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Mortality and loss to follow-up among tuberculosis and HIV co-infected patients in rural southwestern Uganda

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SUMMARY

BACKGROUND: We describe the presentation and outcome of care among patients with tuberculosis (TB) and human immunodeficiency virus (HIV) co-infection from a prospective observational cohort in Uganda.

METHODS: We analysed basic demographics, CD4+ counts, time of initiating antiretroviral therapy (ART), clinical and haematological parameters and outcome of care of 386 patients enrolled between February 2007 and March 2010.

RESULTS: At presentation, 56.7% of the patients were sputum-positive, 89.9% had new TB infection, 62.7% had wasting, 78.7% were anaemic, 72.1% had a CD4+ count of <200 cells/mm^3, 20.2% had pneumonia, 50.3% had oral thrush and 1.3% had Kaposi's sarcoma. Patients developing TB within 3 months of starting ART were less likely to have wasting, to be anaemic or to have a CD4+ count of <100 cells/mm^3. The cure, default and death rates were respectively 54.3%, 24% and 16%. At 8 months, 53 (13.7%) were confirmed dead, 119 (30.8%) were lost to follow-up, 28 (7.3%) were transferred out and 1 (0.3%) had treatment failure. Mortality and loss to follow-up were associated with failure to start ART and having a CD4+ count of <200 cells/mm^3.

CONCLUSION: In Uganda, TB-HIV patients present with severe immune suppression and are at increased risk of death and loss to follow-up, particularly those not on ART. There is need for early identification and improved follow-up of TB-HIV co-infected patients.

KEY WORDS: TB-HIV; mortality; loss to follow-up

THE HUMAN immunodeficiency virus (HIV) pandemic has resulted in an increase in the number of tuberculosis (TB) cases, and TB remains a major cause of morbidity and mortality among persons living with HIV (PLWH).[1–6] In sub-Saharan Africa, persons living with HIV still present late for care with severe immune suppression and with a number of opportunistic infections, notably TB.[4,7]

As many sub-Saharan countries have not yet met the World Health Organization (WHO) targets in terms of TB case detection and cure rates, TB is likely to remain a major cause of morbidity and mortality among PLWH.[8] As of 2007, Uganda's sputum-positive case detection, TB cure and default rates were at respectively 51%, 70% and 13%.[7,9] To improve these statistics, a number of sub–Saharan African countries with a high prevalence of TB and HIV are rolling out TB-HIV collaborative activities aimed at early identification of patients with co-infection and instituting appropriate care to reduce the associated morbidity and mortality.[10]

Studies have described mortality and loss to follow-up among PLWH attending HIV care services at large tertiary care centres.[11] However, limited data have been published on such outcomes among TB-HIV co-infected patients attending large public facilities in high TB and HIV prevalence areas. This study describes the presentation, mortality and loss to follow-up among HIV patients with TB disease attending an integrated TB-HIV clinic at Mbarara Regional Referral hospital (MRRH), Mbarara, Uganda, and explores factors associated with mortality and loss to follow-up.

METHODS

Setting

MRRH is an urban hospital located in Mbarara Municipality, southwestern Uganda. The hospital serves a predominantly rural population of over 1.3 million people, and is the main provider of HIV and TB diagnostic and care services in the region. The rate of TB infection and the prevalence of HIV among active TB patients in Uganda are estimated to be respectively 468 per 100 000 population and 39%.[9] The hospital uses fluorescent microscopy, chest radiography and clinical criteria to diagnose TB. It lacks facilities for sputum culture and drug susceptibility testing (DST). Sputum samples from patients with suspected drug-resistant mycobacteria are sent to the central public health laboratory in Kampala, 260 km from

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Mbarara town, for DST. Newly diagnosed pulmonary TB patients are treated with 2 months of rifampicin, isoniazid (INH), pyrazinamide and ethambutol (EMB) followed by 6 months of EMB and INH.[12] The treatment regimen does not comply with WHO recommendations and the practice is an operational approach as the country transitions to the recommended regimen. The hospital has not started treating drug-resistant TB, and the region lacks a strong community-based directly observed therapy service.

Since 1998, the hospital has been offering both HIV basic care and antiretroviral therapy (ART). As part of routine care, PLWH are regularly screened for TB. The hospital offers provider-initiated HIV counselling and testing (PICT), and patients are offered same-day rapid HIV testing and counselling services.

Since 2006, the hospital has been running an integrated TB-HIV clinic which offers ART, cotrimoxazole for prophylaxis and other components of the basic HIV care package, including diagnosis and treatment of opportunistic infections. The ART regimens are individually tailored, depending on existing comorbidities, particularly anaemia, hepatitis B and any suspected drug interactions. The integrated TB-HIV care clinic uses the existing hospital laboratories and Ministry of Health care tools for TB and HIV care. Every 6 months, patients undergo CD4+ and complete blood count. Organ function and viral load tests are not routinely performed. Patients who develop TB in the HIV clinic are transferred to the integrated TB-HIV care clinic until they achieve cure of TB (Figure 1). The clinic does not offer any transport reimbursements for patients and can only physically track those patients who reside within 30 km.

Study population

Individuals eligible for inclusion in the analysis were patients enrolled for both HIV and TB care in the integrated TB-HIV clinic and who had both HIV infection and TB disease. After ART initiation, patients were followed up at 2 weeks; if they had no symptoms suggestive of drug toxicity, they were reviewed every 30 or 60 days thereafter until they completed their anti-tuberculosis treatment. The TB and ART drugs were subsequently administered at home by their treatment supporter, usually a family member. We measured adherence using a 7-day medication adherence recall and pill count. The study subjects were followed up for the standard 8-month duration of anti-tuberculosis treatment.[12]

Data collection

Data were summarised for patients who were enrolled between February 2007 and March 2010 and were due to complete their anti-tuberculosis treatment in or before December 2010. The data summarised include sex, age, distance between the patient's home and the hospital, date of starting anti-tuberculosis treatment, care entry point, date of HIV testing, timing of TB diagnosis (whether TB was diagnosed

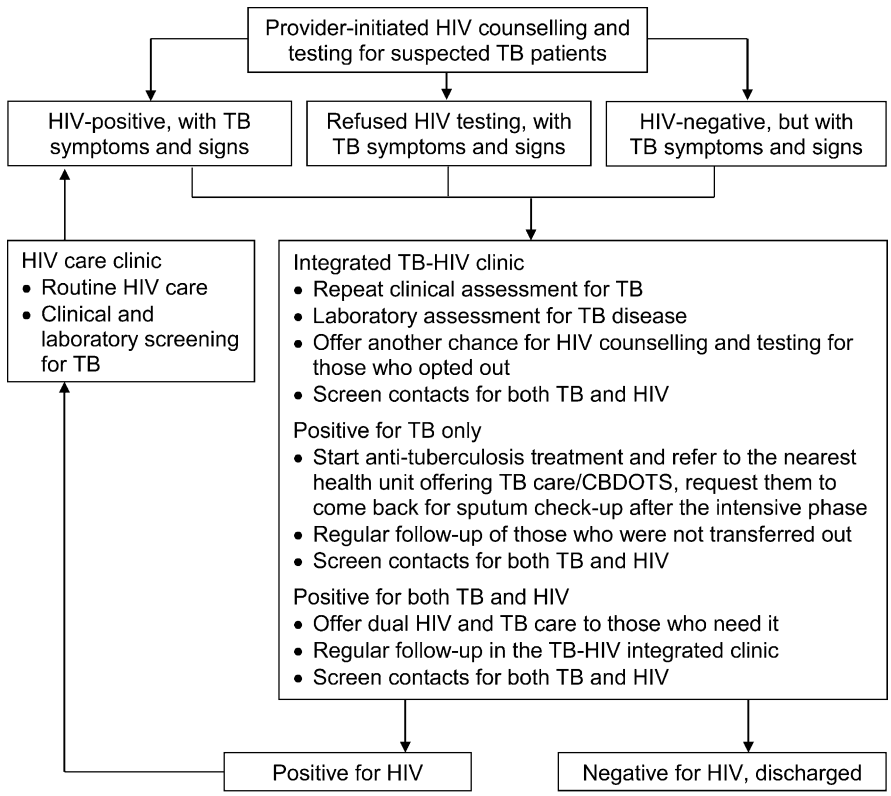

Figure 1 Patient care pathways in and out of the integrated TB-HIV care clinic, Mbarara Regional Referral Hospital, Uganda. HIV = human immunodeficiency virus; TB = tuberculosis; CBDOTS = community-based directly observed treatment service.

within 3 months of ART), other diagnosis at initiation of TB treatment; patient category; risk factors for acquiring TB infection, such as contact with an infected person, poor ventilation, smoking and consumption of alcohol; TB disease classification; TB treatment regimen, initial ART regimen, and date of initiation of ART; clinical parameters such as weight, height, CD4+ count, haemoglobin, white blood cell count, total lymphocyte count at enrolment; last date the patient was seen and outcome of care.

Definitions

Patients were categorised as new, relapse or defaulters as stipulated in the Uganda Ministry of Heath National Tuberculosis and Leprosy guidelines.[12] The disease classification was defined as sputum-positive, sputum-negative, extra-pulmonary or both sputum-positive and extra-pulmonary TB.[12] A patient was classified as underweight if the body mass index was $\leqslant$18.5 kg/m^2, normal if it was 18.5–24.9, overweight if it was 25–29.9 and obese if it was $\geqslant$30.[13] Anaemia was defined as haemoglobin $\leqslant$12 g/dl for women and 13 g/dl for men;[14,15] a white blood cell count of $<$3400 cells/mm^3 was defined as leucopenia,[16] and a total lymphocyte count of $<$1000 cells/μl was defined as lymphocytopenia. The primary outcome of care was classified as completed, cured, transferred out or treatment failure,[3,12] dead if the patient died in the hospital or if death outside the hospital was confirmed by the treatment supporter or patient tracker. Patients were classified as lost to follow-up if they did not return for care, there were no communications within 8 months after initiation of antituberculosis treatment, and we could not confirm whether they were alive, dead or had self transferred out through the patient tracker, treatment supporter or using their personal telephone contact.

The study was approved by the research ethics committee and Institution Review Board of Mbarara University of Science and Technology.

Statistical analysis

We used proportions to describe and present the distribution of baseline demographics and other characteristics of the study population. We used the Cox proportional hazards (CPH) regression methods to determine hazard ratios (and 95% confidence interval) for mortality and loss to follow-up. CPH regression procedures were also used to adjust for confounding. Variables to be included in the multiple regression were chosen based on statistical significance of $P < 0.05$ in the univariate analysis. The survival curves for the patients who received both antituberculosis treatment and highly active antiretroviral therapy and those who did not start ART during antituberculosis treatment were compared using the Kaplan-Meier methods. The time of follow-up was measured from the date of initiation of TB treatment and censored at the date when a patient was cured of TB, transferred out or experienced treatment failure. The primary event for the analysis was mortality or loss to follow-up. Data were analysed using STATA, version 10.0 for Windows (Stata Corp, College Station, TX, USA).

RESULTS

Demographic and other baseline characteristics

A total of 386 TB-HIV co-infected patients were enrolled and followed up for 8 months. Of these, 142 (36.8%) were female. The median age was 33 years

Table 1 Characteristics of TB-HIV co-infected patients attending Mbarara Regional Referral Hospital, February 2007–March 2010 (N = 386)

	n (%)
Female	142 (36.8)
Disease classification	
Sputum-positive pulmonary TB	219 (56.7)
Sputum-negative pulmonary TB	103 (26.7)
Extra-pulmonary TB	49 (12.7)
Both pulmonary and extra-pulmonary TB	15 (3.9)
TB disease status/category	
New	347 (89.9)
Defaulter	15 (3.9)
Relapse	22 (5.7)
Treatment failure	2 (0.5)
Body mass index	
Underweight	242 (62.7)
Normal	138 (35.7)
Overweight	6 (1.6)
ART status	
Receiving ART before developing TB disease	68 (17.6)
Started ART during anti-tuberculosis treatment	160 (41.5)
Did not start ART	158 (40.9)
CD4+ count at enrolment, cells/mm^3	
0–100	193 (50.4)
101–200	83 (21.7)
>200	107 (27.9)
Anaemia	263 (78.7)
Low white blood cell counts	67 (38.5)
Low lymphocyte counts	69 (36.9)
History of other risk factors	
Smoking	168 (43.5)
Poor ventilation	67 (17.4)
Alcohol consumption	255 (66.1)
History of contact	102 (26.5)
Other diagnoses	
Prurigo	40 (10.4)
Pneumonia	78 (20.2)
Kaposi's sarcoma	5 (1.3)
Diarrhoea	82 (21.2)
Fungal infestation	38 (9.9)
Oral thrush	194 (50.3)
Jaundice	2 (0.5)
Distance, km	
0–30	215 (55.7)
>30	171 (44.3)
Care entry point	
Routine HIV testing	101 (26.3)
Adult HIV clinic	248 (64.1)
Lower level health unit	1 (0.3)
Medical ward	23 (6.0)
Out-patients	5 (1.3)
Self refer	8 (2.1)

TB = tuberculosis; HIV = human immunodeficiency virus; ART = antiretroviral therapy.

Table 2 Comparison of patients diagnosed with TB while on ART and those who received anti-tuberculosis treatment prior to initiation of ART in Mbarara Regional Referral Hospital, Uganda

Variable	On ART *n* (%)	Not on ART *n* (%)	OR (95%CI)	*P* value
Nature of TB				
Sputum-positive	39 (57.4)	180 (56.6)	1.03 (0.59–1.81)	0.90
Sputum-negative	22 (32.4)	81 (25.5)	1.44 (0.76–2.56)	0.24
Extra-pulmonary	7 (10.3)	42 (13.2)	0.75 (0.29–1.85)	0.51
Weight category				
Underweight	28 (41.2)	214 (67.3)	0.34 (0.19–0.60)	0.00
Normal weight	38 (55.9)	100 (31.4)	2.76 (1.57–4.88)	0.00
CD4 count, cells/mm^3				
0–100	22 (32.4)	171 (54.3)	0.40 (0.22–0.72)	0.00
101–200	20 (29.4)	63 (2.0)	1.01 (0.53–1.90)	0.98
>200	26 (38.2)	81 (25.7)	1.79 (0.99–3.21)	0.03
Haemotological parameters				
Anaemia	27 (50.9)	244 (86.8)	0.16 (0.08–0.31)	0.00
Low WBC	6 (39.4)	66 (38.4)	1.07 (0.32–3.49)	0.90
Low lymphocyte	4 (26.7)	65 (37.8)	0.60 (0.15–2.15)	0.39

TB = tuberculosis; ART = antiretroviral therapy; OR = odds ratio; CI = confidence interval; WBC = white blood cell.

(interquartile range [IQR] 18–69). Most patients (56.7%) had sputum-positive TB, had new TB infections (89.9%), had wasting (62.7%), were anaemic (78.7%) and severely immune suppressed, with a CD4+ cell count of <200 cells/mm^3 (72.1%). Comorbidities at enrolment among these patients included pneumonia (20.2%), oral thrush (50.3%), diarrhoea (21.2%) and prurigo (10.4%). Five patients (1.3%) had Kaposi's sarcoma (Table 1). The majority of the patients (248, 64.1%) had been referred from the HIV care clinic. All the patients were receiving cotrimoxazole or dapsone for prophylaxis. The baseline demographic features are shown in Table 1.

Use of antiretroviral therapy

Sixty-eight (17.6%) of the patients had started ART 3 months prior to diagnosis and initiation of anti-tuberculosis treatment, 160 (41.5%) started ART during the course of anti-tuberculosis treatment and 158 (40.9%) did not start ART during their anti-tuberculosis treatment. Of the 158 patients who never started ART, 40 (25.3%) completed anti-tuberculosis treatment and were cured, 36 (22.8%) died, 14 (8.9%) were transferred out before starting ART and 68 (43.0%) were lost to follow-up prior to initiation of ART. Among the 160 patients who started ART after initiation of anti-tuberculosis treatment, the median duration before starting ART was 10 weeks (IQR 4–18). Patients who developed TB within 3 months of starting ART were less likely to be wasted, anaemic or have a CD4+ count of <100 cells/mm^3 and were more likely to have a CD4+ count of >200 cells/mm^3 (Table 2). One hundred and twenty-three (31.9%) of the patients received zidovudine (ZDV), lamivudine (3TC) and efavirez (EFV); 44 (11.4%) received ZDV, 3TC and nevirapine (NVP); 43 (11.1%) received tenofovir (TDF), 3TC and EFV; 10 (2.6%) received TDF, emitricitabine and EFV; and 8 (2.1%) received stavudine, 3TC and NVP.

Outcome at 8 months after initiation of anti-tuberculosis treatment

Of the 386 patients, 185 (47.9%) completed 8 months of anti-tuberculosis treatment at the integrated TB-HIV clinic, 53 (13.7%) were confirmed dead, 119 (30.8%) were lost to follow-up, 28 (7.3%) were transferred out and 1 (0.3%) had treatment failure. Two hundred and nineteen patients (56.7%) were sputum-positive. The cure rate among these patients was 54.3%, which was similar to the completion rate. The death and default rates were respectively 16% and 24%, while the rate of treatment failure was 0.5%. Mortality was significantly associated with failure to start ART during anti-tuberculosis treatment and having a CD4+ count of <200 cells/mm^3 (Figure 2 and Table 3). Among those who died, the mean duration from initiation of anti-tuberculosis treatment to death was 67 days (IQR 14–79). Failure

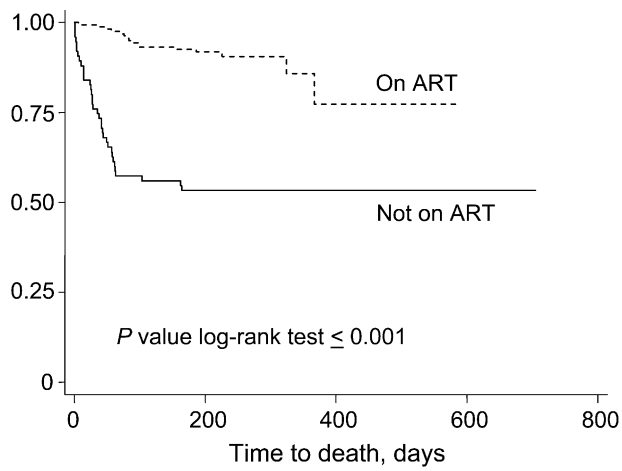

Figure 2 Kaplan-Meier curve to compare probability of mortality among tuberculosis patients receiving ART and those not receiving ART at Mbarara Regional Referral Hospital (*P* value for log rank test < 0.001). ART = antiretroviral therapy.

Table 3 Risk factors for death among TB-HIV co-infected patients in Mbarara Regional Referral Hospital

	Adjusted HR (95%CI)*	*P* value
0–200 CD4+ cells/mm^3 at enrolment	0.36 (0.21–0.62)	0.00
On ART during anti-tuberculosis treatment	7.6 (4.04–14.46)	0.00
Anaemia	0.46 (0.11–2.04)	0.31
Underweight	0.64 (0.30–1.39)	0.27
Living >30 km away	0.99 (0.99–1.00)	0.85

*Adjusted for sex and disease category.
TB = tuberculosis; HIV = human immunodeficiency virus; HR = hazard ratio; CI = confidence interval; ART = antiretroviral therapy.

to start ART during TB treatment and having a CD4+ count of <200 cells/mm^3 at enrolment were associated with failure to complete treatment/loss to follow-up (Table 4).

DISCUSSION

This study shows that most TB-HIV co-infected patients presenting for anti-tuberculosis treatment are likely to be severely immune suppressed, wasted, anaemic and have a number of comorbidities. They are also at increased risk of death and loss to follow-up if they are not started on ART. Although these findings are similar to observations in other sub-Saharan African settings,[3,17] our mortality and loss to follow-up rates were high.

The study population had a median age of 33 years, consistent with observations in other sub-Saharan settings with a high prevalence of TB and HIV.[17,18] The majority of the patients were male. Although we cannot fully explain this observation, it may call for targeted TB prevention interventions among men, but also suggests the need to study the reasons for the lower number of women presenting with TB disease in this cohort, which may include poor access to TB care.

As previously observed in other settings,[4] our patients were severely immune suppressed, with a number of comorbidities, and this may in part explain the high mortality observed in the first 2 months after initiating anti-tuberculosis treatment.[19] In the current study, the mortality rate of 13.7% was much higher than reports from other settings.[17,19] Although this may be explained by late presentation for care due to a number of barriers, such as socio-economic reasons, lack of disclosure, poor access to care, delay in TB diagnosis or delay in HIV testing, which have been documented in other settings and in Uganda,[7,20] it could also be due to a lack of capacity to manage comorbidities and provide essential critical medical care in health systems that are already overstretched by high patient loads, understaffing and lack of expertise and supplies.[21,22]

Table 4 Risk factors for loss to follow-up among 92 patients lost to follow-up from the integrated TB-HIV clinic in Mbarara Regional Referral Hospital

	Adjusted HR (95%CI)*	*P* value
0–200 CD4+ cells/mm^3 at enrolment	0.75 (0.58–0.96)	0.02
On ART during anti-tuberculosis treatment	3.7 (2.49–5.97)	0.00
Anaemia	1.01 (0.88–1.17)	0.85
Underweight	0.95 (0.61–1.48)	0.83
Living >30 km away	1.00 (1.00–1.00)	0.24

*Adjusted for sex and disease category.
TB = tuberculosis; HIV = human immunodeficiency virus; HR = hazard ratio; CI = confidence interval; ART = antiretroviral therapy.

The TB cure rate of 48% in this study population is below the national average.[6] We believe it could be improved by early identification of TB-HIV co-infected patients, initiation of ART and improved management of comorbidities. In the current study, 158 (40.9%) patients never started ART during the 8 months of anti-tuberculosis treatment; of these, 22.8% died and 43.0% were lost to follow-up. The delay in starting ART was attributed to the lack of appropriate ART regimens, fear of high pill burden among patients and lack of proper supporting structures to ensure adherence. These and other barriers have also been observed in other settings.[23]

In the current study, we observed a high rate of loss to follow-up. Similar rates have been noted in HIV care clinics in other African settings.[24,25] Although we did not investigate the causes, loss to follow-up has been associated with severe immune suppression, relocation to other sites, self clinic transfers and the high cost of accessing care.[26] Our findings showed that loss to follow-up was associated with failure to start ART during anti-tuberculosis treatment and having a CD4+ count of <200 cells/mm^3 at enrolment. As TB remains one of the major causes of mortality among PLWH, there is a need to study and address factors leading to loss to follow-up in this population of patients who are more likely to die. Interventions may include moving integrated TB-HIV care services closer to the communities,[27] improving community follow-up of TB-HIV co-infected patients and ensuring that they are started on ART early.[24] Other interventions would include active follow-up of these patients through linking adherence technologies, such as real-time monitoring to patient tracking.[28–30]

Our study had some limitations. Due to lack of funds, we were not able to track patients residing beyond 30 km. We therefore believe some patients classified as lost to follow-up could either have died or self transferred to other TB treatment centres. This may have affected the numbers classified as lost to follow-up, dead or completed and cured. Otherwise, all efforts within our means were used to track patients who did not keep their appointment dates. Most of our patients were not investigated to the desired standard, and we could have missed out on a number of other co-infections among

these patients which we could not easily find on clinical examination.

CONCLUSION

In Mbarara, Uganda, HIV patients with TB disease are likely to present with severe immune suppression and are at an increased risk of death and loss to follow-up, particularly if they are not started on ART within 2 months of initiating anti-tuberculosis treatment. Like others before us,[17,24] we recommend early identification, and improved care and follow-up of these patients.

Acknowledgements

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RÉSUMÉ

CONTEXTE : Nous décrivons la présentation et les résultats des soins chez les patients co-infectés par la tuberculose (TB) et le virus de l'immunodéficience humaine (VIH) à partir d'une cohorte observationnelle prospective d'Ouganda.

MÉTHODES : Nous avons analysé les données démographiques de base, les décomptes de CD4+, le moment de mise en route du traitement antirétroviral (ART), les paramètres cliniques et hématologiques et les résultats des soins chez 386 patients enrôlés entre février 2007 et mars 2010.

RÉSULTATS : Lors de la première consultation, les crachats étaient positifs chez 56,7% des patients, l'infection TB était récente chez 89,9%, la dénutrition chez 62,7%, l'anémie chez 78,7%, des décomptes CD4+ <200 cellules/mm³ chez 72,1%, 20,2% souffraient d'une pneumonie, 50,3% d'une moniliase orale et 1,3% d'un sarcome de Kaposi. Les risques de dénutrition, d'anémie ou de décompte de CD4+ <100 cellules/mm³ sont moins susceptibles d'être présents chez les patients développant une TB dans les 3 mois après le début de l'ART. Les taux de guérison sont de 54,3%, d'abandon de 24% et de décès de 16%. Au 8éme mois, le décès est confirmé chez 53 patients (13,7%), l'abandon chez 119 (30,8%), le transfert vers l'extérieur chez 28 (7,3%) et l'échec du traitement chez 1 patient (0,3%). La mortalité et la perte de vue sont en association avec la non-mise en route de l'ART et avec les décomptes de CD4+ <200 cellules/mm³.

CONCLUSION : En Ouganda, les patients TB-VIH se présentent avec une immunodépression sévère et encourent un risque accru de décès et de perte de vue, particulièrement ceux qui ne sont pas sous ART. Il est nécessaire de veiller à une identification précoce et d'améliorer le suivi des sujets co-infectés TB-VIH.

RESUMEN

MARCO DE REFERENCIA: Se describe la presentación clínica y el desenlace del tratamiento de pacientes coinfectados por el virus de la inmunodeficiencia humana (VIH) y la tuberculosis (TB) en una cohorte poblacional prospectiva en Uganda.

MÉTODOS: Se analizaron las características demográficas, el recuento de linfocitos CD4+, el momento del comienzo del tratamiento antirretrovírico (ART), los parámetros clínicos y hematológicos y el desenlace terapéutico de 386 pacientes inscritos entre febrero del 2007 y marzo del 2010.

RESULTADOS: En el momento de la presentación, el 56,7% de los pacientes tuvo un resultado positivo de la baciloscopia del esputo, en el 89,9% de casos se trató de infecciones tuberculosas nuevas, se observó emaciación en el 62,7% de los pacientes y anemia en el 78,7%, el 72,1% de casos presentó recuentos de linfocitos CD4+ <200 celulas/mm³, el 20,2% neumonía, el 50,3% candidiasis oral y el 1,3% sarcoma de Kaposi. Los pacientes que contrajeron la TB en los 3 primeros meses del ART exhibieron menor probabilidad de emaciación, anemia o recuentos de linfocitos CD4+ <100 celulas/mm³. La tasa de curación fue 54,3%, la tasa de abandono fue 24% y la tasa de mortalidad fue 16%. A los 8 meses se confirmó la muerte de 53 pacientes (13,7%), se habían perdido 119 en el seguimiento (30,8%), se habían transferido 28 pacientes (7,3%) y un paciente presentó fracaso terapéutico (0,3%). La mortalidad y la pérdida durante el seguimiento se asociaron con la falta de ART y con recuentos de linfocitos CD4+ <200 celulas/mm³.

CONCLUSIÓN: En Uganda, los pacientes coinfectados por el VIH y la TB sufren una depresión inmunitaria grave y presentan un alto riesgo de muerte y de pérdida durante el seguimiento, sobre todo los pacientes que no comienzan el ART. Es necesario detectar en forma temprana a los pacientes que padecen de esta coinfección y reforzar su seguimiento.