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MAJOR ARTICLE

Tuberculosis in Visceral Leishmaniasis-Human Immunodeficiency Virus Coinfection: An Evidence Gap in Improving Patient Outcomes?

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Background. Visceral leishmaniasis (VL)-human immunodeficiency virus (HIV) coinfection remains a major problem in Ethiopia, India, and Brazil. Tuberculosis (TB), a treatable factor, could contribute to high mortality (up to 25%) in VL-HIV coinfection. However, the current evidence on the prevalence and clinical impact of TB in VL-HIV coinfection is very limited. In previous reports on routine care, TB prevalence ranged from 5.7% to 29.7%, but information on how and when TB was diagnosed was lacking.

Methods. Field observations suggest that TB work-up is often not done systematically, and it is only done in patients who do not respond well to VL treatment. Here, we advocate high-quality diagnostic studies in VL-HIV-coinfected patients, during which all patients are systematically screened for TB, including a comprehensive work-up, to obtain reliable estimates.

Results. Cost-effective and feasible diagnostic algorithms can be developed for field use, and this can be integrated in VL clinical guidelines.

Conclusions. An accurate diagnosis of TB can allow clinicians to assess its clinical impact and evaluate the impact of early TB diagnosis.

Keywords. visceral leishmaniasis; HIV; tuberculosis; diagnosis; screening.

Visceral leishmaniasis (VL)-human immunodeficiency virus (HIV) coinfection is a persistent or increasing concern in several regions in the world. In countries such as Ethiopia, approximately 15%–20% of VL patients are coinfected with HIV in some parts of the country [1]. In Brazil, HIV coinfection rates are steadily increasing, reaching as high as 10% [2]. For India, the best estimates suggest a prevalence of 5.6% overall, and this increases to 12.8% in males aged 35–44 years [3, 4]. Overall prognosis of VL-HIV coinfection remains poor, especially in Ethiopia, with death rates of 10%–25% [1], and in Brazil, with death rates of approximately 25% [5].

METHODS

Visceral leishmaniasis induces a stage of generalized immunosuppression, and high rates of bacterial infections contribute to death [6, 7]. Human immunodeficiency virus coinfection further exacerbates the underlying immunodeficiency [8]. Human immunodeficiency virus is also one of the strongest risk factors for tuberculosis (TB), and TB is first on the list of opportunistic infections and causes of the immune reconstitution inflammatory syndrome (IRIS) in HIV patients. To decrease the impact of TB in individuals infected with HIV in general, the World Health Organization has recommended several strategies [9]. One strategy includes systematic screening for TB at regular intervals during routine consultations. Specific diagnostic algorithms have also been introduced for timely diagnosis of (smear-positive and -negative) pulmonary TB and extrapulmonary TB [10].

However, in HIV coinfection, TB diagnosis is still missed or delayed. In a recent study from South Africa, TB was diagnosed in 33% of HIV patients admitted to a healthcare facility. More importantly, one third of these patients had disseminated TB, which was diagnosed via blood culture. Futhermore, there was often a delayed diagnosis for disseminated TB, it was rarely found via sputum examination, and patients had a very high mortality rate [11].

The combined immunosuppressive effect of VL and HIV may cause patients in high TB burden areas to be at high risk for reactivation of a latent TB infection, and hence suffer a triple infection. Given the pronounced immunosuppression, they might be more likely to develop disseminated TB, which is particularly challenging to diagnose. Tuberculosis coinfection could be a contributing factor to the persistently high mortality rates in VL-HIV coinfection. However, reliable TB prevalence

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data are limited, and data regarding whether and to what extent TB prevalence affects clinical outcomes are scarce.

RESULTS

Table 1 displays an overview of the main studies from Ethiopia and India that reported TB prevalence and the association with VL treatment outcomes in patients coinfected with VL-HIV between 1990 and 2017. Both of these countries have a high TB burden and relatively high numbers of patients coinfected with VL-HIV, and they both list *Leishmania donovani* as causative pathogen. To our surprise, we did not find studies that evaluated this in Brazil, although the burden of TB and VL-HIV coinfection is also substantial there, and TB has been found to be associated with mortality in patients infected with VL in general [12].

Tuberculosis prevalence in patients infected with VL-HIV ranged between 5.7% and 29.7%. In India, all 3 studies suggested an increased risk of death or treatment failure, reaching statistical significance in the 2 largest cohorts. Although concurrent TB was associated with an increased risk of relapse, this did not reach statistical significance in any of the 3 studies [13–15]. In Ethiopia, findings were more heterogeneous, and several studies only reported crude associations. However, 1 study that reported adjusted associations observed a statistically significant increased risk of poor initial treatment outcomes [16].

Although this is concerning, several critical considerations have to be made regarding these studies. First, none of the studies provided details of the TB diagnostic work-up and the algorithms used nor the adherence to these. Moreover, none reported on the proportion of the types of TB diagnosed. Hence, it is unclear what proportion of patients had confirmed TB versus presumptive TB. Thus, it is unknown to what extent overdiagnosis, underdiagnosis, or delayed diagnosis occurred. Except for 1 study, none of the studies provided information on the timing of the TB diagnosis, whether the patient had been on TB treatment at VL diagnosis, whether the patient was diagnosed at the time of VL diagnosis, or whether the patient was diagnosed during VL treatment.

Observations in the field, and the personal experience of several of the coauthors of this manuscript, suggest that after patients have been diagnosed with VL—and hence have an explanation for the chronic fever—screening for TB is rarely done at VL diagnosis, except on clinical indication (eg, pronounced pulmonary symptoms, marked lymphadenopathy, etc). In contrast, TB work-up will often be done for patients who do not respond well to the VL treatment. Is is not uncommon for TB treatment to be started empirically, often with a diagnosis of "disseminated TB." In that sense, being started on TB treatment might be an indicator of "poor prognosis," which is also true for patients who actually do not have TB. If an empirical TB diagnosis is triggered by a poor response during the first 1 or 2 weeks of VL treatment, the observed association with increased treatment failure or death rates might be partly related to that, instead of a negative effect of TB or the adverse effect of the anti-TB treatment. Basically, the true prevalence of TB in VL-HIV coinfection and the clinical impact remain unclear. This leads to a number of implications and steps forward.

DISCUSSION

High-quality diagnostic studies should be done in patients coinfected with VL-HIV, wherein all patients are systematically screened for TB with a standard algorithm. Within a study setting, the screening process could consist of sputum smear and Xpert MTB/RIF assay (and, ideally, liquid culture), blood culture, possible radiological investigations (chest x-ray and abdominal ultrasound), and additional invasive procedures on indication. This would allow investigators to obtain reliable estimates of TB prevalence. Moreover, by identifying the combination of tests with the highest combined TB yield, this information would also present evidence-based development of cost-effective and feasible diagnostic algorithms (combining clinical and laboratory information) for TB in patients coinfected with VL-HIV.

The inclusion of urine lipoarabinomannan (LAM) testing should also be considered. In patients infected with HIV, the yield was fair for those with low CD4 cell counts [17], which is also the case in most VL-HIV-coinfected patients. Moreover, VL might further increase the yield, irrespective of the CD4 count, by contributing additional immunosuppression. It is possible that because VL can also affect the kidney in various ways, the TB diagnostic yield might be further increased [18]. Xpert testing on urine could be added because both tests combined yield a higher sensitivity [17]. Of interest, most of the cases of disseminated TB in the above-mentioned South African study could be ascertained by urine testing with LAM and Xpert.

If a substantial proportion of TB cases are currently missed at VL diagnosis, there are 3 important implications. First, TB treatment will be started with delays, often when the clinical condition has deteriorated, and this can contribute to increased mortality and perhaps treatment failure. Second, because TB impairs cellular immunity and because the immune status of the patient affects the response to VL treatment, TB coinfection could increase failure rates. Alternatively, if TB is missed at diagnosis and antiretroviral therapy is started on top of VL treatment, then there is a theoretical concern of unmasking TB-IRIS, which can further worsen the patient's condition. Although VL-IRIS is very rare in VL-HIV coinfection [19] and is rarely lethal, it nevertheless merits further research, because excessive generalized immune activation could perhaps contribute to a poorer response to VL treatment. Third, failure to timely diagnose TB poses other patients and healthcare workers at risk of nosocomial transmission.

Table 1. Overview of the Main Studies Reporting on the Prevalence of Tuberculosis and Association With VL Treatment Outcomes in *Leishmania donovani*-Endemic Countries (1990–2017)

Ref	Country, Setting (Healthcare Level), Study Period, Study Design	Study Population Characteristics and Main VL Treatment	TB Diagnosis (Method)	Prevalence, Type, and Timing of TB[a]	Early Treatment Outcomes (Death, Treatment Failure)	Late Treatment Outcomes: Relapse or Relapse-Free Survival	Comments
Ethiopia							
[21, 22]	NW Ethiopia University hospital and MSF supported health center (2011–2015). Single-arm pentamidine secondary prophylaxis trial	74 HIV-infected adults, at high risk of VL relapse; AmBisome 30 mg/kg (±MF); SSG (±PM)	No information	6 of 74 (8.2%) no details on type and timing		Relapse: univariate association during and after PM: OR, 1.9 (95% CI, 0.6–6.6); Not retained in multivariate analysis	Also no significant association with relapse-free survival
[23]	NW Ethiopia, MSF supported health center (2/2008–2/2013) Retrospective cohort study	146 VL-HIV-coinfected adults AmBisome 30 mg/kg (±MF)	WHO guidelines	33 of 145 (22%) no details		Relapse: OR, 1.0 (95% CI, 0.5–2.0)	
[24]	NW Ethiopia, MSF supported health center and district hospital (1/2007–1/2009) Retrospective cohort study	195 VL-HIV-coinfected patients AmBisome 30 mg/kg	No information	58 of 195 (29.7%) no details	Parasitological failure: no association in multivariate analysis OR, 0.7 (95% CI, 0.2–2.2)		In HIV neg: 7.4% (but 80 of 195 included)
[25]	NW Ethiopia, MSF supported district hospital (2003–2006) Retrospective cohort study	Patients not on ART: 161 Patients on ART: 195 First-line treatment: SSG	No information	No ART: No TB: 64% TB before VL: 25% After VL: 8% Before and after: 2.5% On ART: No TB: 41% TB before VL: 40% After VL: 16% Before and after: 2.6%	Death: TB at any time (crude association) Pts not on ART: OR, 2.1 (95% CI, 0.5–8.7) Pts on ART: OR, 1.1 (95% CI, 0.5–2.4)	Relapse: crude OR No ART: TB before VL: 1.3 (95% CI, 0.6–2.9) TB after VL: 0.6 (95% CI, 0.1–2.4) Before and after: 6.3 (95% CI, 1.4–28.0) On ART TB before VL: 1.3 (95% CI, 0.6–2.5) TB after 1.2 (95% CI, 0.5–2.9) Before and after: 3.1 (95% CI, 0.9–10.5)	Two cases of TB IRIS Adjusted associations not reported
[16]	NW Ethiopia University hospital and district hospital (2006–2008) Retrospective cohort study	Adult VL-HIV-infected patients, x% male SSG or AmBisome 30 mg/kg	No information	25 of 92 (27%) no details	Death or failure: adjusted OR for TB, 4.5 (95% CI, 1.5–13.9)		TB prevalence 6% in HIV-negative patients
India							
[13]	MSF supported district hospital, Bihar, India (2007–2012) Retrospective cohort study	159 VL-HIV-coinfected patients, 83% male AmBisome 20–25 mg/kg	No information	9 of 159 (5.7%) no details	Mortality: adjusted OR, 3.9 (95% CI, 1.6–9.5)	Relapse: crude OR: 2.0 (95% CI, 0.5–8.5) Not included in multivariate analysis	
[14]	MSF supported district hospital, Bihar, India (2007–2010) Retrospective cohort study	55 VL-HIV-coinfected patients AmBisome 20–25 mg/kg, 83% male	No information	9 of 55 (16%) no details	Death or treatment failure: significant association in univariate but not in multivariate analysis	Relapse: no significant association in univariate analysis	Death: significant association in univariate analysis (multivariate not done given low number)
[15]	MSF supported district hospital, Bihar, India (2012–2014) Retrospective cohort study	102 VL-HIV-coinfected patients; AmBisome 30 mg/kg + MF 14 days, 75% male	No information	9 of 102 (8.8%) no details	Death: adjusted OR, 5.3 (95% CI, 1.6–17.8)	Relapse: borderline significant: crude OR, 9.5 (95% CI, 0.9–97.9)	Relapse or death: adjusted OR, 7.5 (95% CI, 2.5–22.1)

Abbreviations: ART, antiretroviral therapy; CI, confidence interval; HIV, human immunodeficiency virus; IRIS, immune reconstitution inflammatory syndrome; MF, miltefosine; MSF, Médecins sans Frontières; NW, North-West; PM, paromomycin; Pts, patients; OR, odds ratio; Ref, reference; SSG, sodium stibogluconate; TB, tuberculosis; VL, visceral leishmaniasis; WHO, World Health Organization.

[a]Timing relative to VL diagnosis: whether the TB diagnosis was before, at the time of, or after the VL diagnosis (eg, during VL treatment).

Future studies with reliable TB diagnosis should also evaluate whether TB coinfection—even when readily treated—is indeed associated with poor VL treatment outcomes. If so, the underlying mechanism should be determined, including the assessment of drug-drug interactions and IRIS, to allow investigatgors to design appropriate interventions.

To alter the high mortality rate in patients coinfected with VL-HIV, other opportunistic or coinfections might need to be targeted as well, ranging from cryptococcal meningitis to invasive bacterial infections. For instance, a high prevalence of bacterial sepsis was reported in a small study in Ethiopia, with fairly high rates of bacterial resistance [7]. Because most VL treatment centers do not have access to diagnostic microbiology laboratories, bacterial sepsis might be missed, diagnosed too late, or not treated appropriately. This indicates a low threshold for empirical treatment with antibiotics. Timely initiation of co-trimoxazole is also important; in that respect, recent data from Ethiopia are encouraging [20]. The optimal screening and treatment package for patients coinfected with VL-HIV remains to be defined.

CONCLUSIONS

In conclusion, the prognosis of VL-HIV coinfection remains poor, and concurrent TB infection could be a treatable contributing factor. This calls for quality studies on the TB prevalence and clinical impact on VL treatment outcomes in coinfected patients. At the same time, tests should be peformed for other concurrent infectious diseases.

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