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Akaki Abutidze **April 20, 2012**

Incidence of Tuberculosis After Initiation of Highly Active Antiretroviral Therapy in Georgia; Survival Rate and Risk Factors of Mortality Among HIV-infected Patients with and without Antiretroviral Therapy

By

Akaki Abutidze

Master of Public Health

The Hubert Department of Global Health

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Carlos del Rio, M.D.

Committee chair

Thesis advisor

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By

Akaki Abutidze

M.D. Tbilisi State Medical University, Tbilisi, Georgia, 2005

Thesis Committee Chair**: Carlos del Rio, M.D.**

An abstract of
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Abstract

Incidence of Tuberculosis After Initiation of Highly Active Antiretroviral Therapy in Georgia; Survival Rate and Risk Factors of Mortality Among HIV-infected Patients with and without Antiretroviral Therapy

By
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Background: There is a lack of data on the impact of antiretroviral therapy (ART) on the incidence of Tuberculosis (TB) and survival of HIV/ TB co-infected patients in high TB burden countries of Eastern Europe. The study objective was to determine TB incidence rate among HIV-infected individuals receiving ART and to estimate the independent association between ART use and mortality among HIV-infected individuals in Georgia in years 2008-2009.

Methods: Retrospective cohort study among all HIV-infected patients entering clinical care at National AIDS Center, Tbilisi, Georgia between 01/2008-06/2009. Factors associated with mortality including ART use were assessed utilizing a logistic regression and Cox proportional hazards model.

Results: Of 410 HIV-infected patients, 110 (26.8%) had TB at initial presentation and 49 (11.9%) had a prior history of TB. CD4 count at time of HIV diagnosis among the 410 HIV-infected patients was less than 200 cells/mm^3 in 180 (45.9%). The mean baseline CD4 count was lower in HIV/TB co-infected patients compared with HIV-infected patients without TB (156.9 cells/mm^3 vs. 339.9 cells/mm^3, P<0.0001).

During a total of 776.6 person-years of observation, 4 new cases of TB were diagnosed. The overall TB incidence rate was 5.15/1000 person-years (95% CI=1.64-12.42). The overall mortality rate among HIV/TB co-infected patients was 27.9% in the ART+ group (n=93) and 82.3% in the ART- group (n=17).

HIV/TB co-infected patients who initiated ART after 2 months of TB diagnosis were 2.6 times as likely to die compared to those who initiated ART within 2 months after TB diagnosis (HR: 2.64, CI=1.03-6.75, P= 0.0425). Survival rates at 1, 2 and 3 years after TB diagnosis were approximately 77%, 75% and 75% in ART+ group, compared to 15%, 0% and 0% in ART- group (long-rank test, p<0.0001). In multivariable analysis "not receiving ART" was associated with a higher probability of death (HR= 7.71, CI=3.36-17.68);

Conclusion: TB is the presenting opportunistic infection in over a quarter of HIV-infected patients in Georgia. Recently published randomized trials suggest that starting ART during TB treatment is associated with significantly increased survival. Implementation of ART during TB treatment is critical to improve outcomes for HIV/TB co-infected patients.

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List of Abbreviations

HIV: Human Immunodeficiency Virus

AIDS: Acquired Immunodeficiency Syndrome

TB: Tuberculosis

MDR TB: Multidrug-Resistant Tuberculosis

PTB: Pulmonary TB

XDR TB: Extensively Drug-Resistant Tuberculosis

LTBI: Latent TB infection

TST: Tuberculin skin test

IGRA: gamma interferon release assay

AFB: Acid-fast bacilli

IPT: Isoniazid preventive therapy

CPT: Cotrimoxazole preventative therapy

MARP: Most at Risk Population

IDU: Injecting drug user

MSM: Men who have sex with men

CSW: Commercial sex worker

PLWHA: People living with HIV/AIDS

ART: Antiretroviral therapy

HAART: Highly active Antiretroviral therapy

NNRTI: Non-Nucleoside reverse-transcriptase inhibitors

NRTI: Nucleoside reverse-transcriptase inhibitor

PI: Protease inhibitor

NTP: National TB control program

PCR: Polymerase Chain Reaction

DOTS: directly observed therapy, short-course strategy

WHO: World health organization

UNAIDS: United Nations Programme on HIV/AIDS

CCM: Country coordinating mechanism

VCT: Voluntary counseling and testing

IDACIRC: Infectious Diseases, AIDS and Clinical Immunology Research Center

IRIS: Immune reconstitution inflammatory syndrome

IRR: Incidence rate ratio

Chapter I

Introduction

International Situation in HIV and TB co-infection

HIV-associated Tuberculosis (TB) remains one of the leading causes of morbidity and mortality worldwide. Of the estimated 33.4 million people living with HIV in 2008, nearly 30% were estimated to have latent or active TB infection [1-3]. At the same time, of the 9.4 million cases of incident TB worldwide, an estimated 1.4 million (15%) were co-infected with HIV in 2008 [3]. HIV infection is the strongest known risk factor for TB. High HIV prevalence rates are significantly correlated with high TB incidence rates [4]. HIV-associated TB accounts for a disproportionate share of TB-associated mortality. In 2008, HIV-associated TB accounted for 29% of deaths among incident TB cases [4]. The estimated case-fatality rate of incident TB was more than 2-fold higher for people infected with HIV (37%) than for those without HIV (16%) [1, 4]. The rapid progression of disease due to the failure of immune responses to restrict the growth of *Mycobacterium tuberculosis*, delayed diagnosis and treatment of TB infection due to atypical presentation and lower rates of sputum smear positivity, delayed diagnosis of HIV infection due to stigma or insufficient uptake of HIV testing in TB clinics, delayed start or lack of access to combination Highly Active Antiretroviral Therapy (HAART), and higher rates of multidrug-resistant (MDR) TB (MDR-TB) are some of the factors associated with the higher case-fatality rates of TB among HIV-infected persons [5-8]. TB is the leading cause of death for people living with HIV in low- and middle-income countries. One-

quarter of the estimated 2 million HIV-related deaths worldwide in 2008, was due to TB [3, 4, 9].

HIV-infected patients are 20-30 times more likely to develop TB than those without HIV infection. There is a variation according to HIV prevalence in TB incidence rate ratio (IRR), the relative risk of TB developing in HIV-infected individuals compared to HIV-negative persons. Countries with a generalized HIV epidemic have a TB IRR of 20.6. Countries with concentrated HIV epidemics (HIV prevalence, 0.1% to 1%) have a TB IRR of 26.7, and countries with a low prevalence of HIV infection (HIV prevalence less than 0.1%) have a TB IRR of 36.7 [1, 4]. The relationship between TB IRR and HIV prevalence likely depends on the interaction between local TB incidence and prevalence rates in the general population, TB case detection rates and other linking factors between HIV and TB transmission which increases the likelihood of co-infection [8, 10].

The increased risk of developing TB as well as modified clinical presentation of the diseases is associated with HIV infection. HIV-infected patients are twice as likely to have sputum smear-negative pulmonary TB (PTB) than HIV-negative patients [11]. Extrapulmonary forms of TB are also common among HIV-positive patients. These factors can lead to delayed TB diagnosis, high mortality and represent significant burden for health systems [11, 12].

HIV/TB co-infected patients have higher mortality rate than those without infection, irrespective of CD4 count [6]. An estimated 500,000 cases of MDR-TB occur annually [7], and prevalence among HIV-infected individuals is similar to HIV-negative persons, since MDR-TB strains are not more transmissible and pathogenic in HIV/AIDS

settings. However, compared to general population, delayed diagnosis and inadequate initial treatment contribute to periodic occurrence of MDR-TB in HIV-infected patients [13]. Therefore, rates of extremely drug-resistant (XDR) TB (defined as MDR-TB plus resistance to any fluoroquinolone and at least one of the three injectable second-line drugs capreomycin, kanamycin, and amikacin) have been increasing, with fatal consequences for HIV-coinfected individuals [14].

Addressing the co-epidemics of TB and HIV

WHO, UNAIDS and the Stop TB Partnership have set as a target - a reduction of TB mortality among HIV-infected people by 50% by 2015, compared with 2004 (the year in which TB mortality among HIV-positive people is estimated to have peaked) [4]. To achieve this goal the collaborative TB/HIV intervention activities recommended by WHO to prevent, diagnose and treat TB among HIV-infected patients [15], include HIV testing of all TB patients, the provision of Antiretroviral Therapy (ART) and co-trimoxazole preventive therapy (CPT) to TB/HIV co-infected patients, HIV prevention services for TB patients, **i**ntensified case-finding among People Living with HIV/AIDS (PLWHA), **I**soniazid preventive therapy (IPT) for people living with HIV who do not have active TB, and **i**nfection control in health- care and congregate settings (the latter three activities are referred to as the "Three Is" for HIV/TB).

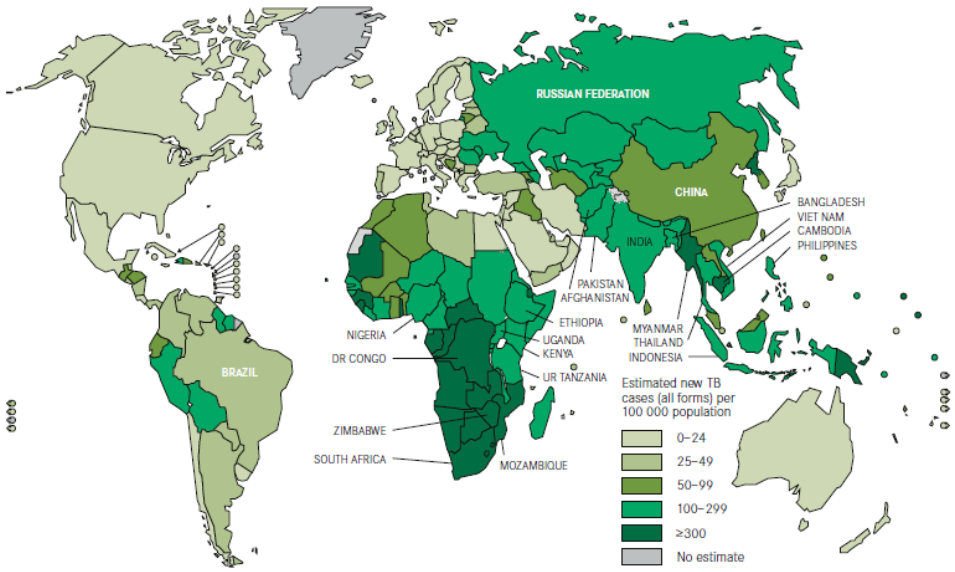
National TB control programs (NTP) are responsible for testing TB patients for HIV and providing CPT to TB/HIV co-infected patients. Intensified case-finding for TB among PLWHA, providing IPT to those without active TB and provision of ART to TB patients living with HIV are typically the responsibility of national HIV programs. If NTPs cannot

provide ART, they are responsible for referring TB/HIV co-infected patients to ART services. According to the WHO latest policy guidance and recommendations, ART should be provided to TB patients co-infected with HIV, irrespective of their CD4 count (and to HIV/AIDS patients with a CD4 cell count <=350) [16].

Global burden of Tuberculosis

TB was declared to be a global emergency by WHO in 1993. In 2010, there were 8.8 million incident cases of TB, 1.1 million deaths from TB among HIV-negative people and 0.35 million deaths from HIV-associated TB [17]. TB incidence in Europe is declining in countries in Western Europe and central Europe, but the burden is still high and increasing in Eastern Europe [18]. Within Europe, the TB incidence varies enormously, from 5 per 100 000 population in Sweden to 181 per 100 000 population in Kazakhstan [20]. Higher rates of TB are associated with socioeconomic crisis, weak health systems, epidemics of HIV and multidrug-resistant TB and poor interventions to control TB among vulnerable populations [18].

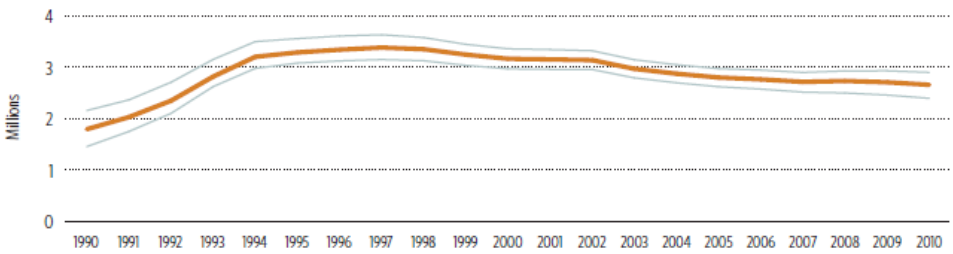
Figure 1: Estimated TB Incidence Rates, 2010. Source: WHO Report 2011.



Global Burden of HIV/AIDS

At the end of 2010, an estimated 34 million people were living with HIV globally [19]. Of them 3.4 million were children under 15 years of age. There were 2.7 million new HIV infections in 2010. Globally, the annual number of newly infected HIV cases is starting to decline, although this varies strongly between regions.

Figure 2: Number of people newly infected with HIV globally, 1990–2010. Source: GLOBAL HIV/AIDS RESPONSE Epidemic update and health sector progress towards Universal Access. Progress report 2011. WHO, UNAIDS, UNICEF.



The annual number of people dying from AIDS-related causes worldwide is also steadily decreasing from a peak of 2.2 million in 2005 to an estimated 1.8 million in 2010. The trends in AIDS-related death also differ. The number of AIDS-related deaths increased more than 10-fold from 2001 to 2010 in Eastern Europe and Central Asia [19]. In the same period, the number of people dying from AIDS-related causes increased by 60% in the Middle East and North Africa and more than doubled in East Asia.

Since 1995, the scale up of ART has averted approximately 2.5 million deaths in low- and middle-income countries with most of the averted deaths having occurred in Sub-Saharan Africa. In addition more than 350,000 children have been prevented from acquiring HIV through the provision of antiretroviral prophylaxis to HIV-infected pregnant women [19].

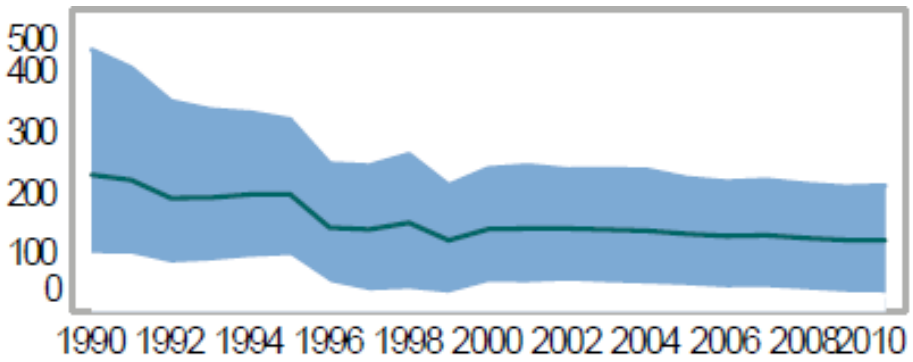
Since 2001, Eastern Europe and Central Asia have had a steep increase in the number of people living with HIV, increasing 250% from an estimated 410,000 in 2001 to 1.5 million in 2010 [19]. Adult HIV prevalence in 2009 was 1% in the Russian Federation and 1.1% in Ukraine. Together those countries account for almost 90% of newly reported HIV infections in this region [20].

The HIV epidemic in Eastern Europe and Central Asia began in the 1990's rapidly spreading among injection drug users (IDUs) and later also among their sexual partners. In Ukraine, 39-50% of the estimated 230,000-369,000 people who inject drugs are believed to be infected with HIV. One third of the 1.5 million to 2 million IDUs in the Russian Federation are living with HIV [20].

TB Epidemiology in Georgia

TB morbidity in Georgia has witnessed an increase between 1992-1996, reaching the highest level in the WHO European region. Compared to 1988, the incidence of TB rose from 29.7 per 100,000 population to 145 per 100,000 population in 1997. After implementation of the National Anti-TB program in 1995-1996, case reporting significantly improved [21]. Although there has been a decline in the TB morbidity rates, the levels are still unacceptably high (107 per 100,000 population, 2010 – WHO, TB profile, Georgia). By the end of 2010, the prevalence rate of TB in Georgia was 118 (27-209) per 100,000 population [22].

Figure 3: Prevalence (rate per 100 000 populations). Source: Georgia Tuberculosis Profile. WHO. www.who.int/tb/data.



After identifying TB as one of the nation's greatest public health threats in the early 1990s, the Ministry of Labor, Health, and Social Affairs, with support from WHO, established in 1995 the NTP of Georgia. In 1997, pilot sites for the Directly Observed Treatment, Short Course (DOTS) implementation were created, and gradually the DOTS strategy, which is the internationally recommended strategy for TB control, was

introduced countrywide. With DOTS case detection rate increased from 58 percent in 2003 to 113 percent in 2007, well over the international target set by WHO of 70 percent. Treatment success rates have also increased steadily since 2003 to reach 75 percent, although it is still below the WHO target of 85 percent (USAID Georgia).

According to WHO, DOTS coverage was 100 percent by 2004 in Georgia. However, providing easy access to TB diagnostics and DOTS services to TB patients is a major challenge. TB prevalence is high among prisoners, who represent a source for the spread of the disease. TB-HIV co-infection rates are low but have increased steadily over the past four years. The TB epidemic in Georgia is characterized by high rates of MDR-TB, including XDR-TB. In 2007, 6.8 percent of all TB cases were MDR-TB [4].

Successful control of TB in Georgia, as elsewhere, requires: (1) rapid identification (case detection) and successful treatment of those with active TB; and (2) stringent infection control procedures to prevent the spread of TB and the development of drug-resistant strains. The Government of Georgia's NTP has made good progress in TB case detection. However, the treatment success rate of 70% is still lower than the WHO target of 85% [21].

The status of HIV/AIDS Epidemic in Georgia

Georgia is categorized as having a low-prevalence HIV epidemic with the estimated HIV prevalence below 0.01%. Based on Spectrum estimation HIV prevalence did not exceed 0.07% by the end of 2008 and 0.08% in 2009. HIV remains concentrated among most-at-risk populations (MARPs) [23].

Since 2006, the number of registered HIV cases has tripled, and, as of the end of March 2012, it reached 3,245. There is a high potential for a rapid rise of HIV infection due to widespread use of injecting drugs and migration between Georgia and neighboring high-prevalence countries such as Ukraine and the Russian Federation. HIV is currently primarily found among the MARPS, which include IDUs; commercial sex workers (CSW); men who have sex with men (MSM); and "bridge" populations - clients of CSW, partners of IDUs, and youth. As of March 2012, injecting drug use accounted for 55% of all cases with a known route of transmission [21].

Estimated HIV prevalence rates among high risk groups are currently below the concentrated epidemic stage (5% or greater within a risk group) but these rates are increasing rapidly. Prevalence rates range from 0.4% to 3.0% among IDUs, 3.7% among MSM, and 0.6% to 1.3% among CSWs (ranges reflect variances in regional prevalence and surveillance) [24]. Most young people do not have accurate knowledge about HIV and some indicators suggest they are initiating illicit drug use and injection at an earlier age than before [25]. Of the 1,940 TB patients who were tested in 2008, 1.3% were HIV-positive. Conversely, approximately 20% to 26% of registered HIV patients also have active TB. Georgia's HIV epidemic is in some part influenced by migration of Georgian citizens to and from Ukraine and the Russian Federation, where HIV prevalence among IDUs ranges from 10% to 66% across cities in Ukraine and from 3% to 70% across cities in the Russian Federation. HIV prevalence in Georgia's conflict region of Abkhazia is almost four times higher than the rest of the country [26].

Several contextual issues influence Georgia's HIV epidemic. Stigma is high and people living with HIV frequently report being rejected by family and friends and even being refused healthcare by health providers. Georgia is in the midst of sweeping changes in its healthcare delivery and financing systems. The state is replacing its vertically aligned specialty care system with a family-medicine-oriented primary care model, privatizing almost all hospitals, and replacing full government funding of healthcare with a new financing system of patient fees, private insurance, and social insurance. These reforms are likely to greatly influence future Government's decisions on HIV prevention and treatment financing and service delivery for people living with HIV[27].

The Policy and Programmatic Response

National efforts have led to a number of key achievements including the establishment of an HIV/AIDS service organizational structure, and the development of an adequate legal, policy and programmatic environment. The State Law on HIV/AIDS was adopted in 1995, with amendments in 2000. In November 2009, a New Law on HIV/AIDS was adopted. Acknowledging that non-discriminatory and protective legislation creates a supportive legal and political environment for scaling up effective HIV/AIDS prevention efforts, initial steps have been taken to revise the anti-drug legislation in Georgia [28]. In response to the "Three Ones" principles that call for the coordination of a National AIDS response around one agreed action framework, the Country Coordinating Mechanism (CCM) became one National Coordinating Authority in May, 2007 taking a leading role in national advocacy for coordinated responses, in development of the

national HIV strategy, policies and legislation, and in monitoring and evaluation of HIV programs nationwide [29].

Since December 2004, Georgia has attained universal access to ART for all registered HIV-infected individuals [29]. Since 2005, Georgia has also ensured universal access to HIV voluntary counseling and testing (VCT) for all pregnant women, including antiretroviral prophylactic treatment free of charge for pregnant women living with HIV/AIDS and their newborns [30].

While the overall HIV prevalence rate in the general population has remained low (0.1%), there are clear indications that prevalence rates in some high risk groups are beginning to increase rapidly and may soon reach the concentrated epidemic stage. A concentrated or more wide-spread HIV epidemic could seriously impede the momentum of Georgia's civil and economic development. Georgia has a rare opportunity, provided to only countries with low prevalence of HIV and at the earliest stages of a potential epidemic, to alter the future course of HIV transmission by conducting a concerted HIV prevention and education effort now. Without more comprehensive prevention outreach efforts, HIV transmission could quickly shift to the general population through heterosexual contact [27].

Rationale:

To quantify the burden of different types of TB that present to care to HIV programs in pre-ART and ART periods is crucial for program managers. It is important to improve our understanding of the epidemiology of TB, the risk factors for developing TB after ART, and risk factors of mortality among HIV/TB co-infected patients. This can help to improve screening strategies to HIV-infected patients, both before and shortly after ART.

TB is one of the most frequent opportunistic infections in HIV-infected patients in Georgia [31]. Factors associated with the occurrence of TB in patients receiving ART and survival rate and risk factors of mortality among HIV/TB co-infected patients with and without ART have never been described in Georgia.

The specific aims of the study were:

1. To describe baseline socio-demographic and clinical characteristics of HIV-infected patients in the country of Georgia between 2008 and 2009.

2. To determine TB incidence rate among HIV-infected individuals receiving ART.

3. To determine the association of socio-demographic and clinical characteristics with mortality among HIV-infected and HIV/TB co-infected patients.

4. To estimate the independent association between ART use and mortality among HIV-infected and HIV/TB co-infected patients.

5. To estimate the independent association between ART use and time to death among HIV-infected and HIV/TB co-infected patients.

Chapter II

Review of the Literature

Impact of HIV on TB manifestations

An increased TB incidence and altered clinical manifestations in the advanced stages are associated with HIV infection. Cutaneous anergy and impaired tissue containment of mycobacteria lead to widespread dissemination of mycobacteria. In patients with latent TB infection, the risk of developing active disease is higher among recently infected persons compared to those with chronic infection but is several hundred-fold higher among persons who acquire HIV. Newly acquired TB infection can rapidly progress to active disease among HIV-positive persons [32].

HIV infection acquired after TB is a significant risk factor for development of active TB due to its effects on immune system. HIV is associated with generalized loss of CD4+ T-lymphocytes, depletion of mononuclear phagocytes, impairment of cell-mediated immune responses to MTB infection, defective chemotaxis and granuloma formation [33].

This increased risk of developing active TB among HIV patients can be decreased by improving the immune status of the patient through highly active antiretroviral therapy (HAART).

Population-based retrospective cohort analysis of adult HIV-infected patients in Brazil conducted by Miranda *et al* (2007) revealed 80% reduction in incidence rate of TB among patients receiving HAART compared to ART-naïve patients.

As described above, HIV co-infection makes clinical presentations and diagnosis of active TB complex. The performance of the Acid-Fast Bacillus (AFB) sputum smear, which is the most widely available TB diagnostic method in resource-constrained settings, becomes limited. As a result of high rates of sputum smear negativity among HIV-infected persons, TB diagnosis can be delayed at HIV/AIDS care settings. This factor significantly increases the risk of TB morbidity and mortality among HIV-infected individuals. Additionally, HIV-infected persons with Latent TB Infection (LTBI) also have a higher risk of reactivation than HIV-uninfected individuals with LTBI [34] due to reduced sensitivity of the tuberculin skin test (TST), especially in those with lower CD4 T-cell counts [34-36].

Screening and Diagnosis of TB in HIV-Infected Patients

Current U.S.P.H.S. guidelines recommend that all HIV-infected persons should be tested for LTBI with either TST or gamma interferon (IFN-γ) release assays (IGRAs) at the time of HIV diagnosis [8, 37, 38].

Chest X-ray (CXR) should be obtained among those patients who test positive in either TST, IFN-γ or IGRA. If the patient has an abnormal CXR or have a normal CXR, but suspicion of TB disease is high (symptomatic and/or originating from countries with high TB burden) the U.S.P.H.S. guidelines recommend that three sputum samples for AFB smear and culture should be obtained in the morning on different days as part of the initial evaluation for suspected pulmonary TB. It is worth mentioning that screening strategy of many national TB programs is based on cough only [39]. Taking into account the fact that majority of HIV-infected individuals with active TB disease are

asymptomatic or do not have specific symptoms, screening based on cough only, will miss many patients whose culture results for TB is positive [39].

In the study by Cain et al., among patients who screened positive for TB but had two negative sputum smears, effective diagnosis was made by only mycobacterial culture [40]. Culture is the "gold standard" for active TB diagnosis, but culture results take 2-6 weeks and this method is not available in many resource-limited settings [41]. In high TB prevalence resource-limited countries, active TB disease is diagnosed by sputum smear microscopy only and culture is not performed. Consequently, the majority of smear negative but culture-confirmed pulmonary TB cases will be missed in these settings.

With regard to extrapulmonary TB among HIV-infected patients, U.S.P.H.S. guidelines recommend AFB smear and culture of tissues or biopsy specimens and blood cultures to diagnose for disseminated TB disease.

At this time, there is a great need for new effective methods for LTBI diagnosis among HIV-infected patients. Currently there are commercially available three IGRAs: QuantiFERON-TB Gold (QFT-G), QuantiFERON-TB Gold In-Tube (QFT-GIT) and T-SPOT.TB, which are approved for the diagnosis of LTBI in HIV-infected patients. These assays detect specific cellular immune response *(*detection of the cytokine gamma interferon) from stimulated T lymphocytes) to antigens expressed in M. tuberculosis. IGRAs are characterized by improved sensitivity and specificity for the diagnosis of TB compared to TST. However, relevant studies concluded that since IGRA rely on immune system, their performance might be impaired in HIV infection [42-44] . Findings from the study by Kaplan J.E., et al. showed that although IGRAs are approved for LTBI

diagnosis, they are not recommended for the diagnosis of active TB among HIV-infected patients. Due to the low sensitivity and negative predictive value of the IGRAs, these assays are not recommended to screen for active TB in high TB prevalence countries. In low TB prevalence countries the specificity and positive predictive value of the IGRAs are not sufficient to rule out active TB disease. Therefore, additional research is needed to determine the utility and cost-effectiveness of these tests in resource-limited settings.

Complexity of treatment of TB and HIV/AIDS co-infection

ART is associated with a decreased incidence of TB. In the study by Lawn et al., evaluating a South African ART program, TB incidence rates decreased during the first 5 years of the program, from 2.25/100 person-years in the first year of treatment to 1.01/200 person years in the fifth year [8, 45]. ART increases CD4 counts, which leads to immunological recovery. Consequently, the incidence of TB decreases particularly in patients with CD4 counts above 500 cells/mm^3 [46-48]. It is worth mentioning that despite ART, HIV-infected patients still had about 10-fold higher risk of TB than HIV-negative patients. Moreover, among HIV-infected patients whose CD4 counts were above 500 cells/mm^3, the incidence rates of TB were still 2-fold higher than those for HIV-negative individuals.

Simultaneous treatment of HIV and TB diseases is challenging. Emphasis has been placed on timing of starting ART, ART regimen and management of the patients for drug-drug interactions, toxicity and diseases outcomes. Based on WHO guidelines the

timing of initiation of ART in these patients should be based on the degree of immunosuppression (CD4 cell counts) [34].

Effect of Highly Active Antiretroviral Treatment (HAART) on tuberculosis epidemiology

HAART revolutionized the care of HIV-infected patients and caused significant reductions in HIV-associated morbidity and mortality, including many of the opportunistic infections. For example, when HIV-infected patients receiving HAART achieved a CD4 counts >200 cells/mm^3, their risk of developing opportunistic infections such as *Mycobacterium avium complex (MAC), Cytomegalovirus, Pneumocystis jirovecii, Toxoplasma gondii, and Cryptococcus neoformans* is generally quite low [48, 49]. However, the data for tuberculosis is not as clear [46, 49].

In HIV-infected patients, even those with minor degrees of immunodeficiency are still at increased risk of developing TB. Accordingly complete normalization of immune function during HAART is required to reduce the risk of TB. However, existing evidence shows that even among patients with good response to HAART, functional immunological deficits usually persist [45, 48], including those specific to *Mycobacterium tuberculosis*.

HAART nevertheless has a major impact on TB incidence among HIV-infected cohorts. Studies conducted in both countries with a low and high prevalence of TB have shown reduction of the risk of TB by 70-90% as a result of HAART use [46, 48, 50-53].

The study by Girardi and colleagues evaluating the burden of TB during 3 years of HAART in cohorts in Europe and North America, showed that HAART resulted in time-dependent reductions in TB incidence during the follow-up. The greatest reduction was observed during the first year of treatment, however the rate continued to decrease with approximately 5-fold reduction between the first and third year [49]. These changes are likely due to increase in CD4 count which are greatest during the first 1-2 years of HAART.

Girardi and colleagues reported high incidence rate of TB in the first 3 months of HAART, which could be explained by the fact that some cases of previously subclinical disease may have manifested as immune reconstitution inflammatory syndrome (IRIS) and also some patients were studied before starting HAART and cultures yielded a positive result only after HAART initiation. In that study low baseline CD4 cell count was an independent risk factor for the development of TB.

A study done in Abidjan led by Seyler and colleagues found that past history of TB was the only independent risk factor for development of TB during HAART [49, 54]. After receiving 6 months or more of TB treatments, 31 patients in the cohort with a past history of TB were cured. However, six patients developed TB during HAART over a median of 26 months of observation. This is an unusual high recurrence rate of TB.

Findings from a similar study conducted in South Africa demonstrated that risk of TB was strongly associated with the level of immunodeficiency before treatment [46].

These data suggest that the risk of TB during the first 3 years of HAART in both low- and high-income countries is associated with the baseline level of immunodeficiency. These findings have crucial implications for antiretroviral treatment programs in low-resources settings.

In a study by Ya Diul M et al., in a sub-Saharan African HIV-infected cohort, TB case-fatality rates were 16-35 % in HIV-infected individuals not receiving ART and 4-9% in HIV-negative patients [55]. Increased mortality in the first month of ART is mainly attributable to TB itself. HIV-infected individuals with the lowest CD4 counts have the highest death rates. A 7 year follow-up study in Malawi showed that before HIV/AIDS treatment, only 11% of patients infected with HIV at TB diagnosis were known to be still alive. About a quarter of deaths were reported within 1 month of TB diagnosis [54].

TB incidence and recurrence in HIV-infected individuals

Several studies from different countries showed that antiretroviral drugs reduce TB incidence in HIV-infected patients by 80% or more [46, 53, 56] with the greatest effect found at the lowest CD4 counts [46]. However, the incidence of TB and recurrence of TB disease among HIV-infected patients with previous HIV/TB co-infection are also high [54].

Findings from the study by Sterling et al., showed that TB risk was highest in the first 3 months of HAART, which might be due to incomplete immune reconstitution (insufficient to prevent disease or unmasking of previously undiagnosed TB). In this study, black race, Hispanic ethnicity, a history of injection drug use, and baseline CD4 lymphocyte count bellow 200 cells/ mm^3 were independent risk factors associated with

TB diagnosis after HAART initiation. The finding that lower CD4 count was significantly associated with early TB risk was consistent with several previous studies [47, 57, 58]. This study supports existing recommendations that screening for TB infection should be focused on HIV-infected patients with low baseline CD4 count or increased HIV-RNA.

In a retrospective cohort study conducted by Bonnet and colleagues [59], which examined the incidence of TB after HAART initiation in HIV-positive patients from five countries with a high TB burden, the authors observed high incidence rates of clinical TB following initiation of HAART, which were likely due to both undiagnosed TB at HAART initiation and subclinical TB developing as a result of IRIS. Their analysis demonstrated high incidence rates of TB among individuals on HAART in five programmes, particularly in the Malawi and Kenya programmes, with pulmonary TB incidence rate of 14.3/100 person-years and 17.6/100 person-years, respectively [59]. The results of this study are in contrast to two recent prospective cohort studies that demonstrated incidence rates of 2/100 person-years (south Africa) and 4/100 person-years (Ivory Coast) respectively [45, 54]. These findings raise operational issues concerning TB diagnosis and treatment on HIV/TB co-infected patients and urgent needs for TB and HIV care integration.

The timing for the initiation of antiretroviral therapy in HIV-infected patients with TB

As mentioned earlier, TB is a major cause of death in HIV-infected patients, especially in resource-limited settings. Despite effective TB treatment, high mortality is observed in

patients with severe immunosuppression [60]. Until recently, there has been a lack of data regarding the timing for starting ART in patients with TB. Most people agreed that ART must be initiated during treatment for TB among HIV co-infected patients [61-63]. However, concerns existed regarding early initiation of ART among HIV-TB co-infected patients, including an increased risk of IRIS, toxic effects of drugs, drug interactions and poor adherence to treatment regimens with a high pill burden.

Recent randomized clinical trials have conclusively answered the question of early versus delayed initiation of ART in adult HIV/TB co-infected patients.

A clinical trial (SAPIT trial) conducted in South Africa by Salim S. Abdool Karim et al., showed that there was no significant difference in the incidence rate of AIDS and death between patients with HIV and active TB infection who received earlier ART vs. later ART. In addition, the authors found a nonsignificant reduction in the incidence of AIDS and death, with a significant increase in the incidence of IRIS in patients with a baseline CD4+ count of less than 50 cells/$mm^{3.}$. However, Havlir and colleagues compared earlier (2 weeks after the initiation of treatment for TB) with later (between 8 and 12 weeks after the initiation of treatment for TB) ART in HIV-infected patients receiving TB therapy [62]. Their study demonstrated non-significant overall reduction in morbidity and mortality associated with AIDS. However, earlier initiation of ART was associated with a lower rate of new AIDS-defining illnesses and death in patients with CD4 cell counts lower than 50 cells/mm^3. Among these patients 15.5% of the patients receiving earlier ART compared with 26.6% of the patients receiving later ART had a new AIDS-defining illness or died (95% CI, 1.5-20.5; P=0.02) [62].

In a third study conducted in Cambodia (CAMELIA trial) conducted by Blanc and colleagues, the researchers determined the effect of earlier (2 weeks after beginning TB treatment) versus later initiation (8 weeks after) of ART on mortality among newly diagnosed 661 HIV/TB co-infected adult patients with no previous exposure to antiretroviral drugs and CD4 counts of 200 cells/mm^3 or less. Results of this study showed that the risk of death was significantly reduced with earlier ART: 18% in the earlier initiation group died compared with 27% in the later-ART group (HR=0.62; 95% CI, 0.44-0.86; P=0.0006). However despite the reduction of HIV mortality, the risk of TB-associated IRIS was significantly increased in the earlier-ART group (HR=2.51; 95% CI, 1.78-3.59; P<0.001) [63].

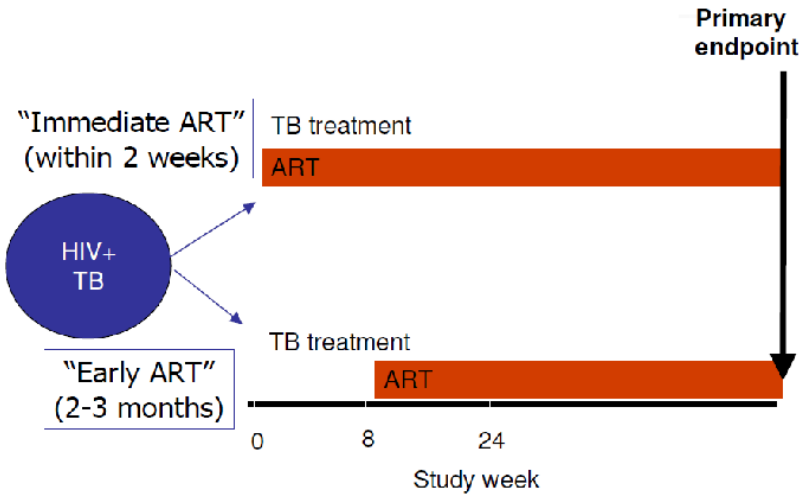
The results of these three randomized clinical trials are complementary. The rate of death in the CAMELIA study (Blank et al.) and the rates of death or AIDS-defining illness in patients with a lower CD4 T-cell counts in the study by Havlir et al., and in the SAPIT study reported by Abdool Karim et al., all suggest that there is a benefit of starting ART earlier rather later ART. "Deferral of the initiation of ART to the first 4 weeks of the continuation phase of tuberculosis therapy in those with higher CD4+ T-cell counts reduced the risks of IRIS and other adverse events related to ART without increasing the risk of AIDS or death" , Dr. Karim and colleagues concluded.

The characteristics of all three clinical trials is shown in the table below. The General schema for CAMELIA, STRIDE and integrated arms of SAPIT is given in Figure 4.

Key characteristics of trials of timing of ART during TB treatment

Study	Setting	Key enrollment criteria	Median CD4 (IQR)	Primary endpoint
CAMELIA	Cambodia	Smear +, CD4<200	25 (10-56)	Death
STRIDE	Multi-national	Clinical TB, CD4<250	77 (36-145)	AIDS or death
SAPIT	South Africa	Smear+, CD4<500	150 (77-254)	AIDS or death

Figure 4: General schema for CAMELIA, STRIDE, and integrated arms of SAPIT.

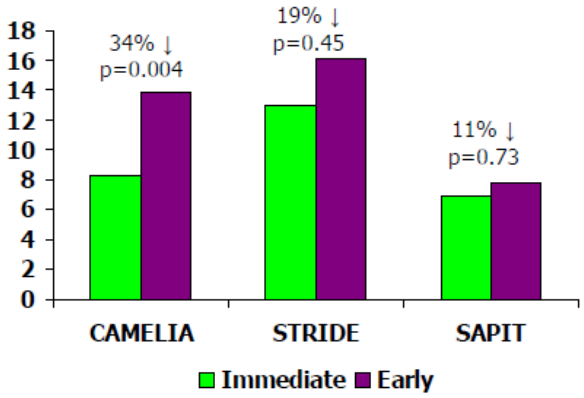


***Source**: TB and HIV co-infection: when to start antiretroviral therapy. Guidelines on when to start therapy in TB and HIV co-infection. Linda-Gail Bekker. CME October 2011 Vol.29 No.10*

All three studies showed significant reduction in death and death/AIDS in patients with CD4 <50 cells/mm^3. CAMELIA: 34% reduction (p=0.004), STRIDE: 42% reduction

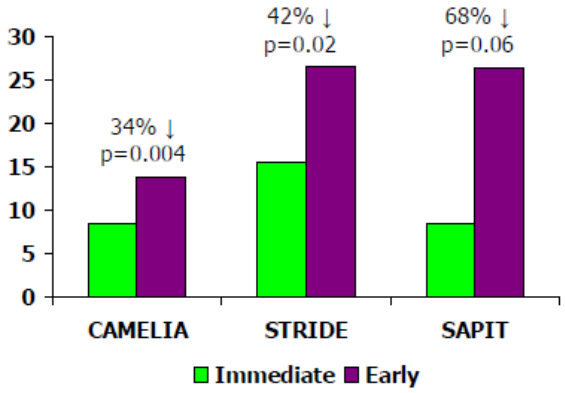
(p=0.02), SAPIT: 68% reduction (p=0.06) (Figs. 2,3). This effect was lost in patients with CD4 >50 cells/mm3 in both STRIDE and SAPIT (Fig. 4).

Figure 5: Effect of ART timing on death (CAMELIA) or death/AIDS (STRIDE, SAPIT)



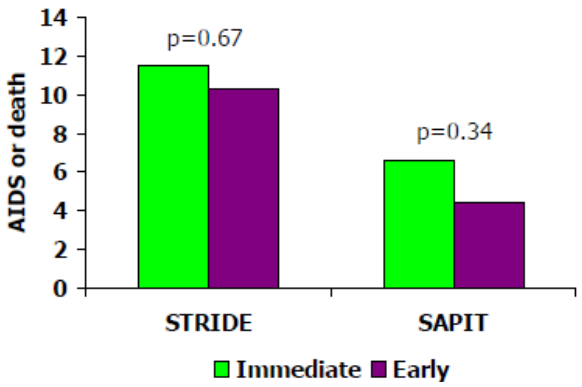
AIDS 2010 abstract THLBB106, CROI 2011

Figure 6: Effects of ART timing in all patients with baseline CD4 counts <50.



AIDS 2010 abstract THLBB106, CROI 2011

Figure 7: Effects of ART timing in all patients with baseline CD4 counts >50.



AIDS 2010 abstract THLBB106, CROI 2011

Chapter III Methods

Study Population

The study population comprised a retrospective cohort of HIV-infected individuals entering clinical care between 01/2008-06/2009 at the Infectious Diseases, AIDS and Clinical Immunology Research center (IDACIRC), in Tbilisi, Georgia, which is the country's referral institution for HIV/AIDS diagnosis, treatment, and care. The medical records of patients were abstracted if the initial facility visit occurred between January 1, 2008 and June 1, 2009 and HIV was diagnosed and confirmed during that period. HIV Western Blot or evidence of HIV viremia (by polymerase chain reaction) were accepted as confirming the HIV diagnosis.

Data abstraction

Variables abstracted included patient demographic characteristics(gender, marital status, education, employment, and usual place of residence), behaviors (tobacco, alcohol and drug use), historical information about TB, imprisonment, routes of HIV acquisition, opportunistic infections at baseline and follow-up visit, other co-morbidities (HBV, HCV and HDV infections, liver cirrhosis, diabetes mellitus, and nephropathy), laboratory variables (baseline CD4 count, plasma HIV-1 viral load and hemoglobin), site of TB, results of acid-fast bacilli (AFB) smear and culture results, susceptibility of M. tuberculosis to anti-TB drugs and ART regimen prescribed and date of initiation of treatment.

Patients were categorized into ART+ group (received ART) and ART- group (did not receive ART) and were followed until death or June 2011.

Ethical considerations

The study was approved by the Institutional Review Board of the Emory University (Atlanta, GA, USA) and the IDACIRC. Patient medical records kept at the facilities contained routinely-collected clinical information and only this data was obtained for the study.

Description of ART Program in Georgia

The National ART Program is coordinated by IDACIRC. Treatment is provided in 5 dedicated facilities countrywide (one national and four regional centers). HIV infected individuals are identified through HIV voluntary counseling and testing (VCT) services and screening programs. Persons with positive screening test results are referred to the IDACIRC for further confirmatory testing and diagnosis (confirmation by Western Blot assay) as well as clinical investigation[29].

HIV infected patients who are not on ART, are evaluated for treatment initiation criteria set by national guidelines every 4 months for timely identification of those in need of treatment. The standard of clinical care of patients receiving ART in Georgia relies on laboratory monitoring of the immune system using CD4 cell counts, of viral suppression using viral loads, and of the development of drug resistance using genotypic testing [26, 30].

All HIV positive individuals eligible for ART based on the national criteria are prescribed an antiretroviral regimen according to the National HIV/AIDS treatment and care guidelines developed based on the protocols and recommendations of WHO, European AIDS clinical society and other organizations. Criteria for the initiation of ART according to the National Guidelines included:

- symptomatic HIV infection (AIDS or severe symptoms),
- CD4 cell count $\leq 200/mm^3$,
- If CD4 cell count is 201-350//mm^3, decision is made upon CD4 decline rate, viral load, and presence of hepatitis co-infection [29].

According to the Georgian National guidelines, the standard of ART monitoring relies upon laboratory monitoring of CD4 count, HIV-1 viral load, and development of resistance based on a resistance-genotype detection when indicated. Virological failure is defined as a plasma HIV-1RNA >400 copies/ml 6 months after initiating ART or plasma HIV-1 RNA >50 copies/ml 12 months after initiating therapy.

At the time that the patients receiving ART were included in our study, treatment was recommended at CD4 cell count $\leq 200/mm^3$ or if the patient had an AIDS defining illness. ART was also recommended if CD4 cell count was $\leq 350/mm^3$, based on the CD4 cell decline rate, a high HIV viral load and co-infection with viral hepatitis.

We classified ART as, (1) a combination of two nucleoside analog reverse-transcriptase inhibitors and one non-nucleoside reverse-transcriptase inhibitor (2 NRTI+1 NNRTI), or

(b). two nucleoside analog reverse-transcriptase inhibitors and one protease inhibitor (2 NRTI+1 PI).

Laboratory Assays. Detection of HIV antibodies was performed by ELISA (third or fourth generation) with further confirmation by Western Blot Assay. HIV-1 RNA level in plasma was measured by commercially available quantitative Polymerase Chain Reaction (PCR) method (Amplicor HIV-1 Monitor test, version 1.5, Hoffmann-La-Roche, Inc.). Since 2006 the Cobas TaqMan HIV-1 test (Real time PCR) has been used for quantification of HIV-1 RNA in plasma, using the Cobas TaqMan 48 Analyser for automated amplification and detection. The test can quantify HIV-1 RNA over a dynamic range of 40-10,000,000 copies/ml. Determination of CD4+ cell count was based on the single-platform immunophenotyping technique using the FACSCalibur flow cytometer (Becton-Dickinson, USA) with four-color direct immunofluorescence reagent MultiTEST CD3/CD8/CD45/CD4. For resistance testing TRUGENE HIV-1 Genotyping Kit with OpenGene DNA Sequencing System (Siemens) was used.

Definitions:

We classified use of ART as begun before TB diagnosis, after TB diagnosis, or never started. Consistent with WHO guidelines for monitoring and evaluating HIV/TB patients, any patient who received at least one dose of ART was considered to be receiving it throughout TB treatment, regardless of adherence or interruptions. We analyzed CD4 count as a categorical rather than a continuous variable. We stratified CD4 count as <50, 51-199, 200-350 and above 350 cells/mm^3. HIV plasma viral load was categorized as ≤100 000 copy/ml and ≥ 100 000 copy/ml.

In terms of residence, urban areas were considered to be the capital city and, where applicable, other big cities with similar socio-economic patterns. Rural areas considered rural districts (small towns and villages). Patients were considered "unemployed" if they had no job, or were a housewife. Education was classified as primary or secondary (including illiterate) and high school or above (college or university).

We have taken a reported smoking rate of less than one pack a day as moderate and a smoking rate of more than one pack a day as excessive. We will use the term "moderate drinkers" to refer to individuals who state that they consume an average of approximately 1 to 4 drinks per day. Excessive alcohol use was defined as five or more drinks on the same occasion on 5 or more days in the past 30 days.

Definition of TB

The following criteria were required for the diagnosis of active TB. Presumptive pulmonary TB: (i) consistent clinical picture (chronic (symptoms lasting three or more weeks) productive cough, haemoptysis, shortness of breath, weight loss, fever, night sweats and fatigue, (ii) presence of AFB mycobacteria on sputum sample or bronchoalveolar lavage, (iii) unsuccessful response to standard antibiotherapy, (iv) successful response to standard antituberculous therapy in one month, and (v) non-microbiological evidence of pneumonia due to any other known pathogen. Presumptive extra-pulmonary TB: (i) Systemic illness with prolonged fever, night sweats, weakness and weight loss. Clinical features of organs involved, e.g. focal lymphadenopathy, cold abscess, sterile pyuria, pericarditis, ascites, pleural effusion, meningitis, arthritis and orchitis, (ii) successful response to standard antituberculous therapy in one month.

"Definitive" TB: Consistent clinical picture and (ii) positive culture for isolation of Mycobacterium tuberculosis of sputum sample or bronchoalveolar lavage ("pulmonary" TB) or positive culture for M. Tuberculosis from cerebrospinal fluid, lymph node aspirate, urine, etc. or histology (e.g. pleural or pericardial biopsy) evidence for extra-pulmonary TB [64].

Smear-positive pulmonary case: A patient with at least two initial sputum smear examinations (direct smear microscopy) AFB-positive; or one sputum examination AFB-positive and radiographic abnormalities consistent with active pulmonary tuberculosis as determined by a physician; or one sputum specimen AFB-positive and culture positive for M. tuberculosis.

Smear-negative pulmonary case: A patient with pulmonary tuberculosis not meeting the above criteria for smear-positive disease. Diagnostic criteria included: at least three sputum smear examinations negative for AFB; and radiographic abnormalities consistent with active pulmonary tuberculosis; and no response to a course of broad-spectrum antibiotics; and a decision by a clinician to treat with a full course of antituberculosis chemotherapy; or positive culture but negative AFB sputum examinations.

Definition of prior, prevalent and incident TB

An episode of TB included any individual who started TB treatment irrespective of smear or culture positivity, similarly it encompassed any notified case of TB in the cohort. Prior TB was defined as any recorded episode of TB treatment before the study enrollment. Prevalent TB was defined as patients receiving TB treatment at ART initiation, including

those already on treatment at programme entry and those diagnosed by pre-ART screening. Incident TB was any new episode of TB treatment after ART initiation.

Definitions of treatment outcomes (WHO):

- **Cured**: A patient who was initially smear-positive and who was smear-negative in the last month of treatment and on at least one previous occasion.
- **Completed treatment**: A patient who completed treatment but did not meet the criteria for cure or failure. This definition applied to pulmonary smear-positive and smear-negative patients and to patients with extrapulmonary disease.
- **Died**: A patient who died from any cause during TB treatment.
- **Failed**: A patient who was initially smear-positive and who remained smear-positive at month 5 or later during TB treatment.
- **Defaulted**: A patient whose TB treatment was interrupted for 2 consecutive months or more.
- **Successfully treated**: A patient who was cured or who completed TB treatment.

Lost to follow-up was defined as no clinic attendance on two consecutive occasions (6 months) and limited tracking of those defaulting treatment was available with telephone calls.

Statistical Analysis:

Categorical variables are described as number (%), and continuous variables as mean (standard deviation (SD)) or median (interquartile range (IQR) according to their distribution). To compare categorical variables the chi-square or Fisher' s exact test were used. Two-sample t-test was used for comparison of continuous variables. These tests were 2-sided. The P values <0.05 was considered statistically significant.

The incidence density rate (IDR) of TB was defined as the number of HIV-infected patients with incident active TB per 1000 patient-years of at-risk follow-up. The at-risk period began at the time of ART initiation and continued to the date of study termination, patient' death, loss of follow-up or the date of the first episode of active TB.

The survival of HIV-infected patients as well as patients with HIV/TB co-infection was determined by the method of Kaplan-Meier, considering survival time in months. Survival time was defined as the time in months between the date of the study entry (for entire HIV-infected cohort) or the date of TB diagnosis (for HIV/TB co-infected patients) and one of the following, whichever the first: date of death, date of lost to follow-up, or the date of the end of the study.

To evaluate the independent effect of ART upon patient mortality, logistic regression models were used. To estimate the independent association between ART and time to death, Cox proportional hazard models were utilized. Graphical and Goodness-of-fit approaches were used for assessing the PH assumption. The CD4+ count was dichotomized as less than 50, 50-199, 200-350 and $\geq$200 cells/mm^3 for both entire cohort

as well as HIV/TB co-infected cohort. HIV viral load was dichotomized as less than 100000 copy/ml and ≥100000 copy/ml. Patient age and hemoglobin level were dichotomized at the mean value for both cohorts. The only covariates were included in the final multivariable model were those significantly associated with the risk of dying and ART use in the bivariate analysis ($p<0.2$) and those that were based on prior evidence. The results of the final model were expressed in terms of Odds Ratio (OR) or Hazard Ratio (HR) and 95% confidence intervals (CI). Analysis was performed with SAS version 9.3 software (SAS Institute, Inc., Cary, NC, USA).

Chapter IV

Results:

Socio-demographic and Clinical characteristics of HIV-infected patients:

A total of 410 HIV-infected patients enrolled at the IDACIRC between 01/2008 -06/2009 were included in the study. However, between January 2008 and June, 2011(study end date), 271 HIV-infected patients received ART. The mean age of the 410 HIV-infected patients was 40.2 years; 289 (70.5%) were male, and the educational level of 350 (85.4%) was less than college/university. At the baseline visit, TB was diagnosed in 110 (26.8%), including pulmonary TB in 90 (21.9%), extrapulmonary in 20 (1.9%), and both pulmonary and extrapulmonary in 4 (1.0%). Of the 90 patients with pulmonary disease, 70 (64.2%) were confirmed by sputum smear and culture. MDR-TB was diagnosed in 13 (11.5%). Forty nine HIV-infected patients had a previous history of TB. The median follow-up time of all HIV-infected patients was 26.5 months. The distribution of antiretroviral regimens in ART+ group was as follows: 2 NRTI+NNRTI in 259 (95.2%) and 2 NRTI+PI in 13 (4.8%) (Table 1). The mean (IQR) CD4 cell count of the 410 patients was 292.7 (95.5-445.0) cells/mm^3 and the mean (IQR) plasma HIV viral load was 436769.5 (22100-384000) copies/ml. Of 410 HIV-infected patients, 180 (45.9%) presented with CD4 count less than 200 at the time of HIV diagnosis.

The median time from baseline visit to ART initiation for the 271 HIV-infected patients who initiated ART was 1 month (IQR 0.4 – 9.6 months). The mean time from baseline visit to ART initiation for HIV-infected patients with CD4 count <200 cells/mm^3 was

significantly lower than those with CD4 count >=200 cells/mm^3 (1.7 months and 10.9 months respectively, P<0.0001).

The mean baseline CD4 count was significantly lower in HIV/TB co-infected patients compared with HIV-infected patients without TB (156.9 cells/mm^3 vs. 339.9 cells/mm^3, P<0.0001). Moreover, significantly more HIV/TB patients had severe immunosupression (CD4 count fewer than 50 cells/mm^3) compared to those without TB at initial presentation (33.4% vs. 12.7%, P<0.0001). Co-infection with hepatitis C virus, liver cirrhosis and opportunistic infections were more prevalent among HIV/TB co-infected patients (P=0.0011, 0.0055, and 0.0105 respectively). HIV/TB patients were also significantly more likely to have a previous episode of TB than those patients without TB (30% vs. 16%, P<0.0001). Baseline socio-demographic and clinical characteristic distribution of HIV-infected patients according to the presence of TB is presented in Table 1b.

During a total of 776.6 person-years of observation, 4 new cases of TB were diagnosed. The overall TB incidence rate was 5.15/1000 person-years (95% CI=1.64-12.42). All 4 cases were pulmonary and definite. MDR-TB was found in 2 patients. The median time from time of ART initiation to TB diagnosis was 17 months (IQR: 7.6 – 19.9 months). All 4 patients were diagnosed with TB after more than 6 months of ART.

Association between Socio-demographic and clinical characteristics and ART use among HIV-infected patients:

Socio-demographic and clinical characteristics of the 410 HIV-infected patients were described and compared between the ART+ (n=271) and ART- (n=139) groups as shown in ***Table 4***. The patients in ART+ group were older (P=0.0098). Patients with CD4 count less than 350 cells/mm^3 were more commonly prescribed ART than those with count ≥ 350 cells/mm^3 (P<0.0001). Drug use and co-infection with Hepatitis B and C were more prevalent in ART+ group compared to ART- group (P=0.0793, P=0.0338 and P=0.0003 respectively). Also, significantly more patients in ART+ group had a previous episode of TB and presented with opportunistic infections (p=0.0057 and P=0.0006 respectively). Patients receiving ART were more likely to have TB at baseline visit than those not on ART (P<0.0001).

Association between Socio-demographic and clinical characteristics and mortality among HIV-infected patients:

Bivariate analysis of factors associated with the risk of dying showed that patients who never started ART were more likely to die compared to those who received treatment, however this association was not statistically significant (OR=1.28, CI=0.75-2.17, p=0.3654). Male patients more commonly died compared to female patients (OR=2.56, CI=1.29-5.08, P=0.0055). Over 40 age group was more likely to have higher mortality (OR=2.21, CI=1.28-3.82, p=0.0046).

Patients with baseline CD4 count less than 50 as well as 50-200 cells/mm^3 and low hemoglobin level were more likely to have increased risk of death (OR=13.34, CI= 5.71-31.1, p<0.0001, OR=3.14, CI= 1.33-7.39, p=0.0088 and OR=3.69, CI=1.89-6.85, p<0.0001 respectively). High HIV-1 viral load was also associated with increased risk of death (OR=3.34, CI=1.76- 6.36, p=0.0002). Illicit drug use, co-infection with hepatitis C and liver cirrhosis were significantly associated with a higher risk of death (OR=2.49, CI=1.19-5.23, p=0.0127; OR=1.65, CI=0.97-2.79, p=0.0609 and OR=6.29, CI=2.91-14.08, p<0.0001 respectively). The excess risk of death was significantly associated with HIV acquisition through drug use (OR=2.19, CI=1.27-3.77, P=0.0045). Diagnosis of TB and other opportunistic infections at baseline visit were also associated with increased risk of death (OR=5.14, CI=2.99-8.83, P<0.0001 and OR=7.74, CI=4.43-13.53, P<0.0001 respectively). Paradoxically, MDR-TB was associated with a lower risk of dying (OR=0.31, CI=0.06-1.47, P=0.1247). History of previous TB episode was protective against death, however the association was not significant (OR=0.65, CI=0.26-1.59, p=0.339***. (Table 3).***

Before we built the multivariable logistic and Cox proportional hazard regression models, multicollinearity diagnostics was conducted to identify the multicollinearity between risk factors. We found that variables illicit drug use and hepatitis C (which were significantly associated with both ART and mortality in bivariate analysis (***Tables 2 and 3)*** were highly correlated and accordingly we decided to include only hepatitis C in the final multivariable model.

Multivariable Analysis (Logistic and Cox proportional hazard regression Analysis) for entire cohort:

We carried out multivariable logistic regression and Cox proportional hazard regression analysis to examine association between ART and death/time to death while controlling other factors. Final multivariable logistic regression and Cox proportional hazard regression models included variables those significantly associated with the risk of death and ART use in the bivariate analysis. Although a previous history was not associated with the risk of death, considering clinical relevance we included this variable into the final model (**Table 5**).

In multivariable logistic regression analysis, controlling for factors associated with death, not receiving ART was strongly associated with increased mortality (OR=7.01 CI= 2.76-18.20). Other factors which remained independently associated with death in the final model included baseline CD4 count <50 cells/mm^3(OR=3.52, CI=1.02-12.13), diagnosis of TB at baseline visit (OR=8.49, CI= 3.69-19.53), opportunistic infections (OR=8.40, CI=3.62-19.57) and a previous history of TB (OR=0.16, CI=0.05-0.55) **Table 5.**

The probability of survival among HIV-infected patients who received and did not receive ART was estimated by the Kaplan-Meier method and is shown in ***Figure 8***. Survival rates at 1, 2 and 3 years were approximately 90%, 85% and 85% in ART+ group and about 80%, 78% and 78% in ART- group; however survival difference was not significant (long-rank test, p= 0.1045). The Cox proportional hazard model was used to compare chance to death between the patients in ART+ group and ART- group. We

found that when controlling those factors (confounders) significantly associated with both ART and death in bivariate analysis, "not receiving ART" was associated with a higher probability of death (HR=8.27, CI= 4.13-16.55); That is, patients who did not receive ART were about eight times as likely to die compared with patients who were treated. The other risk factors associated with a higher probability of death were CD4 count less than 50 cells/mm^3 (HR=4.68, CI=1.57-13.00), CD4 count between 50-199 cells/mm^3 (HR=4.03, CI=1.47-11.03), HIV viral load level ≥ 100 000 copy/ml (HR=2.20, CI= 1.12-4.32), diagnosis of TB at baseline visit (HR= 3.63, CI=2.02-6.52), opportunistic infections at baseline visit (HR=3.85, CI=2.05-7.19) and a previous history of TB (HR= 0.23, CI=0.09-0.62) ***Table 5.***

Baseline Socio-demographic and clinical characteristics of HIV/TB co-infected patients:

As mentioned above, 110 (26.8%) HIV-infected patients had TB at initial presentation. Of them 33 (30%) had a previous history of TB. Ninety three HIV/TB co-infected patients received ART during TB treatment and 17 did not. The median follow-up time for HIV/TB co-infected patients was 22.5 months ***(Table 1a).***

The median time from baseline visit to ART initiation for 93 HIV/TB co-infected patients who started ART was 1.5 month (IQR 0.6 – 5.3 months). The mean time from baseline visit to ART initiation for HIV/TB co-infected patients with CD4 count <200 cells/mm^3 was significantly lower than those with CD4 count >=200 cells/mm^3 (2.9 months and 10.4 months respectively, P<0.0001). Of 110 HIV/TB co-infected patients, 81 (76.4%)

presented with CD4 count less than 200 at the time of HIV diagnosis. Also it is worth mentioning that severe immunosuppression at the time of TB diagnosis was common among these patients (baseline CD4 count <50 cells/mm^3 was observed in 53 (48.2%) patients).

The overall mortality among HIV/TB co-infected patients was 27.9% in ART+ group and 82.3% in ART- group P<0.0001). The median time from TB diagnosis to death for 110 HIV/TB co-infected patients was 3.6 months (IQR: 1.3 – 5.8 months).

The mean CD4+ count was significantly lower among HIV/TB co-infected patients in ART+ group compared to those in ART- group (134.4 cells/mm^3 and 297.1 cells/mm^3, P=0.0029). The patients receiving ART had lower baseline hemoglobin level (P=0.0127). Also, significantly more HIV/TB co-infected patients in ART+ group had hepatitis B and C infections compared to those not receiving treatment (P= 0.0325 and P=0.0292 respectively) ***Table 6.***

Association between Socio-demographic and clinical characteristics and mortality among HIV/TB co-infected patients

Bivariate analysis of factors associated with the risk of death showed that mortality was significantly associated with not receiving ART (P<0.0001), low baseline CD4 count (P=0.0434), low baseline hemoglobin level (P=0.003), illicit drug use (P= 0.1905), liver cirrhosis (P=0.009), a previous history of TB (P= 0.0026) and baseline opportunistic infections (P= 0.0016) ***Table 7***.

Multivariable Analysis (Logistic and Cox proportional hazard regression Analysis) for HIV/TB co-infected cohort:

The risk factors significantly associated with both ART use and mortality from bivariate analysis ***(Tables 6 and 7)*** were included in multivariable logistic and Cox proportional Hazard regression models. In the final multivariable logistic regression model, controlling for factors associated with death, not receiving ART was independently associated with increased mortality (OR=13.9, CI= 2.54-76.44) ***Table 8.***

The mortality rates among 110 HIV/TB co-infected patients who initiated ART at different time points after TB diagnosis are shown in ***Table 9***. At a median follow-up duration of 22.5 months, patients who initiated ART after 2 months of TB diagnosis were 2.6 times as likely to die compared to those who initiated ART within 2 months after TB diagnosis (HR: 2.64, CI=1.03-6.75, P= 0.0425). Stronger effect of ART was found in patients who started ART after 6 months of TB diagnosis compared with those who initiated ART within 6 months after TB diagnosis (HR: 7.93, CI=1.07-58.97, P=0.0431).

The probability of survival among HIV/TB co-infected patients who received and did not receive ART estimated by the Kaplan-Meier method is shown in ***Figure 9.*** Survival rates at 1, 2 and 3 years after TB diagnosis were approximately 77%, 75% and 75% in ART+ group, compared to 15%, 0% and 0% in ART- group and this difference was highly significant (long-rank test, $p<0.0001$). The Cox proportional hazard model was used to examine the independent effect of risk factors on time to death among HIV/TB co-infected patients. We found that when controlling those factors (confounders)

significantly associated with both ART and death in bivariate analysis, “not receiving ART” was associated with a higher probability of death (HR= 7.71, CI=3.36-17.68); That is, patients who did not receive ART were about eight times as likely to die compared with patients who were treated. We found no other covariates to be independently associated with time to mortality in final multivariable Cox proportional model.

Chapter V

Discussion

Patients with HIV infection attending the HIV/AIDS clinics in Georgia during the period January 2008 – June 2009 and did not receive ART had a short survival time. About a third of patients had TB and other opportunistic infections at initial presentation and half of the entire cohort had immunosuppression. In the present study, most patients presented late with low CD4 count (less than 200 cells/mm^3). Most CD4 cell counts were performed when the patients attended at the HIV/AIDS clinic, suggesting that improved screening and VCT is necessary to prevent advanced-stage HIV among TB patients.

In our cohort, the prevalence of hepatitis B was 30.5%, and of hepatitis C was 51.2%. The high prevalence of hepatitis B and/or hepatitis C virus co-infection among HIV-infected patients has previously been reported in Georgia [65]. Hepatitis co-infected with HIV makes ART more complicated. Therefore a proper and early management of hepatitis in parallel with initiation of ART is needed to prevent hepatic-related death among AIDS patients.

To date, combined ART has been widely used for the treatment for HIV-infected patients. A number of studies demonstrate the impact of ART on the survival outcomes in HIV-infected patients with successful immune restoration and reductions in morbidity and mortality [66-68]. However, the data regarding outcomes of concurrent treatment for HIV/AIDS and TB are still limited [69, 70].

The present study is the first cohort study to date in Georgia, documenting improved survival among HIV-infected patients. Herein we can demonstrate the marked difference of survival rate between entire cohort of HIV-infected patients as well as HIV/TB co-infected patients who received and did not receive ART. For HIV/TB co-infected patients who did not receive ART, the majority of them died during the initial phase of TB treatment. The results from our study point out that ART is crucial to improve survival in this population.

For the concurrent treatment of HIV/AIDS and TB, several major concerns should be considered, including optimal timing to initiate ART after TB treatment, drug-drug interactions between TB drugs and ARV drugs, drug toxicities, and IRIS of TB after ART. Previous retrospective studies have shown early initiation of ART in severely immunosuppressed HIV-infected patients with TB is associated with decreased mortality. Dean GL. and colleagues documented clear benefits in prescribing ART to patients newly diagnosed with TB [67]. Another study showed favorable outcomes of both TB and HIV/AIDS treatment when ART was initiated within 2 to 4 months of TB treatment [71].

The potential for ART to induce IRIS in antiretroviral therapy-naïve patients with known active TB disease initially led many experts to recommend deferring ART until the patient had completed at least 2 months of anti-TB therapy. Although concern exists for IRIS in this setting, recent data from three randomized trials – the SAPIT, CAMELIA, and STRIDE [62, 63, 72] studies – have demonstrated that initiation of ART shortly after initiation of anti-TB therapy is associated with lower mortality, especially among HIV-infected persons with a baseline CD4 count less than 50 cells/mm^3. These findings

correspond with the high mortality rates documented in programs that delayed initiation of ART until 2 months or longer after initiation of anti-TB therapy [62].

Our results demonstrate that ART should be initiated within 2 months after TB diagnosis. The early lethality in HIV/TB co-infected patients who received ART after 2 months of TB diagnosis was high (34.8%, 16/46). Also there was a statistically significant difference of mortality between the patients who initiated ART before and after 6 months of TB diagnosis. Accordingly, improvement of survival rate would be achieved by early initiation of ART within the first 6 months of TB diagnosis.

The present study demonstrated that HIV-infected TB patients who did not receive ART had approximately eight times the risk of death compared to those received ART. We found high mortality rates during TB treatment for HIV-infected TB patients and that most patients had markedly advanced immunosuppression. Mortality rates increased as CD4 count declined in our study, yet ART was associated with increased survival at all levels of CD4 count.

Several studies in the United States [73-75] have shown that the median survival time of HIV/TB co-infected patients who did not receive ART, can range from 16 to 23 months depending upon prior history of other AIDS-defining diseases. These studies suggest that these patients have much better prognosis than our patients who did not receive ART.

The concurrent use of ART with anti-TB therapy in HIV/TB co-infected patients significantly reduces the risk of death in the short and long term compared with the risk of death for those receiving only anti-TB treatment. Also, the use of simultaneous ART

and anti-TB therapy significantly reduces the risk of new opportunistic infections compared with that of TB-HIV patients receiving anti-TB therapy alone [76]. It is also worth mentioning that the patients who derive greatest benefits from concomitant therapy are the most immunosuppressed (CD4+ less than 100 cells/mm^3).

The findings of multiple retrospective studies and prospective randomized trials provide compelling evidence that initiation of ART should not be delayed pending completion of TB treatment for HIV/TB co-infected individuals. The most recent WHO guidelines for antiretroviral therapy in adolescents and adults recommend the initiation of HAART between 2 and 8 weeks subsequent to the initiation of TB therapy for severely immunosuppressed co-infected individuals, as defined by a CD4 count <200 cells/mm^3 [76].

Even though the present study was observational rather than a randomized trial, we believe that its findings are valid and relevant for public health policy in Georgia and other developing countries. Observational studies with covariate measurements, adequate sample size and statistical rigor can produce reliable estimates of the impact of an intervention in a population [77]. Using both multivariable logistic and Cox proportional hazard regression analysis, we found convincing evidence that most, if not all, HIV/TB co-infected patients in Georgia should receive ART during TB treatment to reduce mortality.

In this study we observed high incidence of TB during ART period, 5.15 per 1000 person-years. All 4 patients who developed TB after ART initiation had poor adherence

to ARV drugs. The observed high incidence of TB during ART period, and higher incidence of TB in patients with lower CD4 count levels, reflects the high prevalence of TB in Georgia and the increased risk of disease in immunocompromised patients. Overall estimates during the ART period corresponds to those from previous studies conducted in resource-limited settings [48]. Because of the limitations due to a small sample size, we were limited to examine association between risk factors and incidence of TB after ART initiation.

Our study is subject to important limitations. First, considering the nature of retrospective study, the patients' clinical condition may be underestimated and social-economic status was not routinely recorded. Although we adjusted for demographic, clinical and laboratory variables, the association between ART use and survival after TB diagnosis could be confounded by other factors which were not included in our analysis. Some potential risk factors, such as patterns of tuberculin skin test, were not included in the present study. Also, we did not include baseline socio-economic status of patient in the model of mortality analysis. A second limitation is the low sample size and few number of incident cases during ART, which did not allow us to investigate risk factors associated with TB occurrence. Third, future prospective studies are needed to confirm interpretation of the optimal timing to ART, because as mentioned above there are several limitations such as current clinical status of patient, decision of attending physician and socio-economic status.

In conclusion this study demonstrated the significant increase of survival in patients co-infected with HIV and TB who received ART. ART should be initiated as soon as

possible (within the first 8 weeks) after starting anti-TB therapy. It is crucial to expand use of ART to improving the survival of HIV-infected TB patients.

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Tables and Figures

Table 1. Socio-demographic and Clinical Characteristics of the Study Population (n=410)

Continuous variables	**Mean (SD*) [IQR*]**
Age in years	40.2 (10.0) [35.0-46.1]
Baseline CD4 cell count (cells/mm^3)	292.7 (255.1) [95.5-445.0]
Baseline HIV plasma viral load (copies/ml)	436769.5 (104409.9) [22100-384000]
Baseline hemoglobin (g/L)	119.8 (22.8) [102-138]
Categorical variables	**Number (%)**
Gender	
male	289 (70.5)
female	121 (29.5)
Marital Status	
Single	114 (27.8)
Divorced	18 (4.4)
Widowed	18 (4.4)
Married	260 (63.4)
Education	
High school	207 (50.5)
Illiterate	10 (2.4)
Primary or secondary school	133 (32.4)
University	60 (14.6)
Employment	
employed	381 (92.9)
unemployed	29 (7.1)
Residence	
urban	193 (47.1)
rural	217 (52.9)
Tobacco use	
< 1 pack daily	225 (54.9)
>= 1 pack daily	17 (4.2)
no tobacco use	168 (40.9)
Alcohol use	
Excessive	15 (3.7)
Moderate	199 (48.5)
no alcohol use	196 (47.8)
Illicit drug use	38 (9.3)
yes	38 (9.3)
no	372 (90.7)

Table 1. Socio-demographic and Clinical Characteristics of the Study Population (n=410)	
Methadone use	
yes	4 (0.9)
no	406 (99.1)
Diabetes mellitus	
yes	2 (0.5)
no	408 (99.5)
HBV Infection	
positive	125 (30.5)
negative	285 (69.5)
HCV infection	
positive	210 (51.2)
negative	200 (48.8)
HDV co-infection	
positive	3 (0.7)
negative	407 (99.3)
Liver cirrhosis	
yes	27 (6.6)
no	383 (93.4)
Nephropathy	
yes	3 (0.7)
no	407 (99.3)
Imprisonment	
yes	47 (11.5)
no	363 (88.5)
HIV transmission route	
Heterosexual	172 (41.9)
Homosexual	6 (1.5)
IDU	211 (51.5)
Transfusion	1 (0.2)
Maternal infection	14 (3.4)
Other transmission	6 (1.5)
Previous history of TB	
Pulmonary	41 (10.0)
Extra-pulmonary	8 (1.9)
no history of TB	361 (88.1)
TB diagnosis at baseline visit	
pulmonary	90 (21.9)
extra-pulmonary	20 (5.1)
no TB at baseline	300 (73.0)

Table 1. Socio-demographic and Clinical Characteristics of the Study Population (n=410)	
Opportunistic infections at baseline visit	
Cryptococcal disease	10 (2.4)
*PCP**	5 (1.2)
Toxoplasmosis	9 (2.2)
HIV-related lymphoma	3 (0.7)
Kaposis Sarcoma	2 (0.5)
Visceral Leishmaniasis	1 (0.2)
Recurrent pneumonia	10 (2.4)
Herpes zoster	5 (1.3)
Orolabial herpes	2 (0.5)
HIV wasting syndrome	26 (6.4)
Oropharyngeal Candidiasis	24 (5.9)
Other	7 (1.7)
no opportunistic infection	306 (74.6)
ART	
yes	271 (66.1)
no	139 (33.9)
ART Regimen (n=271)	
2 NRTI's + NNRTI	259 (95.2)
2 NRTI's + PI	13 (4.8)
Patient follow-up	
Alive	282 (68.8)
Death	70 (17.1)
Loss to follow-up	58 (14.1)
Sites of TB	
Pulmonary	91 (79.82)
CNS*	11 (9.65)
Lymph node	12 (10.53)
no TB	296 (72.2)
Anti-TB drugs sensitivity	
Drug sensitive	100 (88.5)
MDR-TB*	13 (11.5)
Incident TB cases (during ART period)	4
Median follow-up time	26.5 months

NOTES:
SD: Standard deviation
IQR: Interquartile range
PCP: Pneumocystis pneumonia
CNS: Central nervous system
TB: Tuberculosis
ART: Antiretroviral therapy
MDR-TB : Multi-drug-resistant tuberculosis
NRTI: Nucleoside analog reverse-transcriptase inhibitor
NNRTI: Non-nucleoside reverse-transcriptase inhibitor
PI: Protease inhibitor

Table 1a. Socio-demographic and Clinical Characteristics distribution of HIV-infected patients according to the presence of TB

Risk Factors	**Positive**	**Negative**	**Total**	**P-value**
	(n=110)	**(n=300)**	**(n=410)**	
Continuous variables				
Age in years				
mean	42.9	39.2	40.2	0.0007
median	42.1	39.1	40.1	
interquartile range	37.3-48.1	33.1-45.1	35.0-46.1	
Baseline CD4 cell count				
mean	156.9	339.9	292.7	<0.0001
median	88	295	219.5	
interquartile range	47-200	146-502	95.5-445.0	
Baseline HIV plasma viral load				
mean	780619.3	321342.9	436769.5	0.0002
median	310227	86142	105459.5	
interquartile range	47159-738000	16200-290000	22100-384000	
Baseline hemoglobin				
mean	111.1	122.9	119.8	<0.0001
median	111	125	122	
interquartile range	91-127	108-140	102-138	
Follow-up time				
mean	18.2	24.6	22.9	<0.0001
median	22.5	27.6	26.5	
interquartile range	3.4-30.9	17.7-34.0	11.6-33.1	
Categorical variables		**Number (%)**		
Age				
>40	35 (31.8)	158 (52.7)	193 (47.1)	0.0002

Table 1a. Socio-demographic and Clinical Characteristics distribution of HIV-infected patients according to the presence of TB				
Risk Factors	**Positive**	**Negative**	**Total**	**P-value**
	(n=110)	**(n=300)**	**(n=410)**	
<=40	75 (68.2)	142 (47.3)	217 (52.9)	
Baseline CD4 cell count				
<50 cells/mm^3	37 (33.4)	38 (12.7)	75 (18.3)	<0.0001
50-199 cells/mm^3	47 (42.7)	76 (25.3)	123 (30.0)	
200-350 cells/mm^3	16 (14.5)	66 (22.0)	82 (20.0)	
>350 cells/mm^3	10 (9.1)	120 (40.0)	130 (31.7)	
Baseline HIV viral load				
>= 100,000 copy/ml	68 (71.6)	130 (45.9)	198 (52.4)	<0.0001
<100,000 copies/ml	27 (28.4)	153 (54.1)	180 (47.6)	
Baseline hemoglobin				
<120 g/L	61 (61.6)	114 (40.0)	175 (45.6)	0.0002
>=120 g/L	38 (38.4)	171 (60.0)	209 (54.4)	
Gender				
male	90 (81.8)	199 (66.3)	289 (70.5)	0.0023
female	20 (18.2)	101 (33.7)	121 (29.5)	
Marital Status				
Married	76 (69.1)	220 (73.3)	296 (72.2)	0.3962
Not married	34 (30.9)	80 (26.7)	114 (27.8)	
Education				
Primary and secondary school	45 (40.9)	98 (32.7)	143 (34.9)	0.1212
High school and above	65 (59.1)	202 (67.3)	267 (65.1)	
Employment				
no	103 (93.6)	278 (92.7)	381 (92.9)	0.7347
Yes	7 (6.4)	22 (7.3)	29 (7.1)	
Residence				
rural	67 (60.9)	150 (50.0)	217 (52.9)	0.0502
urban	43 (39.1)	150 (50.0)	192 (47.1)	
Tobacco use				
Yes	74 (67.3)	168 (56.0)	168 (40.9)	0.04
No	36 (32.7)	132 (44.0)	242 (59.1)	
Alcohol use				
Yes	69 (62.7)	145 (48.3)	214 (52.2)	0.0098
No	41 (37.3)	155 (51.7)	196 (47.8)	
Illicit drug use				
Yes	18 (16.4)	20 (6.7)	38 (9.3)	0.0027
No	92 (83.6)	280 (93.3)	372 (90.7)	
Methadone use				

Table 1a. Socio-demographic and Clinical Characteristics distribution of HIV-infected patients according to the presence of TB				
Risk Factors	**Positive**	**Negative**	**Total**	**P-value**
	(n=110)	**(n=300)**	**(n=410)**	
Yes	0 (0)	4 (1.3)	4 (0.9)	0.2242
No	110 (100)	296 (98.7)	406 (99.1)	
Diabetes mellitus				
Yes	1 (0.9)	1 (0.3)	2 (0.5)	0.459
No	109 (99.1)	299 (99.7)	408 (99.5)	
HBV Infection				
Yes	72 (65.5)	213 (71.0)	285 (69.5)	0.2804
No	38 (34.5)	87 (29.0)	125 (30.5)	
HCV infection				
Yes	71 (64.5)	139 (46.3)	210 (51.2)	0.0011
No	39 (35.5)	161 (53.7)	200 (48.8)	
Liver cirrhosis				
Yes	15 (13.6)	12 (4.0)	27 (6.6)	0.0005
No	95 (86.4)	288 (96.0)	383 (93.4)	
Nephropathy				
Yes	0 (0)	3 (1.0)	3 (0.7)	0.2931
No	110 (100)	297 (99.0)	407 (99.3)	
Imprisonment				
Yes	17 (15.4)	30 (10.0)	47 (11.5)	0.125
No	93 (84.6)	270 (90)	363 (88.5)	
HIV transmission				
IDU	72 (65.5)	139 (46.3)	211 (51.5)	0.0006
Other	38 (34.5)	161 (53.7)	199 (48.5)	
Previous history of TB				
yes	33 (30.0)	16 (5.3)	49 (11.9)	<0.0001
No	77 (70.0)	284 (94.7)	361 (88.1)	
Opportunistic infections at baseline visit				
Yes	37 (33.6)	64 (21.3)	101 (24.6)	0.0105
no	73 (66.4)	236 (78.7)	309 (75.4)	
ART				
Yes	93 (84.5)	178 (59.3)	271 (66.1)	<0.0001
No	17 (15.5)	122 (40.7)	139 (33.9)	
ART Regimen				
2 NRTI's + NNRTI	91 (97.8)	168 (93.8)	259 (95.2)	0.1437
2 NRTI's + PI	2 (2.2)	11 (6.2)	13 (4.8)	
Sites of TB at baseline (n=110)				

Table 1a. Socio-demographic and Clinical Characteristics distribution of HIV-infected patients according to the presence of TB				
Risk Factors	**Positive**	**Negative**	**Total**	**P-value**
	(n=110)	**(n=300)**	**(n=410)**	
Extra-pulmonary	23 (21.1)	0(0)	23 (21.1)	
Pulmonary	87 (78.9)	0(0)	87 (78.9)	
Anti-TB drugs sensitivity				
MDR-TB	11 (10.2)	0(0)	11 (10.2)	
Drug sensitive	97 (89.8)	0(0)	97 (89.8)	
Death				
Yes	40 (36.4)	30 (10.0)	340 (82.9)	<0.0001
No	70 (63.6)	270 (90.0)	70 (17.1)	

Table 2. Factors Associated With Death Among HIV-infected Patients (n=410)

Risk Factors	**Death**	**No Death**	**P-value**
	(n=70)	**(n=340)**	
Continuous variables			
Age in years			
mean	43.2	39.6	0.005
median	44.1	39.9	
interquartile range	38.0-49.1	34.0-46.0	
Baseline CD4 cell count			
mean	155.4	316.1	<0.0001
median	68	245	
interquartile range	20-190	120-467	
Baseline HIV plasma viral load			
mean	631029.4	401559.9	0.1237
median	326250	90350	
interquartile range	100000-750000	17377-329184	
Baseline hemoglobin			
mean	100.8	123.1	<0.0001
median	102	124	
interquartile range	81-121	108-140	
Categorical variables	**Number (%)**		
Age			
>40	48 (68.6)	169 (49.7)	0.004
<=40	22 (31.4)	171 (50.3)	

Table 2. Factors Associated With Death Among HIV-infected Patients (n=410)			
Risk Factors	**Death**	**No Death**	**P-value**
	(n=70)	**(n=340)**	
Baseline CD4 cell count			
<50 cells/mm^3	35 (50.0)	40 (11.7)	<0.0001
50-199 cells/mm^3	21 (30.0)	102 (30.0)	
200-350 cells/mm^3	6 (8.6)	76 (22.4)	
>350 cells/mm^3	8 (11.4)	122 (35.9)	
Baseline HIV viral load			
>= 100,000 copy/ml	42 (75.0)	149 (47.3)	0.0001
<100,000 copies/ml	14 (25.0)	166 (52.7)	
Baseline hemoglobin			
<120 g/L	41 (71.9)	134 (40.9)	<0.0001
>=120 g/L	16 (28.1)	193 (59.1)	
Gender			
male	59 (84.3)	230 (67.6)	0.0055
female	11 (15.7)	110 (32.4)	
Marital Status			
Married	47 (67.1)	249 (73.2)	0.3008
Not married	23 (32.9)	91 (26.8)	
Education			
Primary and secondary school	23 (32.9)	120 (35.3)	0.6968
High school and above	47 (67.1)	220 (64.7)	
Employment			
no	68 (97.1)	313 (92.1)	0.1313
Yes	2 (2.9)	27 (7.9)	
Residence			
rural	37 (52.9)	180 (52.9)	0.9898
urban	33 (47.1)	160 (47.1)	
Tobacco use			
Yes	39 (55.7)	203 (59.7)	0.5363
No	31 (44.3)	137 (40/3)	
Alcohol use			
Yes	38 (54.3)	176 (51.8)	0.7006
No	32 (45.7)	164 (48.2)	
Illicit drug use			
Yes	12 (17.1	26 (7.6)	0.0127
No	58 (82.9)	314 (92.3)	
Methadone use			
Yes	1 (1.4)	3 (0.9)	0.6724

Table 2. Factors Associated With Death Among HIV-infected Patients (n=410)			
Risk Factors	**Death**	**No Death**	**P-value**
	(n=70)	**(n=340)**	
No	69 (98.6)	337 (99.1)	
Diabetes mellitus			
Yes	0 (0)	2 (0.6)	0.5206
No	70 (100)	338 (99.4)	
HBV Infection			
Yes	17 (24.3)	108 (31.8)	0.2164
No	53 (75.7)	232 (68.2)	
HCV infection			
Yes	43 (61.4)	167 (49.1)	0.0609
No	27 (38.6)	173 (50.1)	
Liver cirrhosis			
Yes	14 (20.0)	13 (3.8)	<0.0001
No	56 (80.0)	327 (96.2)	
Nephropathy			
Yes	2 (2.9)	1 (0.3)	0.0221
No	68 (97.1)	339 (99.7)	
Imprisonment			
Yes	10 (14.3)	37 (10.9)	0.4163
No	60 (85.7)	303 (89.1)	
HIV transmission			
IDU	47 (67.1)	164 (48.2)	0.004
Other	23 (32.9)	176 (51.8)	
Previous history of TB			
yes	6 (8.6)	43 (12.6)	0.339
No	64 (91.4)	297 (87.3)	
TB diagnosis at baseline visit			
Yes	40 (57.1)	70 (20.6)	<0.0001
No	30 (42.9)	270 (79.4)	
Opportunistic infections at baseline visit			
Yes	43 (61.4)	58 (17.1)	<0.0001
no	27 (38.6)	282 (82.9)	
ART			
Yes	43 (61.4)	228 (67.1)	
No	27 (38.6)	112 (32.9)	0.3654
ART Regimen			
2 NRTI's + NNRTI	43 (100)	216 (94.3)	

2 NRTI's + PI	0 (0)	13 (5.7)	
Table 2. Factors Associated With Death Among HIV-infected Patients (n=410)			
Risk Factors	**Death**	**No Death**	**P-value**
	(n=70)	**(n=340)**	
Sites of TB at baseline (n=110)			
Extra-pulmonary	7 (17.5)	16 (21.6)	0.6023
Pulmonary	33 (82.5)	58 (78.4)	
Anti-TB drugs sensitivity	4 (10.0)	16 (22.9)	
MDR-TB	2 (5.1)	11 (14.9)	0.1247
Drug sensitive	37 (94.9)	63(85.1)	

Table 3. Univariate associations between risk factors and Mortality among HIV-infected Patients (n=410)

Risk Factors	OR*	95% CI*	P-value
Continuous variables			
Age (years)			
mean	1.04	1.01, 1.07	0.0053
median			
interquartile range			
Baseline CD4 cell count			
mean	0.99	0.99, 0.996	<0.0001
median			
interquartile range			
Baseline HIV plasma viral load			
mean	1	1.0, 1.0	0.1416
median			
interquartile range			
Baseline hemoglobin			
mean	0.96	0.94, 0.97	<0.0001
median			
interquartile range			
Categorical variables			
Age			
>40	2.21	1.28, 3.82	0.0046
<=40	ref		
Baseline CD4 cell count			
<50 cells/mm^3	13.34	5.7, 31.1	<0.0001
50-199 cells/mm^3	3.14	1.33, 7.39	0.0088
200-350 cells/mm^3	1.2	0.40, 3.60	0.7401
>350 cells/mm^3	ref.		
Baseline HIV viral load			
>= 100,000 copy/ml	3.34	1.76, 6.36	0.0002
<100,000 copies/ml	ref		
Baseline hemoglobin			
<120 g/L	3.69	1.89, 6.85	<0.0001
>=120 g/L	ref		
Gender			
male	2.56	1.29, 5.08	0.0055

Table 3. Univariate associations between risk factors and Mortality among HIV-infected Patients (n=410)			
Risk Factors	**OR***	**95% CI***	**P-value**
female	ref.		
Marital Status			
Married	1.39	0.77, 2.33	0.3008
Not married	ref.		
Education			
Primary and secondary school	0.89	0.52, 1.55	0.6969
High school and above	ref.		
Employment			
no	2.93	0.68, 12.62	0.1313
Yes	ref		
Residence			
rural	1.03	0.59, 1.68	0.9898
urban	ref		
Tobacco use			
Yes	1.18	0.70, 1.98	0.5366
No	ref.		
Alcohol use			
Yes	1.11	0.66, 1.85	0.7009
No	ref.		
Illicit drug use			
Yes	2.49	1.19, 5.23	0.0127
No	ref		
Methadone use			
Yes	1.63	0.17, 15.88	0.6724
No	ref		
Diabetes mellitus			
Yes	0.96	0.05, 20.22	0.5206
No	ref		
HBV Infection			
Yes	0.69	0.38, 1.24	0.2164
No	ref		
HCV infection			
Yes	1.65	0.97, 2.79	0.0609
No	ref		
Liver cirrhosis			
Yes	6.29	2.91, 14.08	<0.0001

No	ref		
Table 3. Univariate associations between risk factors and Mortality among HIV-infected Patients (n=410)			
Risk Factors	**OR***	**95% CI***	**P-value**
Nephropathy			
Yes	9.97	0.89, 111.51	0.0221
No	ref		
Imprisonment			
Yes	1.36	0.64, 2.89	0.4163
No	ref		
HIV transmission			
IDU	2.19	1.27, 3.77	0.0045
Other	ref.		
Previous history of TB			
yes	0.65	0.26, 1.59	0.339
No	ref		
TB diagnosis at baseline visit			
Yes	5.14	2.99, 8.83	<0.0001
No	ref		
Opportunistic infections at baseline visit			
Yes	7.74	4.43, 13.53	<0.0001
no	ref		
ART			
Yes	ref		
No	1.28	0.75, 2.17	0.3654
ART Regimen (n=271)			
2 NRTI's + NNRTI			
2 NRTI's + PI			
Sites of TB at baseline (n=110)			
Extra-pulmonary	0.77	0.29, 2.06	0.6023
Pulmonary	ref.		
Anti-TB drugs sensitivity			
MDR-TB	0.31	0.06, 1.47	0.1247
Drug sensitive	ref		
NOTES:			
OR: Odds Ratio			
95% CI: Confidence interval			

Table 4. Factors Associated with ART Use Among HIV-infected Patients (n=410)

Risk Factors	**ART**	**No ART**	**P-value**
	(n=271)	**(n=139)**	
Continuous variables			
Age in years			
mean	41.1	38.4	0.0098
median	41.1	38.9	
interquartile range	36.1-47.1	32.0-44.1	
Baseline CD4 cell count			
mean	208.2	461.3	<0.0001
median	158	463	
range	74-288	300-590	
Baseline HIV plasma viral load			
mean	546016.8	223395.9	0.0043
median	154500	35400	
range	47159-537000	9755-176487	
Baseline hemoglobin			
mean	119.6	120.3	0.7815
median	121.5	122	
range	102-136	104-139.5	
Categorical variables	**Number (%)**		
Age			
>40	157 (57.9)	60 (43.1)	0.0046
<=40	114 (42.1)	79 (56.8)	
Baseline CD4 cell count			
<50 cells/mm^3	58 (21.4)	17 (12.2)	<0.0001
50-199 cells/mm^3	111 (40.9)	12 (8.6)	
200-350 cells/mm^3	58 (21.4)	24 (17.3)	
>350 cells/mm^3	44 (16.2)	86 (61.9)	
Baseline HIV viral load			
>= 100,000 copy/ml	99 (40.1)	81 (63.8)	<0.0001
<100,000 copies/ml	145 (59.4)	46 (36.2)	
Baseline hemoglobin			
<120 g/L	120 (46.8)	55 (42.9)	0.4693
>=120 g/L	136 (53.1)	73 (57.1)	
Gender			
male	204 (75.3)	85 (61.1)	0.003
female	67 (24.7)	54 (38.9)	

Table 4. Factors Associated with ART Use Among HIV-infected Patients (n=410)			
Risk Factors	**ART**	**No ART**	**P-value**
	(n=271)	**(n=139)**	
Marital Status			
Married	194 (71.6)	102 (73.4)	0.701
Not married	77 (28.4)	37 (26.6)	
Education			
Primary and secondary school	94 (34.7)	49 (35.2)	0.9095
High school and above	177 (65.3)	90 (64.8)	
Employment			
No	251 (92.6)	130 (93.5)	0.7353
Yes	20 (7.4)	9 (6.5)	
Residence			
rural	146 (53.9)	71 (51.1)	0.5919
urban	125 (46.1)	68 (48.9)	
Tobacco use			
Yes	164 (60.5)	78 (56.1)	0.391
No	107 (39.5)	61 (43.9)	
Alcohol use			
Yes	146 (53.9)	68 (48.9)	0.3418
No	125 (46.1)	71 (51.1)	
Illicit drug use			
Yes	30 (11.1)	8 (5.7)	0.0793
No	241 (88.9)	131 (94.2)	
Methadone use			
Yes	2 (0.7)	2 (1.4)	0.4948
No	269 (99.3)	137 (98.6)	
Diabetes mellitus			
Yes	2 (0.7)	0 (0)	0.3105
No	269 (99.3)	139 (100.0)	
HBV Infection			
Yes	92 (33.9)	33 (23.7)	0.0338
No	179 (66.1)	106 (76.3)	
HCV infection			
Yes	156 (57.6)	54 (38.8)	0.0003
No	115 (42.4)	85 (61.1)	
Liver cirrhosis			
Yes	19 (7.0)	8 (5.7)	0.6279
No	252 (92.9)	131 (94.2)	
Nephropathy			

Table 4. Factors Associated with ART Use Among HIV-infected Patients (n=410)			
Risk Factors	**ART**	**No ART**	**P-value**
	(n=271)	**(n=139)**	
Yes	0 (0)	3 (2.1)	0.0153
No	271 (100.0)	136 (97.8)	
Imprisonment			
Yes	36 (13.3)	11 (7.9)	0.1066
No	235 (86.7)	128 (92.1)	
HIV transmission			
IDU	153 (56.5)	58 (41.7)	0.0048
Other	118 (43.5)	81 (58.3)	
Previous history of TB			
Yes	41 (15.1)	8 (5.8)	0.0057
No	230 (84.9)	131 (94.2)	
TB diagnosis at baseline visit			
Yes	93 (34.3)	17 (12.2)	<0.0001
No	178 (65.7)	122 (87.8)	
Opportunistic infections at baseline visit			
Yes	81 (29.9)	20 (14.4)	0.0006
No	190 (70.1)	119 (85.6)	
Sites of TB at baseline (n=110)			
Extra-pulmonary	19 (19.6)	4 (23.5)	0.7087
Pulmonary	78 (80.4)	13 (76.5)	
Anti-TB drugs sensitivity			
MDR-TB	11 (11.3)	2 (12.5)	0.8933
Drug sensitive	86 (88.7)	14 (87.5)	
Death			
Yes	43 (15.9)	27 (19.4)	0.3654
No	228 (84.1)	112 (80.6)	

Table 5. Multivariable Regression of Risk Factors for Mortality among HIV-infected Patients (n=410).

Risk Factor	**Adjusted Odds Ratio (95% CI)**	**Adjusted Hazards Ratio (95% CI)**
ART		
No	7.01 (2.76-18.20)*	8.27 (4.13-16.55)*
Yes	ref.	ref.
Age (continuous variable)	1.02 (0.98-1.06)	1.02 (0.98-1.05)
Baseline CD4 cell count		
<50 cells/mm^3	3.52 (1.02-12.13)*	4.68 (1.57-13.99)*
50-199 cells/mm^3	2.92 (0.93-9.20)	4.03 (1.47-11.03)*
200-350 cells/mm^3	0.94 (0.26-3.39)	1.36 (0.45-4.16)
>350 cells/mm^3	ref.	ref.
Baseline HIV viral load		
>= 100,000 copy/ml	2.07 (0.91-4.73)	2.20 (1.12-4.32)*
<100,000 copies/ml	ref.	ref.
Gender		
Male	2.46 (0.82-7.35)	*stratified*
Female	ref.	
HCV infection		
Yes	0.67 (0.25-1.76)	0.72 (0.32-1.61)
No	ref.	ref.
HIV transmission		
IDU	1.22 (0.42-3.53)	1.48 (0.62-3.56)
Other transmission route	ref.	ref.
TB diagnosis at baseline visit		
Yes	8.49 (3.69-19.53)*	3.63 (2.02-6.52)*
No	ref.	ref.
Opportunistic infections at baseline visit		
Yes	8.40 (3.62-19.57)*	3.85 (2.05-7.19)*
no	ref.	ref.
Previous history of TB		
Yes	0.16 (0.05-0.55)*	0.23 (0.09-0.62)*
No	ref.	ref.
** P-value<0.05*		

Table 6. Factors associated with ART use Among HIV/TB co-infected Patients (n=110).

Risk Factors	**ART**	**No ART**	**P-value**
	(n=93)	**(n=17)**	
Continuous variables			
Age in years			
mean	43.8	38.2	0.0094
median	43.1	40.1	
interquartile range	38.1-49.1	37.9-44.9	
Baseline CD4 cell count			
mean	134.4	297.1	0.0029
median	88	141	
interquartile range	47-190	18-343	
Baseline HIV plasma viral load			
mean	546016.8	473277.1	0.4338
median	154500	610500	
interquartile range	47159-537000	31600-738000	
Baseline hemoglobin			
*mean**	113.5	96.1	0.005
median	113	95.5	
interquartile range	98-131	81-108	
Categorical variables	**Number (%)**		
Age			
>43	47 (50.5)	7 (41.2)	0.4798
<=43	46 (49.5)	10 (58.8)	
Baseline CD4 cell count			
<50 cells/mm^3	30 (32.3)	7 (41.2)	0.2848
50-199 cells/mm^3	43 (46.2)	4 (23.5)	
200-350 cells/mm^3	13 (13.9)	3 (17.6)	
>350 cells/mm^3	7 (7.6)	3 (17.7)	
Baseline HIV viral load			
>= 100,000 copy/ml	59 (71.8)	9 (64.3)	0.5146
<100,000 copies/ml	22 (27.2)	5 (35.7)	
Baseline hemoglobin			
<111 g/L	56 (49.5)	14 (82.3)	0.0127
>=111 g/L	47 (50.5)	3 (17.7)	
Gender			

Table 6. Factors associated with ART use Among HIV/TB co-infected Patients (n=110).			
Risk Factors	**ART**	**No ART**	**P-value**
	(n=93)	**(n=17)**	
male	78 (83.9)	12 (70.6)	0.1937
female	15 (16.1)	5 (29.4)	
Marital Status			
Married	67 (72.0)	9 (52.9)	0.1171
Not Married	26 (28.0)	8 (47.1)	
Employment			
No	87 (93.5)	16 (94.1)	0.9299
Yes	6 (6.5)	1 (5.9)	
Residence			
rural	58 (62.4)	9 (52.9)	0.4661
urban	35 (37.6)	8 (47.1)	
Tobacco use			
Yes	64 (68.8)	10 (58.8)	0.4194
No	29 (31.2)	7 (41.2)	
Alcohol use			
Yes	58 (62.4)	11 (64.7)	0.8544
No	35 (37.6)	6 (35.3)	
Illicit drug use			
Yes	15 (16.1)	3 (17.6)	0.8769
No	78 (83.9)	14 (82.4)	
Diabetes mellitus			
Yes	1 (1.1)	0 (0)	0.669
No	92 (98.9)	17 (100)	
HBV Infection			
Yes	36 (38.7)	2 (11.8)	0.0325
No	57 (61.3)	15 (88.2)	
HCV infection			
Yes	64 (68.8)	7 (41.2)	0.0292
No	29 (31.2)	10 (58.8)	
Liver cirrhosis			
Yes	13 (13.9)	2 (11.8)	0.8077
No	80 (86.0)	15 (88.2)	
Nephropathy			
Yes	0 (0)	0 (0)	
No	93 (100)	17 (100)	
Imprisonment			

Table 6. Factors associated with ART use Among HIV/TB co-infected Patients (n=110).			
Risk Factors	**ART**	**No ART**	**P-value**
	(n=93)	**(n=17)**	
Yes	17 (18.3)	0 (0)	0.0563
No	76 (81.7)	17 (100)	
HIV transmission			
IDU	62 (66.7)	10 (58.8)	0.5336
Other	31 (33.3)	7 (41.2)	
Previous history of TB			
Yes	28 (30.1)	5 (29.4)	0.9543
No	65 (69.9)	12 (70.6)	
Opportunistic infections			
Yes	31 (33.3)	6 (35.3)	0.8755
No	62 (66.7)	11 (64.7)	
Sites of TB at baseline			
Extra-pulmonary	73 (79.3)	13 (76.5)	0.7903
Pulmonary	19 (20.7)	4 (23.5)	
Anti-TB drugs sensitivity			
MDR-TB	9 (9.8)	2 (12.5)	0.7413
Drug sensitive	83 (90.2)	14 (87.5)	
Death			
Yes	26 (27.9)	14 (82.3)	<0.0001
No	67 (72.1)	3 (17.7)	

Table 7. Factors Associated with Mortality among HIV/TB Co-infected Patients (n=110).

Risk Factor	**Death**	**No Death**	**P-value**
	(n=40)	**(n=70)**	
Continuous			
Age in years			
mean	41.1	43.9	0.0835
median	41.1	43.1	
interquartile range	37.1-46.1	39.1-49.1	
Baseline CD4 cell count			
mean	120.3	173.9	0.1935
median	66.5	103	
interquartile range	26.5-148.5	51-208	
Baseline HIV plasma viral load			
mean	677998.5	831527.6	0.6545
median	485025	259000	
range	11000-751500	35700-716000	
Baseline hemoglobin			
mean	99.3	116.3	0.0001
median	101	116	
interquartile range	81.5-112.5	100-135	
Categorical	**Number (%)**		
Age			
>=43	18 (45.0)	36 (51.4)	0.5184
<43	22 (55.0)	34 (48.6)	
Baseline CD4 cell count			
<50 cells/mm^3	20 (50.0)	17 (24.3)	0.0434
50-199 cells/mm^3	14 (35.0)	33 (47.1)	
200-350 cells/mm^3	3 (7.5)	13 (17.6)	
>350 cells/mm^3	3 (7.5)	7 (10.0)	
Baseline HIV viral load			
>= 100,000 copy/ml	25 (78.1)	43 (68.2)	0.3159
<100,000 copies/ml	7 (21.9)	20 (31.7)	
Baseline hemoglobin			
<111 g/L	31 (77.5))	29 (41.4)	0.0003
>=111 g/L	9 (22.5)	41 (58.6)	
Gender			
male	34 (85.0)	56 (80.0)	0.515
female	6 (15.0)	14 (20.0)	

Table 7. Factors Associated with Mortality among HIV/TB Co-infected Patients (n=110).			
Risk Factor	**Death**	**No Death**	**P-value**
	(n=40)	**(n=70)**	
Marital Status			
Married	26 (65.0)	50 (71.4)	0.4828
Not married	14 (35.0)	20 (28.6)	
Education			
Primary or secondary school	14 (35.0)	31 (44.3)	0.3429
High school and above	26 (65.0)	39 (55.7)	
Employment			
Yes	0 (0)	7 (10.0)	0.5814
no	40 (100.0)	63 (90.0)	
Residence			
rural	23 (57.5)	44 (62.8)	0.4555
urban	17 (42.5)	26 (37.2)	
Tobacco use			
Yes	24 (60.0)	50 (71.4)	0.2212
No	16 (40.0)	20 (28.6)	
Alcohol use			
Yes	25 (62.5)	44 (62.9)	0.9704
No	15 (37.5)	26 (37.1)	
Illicit drug use			
Yes	9 (22.5)	9 (12.9)	0.1905
No	31 (77.5)	61 (84.1)	
Diabetes mellitus			
Yes	0 (0)	1 (1.4)	0.4497
No	40 (100.0)	69 (98.6)	
HBV Infection			
Yes	10 (25.0)	28 (40.0)	0.1131
No	30 (75.0)	42 (60.0)	
HCV infection			
Yes	26 (65.0)	45 (64.3)	0.9402
No	14 (35.0)	26 (37.7)	
Liver cirrhosis			
Yes	10 (25.0)	5 (7.1)	0.009
No	30 (75.0)	65 (92.9)	
Nephropathy			
Yes	0(0)	0 (0)	
No	40 (100.0)	70 (100.0)	

Table 7. Factors Associated with Mortality among HIV/TB Co-infected Patients (n=110).			
Risk Factor	**Death**	**No Death**	**P-value**
	(n=40)	**(n=70)**	
Imprisonment			
Yes	7 (17.5)	10 (14.3)	0.6552
No	33 (82.5)	60 (85.7)	
HIV transmission			
IDU	29 (72.5)	43 (61.4)	0.2423
Other	11 (27.5)	27 (38.6)	
Previous history of TB			
Yes	5 (12.5)	28 (40.0)	0.0026
No	35 (87.5)	42 (60.0)	
Opportunistic infections at baseline visit			
Yes	21 (52.5)	16 (22.9)	0.0016
no	19 (47.5)	54 (77.1)	
ART			
Yes	26 (65.0)	67 (95.7)	
No	14 (35.0)	3 (4.3)	<0.0001
ART Regimen (n=93)			
2 NRTI's + NNRTI	26 (100.0)	65 (97.0)	0.3754
2 NRTI's + PI	0 (0)	2 (3.0)	
Sites of TB at baseline (n=110)			
Extra-pulmonary	7 (17.9)	16 (22.9)	0.549
Pulmonary	32 (82.1)	54 (77.1)	
Anti-TB drugs sensitivity			
MDR-TB	2 (5.3)	9 (12.9)	0.2276
Drug sensitive	36 (94.7)	61 (87.1)	

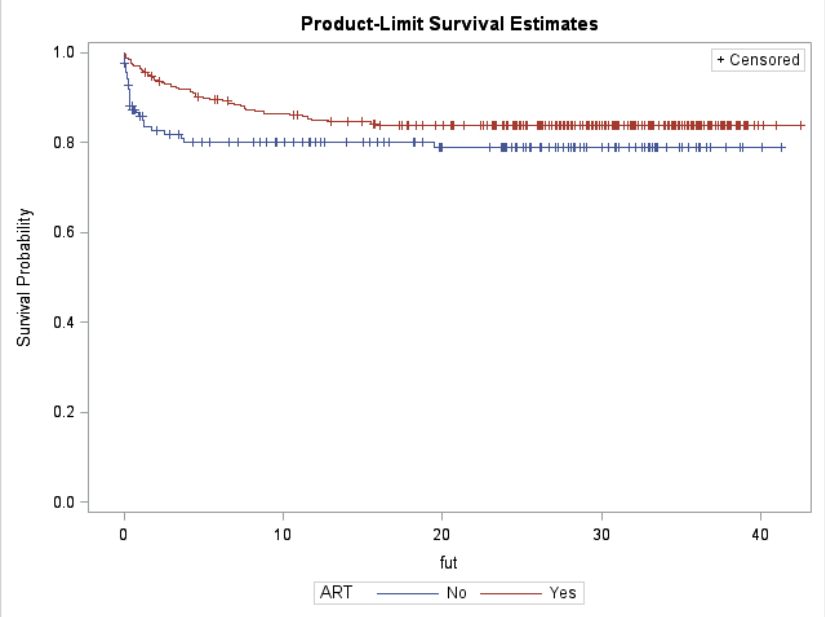
Table 8 Multivariable Regression of Risk Factors for Mortality in HIV/TB co-infected Patients (n=110)

Factor	Adjusted Odds Ratio (95% CI)	Adjusted Hazards Ratio (95% CI)
ART		
No	13.93 (2.54-76.44)*	7.71 (3.36-17.68)*
Yes	ref.	ref.
Age (continuous variable)	0.99 (0.93-1.06)	0.98 (0.94-1.02)
Baseline CD4 cell count		
<50 cells/mm^3	2.11 (0.30-14.74)	0.93 (0.23-3.72)
50-199 cells/mm^3	1.24 (0.19-8.13)	0.71 (0.18-2.78)
200-350 cells/mm^3	0.32 (0.03-3.52)	0.26 (0.04-1.54)
>350 cells/mm^3	ref.	ref.
Baseline hemoglobin		
<111 g/L	3.25 (1.02-10.28)*	2.61 (0.98-6.91)
>=111 g/L	ref.	ref.
Anti-TB drugs sensitivity		
MDR-TB	0.22 (0.03-1.63)	0.45 (0.10-2.00)
Drug sensitive	ref.	ref.
**** P-value<0.05***		

Table 9 Frequency of Death Among 110 HIV/TB co-infected Patients Received ART After TB Diagnosis

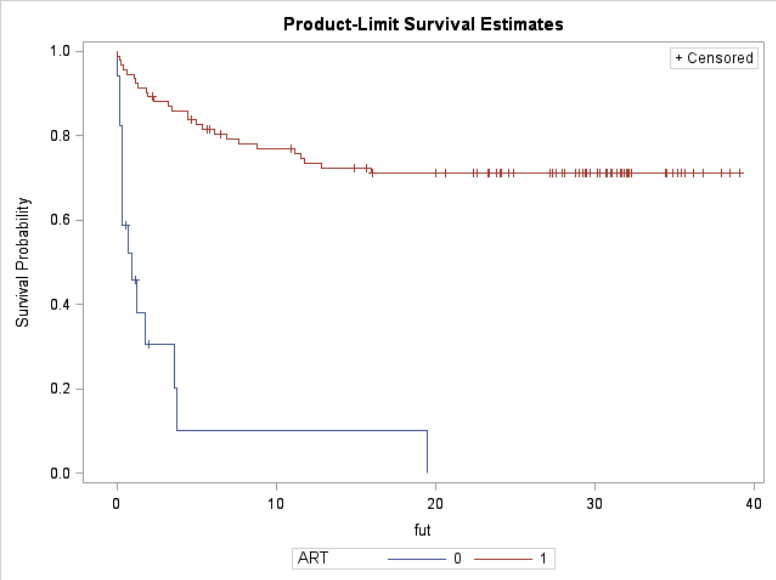
Time From TB Diagnosis to Initiated ART	Death	HR	95% CI	P-value
>2 mo vs <2 mo	34.8% (16/46) vs 15% (6/40)	2.64	1.03, 6.75	0.0425
>4 mo vs <4 mo	32.2% (19/59) vs 11.1% (3/27)	3.25	0.96, 10.99	0.0578
>6 mo vs <6 mo	32.3% (21/65) vs 4.8 (1/21)	7.93	1.07, 58.97	0.0431

Figure 8: Survival rate between HIV-infected patients (n=410) who received and did not receive ART.



Notes:
ART: Antiretroviral Therapy; Fut: Follow-up time (in months)

Figure 9: Survival rate between HIV/TB co-infected patients (n=110) who received and did not receive ART.



Notes: ART: Antiretroviral Therapy (red line- yes, blue line – no); Fut: Follow-up time (in months)

Appendix

Data Form/questionnaire

TO BE COMPLETED BY INVESTIGATOR: **Medical Record: ___ ___ ___ ___**

STUDY ID: ____ ____ ____

Date: _____/_____/_____

Questions:

Section 1. Socio-Demographic Information

1.0 Date of HIV diagnosis: _____/_____/_____

1.1 Date of Birth _____/_____/_____

1.2 Gender: □ Male □ Female

1.3 Current Marital Status:
- □ Married
- □ Single
- □ Divorced/separated
- □ Widowed

1.5 Education Level:
- □ ≥ University
- □ Primary
- □ < Primary
- □ Illiterate

1.6 Employment Status:
- □ Employed
- □ Unemployed
- □ Military
- □ Student
- □ Housewife
- □ Retired

1.7 Residence Location:

□ Urban □ Suburban
□ Rural □ Homeless/Displaced

1.8 Tobacco Use?

□ No □ < 1pack daily □ ≥ 1pack daily

1.10 Alcohol intake?

□ No □ Moderate (1-4 drinks daily) □ Excessive (≥ 5drinks daily)

1.11 Other Illicit Drug use? □ Yes _____ □ No

1.12 Patient Comorbidities:

□ Diabetes □ Cirrhosis □ Pregnancy
□ COPD/Emphysema/Bronchitis
□ Nephropathy □Hepatitis C □ Hepatitis B

1.13 History of imprisonment? □ Yes (release year: _____)
□ No

Section 2. HIV History and Current Presentation

2.1 Date of first HIV center visit: _____/_____/_____

2.1.1 Place of HIV diagnosis:

□ National HIV center (or affiliated HIV clinic)
□ TB Hospital
□ Other hospital or clinic

2.2 Risk Factor for HIV Acquisition (mark all that apply):

□ Unprotected heterosexual sex
□ Unprotected homosexual sex
□ Intravenous drug use
□ Blood Transfusion
□ Maternal Infection
□ None of the above

2.3 Baseline CD4 count: _____ Date: _____/____/_____

2.4 Baseline HIV viral load: _____

2.5 Baseline hemoglobin: _____

2.6 Does patient have history of Tuberculosis?

- □ Pulmonary Tuberculosis
- □ Extra-Pulmonary Tuberculosis
- □ none

2.7 Was patient diagnosed or receiving treatment with of any of the following Opportunistic Infections at baseline visit:

- □ Crytpococcal Disease
- □ Pulmonary Tuberculosis
- □ Extra-Pulmonary Tuberculosis
- □ PCP
- □ Toxoplasmosis
- □ HIV Related Lymphoma
- □ Kaposi Sarcoma
- □ Visceral Leishmaniasis
- □ Recurrent Pneumonia

- □ Other _____

2.8 Baseline Patient Height (meters): _____

Section 3. HIV and ART Follow Up

3.1 Was patient started on ART: □ Yes □ No (go to 3.5)

3.2 Which regimen was patient started on?

- □ 2 NRTI's + NNRTI
- □ 2 NRTI's + PI

3.3 Start date for ART: _____/_____/_____

3.4 Stop date for ART: _____/_____/_____ (leave empty if still on ART)

3.5 CD4 and viral load follow up:

Date of Test	CD4 Count	Viral Load
_____/_____/_____		
_____/_____/_____		
_____/_____/_____		
_____/_____/_____		
_____/_____/_____		

Section 4. Patient Follow Up

4.1 Follow up Date (last clinic visit): ____/_____/_____

4.2 Patient Follow up: □ Alive □ Loss to Follow Up □ Died → Date of Death (_____/_____/_

4.3 Did patent develop any of the following Opportunistic Infections during follow up:

□ **Tuberculosis (go to section 5)**
□ PCP
□ Toxoplasmosis
□ HIV Related Lymphoma
□ Kaposi Sarcoma
□ Visceral Leishmaniasis
□ Recurrent Pneumonia
□ Cryptococcal meninigitis

□ Other _____

Section 5. Tuberculosis Follow Up:

5.1 Date of TB Diagnosis:_____/_____/_____

5.2 Location of Tuberculosis:

□ Pulmonary
□ CNS
□ Lymph Node
□ Other:_____

5.3 How was patient diagnosed with tuberculosis:

□ Clinical diagnosis
□ Positive AFB smear and negative culture
□ Positive AFB smear and positive culture
□ Negative AFB smear and positive culture

5.4 Chest X-ray findings(mark all that apply):

□ Cavitary Lesions
□ Pulmonary infiltrate
□ Miliary Pattern
□ Effusion
□ Other_____

5.5 DST results

□ Drug Sensitive TB
□ INH Mono-Resistant
□ MDR TB
□ XDR-TB

5.6 Outcome of TB treatment:

□ Cured
□ Treatment failure
□ Death
□ Still on treatment

EMORY UNIVERSITY | Institutional Review Board

TO: Akaki Abutidze, MD
Principal Investigator
Global Health

DATE: February 17, 2012

RE: **Expedited Approval**
IRB00055717
Risk Factors for Tuberculosis After Highly Active Antiretroviral Therapy Initiation in Georgia; Survival Rate and Risk Factors of Mortality Among HIV/Tuberculosis Co-infected Patients with and without Antiretroviral Therapy.

Thank you for submitting a new application for this protocol. This research is eligible for expedited review under 45 CFR.46.110 and/or 21 CFR 56.110 because it poses minimal risk and fits the regulatory category F(5) as set forth in the Federal Register. The Emory IRB reviewed it by expedited process on 2/16/2012 and granted approval effective from **2/16/2012** through **2/15/2013**. Thereafter, continuation of human subjects research activities requires the submission of a renewal application, which must be reviewed and approved by the IRB prior to the expiration date noted above.

- A waiver of all elements of informed consent has been granted for this study

Any reportable events (e.g., unanticipated problems involving risk to subjects or others, noncompliance, breaches of confidentiality, HIPAA violations, protocol deviations) must be reported to the IRB according to our Policies & Procedures at www.irb.emory.edu, immediately, promptly, or periodically. Be sure to check the reporting guidance and contact us if you have questions. Terms and conditions of sponsors, if any, also apply to reporting.

Before implementing any change to this protocol (including but not limited to sample size, informed consent, study design, you must submit an amendment request and secure IRB approval.

In future correspondence about this matter, please refer to the IRB file ID, name of the Principal Investigator, and study title. Thank you

Sam Roberts, CIP
Research Protocol Analyst
This letter has been digitally signed

CC:	Del Rio	Carlos	Global Health
	Kempker	Russell	RTP

Emory University
1599 Clifton Road, 5th Floor - Atlanta, Georgia 30322
Tel: 404.712.0720 - Fax: 404.727.1358 - Email: irb@emory.edu - Web: http://www.irb.emory.edu/