TB preventive treatment among pregnant women with HIV

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Running Head: TB preventive treatment policy uptake

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SUMMARY

BACKGROUND: The WHO recommends TB preventive treatment (TPT) for people living with HIV, including pregnant women. Uptake of this policy recommendation in this subpopulation and alignment with WHO guidance is unclear.

METHODS: We conducted a policy review in 38 WHO high TB and TB-HIV burden countries to assess if the uptake of TPT policy among pregnant women living with HIV was in line with the WHO's 2018 Updated and Consolidated Guidelines for Programmatic Management for LTBI. Data sources included TB national guidelines and HIV/AIDS/ART national guidelines, complemented by results from a previous survey on policy uptake held at the WHO.

RESULTS: Uptake of WHO policy to provide TB preventive treatment among women with HIV accessing antenatal care was moderate: 64% (23 of 36 countries) explicitly recommended at least one clinical guideline or policy recommendation on screening, testing or treatment of LTBI among pregnant women living with HIV. There was considerable variation between countries on the stages in pregnancy that TPT should be provided. Two countries (5%) provided clinical monitoring recommendations for pregnant women.

CONCLUSIONS: There is moderate uptake of TPT policy for pregnant women with HIV. Failure to provide TPT as part of antenatal or prevention of mother-to-child services is a missed opportunity for TB control.

KEY WORDS: high burden; TB-HIV countries; latent TB

In 2019, approximately 10 million individuals developed TB and over 1.4 million deaths were attributed to the disease.[1] Women accounted for 32% of these active TB cases. Globally, just under half (43%) of HIV-related TB deaths among adults (age ≥15) were among women. The majority of these HIV-associated TB deaths among women were concentrated in Africa. Put in context, the 2019 incidence of TB among women aged ≥15 years among 30 high TB burden countries was 2,753,700.[2]

Treatment of latent TB infection (LTBI) among those at highest risk of developing active TB is part of the WHO's four pillar End TB Strategy.[3] Since 1998, the WHO has recommended TB preventive treatment (TPT) for people living with HIV (PLHIV).[4] TPT was explicitly recommended for pregnant women with HIV starting in 2011.[4,5] Compared to other age groups, TB disproportionately affects women of reproductive age,[6] with serious consequences to both the mother and the child.[7,8] There is ample evidence documenting the negative impact of TB disease on the overall health of mothers and infants, highlighting the importance of TB prevention among this population.

To inform practice and further guide policy for TPT in pregnant or postpartum women, it is important to review the implementation status of WHO policy for each aspect of the clinical care cascade and management of TPT (screening, testing, treatment). We conducted a desk review to assess the uptake of WHO policy and recommendations on LTBI treatment for pregnant women living with HIV in 38 WHO high TB and TB-HIV countries burden.[5] We assessed 1) uptake of screening, testing and treatment policy for TPT among pregnant women living with HIV, and 2) uptake of specific screening and treatment recommendations, and 3) the rationale for adoption or lack of uptake.

METHODS

Country selection

The WHO has identified three overlapping lists of 30 high burden countries to prioritise elimination efforts for TB, TB-HIV and multidrug-resistant TB (MDR-TB) as part of the End TB Strategy during the period 2016–2020.[9] The respective high TB and TB-HIV burden countries from the lists form the basis of our review, including 38 unique countries from both lists.

Data source inclusion criteria

The primary data source for policy recommendations were TB national guidelines (adults, adolescents, children and infants) and HIV/AIDS/ART national guidelines (adults, adolescents,

children, infants). These data sources were complemented by a secondary data source: a database on latent TB held at the WHO.

As this WHO policy review follows standard methodology for policy desk reviews conducted by the WHO and does not involve collection of human data, ethical permission to conduct this desk review was not deemed necessary; this is consistent with literature reviews.

Data repositories held within the Global TB and HIV Programmes at the WHO were used for this policy review. In addition, a search on the internet and ministry of health webpages was performed in June 2018 to check for updated policy guidelines using English search terms. We were interested in policy guidance issued ahead of the publication of the 2018 programmatic guidance on TPT. Documents and reports by non-governmental organisations, donors or other technical agencies were excluded. We did not restrict our data sources to a publication year, and we included guidelines published before 2011 if this was the latest publicly available guideline. The most recent, relevant national policy for TB and/or HIV/AIDS and ART care were included in this review. Data sources were searched systematically online. Each search was run using the country name in combination with terms for relevant guidelines such as "national tuberculosis guideline", "latent tuberculosis guidelines" and "HIV/AIDS guidelines". All relevant guidelines were pulled and organised into an internal repository. As all policy documents that were used are publicly available documents, institutional review board approval was not required. Data were extracted based on the data source with the most recent year of publication.

Data extraction form

The 2018 Updated and Consolidated Guidelines for Programmatic Management for Latent TB Infection was used as a framework to build a data extraction form with a standardized set of variables to record policy recommendations for PLHIV.[5] The 2018 guidance represents the first consolidated guidance on LTBI management, with significant expansion of target groups and treatment regimens. The following a priori variables were collected: 1) availability of recommendation(s) on programmatic management of LTBI, 2) screening for active TB disease, 3) testing for LTBI, 4) treatment regimens used, 5) availability of monitoring recommendations. Our database was primarily populated with binary variables indicating the absence or presence of a respective policy recommendation. In addition to quantitative data, qualitative data were collected to provide descriptive information on the type of screening method for active or latent TB, options for LTBI treatment, as well as the rationale for adoption of LTBI management policy for pregnant women.

Piloting and data extraction

The extraction form was piloted (using data from three countries) and further modified for clarity prior to finalisation and use. Variable operationalisation was refined, new fields were added and coding questions were reconciled. Data extraction was completed by two reviewers (TD, PW).

Documents that were not in English were translated by authors with language-speaking abilities (TD, PW) or using free online translation software. Sources were considered good quality if the text was entirely legible and language was assessed as clear to both coders (TD and PW). Disagreements between the two primary coders during the data extraction phase were flagged and arbitrated by a third reviewer (MXR). Further disagreements were resolved by consensus.

Qualitative descriptive data on the country's rationale in recommending TB preventive treatment to pregnant women were recorded. For each country that provided a justification for TPT, rationales were organised into groups, which were determined by three reviewers (TD, MXR and YH).

Statistical considerations

Statistical analyses were performed using R programming software (R Computing, Vienna, Austria).[10] Percentages and frequencies were calculated using R. Using the same methodology as Jagger et al., policy recommendations in this paper were reported as percentages, calculated based on a database populated with binary entries (0,1).

RESULTS

Description of countries included

We found policy documents published from 2010 to 2017. Our policy review focused on a total of 38 countries. Primary data were only obtained from a total of 30 countries. Secondary data were used to populate the database for an additional six countries. In total, data for 36 countries were obtained from either national TB policy, HIV/AIDS or ART guidelines, internal WHO questionnaire or database. This represented 30 countries that were on the high TB-HIV burden list (22 of which had an overlapping high TB burden); 8 were on the high TB burden list only. Two countries had no data sources available for this policy review (Guinea Bissau and the Democratic People's Republic of Korea). The figures and tables only reflect countries with available data.

Uptake of current TPT guidance

Of 36 countries included in this review, 23 (64%) included at least one clinical guideline or policy recommendation on screening, testing or treatment of LTBI among pregnant women living with HIV. This included 21 of 29 countries with a high TB-HIV burden, with 16 of these countries also classified as having high TB burdens. The remaining two countries were on the high TB burden list only. Figure 1 compares the availability of recommendations in the high-burden countries specifically for pregnant women living with HIV, compared to recommendations for all PLHIV. Reviewing recommendations along the care cascade for 23 countries, the most frequently identified recommendation was the provision of a specific TPT regimen (61%), followed by a recommended screening method to rule out active TB (39%); nine countries (25%) addressed a testing method for LTBI. Of the countries that specified a testing method for LTBI, the tuberculin skin test was the specified testing method. Among the countries that provided a treatment regimen recommendation, isoniazid preventive treatment (IPT) was mentioned. Among the countries that provided a specific screening method, 36% recommended the use of the WHO's four-symptom screen (cough, fever, weight loss and night sweats) (Figure 2).

Policy reasons for TPT policy and its timing during pregnancy

Reasons to provide TPT to pregnant women with HIV most frequently noted in national guidelines included the following: 1) potential benefits of starting TPT outweighed the harms (progression of disease vs. adverse events), 2) pregnancy was not a contraindication for being on TPT, and 3) IPT could be provided regardless of degree of immunosuppression (pregnancy or CD4 count). A few countries stated other reasons. South Africa recommended TPT be provided based on expert opinion weighing the benefits against harms of providing preventive treatment to pregnant women. For Ghana and Eswatini, the rationale for TPT provision was anchored in their nationwide integration initiatives for maternal, neonatal and child health services (Table 1).

There were considerable differences between countries on the stage of pregnancy that TPT should be provided. Three countries, Kenya, India and South Africa, specified that TPT could be provided "anytime" during pregnancy. Zambia specified that treatment should be provided to "newly pregnant" mothers. Botswana recommended that female clients who become pregnant after 3 months of IPT may continue with isoniazid; clients who have completed less may be discontinued. Brazil recommended TPT after the third month of

pregnancy and Tanzania recommend TPT be started after the first trimester of pregnancy while Cameroon recommended that TPT not be provided before 16 weeks of pregnancy.

DISCUSSION

Our review provides an important baseline to inform our understanding of the uptake of TPT policy and to scale-up preventive treatment for pregnant women living with HIV. There was moderate uptake of TPT policy among pregnant women with HIV for key recommendations across the cascade of care for LTBI. Given that WHO's recommendation on TPT for pregnant women living with HIV was introduced in 2011, the uptake by countries is lower than might be expected between 2011 and the date of our review. Slow uptake of TPT recommendations may, in part, reflect the lack of confidence by programme managers in balancing the harms and benefits of TB prevention in pregnant women. A systematic review across nine studies of the safety of TPT for pregnant and postpartum women found inconsistent associations between reported adverse pregnancy outcomes and TPT.[11] Several observational studies included in that review reported protective effects of TPT with 6 months of isoniazid among pregnant women and no significant increase in adverse events. Specifically, Salazar-Austin[12] and Taylor et al.[13] found a protective association between TPT use and adverse pregnancy outcomes after controlling for potential confounding factors. Similarly, Kalk et al.[14] found that IPT was protective against incidence of TB after 12 months post pregnancy, with an adjusted hazard ratio for TB of 0.71 (95% confidence interval 1,238–1,799/100,000). However, one randomised controlled trial identified an increased risk for adverse pregnancy outcomes from TPT.[15] As noted in the review, in pregnant women at high risk for TB, the maternal and infant risks of developing active TB are likely to outweigh the risks of possible adverse pregnancy outcomes to the mother and child due to TPT. Furthermore, the maternal and infant risks of active TB in multigenerational households pose the additional risk of transmission to other family members and small children. Hamada et al. underscore the need for additional research on this important clinical issue among this high-priority population.[11]

A review on policy uptake is intended as a barometer for implementation and coverage. It should also be acknowledged that it is difficult to assess implementation without monitoring and evaluation (M&E) data. Countries do have M&E plans to support reporting of TB prevalence, prevention and management among PLHIV. Similarly, the WHO does have guidance on recording and reporting all TB-HIV activities for pregnant women living with HIV.[16] While these data are not requested by the WHO for monitoring at the global level, it is nonetheless critical to monitor the uptake of TPT among pregnant women at the national level.

The coverage of TPT among pregnant women in high-burden contexts is unclear; there remains a paucity of data for this risk population. Countries should enhance their M&E system by disaggregating data on pregnancy status at the country level as recommended by the 2017 guidelines on person-centred HIV patient monitoring and case surveillance.[16] Lesotho is the only country identified through this review whose LTBI policy guidance specifically includes reporting of TPT coverage as an indicator in its HIV guidelines. Gaps in the care cascade for LTBI management are difficult to assess without M&E information specific to this population. Linkages with pregnancy registries would strengthen M&E activities within the reproductive maternal and newborn health services.[14]

Varied reasons are provided by countries on the need for, and timing of, TPT offered in the national guidelines reviewed as part of our work. A wide range of reasons underscore the need to clearly convey the benefit-harm trade-off for providing TPT in pregnancy for women, and consequently, their infants. Previous WHO TPT guidelines (2011) recommend that "sound clinical judgement is required for decisions such as the best time to provide IPT to pregnant women".[4] Operational guidance is now available to improve areas of uncertainty, including for clinical evaluation for TB, and eligibility for TPT, and to inform ideal timing of TPT initiation during pregnancy.[17] In addition, tools such as mobile applications to support decision-making for clinicians and pregnant women to confidently start TPT during pregnancy may need further exploration to scale up current recommendations.

While the 2011 and 2018 WHO guidelines do not explicitly single out postpartum women as a subgroup of women with HIV for receiving TPT, the latest guidelines released in 2020 reviewed the safety of TPT in pregnant women and postpartum women and state that appropriate care, such as including pyridoxine supplementation during the antenatal and postnatal periods and during delivery may reduce the risk of adverse pregnancy outcomes. Failure to provide TPT during this period in women with HIV is likely to be a missed opportunity for TB prevention for a number of reasons. Women in the postpartum period are also at high risk of developing TB.[18] There is a substantial risk for poor maternal and birth outcomes due to active disease, as well as the risk of onward transmission to infants and families postpartum if TB is not prevented. WHO guidance for TPT exists for all PLHIV, including women who are pre or postpartum; implementation of current recommendations is warranted. While not a primary objective of this policy review, documents from three countries (Lesotho, Kenya and South Africa) included specific recommendations for postpartum breastfeeding women stating that TPT is safe, suggesting that local policy may exist.

Our review had a few limitations and strengths. The authors were not able to secure missing data from two countries; however, other sources were used, when available from related conference materials following the review. As noted, LTBI guidelines were not available for all 38 countries at the time of data collection. Irrespective of our findings, some recommendations may have emerged as part of a country's national TB programme or through an unidentified source since this review was conducted. Our review does not reflect views since the updated guidance on TPT (policy documents published in or after 2018 were beyond the study remit). Finally, data extraction from documents not in English may have been biased by the primary coder's language proficiency outside of their native language. Study strengths include the extensive variety of sources used in this review. This review also provides, for the first time, an understanding of the gaps in TPT policy for this at-risk population, compared to a broader group of persons with HIV and gives a window on how benefit-harms are perceived, thus highlighting research and policy areas for further attention in future guidelines.

CONCLUSION

We found moderate uptake of TPT policy for pregnant women with HIV. Failure to provide TPT as part of antenatal or prevention of mother-to-child services is a missed opportunity for TB control. Current lack of confidence by programmes to prioritise TB prevention among pregnant women living with HIV needs to be addressed. National programmes should scale up current WHO recommendations, ensuring strengthened capacity to provide TPT and adequate measures for effective monitoring of coverage, timing and completion of TPT and for early detection and management of adverse events.

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References

1 World Health Organization. Global tuberculosis report, 2020. Geneva: Switzerland: WHO, 2020. https://www.who.int/publications/i/item/978924001313

2 World Health Organization. WHO TB incidence estimates disaggregated by age, sex and risk factor. 2020 Dataset. Geneva, Switzerland: WHO, 2020. https://www.who.int/teams/global-tuberculosis-programme/data

3 World Health Organization. The End TB Strategy. Geneva, Switzerland: WHO, 2015. https://www.who.int/tb/strategy/End_TB_Strategy.pdf

4 World Health Organization. Guidelines for intensified tuberculosis case-finding and isoniazid preventive therapy for people living with HIV in resourceconstrained settings. Geneva, Switzerland: WHO, 2011. https://apps.who.int/iris/bitstream/handle/10665/44472/9789241500708_eng.pdf?sequence=1

5 World Health Organization. Latent TB infection: updated and consolidated guidelines for programmatic management. Geneva, Switzerland: WHO, 2018. https://apps.who.int/iris/bitstream/handle/10665/260233/9789241550239-eng.pdf?sequence=1

6 Malhamé I, et al. Latent tuberculosis in pregnancy: a systematic review. PLoS One 2016;11(5):e0154825.

7 Getahun H, et al. Prevention, diagnosis, and treatment of tuberculosis in children and mothers: evidence for action for maternal, neonatal, and child health services. J Infect Dis 2012;205(suppl_2):S216–S227.

8 Mathad JS, Gupta A. Tuberculosis in pregnant and postpartum women: epidemiology, management, and research gaps. Clin Infect Dis 2012;55(11):1532–1549.

9 Floyd K, et al. Use of high burden country lists for TB by WHO in the post-2015 era. Geneva, Switzerland: World Health Organization, 2015. https://www.who.int/tb/publications/global_report/high_tb_burdencountrylists2016-2020.pdf

10 R CoreTeam. R: A language and environment for statistical computing. Vienna, Austria: R Foundation for Statistical Computing, 2018. http://www.R-project.org/

11 Hamada Y, et al. The safety of isoniazid tuberculosis preventive treatment in pregnant and postpartum women: systematic review and meta-analysis. Eur Respir J 2020;55(3):1901967.

12 Salazar-Austin N, et al. Isoniazid preventive therapy and pregnancy outcomes in women living with human immunodeficiency virus in the Tshepiso cohort. Clin Infect Dis 2020;71(6):1419–1426.

13 Taylor, AW, et al. Pregnancy outcomes in HIV-infected women receiving long-term isoniazid prophylaxis for tuberculosis and antiretroviral therapy. Infect Dis Obstet Gynecol 2013; 5

14 Kalk E, et al. Safety and effectiveness of isoniazid preventive therapy in pregnant women living with human immunodeficiency virus on antiretroviral therapy: an observational study using linked population data. Clin Infect Dis 2020;71(8):e351–e358.

15 Gupta A, et al. Isoniazid preventive therapy in HIV-infected pregnant and postpartum women. N Engl J Med 2019;381:1333–1346.

16 World Health Organization. Consolidated guidelines on person-centered HIV patient monitoring and case surveillance. Geneva, Switzerland: WHO, 2017. https://apps.who.int/iris/bitstream/handle/10665/255702/9789241512633-eng.pdf?sequence=1

17 World Health Organization. WHO operational handbook on tuberculosis: module 1: prevention: tuberculosis preventive treatment. Geneva, Switzerland: WHO, 2020. https://apps.who.int/iris/bitstream/handle/10665/331170/9789240001503-eng.pdf

18 Zenner D, et al. Risk of tuberculosis in pregnancy: a national, primary care-based cohort and self-controlled case series study. Am J Respir Crit Care Med 2012;185(7):779–784.

Table TPT: treatment rationale for pregnant women with HIV

Treatment rationale for pregnant women with HIV	Country count (n = 23)
Benefit vs. harms	3
Pregnancy is not a contraindication for TPT treatment	4
TPT should be provided regardless of degree of immunosuppression	9
After ruling out active TB	2
Expert opinion	1
Integration of initiative for maternal, neonatal and child health services	2
Dependent on stage of pregnancy	2

TPT = TB preventive therapy.

FIGURE LEGENDS

Figure 1 Provision of LTBI national policy and clinical guideline recommendations for PLHIV compared to pregnant women in 36 high TB-HIV countries. TPT = TB preventive therapy; PLHIV = people living with HIV; LTBI = latent TB infection.

Figure 2 Existence of recommendations to assess eligibility and treat LTBI among pregnant women living with HIV in 36 high TB and TB-HIV countries. LTBI = latent TB infection.