Correspondence

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Latent tuberculosis infection among adults attending HIV services at an urban tertiary hospital in Malawi

Active tuberculosis (TB) can develop from newly acquired *Mycobacterium tuberculosis* infection or from reactivation of pre-existing latent TB infection (LTBI). Although individuals with LTBI do not have clinical TB symptoms, they are a reservoir for active TB cases and pose a significant challenge to the global effort to eliminate TB. Strategies to reduce the burden of TB vary among countries, and are, in part, determined by the local prevalence of LTBI and active TB [1]. Developing such strategies for sub-Saharan African (SSA) countries is challenging because of the paucity of data on the prevalence of LTBI in the region [2]. To address this knowledge gap, we conducted a cross-sectional study to determine the prevalence of, and factors associated with LTBI among asymptomatic people with HIV (PWH) and healthy, HIV-uninfected adults attending antiretroviral therapy (ART) and HIV voluntary counselling and testing clinics at Queen Elizabeth Central Hospital, a large urban tertiary hospital in Blantyre, Malawi.

All study participants were Malawian adults aged at least 18 years who had received Bacillus Calmette-Guérin vaccination during childhood but had no history of previous TB treatment or clinical and laboratory evidence of active TB. They were tested for LTBI using the QuantiFERON-TB Gold Plus (QFT-Plus) interferon gamma release assay (IGRA) (QIAGEN, Hilden, Germany) according to the manufacturer's instructions. Informed written consent was obtained from all participants and the study protocol was approved by the College of Medicine Research Ethics Committee in Malawi (protocol P.02/18/2356) and the Liverpool School of Tropical Medicine Research Ethics Committee in the UK (protocol 17-032).

We recruited 165 participants, 66 (40%) of whom were PWH. Of the 66 PWH, 55 (83.3%) were on ART. Ten participants, six of whom were PWH, had indeterminate QFT-Plus results and were excluded from further analysis. Of the remaining 155 individuals, 68 [43.87% [95% confidence interval (CI) 35.92–52.06] had positive QFT-Plus results, indicating that they had LTBI. Subgroup analysis by sex revealed that LTBI was more prevalent among males than females [46 of 88 males (52.27%, 95% CI 41.35–63.04) vs. 22 of 67 females (32.84%, 95% CI 21.85–45.40), $P = 0.02$]. However, the prevalence of LTBI was similar across different age groups ($P = 0.82$, Fig. 1a) and between PWH and HIV-uninfected individuals [48.33% (95% CI 35.23–61.61) vs. 41.05% (95% CI 31.06–51.62), $P = 0.37$].

Next, we performed multiple logistic regression to determine if LTBI was associated with age, sex, HIV status, plasma HIV viral load or peripheral blood $CD4^+$ T-cell count. We found that HIV infection, male sex and undetectable HIV viral load were independent risk factors for LTBI [odds ratio (OR) 6.81, CI 1.79–28.66, $P = 0.006$; OR 3.02, CI 1.41–6.77, $P = 0.006$; OR 4.49, CI 1.23–19.36, $P = 0.03$, respectively, Fig. 1b], while age and $CD4^+$ T-cell count were not.

The current study reports a high prevalence of LTBI among adults attending HIV services at an urban hospital in Malawi, a country with high TB and HIV prevalence. Our findings are consistent with previous reports from Nigeria [3] and Zimbabwe [4]. Although HIV infection is a known risk factor for active TB [5], we show that it is also a risk factor for LTBI. The high burden of LTBI among PWH in SSA justifies the WHO recommendation of preventive treatment for LTBI in PWH even in the absence of IGRA or tuberculin skin test results [6].

The high prevalence of LTBI in SSA is likely indicative of high community transmission of TB. Currently, most countries in the region treat PWH with isoniazid preventive therapy (IPT) for 6–36 months [7–9]. Although IPT significantly reduces the risk of LTBI progressing to active TB, its protective effect wanes following discontinuation [10]. Therefore, lifelong IPT would provide PWH with long-lasting protection against active TB. In addition, the high LTBI prevalence among HIV-uninfected adults calls for a review of the public health response to TB in the region. Treatment of LTBI in other at-risk groups should be explored to reduce the reservoir for active TB cases.

We acknowledge that the small sample size and the hospital-based recruitment may limit generalizability of our study findings, therefore large community-based studies are required to determine the community prevalence of LTBI in Malawi. Nonetheless, our participants were ambulatory and reflect the composition of the communities served by the hospital.

In conclusion, the prevalence of LTBI in the study population was high. Males and PWH were at high risk of LTBI. Treating individuals with LTBI in SSA, including lifelong IPT for PWH should complement current active TB case finding strategies to reduce TB incidence and deaths in the region.

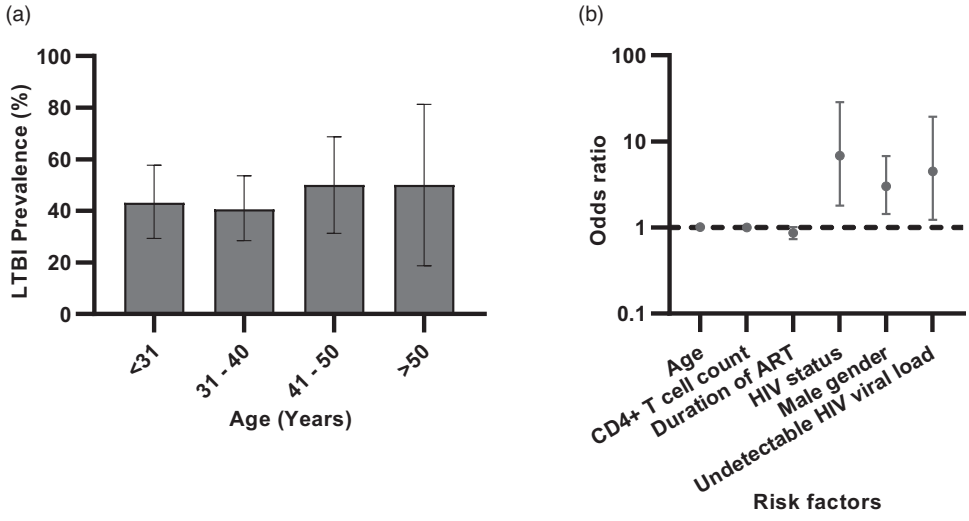

Fig. 1. (a) Prevalence of latent tuberculosis infection according to age. (b) Multivariate logistic regression analysis of risk factors of latent tuberculosis infection. Error bars: 95% confidence interval. *N* = 60 HIV-positive; 95 HIV-negative.

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Conflicts of interest

There are no conflicts of interest.

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OPEN

Doravirine/lamivudine/tenofovir disoproxil fumarate-induced hypertriglyceridemia in a newly diagnosed AIDS patient

A 44-year-old woman (male-to-female) affected by hypertension and asthma with history of unprotected sexual intercourse and inhalatory drug abuse was admitted to the emergency room complaining of nausea, headache, and convulsive status epilepticus. Brain computed tomography (CT) scan showed hypodense lesions in the left parietal lobe and left cerebellar hemisphere, compatible with a central nervous system opportunistic infection. Fourth-generation HIV test was positive and further confirmed by immunoblotting (baseline absolute lymphocyte count 1256 cell/μl; $CD3^+CD4^+$ count 52 cells/μl; $CD4^+/CD8^+$ ratio 0.06 with HIV-1-RNA: 407 000 copies/ml). Intravenous valproic acid, levetiracetam and lacosamide were started as antiepileptic therapy. Furthermore, intravenous mannitol was administered for the reduction of intracranial pressure resulting from cerebral edema. PCR for *Toxoplasma* spp. tested positive on whole blood sample, and even though cerebrospinal fluid analysis was unfeasible because of compressive phenomena on the left brain fourth ventricle, a diagnosis of neurotoxoplasmosis was made. Several active infections were also diagnosed, including severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), hepatitis B virus (HBV) (because of the presence of HBs, HBe antigens, HBe antibodies and HBV-DNA 72UI/ml), cytomegalovirus (with detectable viremia) and pulmonary aspergillosis. Active and latent infection because of *Mycobacterium tuberculosis* was ruled out. Considering the need for prophylactic treatments and the presence of multiple active infections, the patient received secondary prophylaxis for SARS-CoV2 with a single dose of sotrovimab (VIR-7831). Treatment for pulmonary aspergillosis was started with isavuconazole, and trimethoprim–sulfamethoxazole was introduced for the treatment of neurotoxoplasmosis. Prophylaxis for *Mycobacterium avium* complex was also provided with oral azithromycin. Antiretroviral treatment (ART) with doravirine/lamivudine/tenofovir disoproxil fumarate (DOR/3TC/TDF) association as fixed-dose combination single-tablet regimen (Delstrigo-Merck Canada Inc.) was initiated. Nevertheless, during the following routine blood test, an unexpected increase in triglyceride value was noted, which spiked up to 1719 mg/dl on the 15th day after the introduction of DOR/3TC/TDF. No sign or symptom of acute pancreatitis was detected at any time during hospitalization. A differential diagnosis was made between a previously undiagnosed familial hypertriglyceridemia and drug-related toxicity. A complete lipid profile was performed at admission revealing an isolated mild hypertriglyceridemia (admission triglyceride value 276 mg/dl, reference range <150 mg/dl); therefore, the first diagnostic hypothesis was excluded. In an attempt to identify the drug putatively responsible for the sudden increase in triglyceride levels, therapy was simplified with sequential sampling of blood triglycerides. No improvement was observed after isavuconazole, azithromycin or valproic acid suspension. Considering the whole therapeutic scheme, after a literature search for possible interactions and side effects, we safely assumed hypertriglyceridemia as unrelated side effect of any of the remaining drugs, including levetiracetam, lacosamide and trimethoprim–sulfamethoxazole [1,2]. This led us to evaluate the possible involvement of DOR/3TC/TDF. Considering the increased risk of acute pancreatitis because of hypertriglyceridemia, plasma apheresis was suggested. Nevertheless, the patient refused the treatment. The simultaneous interruption of DOR/3TC/TDF together with the introduction of gemfibrozil caused a rapid decrease in triglyceride levels (Fig. 1). According to fenofibrate effect on lowering triglyceride levels, reported, on a sample of 1113 patients with a 4 months median follow-up, a median reduction of triglycerides of 60% ($P < 0.001$) [3]. Conversely, our patient reported a reduction of 87.5% on triglyceride levels in less than 2 weeks, further reinforcing our hypothesis of a drug-induced isolated hypertriglyceridemia.

We therefore proceeded with a treatment re-challenge with DOT/3TC/TDF in combination with gemfibrozil, with a new rapid increase in triglyceride levels, implying a direct effect of DOR/3TC/TDF on triglyceride levels: