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A literature review of current tuberculosis prophylaxis strategies for PLHIV in Namibia

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A Thesis submitted in partial fulfillment of the requirements for the degree of
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ABSTRACT

INTRODUCTION: The HIV and TB co-epidemic remains a big obstacle in reducing PLHIV mortality and morbidity in Namibia. The solution to that has been the implementation of isoniazid preventative therapy (IPT) alongside ART for PLHIV to prevent the development of active tuberculosis. As newer shorter regimens of IPT (3HP) are released it is important to Namibia's Ministry of Health to evaluate the efficacy of these newer IPT regimens prior to their implementation.

OBJECTIVES: The objective of this review is to compare the benefit of 3HP to that of 6-month or continuous (36-month) daily IPT for PLHIV to make future TB prophylaxis recommendations for MOH of Namibia. The review will take into consideration outcomes such as TB incidence, mortality, completion rate, and adverse events.

METHODS: The qualifying studies were randomized controlled trials which consisted of participants being provided with 3HP and daily IPT (6 month or continuous). Only studies that primarily enrolled PLHIV were included in this review. Out of all the results of these studies the interest is in the development of active tuberculosis, mortality, adverse events, and treatment completion rate.

RESULTS: The analysis of the two studies that qualified for this review informs us that 3HP has similar efficacy in preventing active tuberculosis to that of IPT. The Sterling study reported that discontinuation due to hepatotoxicity was significantly higher in the 9-month IPT arm (4%) than in the 3HP (1%) arm. Hepatotoxicity was reported in 1.4% (3/207) of the participants in the 3HP group compared to 6.5% (12/193) of the 9-month IPT groups. Both studies reported a higher completion and adherence rate for 3HP than for 6-month or 9-month IPT. The highest

adherence was reported for the 3HP in the Martinson study at 95.7% whereas 6-month IPT had an adherence rate for only 83.8%.

CONCLUSION: Largely, this review suggests that further research be done to evaluate the complexity of 3HP in different settings with different populations. However, based on these preliminary findings it is preferable for Namibia to adopt 3HP once it is cost-effective to raise their IPT completion rates, increase implementation of IPT in all local sites, and prevent adverse outcomes.

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I. BACKGROUND

WHAT IS TUBERCULOSIS?

Tuberculosis (TB) is one of the top ten leading causes of death worldwide due to a single infectious agent. In 2018 alone, it was responsible for killing 1.5 million people with 10 million people experiencing the illnessⁱ. In addition to affecting so many around the world it can be found in all countries despite being a preventable disease. In an ideal world timely diagnosis and treatment would be available to all thus drastically reducing transmission and severity of the illness. However, due to the lengthy treatment and lack of feasible diagnostic measures that is not necessarily the case. The eradication of TB is complicated by the route of transmission of the bacteria as well as the latent stage of the disease. A latently infected individual will not develop any of the symptoms associated with the illness, and of the latently infected individuals 5-10% will go on to develop the disease. Currently, almost 1.7 billion people around the world are infected with TB and thus are at risk for active tuberculosisⁱ. People with the disease typically exhibit unexplained weight loss, lack of appetite, night sweats, fever and chills. Those with pulmonary tuberculosis will additionally develop chest pain, persistent cough and hemoptysis. Those exhibiting symptoms are considered infectious and capable of spreading the TB bacteria to others. Thus, it is imperative to minimize the development of disease especially for the immunosuppressed.

In 2018, the TB burden in Namibia was 0.524% (524/100,000) with the mortality at 0.064% (64/100,000)ⁱⁱ. However, this number does not capture the whole story of TB associated mortality. Out of the 13,000 individuals affected with TB, 4500 were HIV-positiveⁱⁱ. The fact that

36% of TB patients have an HIV-positive status is alarming. Globally, Namibia remains one of the most HIV prevalent countries. In 2018, the prevalence of HIV in the country was at 11.8% with 2,400 AIDS related deathsⁱⁱ. This highlights that there is a large population of people living with HIV (PLHIV) that are vulnerable to developing tuberculosis. The co-epidemic of HIV and tuberculosis (TB) remains a major public health crisis.

WHY ARE TB AND HIV SO INTERLINKED?

The human immunodeficiency virus (HIV) is an infection in which the CD4 T-lymphocytes are targeted. By preferentially targeting the CD4 lymphocytes the immune system is left weakened. For someone living with HIV the risk of developing TB is 20-37 times greater than for those that are HIV negativeⁱⁱⁱ. For an HIV negative individual, the risk progressing from latent TB to active TB is 10%, but for PLHIV this risk is 30%^{iv}. Thus, HIV remains the strongest risk factor for TB disease progression and severity. An HIV infection increases one's risk of latent TB reactivation. Individuals suffering from a TB and HIV co-infection experience faster disease progression rates and have a higher risk of mortality. There is an inverse relationship between CD4 lymphocyte count and risk of active TB, as CD4 cell count declines the risk for active TB increases. Numerically, this relationship is seen as a 15-20% increased risk of active TB per year for PLHIV with CD4 cell counts of less than 200 cells/ μ l^v. In areas of high prevalence of HIV there remains a need to implement TB control measures in order to keep PLHIV protected as well as stop the TB epidemic.

WHAT ARE THE CURRENT TREATMENT MEASURES FOR PLHIV?

In order to assess the need for further prophylaxis, it is important to first analyze what measures are currently implemented for PLHIV. Through PEPFAR there has been a global scale-up of HIV care all over Africa. This scale-up includes treatment services, in particular, antiretroviral therapy (ART). PEPFAR is currently implemented in Namibia for three strategic areas; prevention of HIV transmission, care and treatment of PLHIV, and strengthening the public health system to effectively and sustainably respond to the epidemic^{vi}. Through PEPFAR, Namibia is trying to achieve the UNAIDS 90-90-90 targets^{vii}. These targets will ensure that 90% of all PLHIV know their status, 90% of those who know their status are on ART and lastly 90% of those on treatment are able to achieve viral suppression^{viii}. The second 90 is important because it is concerning treatment for PLHIV with ART. Currently, all PLHIV in Namibia are eligible for ART upon being diagnosed. Those with a positive HIV test are referred to an ART clinic to be further assessed and to begin the ART regimen. All this effort has given significant results because as of 2018, 76.5% of PLHIV are on ART and 87% of those on ART have viral suppression. This is proof that Namibia is on its way to achieve the UNAIDS 90-90-90 targets. ART is also known to be associated with rapid recovery of mycobacteria-specific immune responses. This leads to decreased mycobacterial growth and at the clinical level has shown to be a powerful TB preventative effect. Since the advent of ART, analysis has shown there to be 65% reduction in TB incidence in PLHIV.

WHAT IS ISONIAZID PREVENTION THERAPY?

However, due to the increased risk of tuberculosis for PLHIV there is a need for more prophylaxis beyond just antiretroviral therapy. Moreover, TB rates still remain relatively high

even after increasing ART uptake among PLHIV; thus, highlighting the need for continued focus on TB control measures. Currently, ART is accompanied by the implementation of isoniazid preventative therapy (IPT). IPT has been widely used as prevention for TB. It eliminates the bacterium from the body by treating latent tuberculosis and preventing new infections from occurring during treatment^{ix}. Alongside ART, IPT provides an additional blanket of protection for PLHIV to prevent tuberculosis. Several studies show that IPT alongside ART provides additional benefits in lowering the incidence of TB than just the implementation of ART alone^x.

(Table 1)

Table 1- List of IPT + ART vs ART alone studies		
Study	Type	Key findings
Edessa 2015 ⁱⁱⁱ	Retrospective cohort study at TASH and ZMH 6-month IPT + ART and ART alone	For ART alone TB incidence: 10/100 PY, For IPT + ART TB incidence: 4.5/100 PY
Badje, TEMPRANO ANRS 12136, 2017 ^{xi}	RCT for 6-month IPT + ART in Cote d'Ivoire	35% reduction in HIV related deaths after initiation of IPT
Golub, THRio, 2007 ^{xii}	Prospective cohort; Brazil	For ART alone TB incidence: 1.9/100 PY, For IPT + ART TB incidence: 0.8/100 PY
Golub, 2009 ^{xiii}	Prospective cohort; South Africa	For ART alone TB incidence: 4.6/100 PY, For IPT + ART TB incidence: 1.1/100 PY
Yirdaw, 2014 ^{xiv}	Retrospective cohort; Ethiopia	For ART alone TB incidence: 0.74/100 PY, For IPT + ART TB incidence: 0.36/100 PY
Rangka, 2014 ^{xv}	RCT; South Africa	For ART alone TB incidence: 3.6/100 PY, For IPT + ART TB incidence: 2.3/100 PY

Table 2- List of continuous IPT vs 6-month IPT studies		
Study	Type	Key findings
Samandari, 2011 ^{xvi}	RCT; Botswana	6-month IPT: 34 cases/989 participants (3.4%) Continuous IPT: 20 cases/1006 (2.0%)

Kunkel, 2016 ^{xvii}	Transmission Dynamic Model; Botswana	Benefits of continuous IPT outweigh the risk of long duration of IPT in reduction of TB incidence and mortality.
Swaminathan, 2012 ^{xviii}	RCT; India	Both regimens were similarly effective, 36 months showed a lower trend of TB incidence. 6 months: 2.4/100py Continuous IPT: 1.6/100py
Hsieh, 2018 ^{xix}	Transmission Dynamic Model, Malawi	Compared to the 6-month IPT program, the continuous IPT can avert at least 6902 more TB cases and prevent 2256 deaths.

Through the analysis of these studies it is clear that when ART is combined with IPT there is greater reduction of mortality for PLHIV. This is due to the fact that IPT lowers the risk of active tuberculosis in high endemic settings for those that are extremely vulnerable (PLHIV). Thus, WHO recommends that IPT be given to all PLHIV in combination with ART starting at the time of diagnosis^{ix}.

The current recommendation is that IPT be given continuously for at least 6 months. Additionally, in high TB endemic areas it is recommended that IPT be given for 36 continuous months. For example, in countries like Botswana, where incidence of TB is at 350 per 100,000, 6 months of IPT can be insufficient. In a randomized, double-blind, placebo-controlled trial conducted in Botswana it was discovered that 36 months of continuous IPT given to PLHIV reduced TB incidence by 43% when compared to 6 months of IPT^{xvi}. It should be noted that this benefit was seen in those with a tuberculin positive test. (39) The Swaminathan randomized clinical trial in India had similar findings in which 712 PLHIV were randomized to receive either 6-month IPT or continuous IPT (36 months)^{xviii}. The results showed a decreased TB incidence for

continuous IPT when compared to 6-month IPT (6 months: 2.4/100py, continuous IPT: 1.6/100py).

In comparison the TEMPRANO study conducted in West Africa, where the incidence of TB is 159 per 100,000 people, concluded that 6 months of ART + IPT has durable protective effect in reducing mortality in PLHIV when taken along with ART^{xi}. After the analysis of current available studies, it can be concluded that the length of IPT is context-specific and can be proportional to the burden of tuberculosis in the country^{ix}. (Table 2)

While 6-month IPT is part of the current WHO guidelines for TB prophylaxis there is another treatment option of 3-month weekly regimen of rifapentine plus isoniazid (3HP) that is recommended for high- or upper-middle-income countries with a TB incidence of <100/100,000. The shorter duration and simplicity offered by the 3 month-once weekly regimen has major appeal for the future of IPT. Since the advent of 3HP in 2011, many studies have confirmed 3HP's effectiveness when compared to alternative IPT regimensⁱ.

Since 3HP, an even shorter course regimen of daily isoniazid and rifapentine for 28 days (1HP) has been formulated. Due to its extremely short regimen it will have even fewer barriers towards implementation and completion rate than 3HP. This shorter regimen is not currently available to be implemented and this will not be further discussed in this reviewⁱ.

OBJECTIVE:

The objective of this review is to compare the benefit of 3HP to that of 6-month or continuous (36-month) daily IPT for PLHIV to make future TB prophylaxis recommendations for

Namibia. The review will take in consideration outcomes such as TB incidence, mortality, completion rate, and adverse events.

II. METHODS

ETHICS STATEMENT:

Ethical approval was not required for this review.

SEARCH STRATEGY:

The search was conducted on the PubMed electronic database. The strategy was to use the terms IPT, rifapentine, 3HP, PLHIV, and RCT. The search was limited to those that were randomized controlled trials and the search span included studies that were published between 1 January 2011 and 1 January 2019. This was done so all studies that were done after the introduction of 3HP can be evaluated. The reference lists of included papers were also checked and reviewed to get additional studies. No language or geographical limitations were applied.

ELIGIBILITY CRITERIA:

The qualifying studies were randomized controlled trials which consisted of participants being provided with 3HP and daily IPT (6 month or continuous). Only studies that primarily enrolled PLHIV were included in this review. Out of all the results of these studies the interest is in the development of active tuberculosis, mortality, adverse events, and treatment completion rate. For the purposes of this review the 6-month IPT and 9-month IPT regimen were considered equivalent. Information taken from each article included study design, comparison groups,

number of participants, and the impact of the intervention through risk ratios. There is however extensive heterogeneity between the study populations, study methods and settings which needs to be taken into consideration when drawing any conclusions^{xx}.

Table 3- List of included studies in this review

Study	Country	Participants
Martinson, 2011 ^{xxi}	South Africa	3HP: 328 6H: 327 Continuous IPT: 164
Sterling, 2016 ^{xxii}	USA, Canada, Brazil, Spain, Hong Kong, and Peru	3HP: 206 9H*: 193

* For the purposes of this review the 6-month IPT and 9-month IPT regimen were considered equivalent.

III. RESULTS

The studies (Table 3) included in this analysis have been analyzed in prior reviews. Since the last systematic review there has not been another study that qualifies for this analysis. However, this review will focus on outcomes of interest (TB incidence, mortality, adverse events, and completion rate) and then will proceed to discuss the feasibility of implementation of 3HP in the Namibia setting.

DESCRIPTION OF INCLUDED STUDIES:

Martinson *et al*-

- The study included randomly assigned South African adults with HIV infection. All participants had a positive tuberculin test and were not initiated on ART. The study arms were: rifapentine (900 mg) and isoniazid (900 mg) weekly for 12 weeks (3HP), rifampin (600 mg) and isoniazid (900 mg) twice weekly for 12 weeks (3HP-2), isoniazid (300 mg)

daily for up to 6 years (continuous isoniazid), and isoniazid (300 mg) daily for 6 months (6-month IPT control group).

- Study population was a Soweto community with high prevalence of HIV infection and tuberculosis. The eligible participants were at least 18 years of age, were not pregnant or breastfeeding and did not have active tuberculosis that was ruled out both through a comprehensive symptom review and through chest radiography. Patients that had previously received tuberculosis preventative therapy were excluded from the study.
- Treatment for the 3HP & 3HP-2 regimen was directly observed in study clinics while the 6-month and continuous IPT were self-administered. Patients were assigned in a randomly generated algorithm format in 2:2:2:1 block for the 4 treatment groups of 3HP, 3HP-2, 6-month IPT and continuous IPT, respectively.

Sterling et al-

- An open-label, randomized noninferiority trial that compared once-weekly rifapentine 600–900 mg plus isoniazid given under direct observation (3HP) with self-administered 9-month daily IPT for participants at high risk for tuberculosis.
- Participants from the United States, Spain, Brazil, Canada and Hong Kong were enrolled from June 2001 and December 2010, additionally participants from Peru and Brazil were enrolled from February 2008 and December 2010. The participants were followed through September 2013. HIV testing was only recommended and not enforced for the enrollment for this trial. Patients (≥ 2 years) with an HIV infection and a positive

tuberculin test (or had close contact with an active tuberculosis case) were enrolled in the study.

- Treatment was allocated in randomized fashion. For household clusters, the first person in the group was randomized to an intervention and the same treatment was given to the rest of the cluster. Those with a suspected positive case of tuberculosis, previous isoniazid therapy, pregnant or breastfeeding were excluded from the study. Participants were followed for 33 months from enrollment and went through a monthly evaluation process. After completion of therapy study visits occurred every 3 months up until the 21st month.

TB INCIDENCE AND MORTALITY:

Table 4- TB incidence and mortality Martinson et al.

Incidence	3HP	3HP-2	Continuous IPT	6-month IPT	All
Cases	24	24	8	22	78
PY follow up	1187.5	1219.7	561.0	1143.9	4112.1
Incidence rate per 100 PY	2.0	2.0	1.4	1.9	1.9

Mortality	3HP	3HP-2	Continuous IPT	6-month IPT	All
Deaths	17	16	8	25	66
PY follow up	1223.6	1269.8	574.2	1180.0	4247.6
Incidence rate per 100 PY	1.4	1.3	1.4	2.1	1.6

The incidence rate of tuberculosis incidence and mortality was not significantly different between the 3HP and 6-month IPT groups. The incidence rate-ratio for incidence and mortality of 3HP was 0.87 when compared to the reference of 6-month IPT (1.0). The p-value was 0.54 signaling that there was no statistically significant difference between the two regimens. In total tuberculosis was diagnosed for 78 patients of which 62 had a confirmed tuberculosis, 11

had probable tuberculosis and 5 had possible tuberculosis. Out of the all participants, 66 patients died during the follow-up. No significant differences in the incidences of tuberculosis or death was seen between all three shorter regimen treatment groups. The rate of tuberculosis and mortality was lower in the continuous isoniazid groups than in the other three groups. (Table 4)

Table 5- TB incidence and mortality Sterling et al.

TB Incidence	3HP	9-month IPT
Total Participants	206	193
TB cases	2	6
Incidence rate per 100 PY	0.39	1.25

There were 2 tuberculosis cases in the 3HP arm in the 517 person-years of follow up and 6 tuberculosis cases in the 481 person-years of follow up for the 9-month IPT arm. Since this was a non-inferiority trial the margin for non-inferiority was defined as the difference in cumulative TB rates of 0.75%. Non-inferiority was reached within the modified intention-to-treat analysis (upper limit of the 95% CI 0.60). Non-inferiority was not reached in the per-protocol analysis (upper limit of the 95% CI 1.47). A previous systematic review conducted a meta-analysis which failed to show a significant difference in the risk for active TB between the two treatment groups. Additionally, there was no significant difference in mortality between the 3HP and 9-month IPT for adults with HIV.

ADVERSE EVENTS:

Martinson *et al* -

The shorter regimens (3HP, 3HP-2, 6-month IPT) all had adverse events likely to occur after the completion of the treatment whereas the continuous regimen saw 87.3% of adverse events occurring in duration of the medication phase. Serious adverse events included grade 3 or 4 toxic effects, death and active tuberculosis. For 3HP arm the rate of adverse events was 8.7 per 100 PY, 3HP-2 had a rate of 10.6 per 100 PY, continuous isoniazid group had a rate of 18.4 per 100 PY and 15.4 per 100 PY for the 6-month isoniazid group. No deaths were reported from the drug regimen itself. This study did report an increase in aspartate or alanine aminotransferase levels during treatment phase. The proportion of participants experiencing this increase was 1.5% in 3HP, 2.4% in 3HP-2, 28% in continuous IPT and 5.5% in 6-month IPT.

Sterling et al -

Discontinuation due to hepatotoxicity was significantly higher in the 9-month IPT arm (4%) than in the 3HP (1%) arm. Hepatotoxicity was reported in 1.4% (3/207) of the participants in the 3HP group compared to 6.5% (12/193) of the 9-month IPT groups. A significantly lower risk of hepatotoxicity is present in participants taking 3HP than in those taking 9-month IPT. The risk of grade 3 or 4 adverse was also lower in patients given 3HP over 9-month IPT regimen.

COMPLETION RATE:

Both studies reported a higher completion and adherence rate for 3HP than for 6-month or 9-month IPT. The highest adherence was reported for the 3HP in the Martinson study at 95.7% whereas 6-month IPT had an adherence rate for only 83.8%. In the Sterling study treatment completion was significantly higher in the 3HP arm than in the 9-month arm. In the 3HP arm

89% (183/206) reported completion whereas only 64% (123/193) reported treatment completion in 9-month IPT arm. This was a statistically significant result as the p-value was less than 0.001. Since there is heterogeneity between the two studies regarding the length of the IPT regimens they are not fully comparable. The point worth noting is that both studies favored 3HP for adherence and completion no matter what it was being compared to^{xx}.

IV. DISCUSSION

The objective of this review was to assess the efficacy of 3HP as an alternative tuberculosis prophylaxis regimen to 6-month IPT. This is an important public health question because for many countries that have high HIV and tuberculosis burden the benefits offered by a shorter and simpler regimen can reduce morbidity and mortality associated with an active tuberculosis infection.

Although, IPT has been a World Health Organization (WHO) recommendation for PLHIV and children <5 years exposed to persons with TB since 1993, global IPT uptake has remained slow. Of the 34.5 million adults living with HIV, only 4.8 million (14%) were ever reported to have been started on IPT since 1993^{xxiii}. Namibia's 2016 HIV Guidelines recommends that all PLHIV in whom TB disease has been excluded should receive 9 months of IPT. Under the U.S. President's Emergency Plan for AIDS Relief, of the 176,126 PLHIV currently receiving ART in Namibia, only 41,612 are recorded as having completed a course of IPT between the end of 2014 and mid 2019. This suggests that 134,514 PLHIV in Namibia remain untreated. Namibia's 2020 PEPFAR target for the number of PLHIV that are expected to complete TPT is 82,042. To achieve this ambitious goal, programmatically a more feasible approach that delivers treatment

widely and successfully will need to be implemented. One avenue is to explore utilizing the isoniazid-rifapentine (3HP) regimen. The shorter course of therapy offers the prospect of improving acceptance and adherence most notably increasing completion rates of IPT in a programmatic setting.

CURRENT IMPLEMENTATION OBSTACLES:

There are many obstacles to IPT implementation, the foremost being adherence to treatment and adverse events.

Adherence is difficult to achieve for the IPT regimen in place today due to the length and rigidity of the therapy. Once a patient starts to feel well it is hard to adhere to a regimen that requires months to complete. In countries worldwide IPT completion rates are between 37% to 95% due to issues with adherence. Namibia faces this issue as well since many of their local sites are below 85% for IPT completion rates. Poor adherence essentially negates any benefit IPT might provide to the patient^{xxiv}. In order to maximize efficacy of the regimen it is important that adherence and completion of the therapy remain a top priority. As discussed in the results section of this review both studies reported higher completion and adherence rates for 3HP when compared to either the 6 or 9-month IPT with statistical significance. The Sterling study is comparable to Namibia because it compared 3HP to 9-month IPT (which is the WHO recommendation for Namibia). In the study, the 9-month IPT arm only reported 64% completion whereas 3HP was at 89%. This is evidence that if 3HP is implemented in Namibia the current completion issues faced by the country can be somewhat alleviated. It is worth considering the differences between the setting of the Sterling study and Namibia when

drawing any conclusions. However, the future of IPT still looks optimistic if we take into consideration the available study data regarding 3HP.

Another notable obstacle in the success of isoniazid preventative therapy is the onset of adverse events. There notable toxicities associated both with isoniazid and ART which make it difficult to understand the causative agent when adverse events occur for PLHIV on IPT^{xxi}. The worst adverse event is isoniazid associated hepatotoxicity. Isoniazid can cause an elevation in liver enzymes, however if it is less than three times the normal amount it is resolvable. This can usually be mitigated through cessation of regimen. The risk for hepatotoxicity increases with age, immunosuppression, hepatitis and consumption of alcohol. Per the WHO recommendations the participants must be thoroughly screened and monitored to avoid cases of hepatotoxicity. However, such monitoring is not always available leaving PLHIV on IPT vulnerable to the onset of adverse events. In both of the studies analyzed in this review lower hepatotoxicity was reported in the 3HP arm than in the 6-month or 9-month IPT arm. Additionally, fewer people discontinued the medication due to hepatotoxicity in the 3HP arm than in the 6-month or 9-month IPT arm. While more studies are needed to fully assess the hepatotoxicity of isoniazid therapy it is clear that taking a potentially strong medication in fewer doses for a shorter regimen is preferable to taking it daily for 6-36 months. Thus, to promote both adherence and reduce hepatotoxicity implementing 3HP in place of 9-month IPT in Namibia is a worthwhile endeavor.

Due to its shorter regimen it can additionally be noted that in countries, including Namibia, where implementation of IPT has been slow 3HP may provide a benefit in reinvigorating the TB prevention treatment program.

EFFICACY:

In terms of efficacy it is clear that 3HP has a similar efficacy in preventing active TB when compared to daily isoniazid therapy through the analysis of onset of tuberculosis cause and all-cause mortality. As discussed it is not only more efficacious but also has a higher treatment completion rate and fewer adverse events. When discussing efficacy, it only applies when comparing 3HP to 6 or 9-month IPT and not continuous IPT. Another systematic review along with a modeling study has reported a lower risk of tuberculosis among participants receiving continuous IPT in the place of 6-month IPT. Thus, further research is needed when deciding between 3HP and continuous IPT^{xx}.

COST-EFFECTIVENESS:

One of the biggest challenges in implementing 3HP is the price. The cost of rifapentine is higher than that of isoniazid. Additionally, since this regimen is not self-administered there is an additional cost associate with directly observed therapy (DOT). The need for additional personal for DOT is a barrier to implementation due to cost and training required. The more flexibility available for any prophylaxis regimen the higher the adherence and lower the discontinuation of the medication. The price of rifapentine is \$6 per dose in the United States, but the price for the countries in need is still far from being cost-effective. Until a decrease in the price is negotiated it remains a huge barrier in broad implementation of 3HP in Namibia^{xx}.

LIMITATIONS:

There are significant limitations in this analysis. In order to provide accurate recommendation for Namibia a 3HP randomized controlled trial needs to be conducted in a similar environment with a similar population. Secondly, the last trial was conducted four years ago, and thus newer data is required to confirm the findings from the previous studies. Additionally, data on children with HIV is limited and thus the conclusions drawn from this review is not applicable on that population. Lastly, there are studies available on the added benefit of continuous IPT. Thus, in order to attain information on how 3HP performs against continuous IPT further studies need to be conducted.

V. CONCLUSION

The analysis of the two studies that qualified for this review inform us that 3HP has similar efficacy in preventing active tuberculosis to that of IPT. In addition, it is also noted that from the data collected in the two studies there are fewer adverse events and higher adherence in the participants receiving 3HP compared to the other regimens. The discussed limitations identify a gap in research regarding the effectiveness of 3HP to that of continuous IPT. Largely, this review suggests that further research be done to evaluate the complexity of 3HP in different settings with different populations. However, based on these preliminary findings it is preferable for Namibia to adopt 3HP once it is cost-effective to raise their IPT completion rates, increase implementation of IPT in all local sites, and prevent adverse outcomes.

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