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Impact of HIV-1, HIV-2, and HIV-1+2 dual infection on the outcome of tuberculosis

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SUMMARY

Background: HIV-1 infection has been shown to impact the outcome of patients with tuberculosis (TB), but data regarding the impact of HIV-2 on TB outcomes are limited. The aim of this study was to assess the impact of HIV types on mortality among TB patients in Guinea-Bissau and to examine the predictive ability of the TBscoreII, a clinical score used to assess disease severity.

Methods: In a prospective follow-up study, we examined the prevalence of HIV-1, HIV-2, and HIV-1+2 co-infection in TB patients in Guinea-Bissau, and the impact on outcomes at 12 months of follow-up. We included all adult TB patients in an observational TB cohort at the Bandim Health Project (BHP) in Guinea-Bissau between 2003 and 2013 and assessed survival status at 12 months after the start of treatment.

Results: A total 1312 patients were included; 499 (38%) were female (male/female ratio 1.6). Three hundred and seventy-nine patients were HIV-infected: 241 had HIV-1, 93 had HIV-2, and 45 were HIV-1+2 dual infected. The HIV type-associated risk of TB was 6-fold higher for HIV-1, 7-fold higher for HIV-1+2 dual infection, and 2-fold higher for HIV-2 compared with the HIV-uninfected. Of the patients included, 144 (11%) died, 62 (12%) among females and 82 (9%) among males (hazard ratio (HR) 0.91, 95% confidence interval (CI) 0.64–1.30; $p = 0.596$). Compared to male patients, female patients were younger (1 year younger, 95% CI 0.5–2; $p = 0.04$), reported a longer duration of symptoms (14 days longer, 95% CI 4–25; $p = 0.003$), and had a higher TBscoreII (0.5 points more, 95% CI 0.3–0.7; $p < 0.001$). More females than males were HIV-infected (36% vs. 25%; $p < 0.001$) and more females had a body mass index (BMI) <15 kg/m^2 (11% vs. 6%; $p < 0.001$) and a mid upper arm circumference (MUAC) <200 mm (13% vs. 7%; $p < 0.001$). HIV infection increased the mortality risk, with HIV-1 infection displaying the highest HR (5.0, 95% CI 3.5–7.1), followed by HIV-1+2 (HR 4.2, 95% CI 2.2–7.8) and HIV-2 (HR 2.1, 95% CI 1.2–3.8). A TBscoreII ≥ 4 was associated with increased mortality (HR 2.2, 95% CI 1.5–3.1). Significantly increased HRs were found for signs of wasting; a BMI <18 kg/m^2 was associated with a HR of 1.8 (95% CI 1.3–2.6) and a MUAC <220 mm with a HR of 3.8 (95% CI 2.7–5.2).

Conclusion: The HIV type-associated risk of TB was much higher for HIV-1 patients and higher but less so for HIV-2 patients, compared with the HIV-uninfected. Clinical severity at presentation was also higher for HIV-infected patients, although less so for HIV-2-infected patients, and all HIV-infected patients had a poorer outcome than the uninfected; mortality was 4–5-fold higher for HIV-1 and dually infected patients and two-fold higher for HIV-2-infected patients. These differences between HIV types did not disappear after adjusting for CD4 count.

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1. Introduction

The global burden of tuberculosis (TB) is falling, but is still considerable. The World Health Organization (WHO) estimated that there were 11 million prevalent cases of active TB and 1.5 million deaths from tuberculosis (TB) worldwide in 2013.[1] The targets for TB control are framed within the United Nations Millennium Development Goals, the main goals being to reduce TB incidence by 2015 and to halve the 1990 TB mortality by 2015, which is now within reach on a global level.[1] Many endemic countries have no reliable health and death registration systems and are therefore not able to assess progress in TB control or trends in the TB burden. Such data are imperative for effective TB control.[2]

A number of factors influence TB risk and outcome, but TB risk is difficult to assess without a known denominator, such as a well-characterized population from which the TB cases are drawn, so cases are not missed. Health and Demographic Surveillance Sites (HDSS) are able to deliver such data, and over the last decades we have followed the TB epidemic in Guinea-Bissau within such an HDSS, The Bandim Health Project. During this period, HIV-2 prevalence has decreased markedly and HIV-1 has increased dramatically.[3] However, in the past decades a stable proportion of approximately one third of TB patients have been co-infected with one or more of the HIV types.[4,5] HIV-1 is known to have a major impact on both the risk of acquiring TB and the outcome of the infection,[6] but little is known regarding the impact of HIV-2 and dual infection.

HIV-2 was discovered 2 years after HIV-1,[7] and has mainly been restricted to West Africa, where an estimated one to two million people are infected with the virus.[8] Compared with HIV-1, HIV-2 is less transmissible (5- to 8-fold less efficient than HIV-1 in early-stage disease and rarely the cause of vertical transmission), and is associated with a lower viral load and a slower rate of CD4+ cell count decline.[9] HIV-2 is associated with a slower clinical progression, but in a proportion of patients it will lead to AIDS with clinical features indistinguishable from the syndrome caused by HIV-1. Yet, the majority of HIV-2-infected individuals survive as long-term non-progressors.[8] Studies of HIV in Guinea-Bissau were initiated early in the epidemic,[7,10] and prevalence studies of HIV in Guinea-Bissau in 1987 showed an HIV-2 prevalence of 9% in adults above the age of 14 years in urban Bissau.[11–13] No HIV-1 infection was found at that time. The first case of HIV-1 infection was identified in 1989, when one case of dual infection of HIV-1+HIV-2 was detected.[11]

Over the last 20 years the two viruses have shown different patterns of spread in the country; the prevalence of HIV-2 seems to be stabilizing or decreasing, while HIV-1 prevalence has been increasing gradually. In contrast to the neighbouring countries of Senegal and Guinea-Conakry, which both have a low HIV-1 prevalence (<1 and 1.5%, respectively), Guinea-Bissau has a prevalence comparable to the levels of the most affected countries in the sub-region, with an HIV-1 prevalence of 4% in the latest survey.[3] This survey found a decreasing HIV-2 prevalence of now 4.4%, but the prevalence was still high (>17% among women) in the age group >45 years.

The lower prevalence of HIV-2 relative to HIV-1 and the restricted dissemination of the HIV-2 epidemic have resulted in limited numbers of studies on the impact of HIV-2 on other infections such as TB. Our data from a high-burden TB area, which is the epicentre of the HIV-2 epidemic, has allowed us to address the impact of having one or more of the HIV types.

HIV co-infection is significant for the disease severity of TB as well as for the prognosis. There are limited data on the impact of HIV-2 on TB from Guinea-Bissau, and these have shown a lower mortality in HIV-2-infected patients,[14] but not when adjusted for CD4 count.[15]

Most studies have looked at the extent of TB infection with a laboratory perspective, using, for example, smear grade or biomarkers such as the sedimentation rate. Few studies have addressed the impact of HIV on TB clinical severity because there has been a lack of standardization of severity. Our group developed the Bandim TBscoreII, which is a clinical tool for the assessment of disease severity based on six signs and symptoms specific to TB disease.[16–18] We have systematically collected information on symptoms and have collected clinical signs for all TB patients enrolled in the TB surveillance system in Bissau. The aim of the present study was to relate this information to HIV data and long-term follow-up data also collected in this cohort, with the overall objective of describing the clinical presentation and severity for TB patients co-infected with HIV-1, HIV-2, and HIV-1+2, as well as to describe differences in mortality of TB patients according to the type of HIV co-infection.

2. Materials and methods

2.1. Study location

The study was conducted in the capital Bissau of the West African country Guinea-Bissau, where the Bandim Health Project has been an HDSS since 1978 (http://www.bandim.org). The research has been based on the prospective collection of demographic and health data by active household visits. Good mapping, numbering of houses, and regular censuses have been performed, making long-term follow-up possible in a country with no civil registration. A central feature of the work in Guinea-Bissau has been the attempt to follow long-term consequences of various infections, health conditions, and interventions.

2.2. Epidemiology and study population

This study was based on a well-defined area consisting of five suburban areas in Bissau (Bandim 1, Bandim 2, Belem, Mindara, and Cuntum). The area has a total population of 102 000 and all individuals living in the area are registered by ID number, age, sex, ethnic group, and socio-economic characteristics. Censuses are performed at regular intervals and information on pregnancies, births, mortality, and migration is collected on a daily basis. Since 1996, a surveillance system has detected all TB cases living in the study area, and long-term follow-up has been possible in the majority of cases. Guinea-Bissau has one of the highest TB incidences in the world (279/100 000).[5] We used the population statistics indicated in this publication on incidence, as well as the HIV prevalence figures from the latest survey in the study area.[3] We estimated the population living with the various HIV types and hypothesized that the influx of new TB patients was minimal (or that their HIV status was similar to the population living in the study area). Hence, we estimated the 5-year TB risk from the population living in the study area in 2006.

2.3. Study design

This was a longitudinal, prospective, cohort follow-up study.

2.3.1. Inclusion criteria

Patients were identified through daily visits by field assistants to the three health centres located in the study area and the national referral TB hospital located next to the study area.

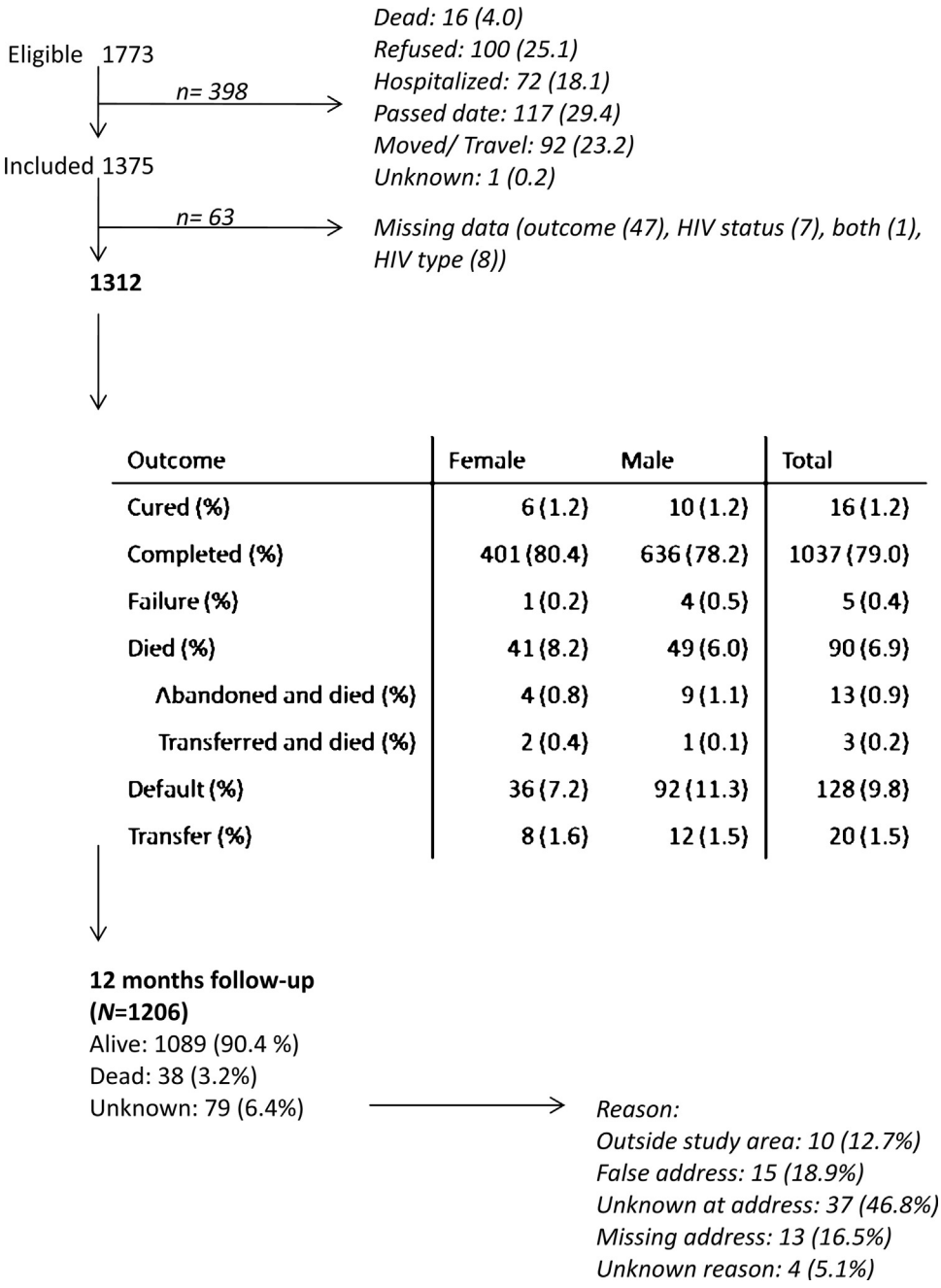
The diagnosis of TB was determined according to the WHO criteria;[19] both smear-positive cases diagnosed on the basis of sputum microscopy for acid-fast bacilli (AFB) and smear-negative cases diagnosed on the basis of clinical criteria after two courses of antibiotics and X-ray were enrolled in the cohort. Extrapulmonary cases were excluded from this study.

TB patients were identified at treatment start, which was often the same day as the diagnosis was made, and invited for consultation and enrolment. During treatment, patients were followed through regular clinical evaluations; after the cessation of treatment, mortality follow-up was conducted through house visits.

2.3.2. Measurements

The severity of TB was assessed using the TBscoreII, recording signs, symptoms, and anthropometry including the presence of cough, chest pain, dyspnoea, and anaemia, body mass index (BMI), and mid upper arm circumference (MUAC), with a maximal score of 8. The TBscoreII has been validated in another cohort and has been grouped into severity classes as follows: I (<2 points), II (2–3 points), and III (≥4 points).[18]

Blood samples were analyzed for HIV at the National Public Health Laboratory in Guinea-Bissau using different tests over the years. In 2003–2008, sera were screened using Enzygnost Anti-HIV 1/2 Plus (Behring Diagnostics GmbH, Marburg, Germany) and reactive sera were confirmed with Capillus HIV-1/HIV-2 (Cambridge Diagnostics, Galway, Ireland), as well as Immunocomb II HIV-1&2 Bispot (Orgenics, Yavne, Israel). From 2008, a new screening test was introduced, the Determine HIV-1/2 (Abbott laboratories, Tokyo, Japan), and HIV type discrimination was performed with SD Bioline HIV 1/2 3.0 (Standard Diagnostics, Kyonggi-do, South Korea). This test has been shown to overestimate the number of dually infected patients,[20] and was replaced in 2012 with First Response HIV-1/HIV-2 WB (PMC Medical, Mumbai, India) and from 2013 with Genie III HIV-1/HIV-2 (Bio-Rad, Steenvorde, France).



Outcome	Female	Male	Total
Cured (%)	6 (1.2)	10 (1.2)	16 (1.2)
Completed (%)	401 (80.4)	636 (78.2)	1037 (79.0)
Failure (%)	1 (0.2)	4 (0.5)	5 (0.4)
Died (%)	41 (8.2)	49 (6.0)	90 (6.9)
Abandoned and died (%)	4 (0.8)	9 (1.1)	13 (0.9)
Transferred and died (%)	2 (0.4)	1 (0.1)	3 (0.2)
Default (%)	36 (7.2)	92 (11.3)	128 (9.8)
Transfer (%)	8 (1.6)	12 (1.5)	20 (1.5)

Figure 1. Flow chart of patients included.

2.4. Antiretroviral treatment (ART)

ART was not widely available before 2007. Since then, all newly diagnosed TB patients with a diagnosis of HIV have been referred to a nearby ART facility for treatment. The vast majority of patients diagnosed with TB in whom the HIV test was positive had no prior knowledge of their HIV status and were therefore not on treatment.

2.5. Statistics

Associations between TB and HIV were evaluated using odds ratios (ORs) and their associated 95% confidence intervals (CIs). Univariate and multivariate analyses were performed using logistic regression methods in Stata v.13 using Cox proportional hazards, with time since the start of treatment as the underlying time variable, adjusted for age and HIV. Univariate analyses were performed separately for men and for women.

2.6. Ethical considerations

Permission for ongoing data collection was obtained from the National Ethics and Health Committee at the Ministry of Health, Bissau. Written information was given to all study participants in the official language of Portuguese and oral information was given to all eligible patients in the widely spoken language of Portuguese Creole. Informed written consent, or a fingerprint in the case of an illiterate subject, has been kept together with the case report forms.

Table 1
Baseline characteristics by HIV status, *n* (%)

	HIV-1	HIV-2	HIV-1+2	Uninfected	*p*-Value
Sex					
Female	114 (47.3)	42 (45.2)	21 (46.7)	322 (34.5)	0.001
Male	127 (52.7)	51 (54.8)	24 (53.3)	611 (65.5)	
Age, years					
15–30	100 (41.5)	14 (15.1)	10 (22.2)	480 (51.5)	<0.001
>30–40	80 (33.2)	29 (31.2)	15 (33.3)	193 (20.7)	
>40–50	39 (16.2)	29 (31.2)	12 (26.7)	127 (13.6)	
>50	22 (9.1)	21 (22.6)	8 (17.8)	133 (14.3)	
Symptom duration					
<2 weeks	12 (4.9)	3 (3.2)	3 (6.7)	34 (3.6)	0.018
2 weeks–2 months	59 (24.5)	22 (23.7)	9 (20.0)	290 (31.1)	
>2–6 months	85 (35.3)	43 (46.2)	11 (24.4)	280 (30.0)	
>6 months	85 (35.3)	25 (26.9)	22 (48.9)	329 (35.3)	
Re-treatment					
No	204 (86.4)	84 (90.3)	40 (88.9)	851 (92.7)	0.022
Yes	32 (28.3)	9 (7.9)	5 (4.4)	67 (9.3)	
TBscoreII >4					
No	115 (50.0)	50 (56.8)	22 (50.0)	536 (58.6)	0.097
Yes	115 (50.0)	38 (43.2)	22 (50.0)	379 (41.4)	
BMI <17 kg/m^2					
No	205 (87.2)	84 (92.3)	39 (88.6)	867 (93.6)	0.009
Yes	30 (12.8)	7 (7.7)	5 (11.4)	59 (6.4)	
MUAC <200 mm					
No	197 (16.8)	81 (6.9)	38 (3.2)	858 (73.1)	<0.001
Yes	37 (15.8)	10 (11.0)	7 (15.6)	65 (7.1)	
CD4 (HIV-infected), cells/mm^3					
< 200	78 (33.5)	36 (33.5)	36 (40.5)	NA	0.626
200–500	40 (17.1)	14 (15.7)	10 (23.3)	NA	
>500	115 (49.4)	39 (43.8)	20 (46.5)	NA	

BMI, body mass index; MUAC, mid upper arm circumference; NA, not applicable.

3. Results

Recruitment began in November 2003 and ended in August 2013. Follow-up was completed in September 2014. We included 1312 patients with TB in our cohort; all patients had completed their anti-TB treatment prior to September 1, 2013. An overview of the patients enrolled in the data analysis is displayed in Figure 1. A total of 379 patients were HIV-infected: 241 had HIV-1, 93 had HIV-2, and 45 were HIV-1+2 dual infected. The mean age of the patients was 35 years (range 15–90 years) and 499 (38%) were females (male/female ratio 1.6).

Characteristics of the patients according to their HIV status are displayed in Table 1. There were more males than females, but the females were more often HIV-infected, in particular with HIV-1, and were younger than males (1 year younger, 95% CI 0.5–2; $p = 0.04$). HIV-1 was the most frequent co-infection, but in the older age groups, HIV-2 was nearly as prevalent and dual infections were more common.

3.1. Tuberculosis incidence

We used the HDSS registry to determine the total population size and calculated the approximate number of HIV-infected using prevalences from an earlier survey in order to estimate the total number of HIV-1, HIV-2, and dually infected subjects in the population. We used the population in 2006 as reported in Lemvik et al.[5] and the HIV prevalences reported in the article by da Silva et al.[3] to estimate the total number of HIV-infected in 2006 (Table 2). In our current TB cohort, we then used the total number of TB patients included in the years 2007–2011 to calculate the 5-year TB risk (Table 2). These estimates led to 6–7-fold higher TB risk ratios (RR) among HIV-1 and dually infected subjects and a 2-fold higher risk for HIV-2 patients (Table 2). Dually infected patients had a 5-year TB RR of 1.3 (95% CI 1.2–1.3) compared with HIV-1 single infected, and the RR for dual-infected vs. HIV-2 patients was 3.4 (95% CI 3.3–3.5). For HIV-1 vs. HIV-2 the RR was 2.7 (95% CI 2.6–2.7).

3.2. Clinical presentation

One hundred and thirteen (9%) were retreatment cases; this was more frequent among HIV-1-infected subjects (28% were retreated). Two thirds of the patients, 880/1312 (67%), had a long duration of symptoms (>2 months) prior to TB diagnosis and this was also associated with HIV status (Table 1).

Table 2
Tuberculosis incidence in the 2006 cohort by HIV type

	Population	HIV-1 estimate based on survey (%)	HIV-2 estimate based on survey (%)	HIV-1+2 estimate based on survey (%)	HIV uninfected estimate based on survey (%)
Male	24 422	879 (3.6)	659 (2.7)	83 (0.34)	22 801 (93.4)
Female	28 432	1194 (4.2)	1108 (3.9)	165 (0.58)	25 965 (91.3)
Total	52 854	2073	1767	248	48 766
TB cases 2007–2011	638	118	38	18	464
5-year risk/100 000	1207	5692	2150	7258	951
RR of TB (95% CI)	-	6.6 (5.9–6.2)	2.3 (2.2–2.4)	7.7 (7.5–7.8)	1

TB, tuberculosis; RR, relative risk; CI, confidence interval.

Most patients had a severe clinical presentation at diagnosis; the mean TBscoreII was 3.6 (95% CI 5.5–3.7) and 43% (554/1277) of the patients had a TBscoreII ≥4, which is defined as high severity.[18] Among HIV-1-infected patients, 50% (115/230) had a TBscoreII ≥4; for HIV-2 this was 43% (38/88) and for those with a dual infection it was 50% (22/44). Nutritional status constitutes a major part of the TBscoreII, and both BMI and MUAC were markedly low in a high proportion of patients and significantly associated with the HIV type; patients with HIV-1 and the dually infected had particularly low BMI and MUAC (Table 1).

Compared with the men, the women had a longer duration of symptoms (14 days longer, 95% CI 4–25; $p = 0.003$), a significantly higher TBscoreII (0.5 points more, 95% CI 0.3–0.7; $p < 0.001$), and more had a BMI <18 kg/m^2 (48% vs. 38%; $p = 0.003$) and a MUAC <220 mm (31% vs. 19%; $p < 0.001$) (Table 3).

3.3. Outcome

The standard TB outcomes are displayed in Figure 1; the proportion of successful treatment (cure or completed) was close to the WHO goal of 85% (80%). During the treatment period, a total of 106/1312 (8%) patients died, and during the entire 12-month follow-up period, 144/1312 (11%) died (Table 4). Patients above the age of 30 years had a higher risk of dying, in particular those aged >50 years (HR 2.8, 95% CI 1.7–4.4). All HIV single and dual infected patients had significantly increased mortality (Table 4), with an adjusted HR above 2 for HIV-2 and nearly 5 for HIV-1 and dual infection. Mortality according to the HIV type is displayed in Figure 2. When adjusting for CD4 count at TB diagnosis, we found that this changed the mortality by HIV type only a little, and the adjusted HR for death for HIV-2 vs. HIV-1 was 0.49 (95% CI 0.27–0.89).

As expected, we found a marked excess mortality for patients presenting with a high TBscoreII (Figure 3). The mortality rate ratio for patients with a high severity at inclusion was twice as high as for patients with a low severity. This was also seen after adjusting for CD4 count, which was only decreased for the HIV co-infected patients.

Treatment outcome did not differ significantly by gender (Figure 1). However, the tendency was that more females than males completed treatment/died and more males than females abandoned treatment.

Table 3
Risk factors by gender

	Female (%) $n = 499$	Male (%) $n = 813$	All (%) $n = 1312$	p-Value for difference
Age, years				
15–30	253 (50.7)	351 (43.2)	604 (46.0)	0.041
>30–40	105 (21.0)	212 (26.1)	317 (24.1)	
>40–50	71 (14.2)	136 (16.7)	207 (15.8)	
>50	70 (14.0)	114 (14.0)	184 (14.0)	
HIV				
Uninfected	322 (64.5)	611 (75.2)	933 (71.1)	0.001
HIV-1	114 (22.9)	127 (15.6)	241 (18.4)	
HIV-2	42 (8.4)	51 (6.3)	93 (7.1)	
HIV-1+2	21 (4.2)	24 (2.9)	45 (3.4)	
Symptom duration				
<2 weeks	19 (3.8)	33 (4.1)	52 (3.9)	0.005
2 weeks–2 months	117 (23.5)	263 (32.4)	380 (28.9)	
>2–4 months	177 (35.5)	242 (29.8)	419 (31.9)	
>4 months	186 (37.3)	275 (33.8)	461 (35.1)	
Re-treatment	41 (8.2)	72 (8.9)	113 (8.6)	0.756
TBscoreII ≥4	242 (48.5)	312 (38.4)	575 (42.2)	<0.001
BMI <18 kg/m^2	241 (48.3)	334 (41.1)	575 (43.8)	0.003
MUAC <220 mm	150 (30.6)	156 (19.2)	306 (23.3)	<0.001

BMI, body mass index; MUAC, mid upper arm circumference.

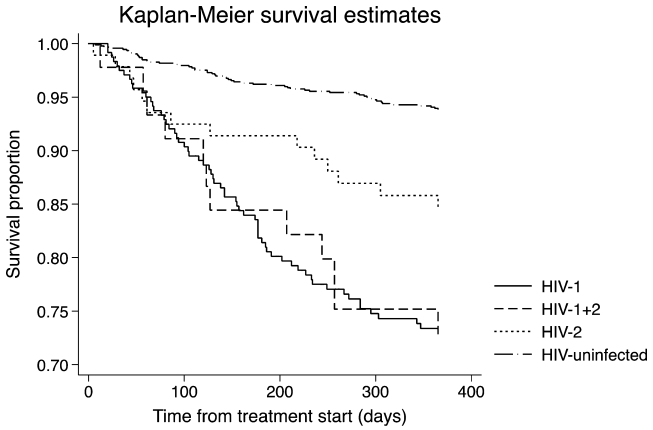


Figure 2. Survival according to HIV status.

4. Discussion

With the use of HDSS data on the population and existing HIV prevalence survey data, we were able to demonstrate the different TB risks according to the type of HIV infection. The outcome differed substantially by HIV status, even when adjusting for CD4. We found that the outcome of having TB is poorer when the subject is HIV-infected, mostly for HIV-1 and those with HIV-1+2 dual infections, but also for HIV-2. The TBscoreII prediction of mortality was not influenced by HIV status.

The higher TB risk for those with a dual infection could be interpreted as a sign of dual infection being worse than HIV-1 single infection. However, this may not necessarily be the case. Esbjörnsson et al. have shown protective effects of having HIV-2 prior to HIV-1,[21] and while several other reports have shown that the dually infected have similar mortality to those with an HIV-1 single infection,[22] it is most likely because of the time point at which the dually infected are diagnosed,[9] which is often at a time of advanced HIV disease, such as in these patients with active TB. With the data available we cannot clarify whether the dually infected patients were first infected with HIV-2 and whether this delayed their progression to AIDS.

Previous studies have shown increased mortality for HIV co-infected TB patients,[14,23–25] increased age,[23–30] and wasting,[14,25,31] which is in line with our findings. However, data on the relationship between clinical severity and mortality are sparse and the availability of clinical severity data in this study is a strength.

Gender differences in TB severity and treatment outcome are seldom assessed. While women are less likely to be diagnosed with TB[32–36] and referred to treatment, they are shown to follow through at higher rates than males,[33–37] and are more often HIV co-infected.[34] The latter two observations are also reflected in our data. The increased severity shown here could reflect the delay in health-seeking/referral to treatment and the increased HIV co-infection amongst females. Further, it has been suggested that females progress to disease at earlier ages,[38] which could be the reason for the age difference in our cohort.

A strength of this study is that it is by far the largest cohort of TB patients with HIV-2 and dual co-infection reported. Our findings are in contrast to those of van der Sande et al. from a large Gambian HIV cohort with several HIV-2 and dually infected patients, of whom 368 were diagnosed with TB.[15] They also found large survival differences between the HIV-1 and HIV-2 infected, but the difference disappeared when adjusting for CD4 count, suggesting that it is the degree of advanced HIV disease that is important, rather than the HIV type. HIV-2 has a slower and more infrequent progression towards immunodeficiency, and the findings of van der Sande et al. suggest that HIV-2 patients with advanced

Table 4
Risk factors for death

	Number of individuals, *n* (*N* = 1312)	Number of deaths, *n* (%) (*n* = 144; 11%)	Person-years of exposure	Deaths/ person-years	Crude HR (95% CI)[a]	Adjusted HR (95% CI)[b]
Sex						
Female	499	62 (12.4)	453.3	62/453.3	1	1
Male	813	82 (10.1)	735.8	82/735.8	0.81 (0.59–1.13)	0.94 (0.67–1.31)
Age, years						
15–30	604	37 (6.1)	562.7	37/562.7	1	1
>30–40	317	47 (14.8)	278.0	47/278.0	2.55 (1.66–3.93)	1.88 (1.21–2.91)
>40–50	207	26 (12.6)	185.2	26/185.2	2.12 (1.28–3.50)	1.60 (0.96–2.66)
>50	184	34 (18.5)	163.2	34/163.2	3.15 (1.98–5.01)	2.76 (1.73–4.40)
HIV						
Uninfected	933	56 (6.0)	875.0	56/875.0	1	1
HIV-1	241	62 (25.7)	193.8	62/193.8	4.89 (3.41–7.02)	4.97 (3.46–7.14)
HIV-2	93	14 (15.1)	82.9	14/82.9	2.62 (1.46–4.71)	2.10 (1.16–3.80)
HIV-1+2	45	12 (26.7)	37.4	12/37.4	4.94 (2.65–9.21)	4.19 (2.24–7.84)
CD4 count[c], cells/mm^3						
>500	127	20 (15.8)	108.5	20/108.5	1	1
200–500	64	7 (10.9)	59.8	7/59.8	0.64 (0.27–1.51)	0.64 (0.27–1.52)
<200	174	61 (35.1)	133.3	61/133.3	2.43 (1.47–4.03)	2.47 (1.49–4.09)
Symptom duration						
<2 weeks	52	3 (5.8)	49.4	3/49.4	1	1
2 weeks–2 months	380	34 (8.9)	348.7	34/348.7	1.61 (0.49–5.23)	2.05 (0.63–6.67)
>2–4 months	419	42 (10.0)	381.8	42/381.8	1.80 (0.56–5.81)	1.97 (0.61–6.37)
>4 months	461	65 (14.1)	409.2	65/409.2	2.60 (0.82–8.28)	2.92 (0.92–9.31)
Re-treatment						
No	1179	124 (10.5)	1071.2	124/1071.2	1	1
Yes	113	20 (17.7)	98.9	20/98.9	1.74 (1.09–2.79)	1.24 (0.77–2.00)
TBscoreII ≥4						
No	723	51 (7.1)	676.7	51/676.7	1	1
Yes	554	84 (15.2)	484.1	84/484.1	2.29 (1.62–3.24)	2.16 (1.53–3.06)
BMI <18 kg/m^2						
No	721	56 (7.8)	667.8	56/667.8	1	1
Yes	575	81 (14.1)	510.8	81/510.8	1.88 (1.34–2.65)	1.83 (1.30–2.58)
MUAC<220 mm						
No	986	68 (6.9)	919.4	968/919.4	1	1
Yes	306	75 (24.5)	251.1	75/251.1	3.99 (2.88–5.45)	3.76 (2.69–5.23)

HR, hazard ratio; CI, confidence interval; BMI, body mass index; MUAC, mid upper arm circumference.
[a] Time since start of treatment as the underlying time variable.
[b] Time since start of treatment as the underlying time variable, adjusted for age and HIV.
[c] Only HIV-infected, *n* = 379.

disease are at the same risk as HIV-1 and dually infected patients at the same stage. Our study population is markedly different, being a TB cohort in which some have HIV; the Gambian cohort comprised HIV patients some of whom were diagnosed with TB. Hence, in our population there were more patients with advanced disease in which TB was a part of AIDS, also among the HIV-2 infected, with a similar proportion as among the HIV-1-infected (one third of the patients) having a CD4 count below 200 cells/mm^3. Adjusting for low CD4 did not, therefore, change estimates much, and our results indicate that even at the same low CD4 levels, HIV-2 is still associated with a survival benefit with simultaneous TB compared with HIV-1–TB-co-infection.

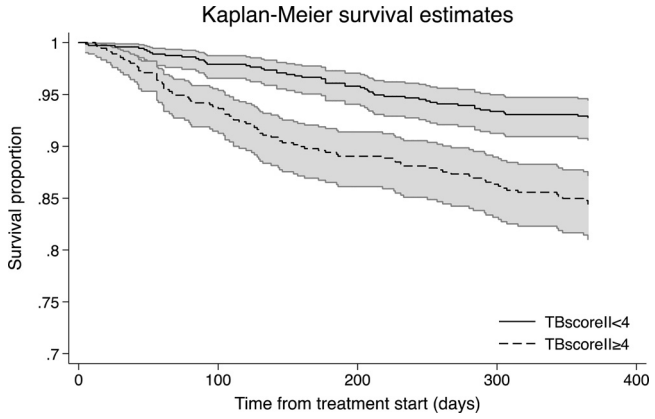


Figure 3. Mortality according to clinical severity at TB treatment start, with 95% confidence intervals.

A weakness of this study is that we did not have individualized data on HIV status in the background population, but used survey data to estimate the number infected. Our TB incidence by HIV type is therefore based on the observation of TB cases over a 5-year period and knowledge of the size of the population, as well as the distribution of HIV types, and not on real-time observation of TB risk in a cohort of HIV-infected subjects. This is an approximation, and so is the presumption that most of the TB patients enrolled in our cohort were long-term residents in the study area. There may have been some influx of HIV-infected patients from villages into the capital Bissau to seek treatment, and this could have biased our estimation towards a higher risk of TB among HIV-infected subjects than was actually the case. However, we know that only a minority of the TB patients had recently migrated into the study area, so we consider this is minor source of bias.

Another limitation of this study was the lack of confirmatory HIV type discriminatory testing for the entire study period. In the last part of the study, the confirmation of HIV type was done using a second Bioline, which has been shown to be inaccurate, in particular with regard to HIV-1+2 dual infection.[20] There may therefore be patients identified as HIV-1 single infection in our data, who are in fact dually infected. This potential bias likely did not have a major impact on our findings since the differences between HIV-1 and dually infected subjects were small.

Our findings underline the importance of immediate referral to ART facilities for treatment for TB patients newly diagnosed with HIV, regardless of the type. HIV co-infected patients presented with a more severe clinical status and displayed excess mortality even in the first month of TB treatment. Hence, rapid HIV diagnosis for all new TB patients is of the utmost importance. We also found that the TBscoreII was an easily obtainable measure to identify which patients were at risk, unaffected by HIV status, and this could be used in the triage of patients.

In conclusion we have documented that the HIV type-associated risk of TB is 6-fold higher for HIV-1-infected patients, 7-fold higher for the HIV-1+2 dually infected, and 2-fold higher for HIV-2 single infected, compared with the HIV-uninfected. Clinical severity at presentation was also higher for the HIV-infected, mostly for HIV-1 and dually infected patients and least for the HIV-2 infected. All HIV-infected subjects had poorer outcomes than the uninfected, with a 4–5-fold higher mortality for HIV-1 and dually infected patients and 2-fold higher for the HIV-2 infected, although the differences between HIV types disappeared after adjusting for CD4 count.

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Ethics: The data were collected with informed consent from the patients and the data collection was approved by the local ethics committee in Bissau and by the Danish National Committee on Biomedical Research Ethics, as stated in the Methods section of the manuscript.

Conflict of interest: We declare that none of the authors has a conflict of interest.

References

1. World Health Organization. Global tuberculosis control: surveillance, planning, financing. WHO Report 2013. WHO/HTM/TB/2014.08. Geneva, WHO; 2014.
2. Dye C, Bassili A, Bierrenbach AL, Broekmans JF, Chadha VK, Glaziou P, et al. Measuring tuberculosis burden, trends, and the impact of control programmes. *Lancet Infect Dis* 2008;**8**:233–43.
3. da Silva ZJ, Oliveira I, Andersen A, Dias F, Rodrigues A, Holmgren B, et al. Changes in prevalence and incidence of HIV-1, HIV-2 and dual infections in urban areas of Bissau, Guinea-Bissau: is HIV-2 disappearing? *AIDS* 2008;**22**:1195–202.
4. Gustafson P, Gomes VF, Vieira CS, Rabna P, Seng R, Johansson P, et al. Tuberculosis in Bissau: incidence and risk factors in an urban community in Sub-Saharan Africa. *Int J Epidemiol* 2004;**33**:163–72.
5. Lemvik G, Rudolf F, Vieira F, Sodemann M, Ostergaard L, Rodrigues A, et al. Decline in overall, smear-negative and HIV-positive TB incidence while smear-positive incidence stays stable in Guinea-Bissau 2004–2011. *Trop Med Int Health* 2014;**19**:1367–76.
6. Zumla A, Raviglione M, Hafner R, von Reyn CF. Tuberculosis. *N Engl J Med* 2013;**368**:745–55.
7. Clavel F, Guetard D, Brun-Vezinet F, Chamaret S, Rey MA, Santos-Ferreira MO, et al. Isolation of a new human retrovirus from West African patients with AIDS. *Science* 1986;**233**:343–6.
8. Rowland-Jones SL, Whittle HC. Out of Africa: what can we learn from HIV-2 about protective immunity to HIV-1? *Nat Immunol* 2007;**8**:329–31.
9. Esbjornsson J, Mansson F, Kvist A, Isberg PE, Nowroozalizadeh S, Biague AJ, et al. Effect of HIV-2 infection on HIV-1 disease progression and mortality. *AIDS* 2014;**28**:614–5.
10. Fultz PN, Switzer WM, Schable CA, Desrosiers RC, Silva DP, McCormick JB. Seroprevalence of HIV-1 and HIV-2 in Guinea Bissau in 1980. *AIDS* 1988;**2**:129–32.
11. Poulsen AG, Aaby P, Gottschau A, Kvinesdal BB, Dias F, Molbak K, et al. HIV-2 infection in Bissau, West Africa, 1987–1989: incidence, prevalences, and routes of transmission. *J Acquir Immune Defic Syndr* 1993;**6**:941–8.
12. Holmgren B, Andersson S, Harding E, Schim van der Loeff M, Vastrup P, Aaby P, et al. Increased prevalence of HTLV-1 among HIV-2-infected women but not HIV-2-infected men in rural Guinea-Bissau. *J Acquir Immune Defic Syndr* 2002;**30**:342–50.
13. Poulsen AG, Kvinesdal B, Aaby P, Molbak K, Frederiksen K, Dias F, et al. Prevalence of and mortality from human immunodeficiency virus type 2 in Bissau, West Africa. *Lancet* 1989;**1**:827–31.
14. Gustafson P, Gomes VF, Naucler A, Vieira CS, Samb B, Aaby P, et al. Clinical predictors for death in HIV-positive and HIV-negative tuberculosis patients in Guinea-Bissau. *Infection* 2007;**35**:69–80.
15. van der Sande MA, Schim van der Loeff MF, Bennett RC, Dowling M, Aveika AA, Togun TO, et al. Incidence of tuberculosis and survival after its diagnosis in patients infected with HIV-1 and HIV-2. *AIDS* 2004;**18**:1933–41.
16. Wejse C, Gustafson P, Nielsen J, Gomes VF, Aaby P, Andersen PL, et al. A clinical score system for monitoring tuberculosis in a low-resource setting. *Scand J Infect Dis* 2008;**40**:111–20.
17. Rudolf F, Joaquim LC, Vieira C, Bjerregaard-Andersen M, Andersen A, Erlandsen M, et al. The Bandim tuberculosis score: reliability and comparison with the Karnofsky performance score. *Scand J Infect Dis* 2013;**45**:256–64.
18. Rudolf F, Lemvik G, Abate E, Verkuilen J, Schon T, Gomes VF, et al. TBscore II: refining and validating a simple clinical score for treatment monitoring of patients with pulmonary tuberculosis. *Scand J Infect Dis* 2013;**45**:825–36.
19. Harries AD, Maher D, Graham S. TB/HIV: a clinical manual. 2nd ed. WHO/HTM/TB/2004.329. Geneva: WHO; 2004.
20. Honge BL, Bjarnason Obinah MP, Jespersen S, Medina C, Te Dda S, da Silva ZJ, et al. Performance of 3 rapid tests for discrimination between HIV-1 and HIV-2 in Guinea-Bissau, West Africa. *J Acquir Immune Defic Syndr* 2014;**65**:87–90.
21. Esbjörnsson J, Mansson F, Kvist A, Isberg PE, Nowroozalizadeh S, Biague AJ, et al. Inhibition of HIV-1 disease progression by contemporaneous HIV-2 infection. *N Engl J Med* 2012;**367**:224–32.
22. Prince PD, Matser A, van Tienen C, Whittle HC, Schim van der Loeff MF. Mortality rates in people dually infected with HIV-1/2 and those infected with either HIV-1 or HIV-2: a systematic review and meta-analysis. *AIDS* 2014;**28**:549–58.
23. Kirenga BJ, Levin J, Ayakaka I, Worodria W, Reilly N, Mumbowa F, et al. Treatment outcomes of new tuberculosis patients hospitalized in Kampala, Uganda: a prospective cohort study. *PLoS One* 2014;**9**:e90614.
24. Millet JP, Orcau A, Rius C, Casals M, de Olalla PG, Moreno A, et al. Predictors of death among patients who completed tuberculosis treatment: a population-based cohort study. *PLoS One* 2011;**6**:e25315.
25. Waitt CJ, Squire SB. A systematic review of risk factors for death in adults during and after tuberculosis treatment. *Int J Tuberc Lung Dis* 2011;**15**:871–85.
26. Gutierrez PD, Fernandez MC. Vitamin D2 in cutaneous tuberculosis; (progress report). *Acta Med Philipp* 1950;**7**:55–9.
27. Duarte EC, Bierrenbach AL, Barbosa da Silva Jr J, Tauil PL, de Fatima Duarte E. Factors associated with deaths among pulmonary tuberculosis patients: a case–control study with secondary data. *J Epidemiol Community Health* 2009;**63**:233–8.
28. Feng JY, Su WJ, Chiu YC, Huang SF, Lin YY, Huang RM, et al. Initial presentations predict mortality in pulmonary tuberculosis patients—a prospective observational study. *PLoS One* 2011;**6**:e23715.
29. Kourbatova EV, Borodulin BE, Borodulina EA, del Rio C, Blumberg HM, Leonard Jr MK. Risk factors for mortality among adult patients with newly diagnosed tuberculosis in Samara, Russia. *Int J Tuberc Lung Dis* 2006;**10**:1224–30.
30. Lefebvre N, Falzon D. Risk factors for death among tuberculosis cases: analysis of European surveillance data. *Eur Respir J* 2008;**31**:1256–60.
31. Sacks LV, Pendle S. Factors related to in-hospital deaths in patients with tuberculosis. *Arch Intern Med* 1998;**158**:1916–22.
32. Begum V, de Colombani P, Das Gupta S, Salim AH, Hussain H, Pietroni M, et al. Tuberculosis and patient gender in Bangladesh: sex differences in diagnosis and treatment outcome. *Int J Tuberc Lung Dis* 2001;**5**:604–10.
33. Karim F, Ahmed F, Begum I, Johansson E, Diwan VK. Female–male differences at various clinical steps of tuberculosis management in rural Bangladesh. *Int J Tuberc Lung Dis* 2008;**12**:1336–9.
34. Kivihya-Ndugga LE, van Cleeff MR, Ng'ang'a LW, Meme H, Odhiambo JA, Klatser PR. Sex-specific performance of routine TB diagnostic tests. *Int J Tuberc Lung Dis* 2005;**9**:294–300.
35. Ramsay A, Bonnet M, Gagnidze L, Githui W, Varaine F, Guerin PJ. Sputum, sex and scanty smears: new case definition may reduce sex disparities in smear-positive tuberculosis. *Int J Tuberc Lung Dis* 2009;**13**:613–9.
36. Uplekar MW, Rangan S, Weiss MG, Ogden J, Borgdorff MW, Hudelson P. Attention to gender issues in tuberculosis control. *Int J Tuberc Lung Dis* 2001;**5**:220–4.
37. Hudelson P. Gender differentials in tuberculosis: the role of socio-economic and cultural factors. *Tuber Lung Dis* 1996;**77**:391–400.
38. Holmes CB, Hausler H, Nunn P. A review of sex differences in the epidemiology of tuberculosis. *Int J Tuberc Lung Dis* 1998;**2**:96–104.