Operational aspects of diagnosing and treating tuberculosis and HIV infection in Ugandan urban areas
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Chapter 1

General Introduction
1.1 Tuberculosis and HIV infection

Tuberculosis (TB) is an ancient disease caused by *Mycobacterium tuberculosis* that has infected humans for hundreds of years.¹ The infection with Human Immunodeficiency Virus (HIV) that eventually leads to Acquired Immune Deficiency Syndrome (AIDS) was first discovered and described in the early 1980s.² Despite the recent advances in medicine and technology, TB and HIV infection continue to inflict a heavy burden on many populations of the world, killing about 1.4 and 1.7 million people respectively in 2011.³,⁴ In sub-Saharan Africa which bears the biggest burden of TB/HIV co-infection, the proportion of TB patients infected with HIV is variously reported to be between 31% and 80%.⁵,⁶,⁷,⁸ Global efforts to combat these two diseases are enshrined in the Millennium Development Goal (MDG) number 6: “to have halted, and begun to reverse the incidence of TB and HIV by 2015”. The World Health Organization (WHO) and Stop TB partnership have, in addition to the MDG, set a target “to halve the 1990 TB prevalence and mortality levels by 2015”.⁹ Since 2005 two global plans have been developed to accelerate attainment of these TB targets.¹⁰,¹¹ Around the same period the Joint United Nations Programme on HIV/AIDS (UNAIDS) introduced a strategy to halve all new HIV infections by 2015 as one of the major goals.¹² Although the MDG target to halt and reverse the TB epidemic by 2015 has already been achieved,³ that for HIV infection has not yet been achieved; and several challenges for both diseases still remain. HIV affects the natural course of TB posing diagnostic difficulties. In order to prevent early as well as late HIV morbidity, early initiation of combination antiretroviral therapy (cART) has been recommended.¹³ The diagnosis of TB at any stage of CD4 level as an indication for starting cART has been included in several recent treatment guidelines.¹⁴,¹⁵ As a result, patients are often prescribed dual therapies for TB and HIV infection and the overlapping drug toxicities and drug-drug interactions¹⁶ from these therapies may result in poor adherence to either of the treatments. One of the ways of accelerating the achievement of the MDG is to address diagnostic delays, poor adherence and abandonment of treatment.

1.2 Urbanization, tuberculosis and HIV infection

The average African country’s urban population has grown by 5.2% per annum in the last three decades mainly as a result of rural-urban migration.¹⁷,¹⁸,¹⁹,²⁰ Unfortunately, this migration was not accompanied by the economic growth that would be expected; instead the GDP per capita fell at an estimated rate of 0.66% per annum.¹⁸ This distorted transition means that urbanization occurred without generating the anticipated resources and employment.
opportunities hence putting a heavy burden on the available limited resources. Currently up to two thirds of African urban dwellers live in informal settlements with inadequate transport, water, sanitation, electricity, education and health services.\textsuperscript{18,21,22}

Rural-urban migration has been reported to present several challenges: social ties and communities are disrupted; inadequate job opportunities or having a paid job that does not meet the demands of daily life may be worse than having one’s own farm in the village.\textsuperscript{23} In urban areas there are also increased opportunities for disease transmission and consequently high HIV infection and TB rates.\textsuperscript{24,25,26,27} A few studies have found no difference in HIV incidence or prevalence between urban and rural residents.\textsuperscript{28,29} However, data on these urban-rural differences in sub-Saharan Africa are still limited. When afflicted by TB or HIV infection the health care needs of these rural-urban together with international migrants are not well taken care of.\textsuperscript{30,31}

1.3 Tuberculosis and HIV in Uganda
Uganda is a low developed land-locked country in East Africa, situated 4°12’N and 1°29’S of the Equator and 29°34’E and 35°0’E of the Greenwich Meridian, with an estimated 2012 mid-year population of 34.1 million, 15% of whom live in the urban areas.\textsuperscript{32} With an estimated TB incidence of 195 per 100,000 and prevalence of 183 per 100,000 in 2011, Uganda is one of the 22 high-burden countries that account for 80% of the TB cases each year.\textsuperscript{3} Mortality due to TB was estimated at 15/100,000 population. The HIV prevalence among adults aged 15-49 years is estimated at 6.7%\textsuperscript{33} and up to 85% of the adult population is not aware of their HIV status.\textsuperscript{34} Worse still, an estimated 80% of HIV-infected adults are unaware of their infection.\textsuperscript{4,35} Estimates by the Uganda AIDS Commission showed that about 1.2 million Ugandans were living with HIV/AIDS, about 540,094 were eligible for cART and 290,971 (53%) adults and children had initiated cART by 2011.\textsuperscript{36} The Uganda government is committed to further reducing the number of patients in need of cART but not receiving it by initiating an additional 100,000 persons on cART in the fiscal year 2012/2013.\textsuperscript{37}

1.4 Tuberculosis and HIV in Kampala
Kampala, the capital city, lies across the equator in central Uganda. The city has an estimated resident population of 1.72 million people\textsuperscript{32} with an annual population growth of 4.1% (compared to the national average of 3.4% in 2002).\textsuperscript{38} The day population is nearly double the
resident population because of its position as the country’s central business hub. The average household size is 3.9 versus the national average of 5.2 and 35% are female headed households. The overall unemployment rate in Kampala city and its environs is 13% and about 52% of those of the work force are in self employment. The employment to population ratio (EPR) for persons aged 14-64 years is 65% as opposed to the national average of 75%. The city has a disproportionately heavy TB burden with an estimated TB prevalence of up to 4,500 per 100,000 in some slum areas of the city, which is much higher than the estimated national prevalence of 183 per 100,000. The city also has a heavy HIV burden. HIV prevalence among the 15-49 year olds was estimated at 6.9% in 2011. HIV prevalence rises to nearly 30% in certain sub-populations. The prevalence of HIV infection among smear-positive TB patients attending urban primary care clinics is estimated at 32%. Higher TB/HIV co-infection levels of 40-50% have been reported among patients seeking care at the national referral hospital in the city.

1.5 Challenges of diagnosing and treating tuberculosis and HIV

The first challenge of diagnosing TB lies in the fact that a sizeable proportion of patients in countries with high TB incidence do not seek medical attention for their symptoms early enough. A high proportion of those who choose to seek medical care do so late in the natural history of the disease. In sub-Saharan Africa diagnostic delay for TB is highly variable and setting-specific, ranging from a 6 weeks to 12 weeks. TB in many cases has an insidious onset with initially few non-specific symptoms so that patients may seek care late and the health care workers for the same reason may not think of TB when the patient presents. The primary method, sputum smear examination, currently used most for diagnosing TB in low resource-limited settings has limited sensitivity; the patient may visit the TB diagnostic facility several times before achieving a diagnosis of TB.

Assessing diagnostic delay in HIV disease is a bit more difficult due to the long latency period and the subtle and insidious onset of the disease symptoms that can stretch for several months or even several years. Most HIV infections are symptomless until quite substantial immunological damage has occurred. In terms of diagnostic delay, 40% or more of HIV-infected patients have advanced disease at the time of HIV diagnosis. A study carried out in two tertiary hospitals in Uganda, showed that although HIV test uptake was high at 98% among admitted patients, 81% of these patients were being tested for HIV infection for the
Among patients who were tested for HIV during hospitalization in an urban tertiary hospital, 64% turned out to be HIV infected.\textsuperscript{53} Waiting to be tested for the first time for HIV infection until admission in a tertiary institution means a quite substantial delay. Additional challenges are present regarding the optimal timing for initiation of cART among patients co-infected with TB.\textsuperscript{55,56}

The second challenge in the diagnosis and treatment of these two diseases is getting people to take diagnostic tests and get test results. The success of any TB (and possibly to some extent HIV) control programme lies in detecting the cases and starting eligible patients on good quality treatments. In primary health care programmes it is crucial that HIV patients are diagnosed early in their disease process to avoid challenges of deciding when to start treatments in the setting of co-infections and vice versa.\textsuperscript{57,58,59} Moreover cART reduces mortality among TB patients.\textsuperscript{60,61,62,63} Despite the adoption by many countries of the WHO provider initiated HIV testing and counseling guidelines, uptake of HIV testing is still low in outpatient departments, also among TB patients.\textsuperscript{64,65,66} A study in Ethiopia found missed opportunities for HIV diagnosis in 52% of patients.\textsuperscript{67}

The third challenge in the TB and HIV treatment programmes is to maintain those patients on treatment who have initiated therapy. High defaulting levels from anti-tuberculosis treatment (range 11-30%) have been reported in Africa.\textsuperscript{68,69,70} Similar to what is seen in TB treatment, between 16% to 26% on cART have been lost to follow-up within three years of starting cART in resource-limited settings.\textsuperscript{71,72,73,74} Data concerning defaulting or loss to follow up from ART programmes are still limited.

The fourth challenge in treating TB and HIV diseases is the poor adherence to treatments among those patients who do not abandon their treatments. Despite the high adherence levels reported for patients who remain on their cART or TB treatments,\textsuperscript{75,76} a sizeable proportion of patients adhere poorly to their treatments. Importantly, the on-and-off interruptions in medications result in drug resistance.\textsuperscript{77,78} Good adherence to TB treatment is essential for cure from the disease and plays a crucial role in TB control. Similarly, good adherence to cART is critical for achieving viral suppression and good clinical outcomes.
1.6 Study site
Kampala Capital City Authority (KCCA) is the institution in charge of planning and organizing the capital city. The name of this institution was changed from Kampala City Council to KCCA by an Act of the Ugandan Parliament in 2010. KCCA operates ten public primary health care facilities that offer a broad spectrum of outpatient services including smear microscopy, TB treatment, as well as HIV testing, prevention, care and treatment. We conducted observational studies in Kampala city at three of these KCCA health care facilities: the health centres of Kiruddu, Kisenyi and Kiswa. Kiruddu health centre is located in a semi-rural residential area. Kisenyi health centre is located in the middle of a densely populated low-income area. Kiswa health centre is located in an industrial area of the city.

Our operational studies were conducted under the INTERACT program. The Infectious Diseases Network for Treatment and Research in Africa (INTERACT) is a collaboration between Ugandan, Rwandan, Belgian, Irish and Dutch researchers and institutions and was formed in 2005 with a major objective of building sustainable capacity to conduct research in the poverty-related diseases namely HIV/AIDS, malaria and tuberculosis. INTERACT started by building capacity at the three KCCA clinics to offer better laboratory services for TB. The collaboration also offered additional space in terms of temporary containers.

The National Tuberculosis and Leprosy Control Programme (NTLP) is headed by a programme manager and organized as follows: the country is divided in 9 operational zones (Kampala being one of them), each headed by a zonal TB supervisor. These zonal supervisors report to the Programme manager of NTLP. Zones are divided into districts; district supervisors report to the zonal TB supervisor. The districts are divided into divisions. The divisional TB supervisors support the Diagnostic and Treatment Units (DTUs) in all TB control activities and ensure that routine data are collected and submitted in a timely manner. DTUs are government or private health units designated by the NTLP to offer TB diagnosis and treatment. There are 38 DTUs in Kampala city. The NTLP collects routine data from these DTUs. The health unit TB and laboratory registers at every DTU provide the source data. There is also a TB register at the Division level that captures data from the clinics. The zonal and district supervisors provide technical support and guidance to the big hospitals and accredited private clinics in the city. Every health facility designates a staff member in charge
of TB activities. The NTLP distinguishes the following standardized outcomes: cured, treatment completed, died, transferred-out, defaulted, and treatment failure.

At the time of our studies (2007-2010), patients attending the KCCA clinics were normally self-referred from home, referrals from private practitioners or down referrals from hospital for continuation of treatment. The standard procedure of diagnosing pulmonary TB in Uganda at the time was that all patients with cough for two weeks or longer were requested to submit three sputum samples. The first was on the spot, the second was an early (next) morning sample, while the third was a sample on the spot again. A standardized eight month treatment regimen with Ethambutol (E) and Isoniazid (H), Rifampicin (R) and Pyrazinamide (Z) for the first two months and EH for the subsequent 6 months was offered to patients with confirmed TB diagnosis. TB is treated according to the National Tuberculosis and Leprosy Control Programme (NTLP) guidelines with once daily dosing using fixed dose combinations. The health centres implement an urban model of Community Based Directly Observed Treatment Short course (CB-DOTS) in which the patient is given the option to choose a family member or friend to supervise swallowing of medicines.

The National HIV/AIDS control programme is headed by the HIV/AIDS control programme manager. In Kampala the HIV/AIDS Focal Person coordinates, monitors and supervises all the HIV/AIDS activities in the city; he/she reports to the national control programme manager. Until recently, HIV testing in Uganda was based on a voluntary request from the patient to be tested (“opt-in approach”) at static testing centres and, later on, during outreach services. In 2005 a new policy was adopted in Uganda that advocated a shift to an “opt-out” testing approach, in which the health care provider offers an HIV test as part of the routine investigations for any disease condition. Provision of cART had been available to patients since 2000 on a limited scale mainly in research settings and private practice. The Uganda government, through the Ministry of Health, embarked on the roll-out of free cART provision in 2004 beginning with the big hospitals. By the time provision of cART was introduced in the KCCA health centres in 2005, two research centres (Joint Clinical Research Centre and Infectious Diseases Institute [IDI]); the national referral hospital (Mulago); two tertiary private hospitals (Nsambya and Mengo) and three non-governmental organizations (The AIDS Support Organization, Mbuya outreach and Kamwokya Christian Caring Community) were already providing antiretroviral drugs to a wider selection of patients. In 2006 IDI, with
a grant from the United States Centers for Disease Control & Prevention, embarked on the process of supplementing government efforts of rolling out cART to all the remaining KCCA health centres through building clinics’ capacity to offer quality HIV care and treatment services.

At the time of recruiting for our studies provision of cART had just been rolled out to the three KCCA health centres; roll-out into all other clinics was on-going. By 2008 about 540 patients had initiated cART and about 2000 patients were on co-trimoxazole prophylaxis at KCCA health centres. Stable patients were down referred from IDI to the KCCA health centres. ART eligible patients were treated according to the national ART treatment guidelines which have since been revised. The commonest regimens offered then were: stavudine (d4T) + lamivudine (3TC) + nevirapine (NVP), and zidovudine (AZT) + 3TC+ efavirenz (EFV) or AZT + 3TC + NVP.

KCCA health centres directly refer complicated TB cases to Mulago hospital, which houses the national tuberculosis treatment centre. The hospital also down refers stable patients to KCCA health centres for continuation of treatment. IDI, the center of excellence for HIV care in Uganda, is located at the Mulago hospital complex and has similar relationships with KCCA health centres as the national tuberculosis treatment centre.

1.7 Rationale for each of the studies
We conducted six studies to examine operational aspects of diagnosing and treating TB and HIV infection in the routine setting of government clinics, in which we tried to intervene as little as possible. Several trials had been conducted in research settings in Kampala city, including at the national referral hospital. Our studies sought to examine operational aspects that are important at the peripheral level of the urban health services. The main objectives of the studies were to describe and quantify operational challenges and define potential targets for addressing these challenges. The rationale and scope of the studies are described below.

A. Starting patients on treatment
Prompt diagnosis of TB identifies the infectious cases from the pool of patients. Instituting prompt and effective treatment means that the transmission of TB is interrupted. Delayed diagnosis of TB results in extensive disease and increased mortality.\textsuperscript{80} Delayed diagnosis and
treatment would also lead to increased duration of infectiousness.\textsuperscript{81} There is paucity of data regarding diagnostic delay among patients seeking care at primary health care facilities in urban areas. We conducted a study to quantify this diagnostic delay and the factors associated with this delay among patients newly diagnosed with smear-positive PTB at the three KCCA health centres (Chapter 2).

Establishing early HIV diagnosis among TB patients facilitates initiation of prophylactic treatments to improve treatment outcomes and patient survival.\textsuperscript{82,83} Provision of cART to TB patients is now one of the known strategies for TB control.\textsuperscript{56,84,85} An HIV counseling and testing policy had been adopted in Uganda in 2005.\textsuperscript{86} Data were limited on how far the policy had been implemented at the primary care level. We conducted a study to look at the HIV test uptake and its associated factors among TB patients in this urban setting (Chapter 3).

In Uganda, studies have shown that between 30\% and 50\% of HIV patients present at ART clinics with severe immune suppression (CD4 count $< 200$ cells/$\mu$L).\textsuperscript{87,88} However, most of these studies had been carried out in research settings, university teaching hospitals and non-governmental hospitals. No study had yet been conducted in a routine public primary care setting. Previous studies largely focused on patients accessing HIV care services late (with advanced disease). Few studies had looked at late start of cART among patients already registered with the health services. We conducted a study to examine the late start of cART in this urban setting and factors associated with this late start under routine conditions (Chapter 4).

**B. Maintaining patients on treatment**

The TB control programme in Kampala city faces a huge challenge of retaining patients on their anti-tuberculosis treatment. According to unpublished data from the NTLP defaulting levels of up to 16\% have been reported for Kampala against the national average of 11\%. Patients stopping treatment soon after initiation have an increased risk of not being cured; patients stopping later in the course of treatment have an increased risk of TB relapse. There is a possibility that such patients continue spreading the infection to others. Defaulting as reported by TB control programmes is based on missing two consecutive monthly clinic visits. In reality some of these patients may have died, or continued treatment elsewhere. To fully understand the magnitude and pattern of this defaulting, one has to correct the reported
defaulters “rates” (not true rates, but really proportions) for deaths and continuation of treatment elsewhere, based on an active follow-up of defaulted patients. Chapter 5 presents a study to quantify defaulting levels and factors associated with the defaulting in Kampala city.

One of the goals of effective TB case management is to achieve a high level of adherence by direct observation of treatment and thereby averting the development of drug resistance. Some studies have looked at defaulting as a proxy for adherence. However, the two phenomena are of public health importance in different ways: a patient who defaults from treatment, i.e. stops treatment, may not get cured while a patient who keeps on interrupting treatment may eventually develop drug-resistant TB. We conducted a study among new TB patients who started TB treatment in an urban setting, with health facilities offering community CB-DOTS with a volunteer treatment supporter. We followed-up these patients to study adherence to treatment, and factors that affected adherence (Chapter 6).

In the absence of a cure for HIV/AIDS, the only practical choice is to ensure that available treatment options are used effectively; hence the call for good adherence. Good adherence to cART is critical in achieving virologic suppression and prolonging life. Good virologic suppression will forestall continuing damage to the immune system and help prevent opportunistic infections and other diseases such as cancers. Earlier studies have shown high adherence levels in sub-Saharan Africa. However, few studies have been conducted in primary health care facilities. The sixth study sought to explore issues surrounding adherence to cART, again in an urban primary health care setting (Chapter 7).

Finally the implications of these studies, recommendations and targets for interventions are discussed in chapter 8.
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