Aspects of tuberculosis and HIV diagnosis, care and treatment in Rwandan health facilities: operational studies
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Chapter 9

General discussion and conclusions
Introduction
This thesis reports on operational aspects of TB and HIV diagnosis, care and treatment in Rwandan health facilities. In this last chapter we discuss the main findings from the studies reported in this thesis and try to make interpretations of these findings. We will draw conclusions from the results and provide recommendations for public health practice and for further research.

TB studies
We conducted an assessment of the performance of the Rwandan TB control program on sputum completion rate (defined as the coverage of sputum microscopy for PTB + cases at the end of the 2-month intensive treatment phase) and the sputum conversion rate (SCR) defined as the proportion of patients who had become smear negative out of all of those who had a 2-month smear microscopy done in a cohort of patients diagnosed and treated between January and June 2006 (chapter 2). The association of sputum completion and SCR with health facility factors was also examined (chapter 2 and chapter 3). We also assessed the determinants of adherence to TB treatment, TB mortality and the independent effect of adherence on mortality in a cohort of new adult patients diagnosed at 48 clinics between January and March 2007 (chapter 3).

Sputum completion and SCR
Our findings indicate that the sputum completion rate was too low; sputum microscopy after the initial phase of TB treatment was done for 80% of the patients (chapter 2). This represents a sub-optimal performance by the national TB program. Routine follow-up microscopy for all TB patients after 2 months of the initial phase of TB treatment is mandatory. It is an operational indicator that is useful for measuring the quality of treatment supervision in the initial phase. Prolonging the initial phase of TB treatment for an extra month among patients with positive sputum microscopy after 2 months of treatment is one of the measures to prevent the emergence of drug resistance that could occur through exposure of replicating bacterial populations to just two drugs.¹ Failing to perform follow-up sputum microscopy for 20% of patients by program staff has prevented an extension of the initial phase for an extra month among some patients for whom this was indicated. This finding demonstrates a missed opportunity for better treatment outcomes.
We found that the SCR was adequate at 82% and 80% from the two cohorts we studied (chapters 2 and 3 respectively) given that rates above 75% are regarded as good for well functioning programs.² Similar results were obtained from other studies where sputum conversion rates ranged between 80-93%.³-⁴ Although our finding reflects a well functioning program, it is also indicative of potential room for improvement. We found that the busiest clinics and clinics located in rural areas were
significantly more prone to have poor completion and conversion rates (chapter 2). Failure to convert at 2 months treatment was significantly associated with baseline smear grade and HIV infection (chapter 3). From the study by Hassling et al. smear grading and extensive parenchymal involvement were both identified as predictors of smear conversion at two months.3 One study from South Africa reported that important factors associated with delayed sputum culture conversion after 2 months were baseline time to detection, smoking, and cavities and W-Beijing genotype.4 More efforts should be placed in ensuring the availability of additional staff to busy clinics particularly those located in rural areas; regular training may increase staff compliance to treatment guidelines and quality of patient follow up. It would be worthwhile to conduct a larger study examining both patient level factors as well as clinic factors associated with sputum completion rate and SCR.

Determinants of TB treatment adherence
We found that HIV infected TB patients that did not start combination anti-retroviral therapy (cART) were more likely to be non-adherent (defined as taking less than 90% of the expected TB medication doses) (chapter 3). Non-adherence to TB medications has been reported in other studies7,8 and may be explained by the fact that those on cART get regular follow up with adherence counselling. Similar studies from Uganda found that these patients are characterized by weak social ties such as daily alcohol drinking, change of residence, lack of social support or unemployment.9,10 Recently, Gray and Cohn reviewed the atypical clinical manifestations of TB linked to HIV, overlapping drug toxicities, drug–drug interactions, and concerns about adherence among co-infected patients.11 Efforts to monitor the development of TB clinical signs among HIV patients and timely initiation of cART may improve health outcomes among these patients. Simplified algorithms need to be developed to identify and monitor patients at higher risk of non-adherence.7 Interventions such as training of TB program personnel on enhanced treatment compliance counselling may improve adherence.7

Determinants of TB mortality
From our study (chapter 3), the determinants for mortality were older age, smear-negative and extrapulmonary TB, and HIV infection. Similar findings were observed in studies from Ethiopia, Malaysia and Thailand; mortality was high among TB-HIV co-infected patients.12-14 Poor adherence to TB treatment had an independent effect on mortality. This suggests that improving adherence is important to prevent mortality in these patients. Health care interventions such as enhanced individual counselling may improve treatment adherence, improved patient tracking, linkage to care,
and an effective referral system from point of testing to the cART clinic, may improve treatment outcomes.\textsuperscript{15,16}

**Provider-initiated Testing and Counselling (PITC)**

PITC has been proposed by WHO and UNAIDS as a way to increase HIV testing, to make an HIV diagnosis sooner after infection, to increase the awareness of individuals of their own HIV status, and to enable an earlier start of cART. In Chapters 4 to 7, we report on the results of a large study conducted in eight health facilities in which PITC was introduced. We studied various aspects of PITC, like the acceptability of PITC for health care workers and for clinic attendees, the effectiveness of PITC to increase test-uptake and case finding, the time to enrolment and linkage to care and treatment after HIV diagnosis, the stage of HIV infection at the time of HIV diagnosis and whether that changed during PITC, time to start of cART, and factors associated with timely linkage to care among attendees in eight Rwandan health facilities in the period 2009-2010.

**Is PITC acceptable to health care workers and attendees?**

We examined the acceptability of the PITC, the reasons for being or not being tested for HIV and factors associated with having been tested on the day of the interview among attendees (chapter 4). We found that PITC was highly acceptable (>95%) to both the health facility attendees and health care staff. The high acceptability rate from our study is consistent with the results from a Botswana study in two large tertiary hospitals and a population-based study in Uganda.\textsuperscript{17,18} The reasons for accepting an HIV test from our study were also consistent with those from the Ugandan study; the desire to know one’s HIV status and the offer of PITC by health care staff were the most common reasons for accepting an HIV test.\textsuperscript{18} Known HIV status and no test offer by health care staff were the most common reasons for not being tested. Although PITC appeared to increase HIV testing rates, it is important to note the challenges that come with it. We found that it increased the health care workers’ workload and the waiting time for patients in our study. Patient overload was cited as a barrier for effective provision of PITC by health care workers from a Tanzanian study.\textsuperscript{19} Based on our findings and studies from other countries, PITC seems acceptable to both health care workers and attendees.

**Does PITC lead to increased HIV test uptake and case finding?**

HIV testing uptake during the routine practice was assessed in comparison with the test-uptake during the intervention period when PITC was introduced at the outpatient and family planning departments (chapter 5). We found that PITC led to a shift of HIV testing from VCT department to
the OPD and a higher overall test uptake in the six intervention sites in the OPD. Similar findings from a study in South Africa\textsuperscript{20} and a systematic review by Kennedy et al\textsuperscript{21} suggest PITC leads to increased uptake of HIV testing compared with routine practice. During the PITC intervention period the proportion of OPD attendees that were tested increased significantly. We also assessed the effect of PITC on HIV case finding by comparing routine practice, when VCT was mainly used as the testing approach, with the PITC implementation phase. PITC did not lead to increased HIV case finding in our study. Studies from Uganda\textsuperscript{18,21} and South Africa\textsuperscript{23} reported increased HIV case finding due to PITC. One of the Ugandan studies was conducted between November 2004 February 2006 among a population that attended two tertiary hospitals that had a high HIV burden. The other study was conducted among outpatients that attended a rural hospital between February and June 2008. The South African study was done in an urban hospital outpatient population in 2005. The discrepancy of results of our study to the above-mentioned studies may be explained by differences in HIV prevalence rates and the way health care is differently organized in these three countries. Generally, the HIV prevalence in the Ugandan and the South African populations is higher (7.2\% and 17.9\%) than that of the Rwandan population (3.0\%).\textsuperscript{24} Secondly, the access to care and treatment in Rwanda is above 80\%\textsuperscript{25,26}, many health facility attendees reported previous testing and therefore further expansion of testing identifies only few additional cases. The rapidly decreasing trend of new HIV infections in Rwanda compared to other countries in the region may account for the observed variation in case finding rates.\textsuperscript{27} Based on our findings, PITC appeared to increase testing rates but seems ineffective for increasing HIV case finding in Rwanda.

\textbf{Does PITC lead to increased usage of HIV care and treatment?}

Timely linkage to eART is critical for reducing HIV-related morbidity, mortality and transmission.\textsuperscript{28} We describe the time to enrolment and linkage to care and treatment after HIV diagnosis during routine care when PITC was not operational (chapter 6). We found that less than 50\% of the patients had enrolled to care and treatment within 90 days after HIV diagnosis. This finding is consistent with several studies that identified low rates of enrolment despite improved access to HIV services.\textsuperscript{29-32} We also identified that there was significant variation by study site in enrolment; this suggests an effect of health facility such as insufficient staff that are overwhelmed by an overload of patients. Re-organizing health services delivery and providing more health care workers particularly at the busy clinics may improve enrolment rates.\textsuperscript{33} Patients were likely to enrol at facilities with ART clinics compared those diagnosed at facilities that referred patients to off-site ART clinics. More operational studies to identify effective solutions so that a greater proportion of infected individuals can benefit from long-term eART are needed.\textsuperscript{34,35} In the same cohort, we also assessed the stage of
HIV at the time of diagnosis and start of cART. In Rwanda the HIV care and treatment guidelines recommend three eligibility criteria for cART initiation: clinical stage, immunological state and social status. We found that only few patients were in very advanced stage of infection (none were in WHO stage 4 and only 9% had a CD4 count below 100 cells/mm$^3$). This finding may not be surprising given that access to free HIV testing and treatment services is remarkably high in Rwanda. In the same cohort, we identified that a low proportion of the eligible patients (56%) had started ART after 90 days of HIV diagnosis. This finding is unexpected since Rwanda is ranked among the top three countries with high cART coverage. It must be interpreted with caution, as it is dependent on linkage-to-care after HIV diagnosis; a low enrolment rate to pre-ART care affects treatment initiation. Interventions that enable effective patient tracking between the point-of-testing to pre-ART care and treatment initiation must be reinforced. These may include WHO clinical staging and CD4 count determination on the same day of HIV diagnosis, use of family and community engagement as well as use of longitudinal medical records.

We also examined the proportion of HIV infected patients that linked to cART care in the PITC intervention phase, and examined factors associated with non-linkage, with advanced HIV stage, and with start of cART (chapter 7). We assessed whether these indicators differed significantly between the pre-PITC and the PITC phase. We found a suboptimal linkage to pre-ART care and cART in both pre-PITC and PITC phases. This may be explained by the fact that we identified from our cohort that only few patients had an advanced HIV stage, yet it is an important determinant of both linkage-to-care and start of treatment. Indeed from our study, patients diagnosed at TB department were more likely to have a high WHO stage, however they constituted only 17.2% of the 325 patients whose staging was available. We also found that psychosocial and health-services related factors contributed to non-enrolment to HIV care and treatment. In the same cohort, PITC appeared to be associated with non-enrolment within 90 days of HIV diagnosis. Our data indicate that some patients diagnosed with HIV were already enrolled into care but sought re-testing partly because they thought the infection had been cured through prayers. Others retested due to denial of their HIV status (mostly due to stigma and non-disclosure) while others had already enrolled into HIV care and treatment at different health facilities. Long waiting time at busy clinics, not being told to return for clinical staging and CD4 count measurement, failure to meet a health care provider on the day of the clinic visit and non-functioning laboratories were some the reasons reported for non-enrolment. Our results are also consistent with other studies conducted in similar settings. One study assessed the effectiveness of care for HIV-positive patients between HIV diagnosis and linkage to cART services in South Africa and found that only 47% of the eligible patients were
referred to cART services. In a large cohort study of HIV patients in Zambia PITC did not facilitate timely linkage to care compared to VCT. Although our survey among the non-enrolled patients revealed an underestimate of the actual proportion of patients linking to pre-ART care, timely linkage to care remained suboptimal nonetheless. Our findings strongly suggest the need to improve the quality of individual patient counseling and patient tracking to improve linkage to care. These findings add considerable weight to initial results we report in chapter 6, as well as those from a systemic review of PITC programs in sub-Saharan Africa that focused on interventions and resources to improve pre-ART linkage to care.

**Prevalence and determinants of discordant response to cART**

The prevalence and determinants of discordant treatment responses (defined as good virological response but a poor immunological response to cART or vice versa) 12 months after start of cART in a Rwandan prospective cohort from nine rural health facilities were also studied (chapter 8). We found that 29% of the patients experienced immunological discordant treatment response. Our results are comparable with those from a South African study that observed 37% of the patients having failed to restore CD4 cell counts within 12 months of cART. The implication of these results is that a large proportion of patients do not achieve adequate immunological response yet CD4 cells measurement is the most likely and available parameter for biological monitoring for patients in limited resource settings. We found that discordancy was significantly associated with older age (above 35 years) and longer travel times to the clinic in our study. A South African study also reported older age and nadir CD4 cell count at cART initiation as predictive factors for discordant virological and immunological responses to cART. Both older age and CD4 count at initiation were predictors for discordancy in the Zambian study but in our cohort, baseline CD4 count did not have any effect. Regression to the mean, random and individual variation of CD4 counts may explain this contradictory finding. The association of travel time with retention in care, viral load suppression and CD4 change in this cohort has been described and its effect on discordancy could possibly be explained by fluctuation in treatment adherence. In places where viral load monitoring is not routinely done, cART monitoring is dependent on CD4 count and a limited increase may be incorrectly interpreted as treatment failure and patients may unnecessarily be switched to costly second line regimens. To avoid this, point-of-care VL tests are needed in public health clinics to differentiate between cART failure and a discordant treatment response.
Policy implications

Despite very good performance of the Rwanda national TB control program, our study on sputum completion and conversion rates highlights challenges related to follow up of patients particularly during the initial phase of TB treatment. This suggests need for more efforts to improve the compliance of health providers to standard diagnostic and TB treatment guidelines during the initial treatment phase. The low sputum completion rate observed in our study was associated with patient overload at the busiest clinics. Health facilities frequently visited by high numbers of patients should be prioritized with respect to staffing and other interventions that improve health workers’ performance. The finding that patients with smear-negative TB had a high risk of death further suggests the need to systematically test for HIV infection and follow closely this group of patients. Interventions to increase early identification of TB cases and close monitoring of older age male patients could considerably increase the sputum conversion rates and improve TB treatment outcomes.

Our studies suggest that PITC was highly acceptable among health facility attendees and health care providers. It also increased HIV test uptake, an important entry point towards prevention, timely care and treatment, but it did not lead to a significant increase in case finding. Furthermore, PITC appeared to increase workload for the health care providers and led to longer waiting times for patients. In the end, the limited number of extra cases identified during PITC was less likely to enrol in HIV and treatment. Further research taking into consideration countries with different HIV profiles such prevalence, population testing rates, and ART coverage is warranted.

Committing additional resources to support adequate staffing, regular training and motivating health care providers may solve the service-related challenges.

Due to the high rates of discordant treatment responses among patients on cART, rigorous monitoring for clinical signs particularly among older age patients and low-cost VL tests should be introduced to mitigate the unwarranted treatment changes to second line regimen in settings with limited resources.

Recommendations for further research

1. Due to the importance of sputum completion and sputum conversion rates after 2 months of initial treatment as predictors of eventual cure and treatment implications in case of failure to convert, we recommend operational research to test the feasibility and
effectiveness of standard operating procedures that may increase staff compliance to systematic sputum microscopy at the end of the initial treatment.

2. There is need operational research to enhance early detection of the common secondary pathologies superimposed on TB as well exploring innovative approaches to that may improve TB treatment adherence.

3. We recommend studies into feasibility and effectiveness of same day WHO clinical staging, CD4 count determination and enhanced individual counseling to improve timely linkage to pre-ART care and cART.

Conclusions
To respond to unresolved research questions, we conducted operational studies on the diagnosis, care and treatment of TB and HIV in Rwanda. We identified and recommend clinical and public health interventions that could improve the performance of TB and HIV control programmes. National TB control programmes should prioritize strategies to improve TB treatment outcomes particularly treatment adherence. Our findings and those from earlier studies suggest that PITC was highly acceptable and led to increased HIV test-uptake. We did not detect an effect of PITC on HIV case finding; nonetheless it remains the best available model to effectively enhance diagnosis of more HIV patients in the early stages of their infection. Further, due to the growing number of patients on prolonged cART, use of low-cost point of care VL tests should be prioritized to avoid unwarranted treatment changes to second line regimens in resource limited settings.

References


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