Published in final edited form as:

J Acquir Immune Defic Syndr. 2012 June 1; 60(2): e29–e35. doi:10.1097/QAI.0b013e318251aeb4.

Integration of HIV and TB services results in improved TB treatment outcomes and earlier, prioritized ART initiation in a large urban HIV clinic in Uganda

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Abstract

Background—WHO recommends that treatment of TB in HIV-infected patients should be integrated with HIV care. In December 2008, a separate, outdoor integrated TB/HIV clinic was instituted for attendees of a large urban HIV clinic in Uganda. We sought to evaluate associated TB and HIV treatment outcomes.

Methods—Routinely collected clinical, pharmacy and laboratory data was merged with TB clinic data for patients initiating TB treatment in 2009 and with TB register data for patients in 2007. TB treatment outcomes and (timing of) ART initiation in ART-naïve patients (overall and stratified by CD4+ T cell [CD4] count) in 2007 and 2009 were compared. Nosocomial transmission rates could not be assessed.

Results—346 patients were initiated on TB treatment in 2007 and 366 in 2009. Median CD4 counts at TB diagnosis did not differ. TB treatment cure or completion increased from 62% to 68%, death or default decreased from 33% to 25% ($P<0.001$). Fewer ART naïve TB patients were initiated on ART in 2009 versus 2007 (57% and 66%, $P=0.031$), but this decrease was only in patients with CD4 counts $>250/\text{mm}^3$ (19% versus 48%, $P=0.003$). More patients were started on ART during TB treatment (94% versus 78%, $P<0.001$). Moreover, the majority were now initiated during intensive phase (60% versus 23%, $P<0.001$).

Conclusions—Integration of TB and HIV care has led to improved TB treatment outcomes and earlier, prioritized ART initiation. This supports roll-out of a fully integrated TB/HIV service delivery model throughout high-prevalence TB and HIV settings.

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Data was presented in part at the 6th IAS Conference on HIV Pathogenesis, Treatment and Prevention (17-20 July 2011, Rome, Italy) and was published in the abstract book of this conference (TUPE472 and WEPDD0103).

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Keywords

HIV/AIDS; tuberculosis; integrated TB/HIV care; operational research; resource-limited setting

Introduction

Tuberculosis (TB) is the leading cause of death in HIV-infected patients and HIV-infection is the most important risk factor for developing active TB¹⁻². The dual epidemic of TB and HIV is cause for great concern, especially in sub-Saharan Africa where 80% of the burden of co-infection resides and health systems are already weak and overstretched^{1,3}.

To decrease the joint burden of HIV and TB disease, the World Health Organization (WHO) formulated a strategic framework for collaborative TB/HIV activities⁴. These activities focus on reducing the burden of TB among HIV-infected patients by the “three I’s”: intensified case finding, isoniazid preventative therapy and infection control. Decreasing the burden of HIV in TB patients is to be done by providing HIV counseling and testing, the use of co-trimoxazole and by introducing antiretroviral therapy (ART). Based on evidence from several randomized controlled trials showing reduced mortality⁵⁻⁸, recent guidelines state that co-infected patients should be initiated on ART as soon as possible after TB treatment initiation⁹. These trials showed that the greatest benefit of early ART initiation was realized in patients with CD4+ T cell (CD4) counts <50 cells/mm³. In order to fully implement these collaborative activities integration of health systems for HIV and TB service delivery should be in place, although there is a lack of consensus on how to implement this integration¹⁰.

Uganda is among the 22 WHO TB high-burden countries and has an HIV prevalence of 6.4%^{3,11}. The proportion of TB patients tested for HIV rose from 30% in 2005 to 71% in 2009, and HIV-positivity of those tested was 54% in 2009. National policy guidelines for collaborative TB/HIV activities were formulated in 2006, but have been slow to be implemented¹².

In December 2008, a separate, outdoor integrated “One-Stop Shop”¹⁰ TB/HIV clinic was instituted for attendees of the HIV clinic at the Infectious Diseases Institute, to improve the TB treatment completion rate, to standardize diagnosis and care in co-infected patients and to reduce nosocomial transmission of TB. Our objective was to investigate whether integrating HIV and TB care results in improved patient management, measured by improved TB treatment outcomes (survival and treatment completion) and by prompt ART initiation in eligible patients according to the Ugandan Ministry of Health Guidelines. We evaluated these outcomes before and after the implementation of this clinic, by comparing the years 2007 and 2009.

Methods

Setting

The Infectious Diseases Institute (IDI) at the Makerere University College of Health Sciences in Kampala, Uganda, is a large urban HIV clinic, which has registered more than 26,000 patients, and provides free outpatient care to more than 10,000 HIV-infected patients. In general, patients on ART are seen every 4 weeks and CD4 counts are performed every 6 months. At the time of this evaluation and in accordance with the national guidelines of the Ugandan Ministry of Health, all patients received daily co-trimoxazole prophylaxis irrespective of their CD4 count, and ART was initiated in patients with WHO stage IV disease or a CD4 count <250 cells/mm³¹³. For HIV-infected patients with active tuberculosis, the CD4 threshold for ART initiation was 350 cells/mm³. In TB patients with

CD4 counts <200 cells/mm³, ART was to be initiated during the intensive phase of TB treatment.

Available investigations for TB include sputum microscopy, chest radiology, abdominal ultrasonography, and fine-needle aspiration of lymph nodes for acid fast bacilli microscopy. No routine mycobacterial culture facilities are available. Diagnosis is made on the basis of these investigations, but very often on clinical judgment alone.

Treatment for TB is offered at IDI. Drugs are provided by the National TB and Leprosy Program (NTLP) and treatment follows their guidelines which were consistent over the study periods: for new cases, treatment consisted of a 2-month intensive phase with a combination of rifampicin, isoniazid, ethambutol and pyrazinamide (RHZE), followed by a 6-month continuation phase with isoniazid and ethambutol¹⁴. Retreatment cases were treated with the category II regimen in which streptomycin is added to the 2-month intensive phase, followed by a month of RHZE, and a 5-month continuation phase of a combination of rifampicin, isoniazid, and ethambutol. Follow-up of treatment was done according to NTLP standards with repeat sputum smears at the end of intensive phase, at 5 months and at the end of treatment to determine treatment outcome in pulmonary TB patients. Isoniazid preventative therapy was not being prescribed.

Organization of TB care before integration

Until 2008, TB screening and diagnosis was not done systematically and was performed at the discretion of medical officers during routine HIV follow-up visits. After diagnosis of active TB, treatment and follow-up according to the NTLP guidelines was provided by a TB nurse who was based in the pharmacy area, while HIV care remained the responsibility of the medical officers. Directly Observed Therapy (DOT) or tracing of patients lost to follow-up was not done.

Creation of integrated TB/HIV program

In August 2008 a group of health care workers formed a TB working group. Its goals were to improve diagnosis and care for co-infected patients at IDI, and to improve infection control for both patients and clinic staff. This group laid the groundwork for a more integrated TB/HIV service and created evidence-based standard operating procedures for diagnosis and management of TB in HIV-infected patients, a set of “self-learning” TB/HIV clinic management forms (see supplemental data) and a database for monitoring and evaluation of the integrated service. To optimize infection control, the clinic was separated in an outdoor space to take advantage of natural ventilation and UV light.

In December 2008, an outdoor integrated TB/HIV clinic was set up on the IDI grounds. In this clinic, TB suspects and patients diagnosed with TB can access care for both diseases simultaneously, by the same staff. Care was provided by a trained team of 2 medical officers, 2 nurses and a nurse-counselor, who were trained and supervised by a senior medical officer and assisted in logistic and health education tasks by a peer supporter. The HIV/TB clinic team members were permanent with the exception of one medical officer, belonging to a rotating pool of medical officers in the general HIV clinic as a capacity building initiative. Logistical and improvement issues as well as difficult cases were discussed at weekly team meetings.

General HIV clinic personnel were trained to recognize common TB symptoms and to direct patients suspected to have TB to the integrated clinic for assessment. Standardized TB diagnosis, treatment initiation and follow-up were reinforced by the use of “self-learning” TB/HIV clinic management forms. This set of six forms guides clinicians in the appropriate management of the co-infection and includes all TB program definitions and algorithms for

switching or initiation of ART in patients with active TB (see Documents, Supplemental Digital Content 1 and 2, for examples of the TB/HIV clinic diagnosis form and treatment initiation checklist). These forms together with all clinical information on TB are kept in the “master” HIV clinic patient file. In 2009, tracing of patients lost to follow-up was done on an approximately two-weekly basis by phone tracing by the nurse-counselor in the TB clinic. DOT was not practiced. After completion of TB treatment or after exclusion of active TB, the patient is referred back to the general HIV clinic. See Figure, 1 for a schematic of integration of care in both models.

Data collection

Scheduled clinic appointments took place every 4 weeks and data on clinical parameters, ART and adherence, WHO stage, toxicities and opportunistic infections was routinely collected into a database. Laboratory data was directly downloaded electronically. A team of trained nurses and medical officers performed data verification with the patient's medical notes and auditing of this database as part of regular clinic monitoring and evaluation.

TB treatment specific data was collected in the NTLP registers. This included data on demographics, investigations performed, type of TB diagnosed, date and category of TB treatment initiated, HIV status, medication used (co-trimoxazole or ART), follow-up visits and investigations, adherence and treatment outcome. The NTLP register data for 2007 was entered into a separate database. Data generated by the TB/HIV clinic forms was entered into a TB/HIV clinic database, which included data on demographics, TB symptoms, in addition to the data captured in the NTLP register. For the sake of this analysis, the TB/HIV clinic database for patients initiating TB treatment in 2009 and the NTLP register data for patients in 2007 were appended and merged with the routinely collected clinical, pharmacy and laboratory data. A review of the TB registers and records of all patients treated for TB in 2007 and 2009 was carried out to validate the information in both datasets.

Ethical approval

The collection and use of this clinical data has been approved by the Institutional Review Boards of IDI, Makerere University College of Health Sciences and the Uganda National Council for Science and Technology. De-identified data for our study was extracted from these databases and analyzed.

Study design, selection criteria, outcomes and definitions

A retrospective cohort study design was used. All patients initiating TB treatment at the IDI in 2007 and 2009 were selected for comparison. The primary study outcome was TB treatment outcome according to WHO definitions: cure, completion, death, default, transfer-out and failure¹⁵. Secondary study outcomes were the proportion, timing and outcomes of ART initiation in ART-naïve TB patients (overall and stratified by CD4 count at TB diagnosis). CD4 counts at TB diagnosis were the closest recorded values to the date of TB diagnosis, maximum 90 days pre and 90 days post TB treatment initiation. For outcomes after ART initiation, a combined definition of death or lost was used, as mortality ascertainment was unreliable in 2007. In 2009, this was improved secondary to a file inactivation and loss to follow-up ascertainment exercise.

Statistical methods

Proportions and medians of outcomes in 2007 (before implementation of the clinic) and 2009 (after) were compared using Chi-squared and two-sample Wilcoxon rank-sum tests, respectively. Time to ART initiation was analyzed using survival analysis: Kaplan-Meier curves were generated and compared using the log-rank test. All statistical tests were two-

sided at an α value of 0.05 and were conducted using STATA version SE 11.1 (College Station, Texas, USA).

Results

A total of 346 patients were initiated on TB treatment at IDI in 2007 and 366 in 2009. Baseline characteristics are summarized in Table 1. In 2009, more patients were diagnosed with extrapulmonary TB; more patients were on ART at TB diagnosis in 2009 and their median time between ART initiation and TB diagnosis was longer.

TB treatment outcomes

Overall, patients who completed treatment increased from 62% in 2007 to 68% in 2009, and patients who died or defaulted decreased from 33% to 25% (Table 2). Although the proportion of deaths increased, the proportion of patients defaulting TB treatment decreased. Of those, a high proportion defaulted during the intensive phase (59% in 2007 and 47% in 2009) (see Figure, Supplemental Digital Content 2, which illustrates timing of default of TB treatment in 2007 and in 2009). In 2007, defaulters were more likely to reside outside Kampala district as compared to non-defaulters (49% versus 33%, $P=0.04$). In both years we observed an increasing numbers of patients defaulting TB treatment during the rainy season (November).

ART initiation in TB patients and associated outcomes

Fewer ART naïve TB patients were initiated on ART in 2009 versus 2007 (Table 2), but this decrease was only in patients with higher CD4 counts (as a result of limited total ART slots). Of the patients initiated on ART, more were started during TB treatment than after completion (94% in 2009 versus 78% in 2007, $P<0.001$). Moreover, the majority was started on ART during intensive phase with the median time to ART initiation decreasing from 103 to 45 days. The earlier ART initiation was specifically in the group of patients with CD4 counts <100 cells/mm³ (Figure 2).

There was no difference in survival and retention of ART-naïve patients who were initiated on ART (Table 2). Interestingly, among those not initiated on ART, fewer patients died or became lost to follow-up, which was mainly due to the improvement in outcomes in the intermediate CD4 count group (see Figure 3).

Discussion

Complete integration of TB and HIV care in our urban HIV clinic contributed to an increase in the proportion of patients who completed TB treatment alive and to a decrease in treatment default. It also led to earlier and more prioritized ART initiation in ART-naïve HIV-infected patients diagnosed with TB with a decrease in the time to initiation of ART, especially in patients with a CD4 count <100 /mm³ who are most likely to benefit from timely ART initiation⁶⁻⁸.

Different models of integrated delivery of TB and HIV care in resource-limited settings have been described in the literature. Legido-Quigley et al. performed a systematic review of 60 papers and 70 abstracts describing HIV and TB service integration in low- and middle-income countries, and categorized these into 5 models: a TB clinic with referral for HIV testing and treatment; a TB clinic with on-site HIV testing but with referral for HIV treatment; an HIV clinic with referral for TB testing and treatment; an HIV clinic with on-site TB screening and with referral for TB treatment and a “single facility” with provision of TB and HIV services in the same clinic¹⁰. They also described benefits and weaknesses of the different models. These range from easy implementation but failing referral mechanisms

due to poor communication in less integrated models to improved staff morale and retention, but more logistical challenges such as human resource limitations, increased need for staff training and additional infrastructure in models with higher levels of integration.

Despite the rationale for integrated service delivery, the evidence to support it is limited^{4, 10}. Few reports include TB and/or HIV treatment outcomes¹⁰. Decreased default rates after integrating TB services into home-based care were found in Zambia.¹⁶ Two studies of fully integrated care models in Kenya (HIV services added to a TB clinic) and Malawi (TB services added to an HIV clinic) found no decrease in TB treatment default but an increase in ART usage¹⁷⁻¹⁸. To our knowledge, our evaluation of our integrated clinic model study is the first to present results on ART prescribing behavior including timing of ART initiation.

We feel several aspects were crucial to the success of the integrated care delivery in our clinic. The formation of a dedicated team of health care workers who were convinced of the need for integrated care was paramount. Weekly team meetings and opportunities for personal growth motivated team members and gave them a feeling of empowerment. Training of the TB/HIV clinic staff by the learning forms allowing continuous repetitive emphasis on core treatment concepts, having one clinician take care of both diseases and continuous quality improvement by ongoing supervision by senior team members were essential to the delivery of high-quality standardized care. The setup of a compact open air clinic with few staff members allowed for easy communication and treatment continuity for the patients.

The recently concluded TB-Control Assistance Program (TB-CAP) to strengthen TB/HIV collaboration in Uganda recommended a health service delivery model based on offering comprehensive TB and HIV services in one health facility¹⁹. At baseline, our clinic represented the siloed situation of the highly standardized TB care setting with minimal communication with the more patient-centered HIV care setting²⁰. Our results offer an insight into TB and HIV care outcomes that are attainable by integrating services for both diseases. Our model would need to be adapted further for general out patients settings which include HIV-uninfected patients. We are currently testing this in a WHO funded TB REACH project. As suggested by others, having a point person responsible for TB/HIV integrated care in each health center will help continued communication between the TB and the HIV health care systems^{18, 21}. In our view, there is no need for separate staff; in a traditional setting with separate TB and HIV outpatient clinics, usually run on different days, staff from these could be trained and deployed on separate TB/HIV outpatient clinic days.

The proportion of patients defaulting TB treatment in sub-Saharan Africa varies from 11.3% to 29.6%²²⁻²⁶, and could be higher in HIV-positive patients. As mentioned earlier, two integrated care models reported different effects on default rates¹⁶⁻¹⁷. In our clinic, active tracing of patients who missed their appointment improved ascertainment of patients' outcomes. The increase in proportion of deaths in 2009 compared to 2007 is likely attributable to this improved ascertainment rather than a real increase in mortality; a large proportion of patients classified as lost to follow-up before the intervention might have died. However, more effort is needed to reduce loss to follow up; 10% of patients still did not complete TB treatment after integration of services. Contrary to other studies the majority of our patients default during the intensive phase²²⁻²⁶, suggesting that interventions during the first 2 months of treatment could drastically reduce the number of patients lost to follow-up in our clinic.

Recent evidence strongly suggests that initiation of ART during TB treatment rather than after completion of TB treatment leads to improved survival, and that patients with very low

CD4 counts (<50 cells/mm³) should be started on ART within 2-4 weeks after initiation of TB treatment⁵⁻⁸. This evidence has been incorporated into the WHO ART guidelines⁹. Our results show that integrating HIV and TB care feasibly allows for timely initiation of ART (the time to ART initiation reduced from 103 to 45 days). Restricted funding and therefore ART availability prohibited initiation of all TB patients on ART in our setting, but trained medical staff were able to appropriately assess ART eligibility and triage ART access which led to a more prioritized ART initiation in patients most in need of ART. Interestingly, no difference in mortality and loss-to-follow-up was seen in patients who had been initiated on ART across periods. Improvement in these outcomes was found in patients not initiated on ART, particularly in the intermediate CD4 count group. The small numbers prompt careful interpretation; we attribute this to an overall higher quality of care after the integration.

National guidelines formed the basis of the TB and HIV care provided both before and after implementation of the integrated clinic, and had not changed between 2007 and 2009 with respect to any of the reported outcomes. Data to support ART initiation during TB treatment came out early 2009²⁷, which might have increased awareness among clinicians to adhere to existing national guidelines. However, we feel that the most important factor underlying the more timely ART initiation in 2009 was that the ART prescribing clinician and the TB treating clinician were the same.

The integrated clinic was set up with a minimal use of resources, of which the majority was used for the construction of the outdoor clinic specifically for improvement of infection control, an outcome which we could not measure. Although we lack data on nosocomial TB transmission rates, we believe the creation of an outdoor waiting area and clinic could have averted infections compared to the situation prior to integration. The additional cost to provide the integrated care service was minimal and consisted mainly of efforts to create training, clinic, monitoring & evaluation materials, and to train the HIV/TB clinic staff. Other limitations of our analysis were the use of routinely collected data with issues of missing data and outcome ascertainment. Data on the type of TB diagnosed and TB treatment outcomes were collected differently in 2007 and 2009. The digitalized NTLP register was used in 2007 and the new clinic database validated by the NTLP register in 2009. The HIV and laboratory data was uniformly collected across both study periods, however. The data in both datasets underwent extensive validation through cross-checking with the clinical notes. Therefore, we do not think these differences could explain the observed outcome differences between the two years.

In conclusion, the integration of TB and HIV care in our large, urban HIV clinic has led to improved TB treatment outcomes and earlier and more prioritized ART initiation. There is need for data on nosocomial TB transmission rates in integrated care settings. This data supports the roll-out of a fully integrated TB/HIV service delivery model throughout high-prevalence TB and HIV settings.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We thank the IDI TB working group for their endless motivation to improve TB care in our clinic. In particular we wish to acknowledge the invaluable contributions of Immaculate Ariko, Jennifer Kisakye, Isaac Lwanga and Eli Kyolaba. We also wish to thank IDI senior management, in particular Andrew Kambugu as the head of the prevention, care and treatment department, for their support, Victor Afayo and the rest of the IDI data management and validation team for their efforts in collecting and improving the quality of our data, and the Yale International Bulldog students of 2008 and 2010 (Betsy Lee, Ambika Bushan, Ryan Park, Abraar Karan and Nikia McFadden)

for collecting and validating the 2007 and 2009 TB clinic data. We are grateful to the INTERACT program, in particular to Nadine Pakker, for its support in the realization, training and staffing of the integrated clinic.

Conflicts of Interest and Source of Funding:

This work was done as part of the Infectious Diseases Network for Treatment and Research in Africa (INTERACT) program, financially supported by the Netherlands Organization for Scientific Research – WOTRO Science for Global Development: NACCAP [grant number W 07.05.20100] and the European Union [grant number SANTE/2006/105-316]. SMH receives monetary support through these grants. YCM receives salary support from the National Institutes for Health (grant numbers HHSN272200900050C & RFA-TW-10-008).

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Figure 1.
Schematic of integration of care in both models (2007 and 2009).

Figure 2.

Kaplan Meier survival curve of time to ART initiation stratified by CD4 count at TB diagnosis and by year of TB diagnosis. Log-rank tests of equality of survivor-functions was $P<0.001$, $P=0.207$ and $P=0.121$ for the lowest to the highest CD4 group, respectively.

NOTE ART, antiretroviral therapy; TB, tuberculosis.

Figure 3.

TB treatment outcomes of ART naïve patients, stratified by ART initiation and by CD4 count at TB diagnosis).

Numbers included (from left to right): 17/19 and 8/10; 38/53 and 29/34; 17/19 and 8/10. For the no ART group: 1/20 and 0/14; 3/14 and 10/17; 11/21 and 23/43.

Table 1

Baseline characteristics.

	2007 (n=346)	2009 (n=366)	P-value
Sex (female, %)	174 (50.3)	191 (52.2)	0.613
Age (years, mean [SD])	37.0 (8.7)	36.8 (8.5)	0.804
Type of TB (n [%]) ^a			<0.001
Smear positive	121 (35.0)	124 (33.9)	
Smear negative	101 (29.2)	80 (21.8)	
Extrapulmonary	114 (33.0)	162 (44.3)	
ART at TB diagnosis (n [%])			0.031
ART naïve	243 (70.2)	229 (62.6)	
On ART	103 (29.8)	137 (37.4)	
Median time between ART initiation and TB diagnosis (days [IQR])	229 (76, 552)	394 (105, 1138)	0.006
CD4 counts at TB diagnosis (cells/mm ³ , median [IQR]) ^b			
All	132 (54, 231)	147 (43, 311)	0.146
ART naïve	130 (49, 228)	126 (38, 289)	0.587
On ART	136 (61, 239)	196 (73, 334)	0.084
CD4 counts at TB diagnosis (cells/mm ³ , n [%]) ^b			0.095
<100	97 (28.0)	104 (28.4)	
100-249	91 (26.3)	76 (20.8)	
250	55 (15.9)	84 (22.4)	
CD4 counts at TB diagnosis (ART-naïve patients, cells/mm ³ , n [%]) ^b			0.123
<100	75 (30.9)	79 (34.5)	
100-249	67 (27.6)	51 (22.3)	
250	40 (16.5)	53 (23.1)	

TB, tuberculosis; ART, antiretroviral therapy; SD, standard deviation; IQR, interquartile range.

^aData on type of TB was not available for 10 patients in 2007.^bData on CD4 count at TB diagnosis was not available for 207 patients: 103 in 2007 (61 ART naïve and 42 on ART) and 104 in 2009 (46 ART naïve and 58 on ART); CD4 counts were closest recorded values to the date of TB diagnosis, maximum 90 days pre and 90 days post TB treatment initiation.

Table 2

Overall treatment outcomes and ART initiation in 2007 and 2009.

All patients	2007 (n=346)	2009 (n=366)	P-value
TB treatment outcome (n [%])			<0.001
Completed/Cured	215 (62.0)	251 (68.2)	
Dead	10 (2.9)	56 (15.2)	
Default	104 (30.0)	35 (9.5)	
Failure	0 (0.0)	2 (0.5)	
Transfer-out	14 (4.0)	15 (4.1)	
Other	4 (1.1)	9 (2.5)	
ART naïve patients	2007 (n=243)	2009 (n=228)	P-value
ART initiation (n [%])			0.034
No	82 (33.7)	99 (43.2)	
Yes	161 (66.3)	130 (56.8)	
ART initiation by CD4 category (n [%]) ^a			
<100	55 (73.3)	65 (82.3)	0.181
100-249	53 (79.1)	34 (66.7)	0.128
250	19 (47.5)	10 (18.9)	0.003
Timing of ART initiation (n [%])			<0.001
Intensive phase	37 (23.0)	78 (60.0)	
Continuation phase	88 (54.7)	44 (33.9)	
After completion	36 (22.3)	8 (6.1)	
Time to ART initiation by CD4 category (median [IQR])			
<100	67 (42, 103)	28 (14, 45)	<0.001
100-249	105 (73, 201)	91 (56, 178)	0.186
250	320 (178, 647)	187 (21, 238)	0.010
Outcomes in patients not started on ART (n [%])			0.013
Completed/Cured	24 (29.3)	46 (46.5)	
Death or lost	52 (63.4)	41 (41.4)	
Other ^b	6 (7.3)	12 (12.1)	
Outcomes in patients started on ART (n [%])			0.765
Completed/Cured	124 (77.0)	104 (80.0)	
Death or lost	30 (18.6)	20 (15.4)	
Other ^b	7 (4.4)	6 (4.6)	

^aProportions of patients started on ART in that CD4 count category (proportions not started are not shown); data on CD4 count of 54 ART initiators was not available (34 in 2007 and 21 in 2009); t-tests were performed per CD4 count category.

^bTransfer-out, failure and other (doctor's decision to stop TB treatment).