One of our studies showed that unemployment was associated with late start of cART (chapter 3). Findings of the study on adherence to cART showed an association between poverty and poor adherence (chapter 7). An earlier study carried out in the same city, Kampala, reported similar findings.22 A study carried out in a high risk urban population Nairobi, Kenya also found poverty to be associated with poor adherence.51 However, poverty was not significantly associated with TB diagnostic delays, late of cART, defaulting from TB treatment or poor adherence to TB treatment. This could reflect that these problems in patient management are not so much associated with poverty as with indicators of social instability. It could also be that the method we used for measuring household wealth (and thereby poverty) based on asset scores, has insufficient discriminatory value for differences in economic status within the urban patient populations we studied. As this method assigns a score to households based on e.g. characteristics of the dwelling and assets (such as TV, car or motorcycle) owned or present in the household, the patients’ possessions or circumstances in our study may have been too similar to detect relatively small differences that may nonetheless be relevant for their behaviour with regard to health seeking and treatment completion and adherence.

**Targets for Intervention/Policy implications:**
Our studies indicated a number of shortcomings in the functioning of the health system, and several of these, point to possible interventions. In order to reduce diagnostic delays among
TB suspects the NTLP should increase the number of DTUs by strengthening the public-private mix of TB management. A recent study carried out in South Africa, comparing four rural and urban communities, showed that inhabitants of urban communities preferred to visit a private medical doctor if there were no restrictions such as lack of money or transport as compared to rural inhabitants who preferred to visit health clinics. Health care consumption habits of Kampala’s urban dwellers would not be expected to differ very much. Capacity for a well selected number of private providers such as private doctors and private midwives should be built to offer diagnosis and treatment of TB and participate in the requisite quality assurance and monitoring system. This will increase access to TB services and reduce health services delays. A second strategy would be to re-orient drug shop and pharmacy attendants to TB control services and provide them a standard operating procedure (SOP) tool to identify TB suspects early. The level of awareness for suspecting TB among female patients should be raised among the KCCA health staff through re-orientation in TB diagnosis and treatment. Together this would go a long way in reducing missed opportunities. A third strategy would be to carry out massive sensitization campaigns, peer to peer education, film shows, electronic and print media. This would help raise the level of awareness about TB in the community and has the potential to reduce patient’s delay. A fourth strategy would be to develop a sensitive screening tool to identify TB cases much earlier than the current one of cough for two or more weeks.

The HIV counseling and testing (HCT) policy was adopted by the Uganda Ministry of Health in 2005. While the NTLP and KCCA had taken HCT on as their policy, implementation of that policy was apparently lagging behind or weak. The KCCA staff should implement the HCT policy in order to increase the test uptake among TB patients. All TB suspects should be offered HIV testing as part of the diagnostic work up. Secondly, clinic staff should be re-oriented on offering HCT. And thirdly, SOPs on how a health care provider initiates HIV testing and counseling should be written, tested and then implemented in all TB consulting rooms and other departments at the KCCA health centres.

The finding that more than a third of the patients in the HIV services were initiated on cART in 2008 and 2009 at advanced levels of CD4 count decline suggests that there is no mechanism to identify patients who become eligible to start ART. A first intervention would be to introduce clear SOPs that take into account emergency start of cART and limit the
number of counseling sessions. Secondly the clinical teams at the KCCA health centres should be re-oriented in patient management, timely laboratory and clinical monitoring and timely response to laboratory results. A third possible intervention to address the problem of late start of cART is to build and use an electronic database that can flag patients whose CD4 counts have dropped below the cut-off value to start cART. Fourth, implementing couple HIV counseling and testing could possibly increase the number of persons who test for HIV and enter care early. Finally, offering HIV testing services at home has the potential to identify HIV-positive patients early and hence facilitate early entry into care.

From both our follow-up studies on TB treatment in the urban setting, it appears that adherence to TB treatment is not a big problem. Although we cannot rule out social desirability bias, we showed that once the patients do not default and remain on treatment, adherence levels are very high. The discrepancy in defaulting levels between programme reporting and after adjustment from follow-up visits highlights the challenges in patient retention, tracking and follow-up under programme conditions. The default from TB treatment study showed that one of the factors contributing to defaulting from TB treatment in the city was a change of residence. We recommend that HCWs enquire about plans of patients to move house, and, if patients are intending to move, to discuss options of continuation of treatment elsewhere. Tuberculosis control programmes should facilitate regular contact between patients and their treatment supporters as a way of improving direct observation of treatment. Counseling should be strengthened and intensified in the TB services to the level that approaches adherence counseling for ART, although this calls for additional human resources or task shifting, the benefit of which has already been demonstrated in a large urban HIV clinic in Kampala. Intensified counseling for TB patients and their treatment supporters can potentially be achieved through strengthening TB/HIV collaborative activities. Such counseling should be comprehensive and holistic to address underlying problems such as alcoholism, unemployment, poverty, homelessness, stigma and lack of social support that are not readily evident to the clinician.

In order to capture reliable TB treatment outcomes, the NTLP should build both health facility and community capacity to track patients interrupting their treatments before they are categorized as defaulters and put them back on treatment. Secondly to reduce the possibility of the defaulting, clinicians should assess the possibility of shifting for the patient and actively
make appropriate arrangements about the nearest place where the patient could get treatment and follow-up. Thirdly it may be wise to invest in mobile TB services in all the five divisions of the city so as to cater for the mobile urban dwellers. Fourth, building a strong electronic database with an aim of considering patients who miss their clinic appointment as self-transfers until updated from active follow-up, would reduce on the defaulting levels. Such a database would help in active defaulter tracing. A recent study carried out in Kampala showed that electronic medical records and same day tracking improved adherence to clinic appointments in a community HIV care program. Active defaulter tracing can be performed physically or through text messaging. And finally since Kampala bears the biggest TB burden, offering TB treatment cards with a colour different from the rest of the cards offered elsewhere in the country, may facilitate quick data reconciliation and validation of treatment outcomes.

High adherence levels to cART were recorded in our study. However, the recent change in cART eligibility criteria is likely to put an additional strain on the already overstretched staff at the HIV services. Human resources should be increased to cope with the anticipated increase with client numbers so that the quality of HIV care in general and cART adherence counseling in particular is not diluted. Providing social support and improving incomes of HIV-positive persons and their families will also increase their adherence to cART. Mobilizing and coordinating community-based organizations, non-governmental organizations and the private sector to participate in strengthening and implementation of TB/HIV collaborative activities will also increase adherence to cART.

**Strengths of the studies:**

Our studies had several strengths. First and foremost the studies were either cross-sectional studies nested in longitudinal studies or follow-up studies themselves. The longitudinal design to some extent reduced the effect of recall bias would have on our study results. The study designs also offered us near-complete datasets, with no significant data losses. Our studies were carried out in routine settings with minimal intervention. Few studies have been carried out in routine settings at primary care clinics. This is important since much of the TB and HIV care services follow a public health approach in which the big bulk of patients are treated at the primary care clinics. It is at this level of care that comprehensive and efficient interventions can and need to be implemented. For example in the study on default from TB
treatment, patients were not traced until they were reported by the clinic as defaulters. We used program relevant definitions and cut-offs in order to provide suitable evidence for policy in the low income countries.

**Limitations of the studies**

Our studies had limitations. Substantial amounts of data were collected from patient reports. However, often the data from the patient report were triangulated with or backed by data from the clinical records. These studies were conducted in public settings and may not have captured the whole picture of the urban health system. Since in Uganda provision of the TB and HIV services is mainly carried out in the government health units with the private sector playing a limited role, the findings from these studies largely represent the actual situation of operational issues of diagnosing and treating TB and HIV infection in Kampala city. Because of different population dynamics, disease burden, cultural settings and level of development, our results may not necessarily be generalisable to other cities in the region. However, when it comes to studying behavioral variables such as defaulting and adherence, there are some characteristics or phenomena that are universal and don’t vary much across settings e.g. alcoholism, personality traits and poverty. In this respect these findings can be very helpful in programme planning.

**Conclusions**

We conducted operational studies in the diagnosis and treatment of TB and HIV infection in urban areas in Uganda. We found similar issues defining challenges in the management of both disease conditions that were largely patient related and not easily amenable to intervention. Several of our studies highlighted alcohol use, sex and social instability as contributory factors to operational issues in the diagnosis and treatment of TB and HIV infection in urban areas. However, we identified several health services-related factors that are amenable to intervention for both TB and HIV infection. We therefore, recommend that any solution to solve some of these issues should continue to target both diseases and not one in isolation of the other.
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