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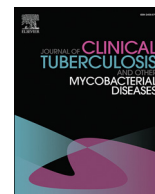
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# Tuberculosis preventive therapy (TPT) to prevent tuberculosis co-infection among adults with HIV-associated cryptococcal meningitis: A clinician's perspective

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## ABSTRACT

As part of the END TB strategy, the World Health organization (WHO) recommends provision of tuberculosis preventive therapy (TPT) to all people at high risk of developing active TB disease. Patients with HIV-associated cryptococcal meningitis are severely immunocompromised and therefore should be eligible for TPT. In this commentary we discuss the challenges associated with starting tuberculosis preventive therapy in patients with HIV associated cryptococcal meningitis in a clinical setting, we highlight the benefit, existing gaps and research opportunities of tuberculosis preventive therapy in this patient population.

## 1. Introduction

Tuberculosis (TB) is the leading cause of death from a single infectious agent. In 2018, an estimated 1.5 million people died from TB, of which 251,000 were people living with human immunodeficiency virus (HIV) [1]. Cryptococcal meningitis is the leading cause of meningitis among people living with HIV (PLWHIV) accounting for 15–20% of AIDS related mortality [2]. Cryptococcus and TB co-infection amongst PLWHIV is common and is associated with an increased risk of mortality [3]. For instance, in Uganda, TB was treated or confirmed in around one fifth (21% and 22% respectively) of patients with HIV-associated cryptococcal meningitis [3,4].

In order to meet the 2025 End TB strategy goal of reducing the incidence of TB by 50% compared to 2015, one of the strategies recommended by the World Health Organization (WHO) is the use of Tuberculosis Preventive Therapy (TPT) among people living with HIV in whom active TB has been excluded regardless of their TB history, level of immune suppression or ART status [5]. TPT is effective and safe for treatment of latent TB infection (LTBI) among PLWHIV and thus prevents progression to active TB infection in this population [6–9]. The WHO currently recommends: 6 or 9 months of daily isoniazid monotherapy (6H or 9H), 3-months regimen of weekly rifampentine plus

isoniazid (3HP), 3 months regimen of isoniazid plus rifampicin (3HR), 1-month of daily rifampentine plus isoniazid (1HP) or 4 months of daily rifampicin alone (4R) as TPT regimens [10].

Despite this, implementation of TPT has been suboptimal globally including amongst cryptococcal meningitis cohorts. In 2018, 862,000 PLWHIV fell ill with TB moreover its estimated that only 49% of people newly enrolled in HIV care received TPT [5,11]. In the same year, of the 30 high TB/HIV burden countries, 15 did not report any provision of TPT; and in the 15 countries that provided data, coverage among people newly enrolled in HIV care varied considerably from 10% in Indonesia to 97% in Russia Federation. Barriers to implementation of TPT include concerns about adherence, loss to follow up, drug toxicity and emergence of drug resistance [11]. In this article we discuss the clinical challenge of rolling out TPT among individuals with advanced HIV-associated cryptococcal meningitis.

## 2. Discussion

### 2.1. Rationale for utilization of TPT among HIV associated cryptococcal meningitis

Patients with HIV associated cryptococcal meningitis are severely

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immune suppressed with majority having a CD4 cell count < 50 cells/mm<sup>3</sup> [2,12]. Consequently, they are at a high risk of TB-related morbidity and mortality [13]. TPT in persons with HIV and a CD4 count < 500 cells/mm<sup>3</sup> confers an independent but additive effect to ART in preventing progression to AIDS and active TB incidence [8].

## 2.2. Clinical decision challenges facing utilization of TPT among HIV associated cryptococcal meningitis

### 2.2.1. Active TB diagnostic dilemma in HIV associated cryptococcal meningitis

WHO recommends the use of clinical symptoms or radiology to rule out active TB prior to initiation of TPT in resource limited settings [10]. Briefly, symptom screen includes asking patients about the presence of cough, fever, weight loss, and night sweats. However, there is an overlap between symptoms suggestive of TB and those related to cryptococcal meningitis; In a cohort of 230 Zambian adults with HIV-associated cryptococcal meningitis 210 (91%) had fever, 208 (90%) reported weight loss and 206 (90%) were wasted [14]. Cough is also a reported symptom in pulmonary cryptococcal infection [15]. Similarly, radiological finding like abdominal lymphadenopathy, pulmonary cavitation, pleural effusion in active TB infection are nonspecific and have been reported in disseminated cryptococcal infection [16]. This implies that highly sensitive and specific diagnostic tests are required to rule out active TB in this high-risk population.

Moreover, a definitive microbiological TB diagnosis in patients with advanced HIV-associated cryptococcal meningitis patients is challenging. The most common form of TB in advanced HIV is extra-pulmonary TB; including abdominal, pleural, genitourinary and central nervous system [16,17]. With the exception of Tuberculous meningitis, other forms of extra pulmonary TB often require a tissue diagnosis, which may be challenging to obtain in resource poor settings. In addition, sensitivity of Xpert MTB/RIF Ultra (Xpert Ultra) is low for extra pulmonary specimens: pooled Xpert Ultra sensitivity of cerebrospinal fluid, pleural fluid, and urine is 71.1%, 50.9%, 50–82.7% respectively [18,19]. Although urine TB-lipoarabinomannan (LAM) is more sensitive in advanced HIV, it has a highly variable sensitivity of 13–93% depending on CD4 count [20]. In fact, significant diagnostic disparities between Xpert MTB/RIF Ultra and the Alere TB-lipoarabinomannan (LAM) assay have been reported among patients with advanced HIV suspected of meningitis and TB [4]. Given the above, reliance on non-specific symptoms and TB diagnostics with low sensitivity leads to missed TB diagnoses, therefore more accurate or combination of diagnostics tests to reasonably rule out active TB in this population prior to TPT initiation is warranted. As a result, we recommend delayed initiation of TPT in these patients is until TB co-infection is ruled out. Further research into the optimal screening strategy for active TB amongst patients with HIV-associated Cryptococcosis is warranted.

### 2.2.2. TPT and HIV associated cryptococcal meningitis drug interaction and toxicities

To date there are no studies to evaluate the safety of TPT use during the induction and maintenance phases of cryptococcal meningitis treatment with or without ART in HIV infected patients. Isoniazid and fluconazole are metabolized by the liver and they are associated with mild to severe hepatotoxicity [21,22]. When used alone rifamycins (rifampicin and rifapentine) are safe however in combination with other anti-tuberculous drugs they are associated with an increased risk of hepatotoxicity [23]. Therefore, the co-administration of isoniazid, rifamycins and high dose fluconazole during the induction and consolidation phases of cryptococcal meningitis treatment may increase the risk of drug induced hepatotoxicity in these patients.

Hepatotoxicity has also been reported among patients taking anti-retroviral therapy (ART) and TPT [24], which may be exacerbated by high dose fluconazole. No safety concerns were observed with nevirapine and efavirenz based ART regimens with isoniazid monotherapy

TPT [25]. However, dolutegravir based regimens which are now the recommended first line ART, were found to cause cytokine mediated drug reactions when issued to healthy participants in combination with weekly isoniazid and rifapentine [26]. A follow up study among HIV patients shows contradicting results with no grade 3 and above adverse effect reported yet [27]. Nonetheless this study population had a median CD4 638cells/mm<sup>3</sup> and had attained viral suppression prior to dolutegravir, isoniazid and rifapentine initiation which may not be the case in routine care for HIV-associated cryptococcal meningitis. Therefore, as noted above these drug interactions and toxicities warrant continuous patient monitoring and clinical trials to establish safety of TPT among HIV associated cryptococcal meningitis patients in high TB incidence places.

### 2.2.3. Pill burden

A combination therapy of anti-fungal; amphotericin B, flucytosine and fluconazole is associated with a higher early fungicidal activity and thus recommended for cryptococcal meningitis induction phase treatment [28]. There is the critical issue of high pill burden when patients receiving induction phase treatment are also given oral supplementary magnesium and potassium, paracetamol, and in some cases, anti-seizure medication. In addition, patients also receive co-trimoxazole prophylactic treatment. We hypothesize that the adherence to medication in these patients will be poor incase IPT is started during induction therapy due to a high pill burden.

### 2.2.4. Isoniazid resistance

Isoniazid is a key component of all except one (4 months Rifampicin only) TPT regimens recommended by WHO [10]. Unlike rifamycins, isoniazid has been reported to increase the risk of INH-resistance TB following isoniazid preventive therapy [29]. For this reason, there is a need for continuous monitoring for INH resistance in the population and utilization of short course combination TPT regimens.

## 3. Conclusion

In conclusion, patients with HIV-associated cryptococcal meningitis are at a higher risk of developing active TB disease, as they usually severely immunosuppressed and as such they are more likely to benefit from TB preventive therapy. However, excluding active TB in a population with advanced HIV disease and disseminated Cryptococcosis is challenging. As a result, there is concern for inadvertent isoniazid monotherapy as TPT, which potentially predisposes patients to developing isoniazid resistant TB when isoniazid monotherapy is used for TPT. Further, concomitant induction treatment for cryptococcal meningitis and TPT initiation may be complicated by drug-drug interactions and pill burden that could hamper adherence. Coupled with lack of data demonstrating mortality benefit of TPT in a population that is already at 59–81% risk of death from cryptococcal meningitis [2], the challenges articulated above warrant an individualized approach to TPT in cryptococcal meningitis patients. We recommend that clinicians assess for TPT eligibility utilizing individualized approach and a combination of diagnostics tests (both laboratory and radiology). We also recommend utilization of short course combination TPT regimens and continuous monitoring for drug resistance, interactions and adverse effects during TPT. There is also need to perform randomized controlled trials evaluating the effectiveness and safety of TPT regimens among patients with advanced HIV disease and cryptococcal meningitis.

## 4. Authors' contributions

Manuscript conception and first draft was done by JK. MKR, EK, KS, JE, LT, EM, FVC, and DBM revised and edited drafts. FVC and DBM also offered mentorship and final approval of version to be submitted.

## 5. Ethical considerations

The development of this manuscript did not involve human subjects or animal experiments due to the nature of this manuscript as a clinical perspective article.

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## Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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## References

- [1] World Health Organisation, G., Switzerland., Global tuberculosis report 2019. <https://apps.who.int/iris/bitstream/handle/10665/329368/9789241565714-eng.pdf?ua=1>, 2019. (Licence: CC BY-NC-SA 3.0 IGO.) [accessed 28th July 2020].
- [2] Rajasingham R, Smith RM, Park BJ, et al. Global burden of disease of HIV-associated cryptococcal meningitis: an updated analysis. *Lancet Infect Dis.* 2017;17(8):873–81. [https://doi.org/10.1016/S1473-3099\(17\)30243-8](https://doi.org/10.1016/S1473-3099(17)30243-8).
- [3] Rutakingirwa MK, Cresswell FV, Kwizera R, et al. Tuberculosis in HIV-Associated Cryptococcal Meningitis is Associated with an Increased Risk of Death. *J Clin Med.* 2020;9(3):781. <https://doi.org/10.3390/jcm9030781>. Published 2020 Mar 13.
- [4] Cresswell FV, Ellis J, Kagimu E, et al. Standardized Urine-Based Tuberculosis (TB) Screening With TB-Lipoarabinomannan and Xpert MTB/RIF Ultra in Ugandan Adults With Advanced Human Immunodeficiency Virus Disease and Suspected Meningitis. *Open Forum Infect Dis.* 2020;7(4):ofaa100. Published 2020 Mar 24. doi:10.1093/ofid/ofaa100.
- [5] WHO, World Health Organisation Global Tuberculosis Report, Executive summary 2019. [https://www.who.int/tb/publications/global\\_report/GraphicExecutiveSummary.pdf?ua=1](https://www.who.int/tb/publications/global_report/GraphicExecutiveSummary.pdf?ua=1) [accessed 28th July 2020].
- [6] Swindells S, Ramchandani R, Gupta A, et al. One Month of Rifampentine plus Isoniazid to Prevent HIV-Related Tuberculosis. *N Engl J Med.* 2019;380(11):1001–11. <https://doi.org/10.1056/NEJMoa1806808>.
- [7] Grant AD, Mngadi KT, van Halsema CL, Luttig MM, Fielding KL, Churchyard GJ. Adverse events with isoniazid preventive therapy: experience from a large trial. *AIDS.* 2010;24(Suppl 5):S29–36. <https://doi.org/10.1097/01.aids.0000391019.10661.66>.
- [8] TEMPRANO ANRS 12136 Study Group, Danel C, Moh R, et al. A Trial of Early Antiretrovirals and Isoniazid Preventive Therapy in Africa. *N Engl J Med.* 2015;373(9):808–822. doi:10.1056/NEJMoa1507198.
- [9] Zenner D, Beer N, Harris RJ, Lipman MC, Stagg HR, van der Werf MJ. Treatment of Latent Tuberculosis Infection: An Updated Network Meta-analysis. *Ann Intern Med.* 2017;167(4):248–55. <https://doi.org/10.7326/M17-0609>.
- [10] WHO, WHO operational handbook on tuberculosis. Module 1: prevention - tuberculosis preventive treatment. Geneva: World Health Organization; 2020. Licence: CC BY-NC-SA 3.0 IGO. <https://apps.who.int/iris/rest/bitstreams/1272664/retrieve>. [accessed 28th July 2020].
- [11] WHO and G. World Health Organisation, Switzerland., Country profiles for 30 high tb burden countries. [https://www.who.int/tb/publications/global\\_report/tb19\\_report\\_country\\_profiles\\_15october2019.pdf?ua=1](https://www.who.int/tb/publications/global_report/tb19_report_country_profiles_15october2019.pdf?ua=1) [accessed 28 July 2020].
- [12] Boulware DR, Meya DB, Muzoora C, et al. Timing of antiretroviral therapy after diagnosis of cryptococcal meningitis. *N Engl J Med.* 2014;370(26):2487–98. <https://doi.org/10.1056/NEJMoa1312884>.
- [13] Kaplan R, Hermans S, Caldwell J, Jennings K, Bekker LG, Wood R. HIV and TB co-infection in the ART era: CD4 count distributions and TB case fatality in Cape Town. *BMC Infect Dis.* 2018;18(1):356. Published 2018 Jul 31. doi:10.1186/s12879-018-3256-9.
- [14] Mwaba P, Mwansa J, Chintu C, et al. Clinical presentation, natural history, and cumulative death rates of 230 adults with primary cryptococcal meningitis in Zambian AIDS patients treated under local conditions. *Postgrad Med J.* 2001;77(914):769–73. <https://doi.org/10.1136/pmj.77.914.769>.
- [15] Chang WC, Tzao C, Hsu HH, et al. Pulmonary cryptococcosis: comparison of clinical and radiographic characteristics in immunocompetent and immunocompromised patients. *Chest* 2006;129(2):333–40. <https://doi.org/10.1378/chest.129.2.333>.
- [16] Zaidi M, Qureshi S, Shakoor S, Fatima S, Mir F. Abdominal Lymphonodular Cryptococcosis in an Immunocompetent Child. *Case Rep Pediatr.* 2015;2015:347403 <https://doi.org/10.1155/2015/347403>.
- [17] Gupta RK, Lucas SB, Fielding KL, Lawn SD. Prevalence of tuberculosis in post-mortem studies of HIV-infected adults and children in resource-limited settings: a systematic review and meta-analysis. *AIDS.* 2015;29(15):1987–2002. <https://doi.org/10.1097/QAD.0000000000000802>.
- [18] A Andama A, Jaganath D, Crowder R, et al. Accuracy and incremental yield of urine Xpert MTB/RIF Ultra versus Determine TB-LAM for diagnosis of pulmonary tuberculosis. *Diagn Microbiol Infect Dis.* 2020;96(1):114892. doi:10.1016/j.diag-microbio.2019.114892.
- [19] Kohli M, Schiller I, Dendukuri N, et al. Xpert® MTB/RIF assay for extrapulmonary tuberculosis and rifampicin resistance. *Cochrane Database Syst Rev.* 2018;8(8):CD012768. Published 2018 Aug 27. doi:10.1002/14651858.CD012768.pub2.
- [20] Minion J, Leung E, Talbot E, Dheda K, Pai M, Menzies D. Diagnosing tuberculosis with urine lipoarabinomannan: systematic review and meta-analysis. *Eur Respir J.* 2011;38(6):1398–405. <https://doi.org/10.1183/09031936.00025711>.
- [21] Metushi I, Uetrecht J, Phillips E. Mechanism of isoniazid-induced hepatotoxicity: then and now. *Br J Clin Pharmacol.* 2016;81(6):1030–6. <https://doi.org/10.1111/bcp.12885>.
- [22] Muñoz P, Moreno S, Berenguer J, Bernaldo de Quirós JC, Bouza E. Fluconazole-related hepatotoxicity in patients with acquired immunodeficiency syndrome. *Arch Intern Med.* 1991;151(5):1020–1. <https://doi.org/10.1001/archinte.1991.00400050150032>.
- [23] Verbist L, Rollier F. Pharmacological study of rifampicin after repeated high dosage during intermittent combined therapy. II. Bilirubin levels and other biochemical determinations. *Respiration.* 1971;28:17–28. <https://doi.org/10.1159/000194958>.
- [24] Ngongondo M, Miyahara S, Hughes MD, et al. Hepatotoxicity During Isoniazid Preventive Therapy and Antiretroviral Therapy in People Living With HIV With Severe Immunosuppression: A Secondary Analysis of a Multi-Country Open-Label Randomized Controlled Clinical Trial. *J Acquir Immune Defic Syndr.* 2018;78(1):54–61. <https://doi.org/10.1097/QAI.0000000000001641>.
- [25] Tedla Z, Nyirenda S, Peeler C, et al. Isoniazid-associated hepatitis and antiretroviral drugs during tuberculosis prophylaxis in hiv-infected adults in Botswana. *Am J Respir Crit Care Med.* 2010;182(2):278–85. <https://doi.org/10.1164/rccm.200911-1783OC>.
- [26] Brooks KM, George JM, Pau AK, et al. Cytokine-Mediated Systemic Adverse Drug Reactions in a Drug-Drug Interaction Study of Dolutegravir With Once-Weekly Isoniazid and Rifampentine. *Clin Infect Dis.* 2018;67(2):193–201. <https://doi.org/10.1093/cid/ciy082>.
- [27] Dooley KE, Churchyard G, Radojka M, Savic RM, et al., safety & pk of weekly rifapentine/isoniazid (3hp) in adults with hiv on dolutegravir. Conference on Retrovirals and Opportunistic Infections (CROI), 2020.
- [28] Tenforde MW, Shapiro AE, Rouse B, et al. Treatment for HIV-associated cryptococcal meningitis. *Cochrane Database Syst Rev.* 2018;7(7):CD005647. Published 2018 Jul 25. doi:10.1002/14651858.CD005647.pub3.
- [29] Balcells, M.E., et al., Isoniazid preventive therapy and risk for resistant tuberculosis. *Emerg Infect Dis.* 2006. 12(5): p. 744-51.