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THE EFFECTIVENESS OF 3HP ON TREATMENT OF LATENT TB INFECTION IN ADOLESCENT AND ADULT PLHIV IN TANZANIA: A SYSTEMATIC REVIEW

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Abstract:

Background: is the commonest opportunistic infection in PLHIV, People who harbor LTBI are the important reservoirs of active TB disease. LTBI treatment is intended to prevent progression of LTBI from dormant state to active TB disease there by reducing the burden of morbidities and mortalities in PLHIV. WHO recommends the use of shorter regimens including 3HP in treating LTBI to people at risk of developing active TB disease. This study aimed at reviewing the effectiveness of 3HP on treatment of LTBI in adolescent and adult PLHIV

Methodology: This is a secondary review literature study where an electronic database search was conducted from 11th March, 2024 to 22nd April, 2024 searching for RCTs on treatment of LTBI in adolescents and adults PLHIV using 3HP conducted from 2010 to 2024 from Embase, Medline, PubMed, EBSCO, Cochrane database and ClinicalTrial.gov, Google Scholar, clinicalTrials.gov, International Clinical Trials Registry, Network Digital Library of Theses and Dissertations and the University of South Wales Library. The primary outcomes were the free survival Tuberculosis and treatment completion rates.

Results. A total of 4 studies were identified that was included in data analysis where three studies compared 3HP with 6/9H in their studies and one study only used 3HP in the analysis of the primary outcome. Three studies were conducted in Africa and one in different continents. The studies showed 3HP to be effective in treatment of LTBI by preventing the development of active tuberculosis with reduction in mortalities. 3HP was associated with higher completion rates with higher adherence rates compared to longer duration treatments.

Conclusion: 3HP proved to effective in treating LTBI in PLHIV by preventing development of active TB disease and reducing the all cause mortalities with demonstration of high compliance and completion rates, the gap remains as to what duration do 3HP provide the protective effect.

Key Words: -Rifapentine plus Isoniazid, TPT, IPT, TB Preventive Therapy, Latent tuberculosis Infection, Active tuberculosis disease, Adults, Adolescents, People Living with HIV, Efficacy, Effectiveness, Effect

1.0.INTRODUCTION

Tuberculosis (TB) is the commonest opportunistic infection and leading causes among the People Living with HIV (PLHIV). In 2022 WHO out of 10.6 M people who have TB out of 7,950 million where the PLHIV that resulted to 671,000(24.9%) deaths[1,2] . In Sub-Saharan Africa countries out of 2.5 million people who had TB disease, 461,000 (18.6%) people were PLHIV, that resulted to a total death of 114,000 which accounting for 68.3% which is more than half of all global TB deaths [2]

Latent Tuberculosis Infection (LTBI) explained as factor that increase the risk of TB infection among the PLHIV .About one in four of the global population lives with LTBI and transmitting TB disease[3,4] Presence of LBTI to PLHIV results to weakened immune system gives a chance to multiplication of the bacteria that eventually leads to progression of LTBI to active TB disease [5]. PLHIV are 20 times more at risk of developing active tuberculosis with approximately 40% advancing into active tuberculosis disease [6].

Preventing new infections and progression to active tuberculosis after being infected is very important in minimizing the burden of the disease and the associated mortalities. Among the modalities used to prevent active TB disease is through treatment of LTBI, this helps to minimize the risk of dormant mycobacterium tuberculosis (MTB) bacilli activation which might progress to active TB disease[7].

The treatment of LTBI was among the strategies recommended by WHO through the END TB strategy put in 2015 whereby the targets hasto be reached by 2035. The aims of the strategy are to reduce the incidence of TB by 90%, TB related deaths by 95% and reducing the TB related costs to families that suffer TB disease to 0%. Where pillar number I was a patient centered TB care and prevention through early diagnosis of TB disease, treatment of all people with TB disease and preventive treatment (treatment of LTBI) of people at higher risk of TB including PLHIV[8]

Previous World Health Organization (WHO) recommended the use of isoniazid for 6 to 12 months as the prevention therapy or treatment of LTBI which was proven to decrease the possibility of progression to active TB disease by 60% to 90%[9]. Current the WHO recommend the use of Rifapentine plus Isoniazid (3HP) as one of the preferred TPT regimes for treatment of LTBI.The Drug proven positive result to protect people with LTBI from progressing to active tuberculosis with the reduction in mortalities to PLHIV , regardless of Antiretroviral therapy (ART) use[10].The duration for the new regimen was three months (3HP) being used once a week with only 12 doses taken to complete the course of treatment in age group > 2 years. (WHO,2018). 3HP can be delivered through Direct Observed Therapy (DOT) at the health facility observed by health care provider or through Self-Administered Technique (SAT) at home by a patient with the help of a relative or oneself,[11].

The shorter duration for use, few doses required to be taken (36 doses only) and few tolerated side effects, make 3HP to be more accepted by clients and health care providers. Hence, making most of the prescribed doses to be taken with higher completion rates improving the effectiveness of 3HP in treating LTBI,[12]. For the drugs (3HP) to be effective the person should take at least 11 out 12 doses (more than 90%) within a period 120 days[13]. However, other factors need to be taken into consideration, like accessibility, availability and costs related to getting the drugs. 3HP has been proved to be more cost effective due to less visits to the health facility than 6H contributing to higher acceptance ~~a~~ compliance assuring the effectiveness, (Yuen C, et al, 2021). This systematic review aimed to understand the effectiveness of 3HP on treatment of LBTI in adolescent and adult PLHIV in Tanzania.

2.0. NEED OF THE STUDY.

WHO recommend the use of Rifapentine plus Isoniazid (3HP)regimen as one of the preferred TPT regimen for treatment of LTBI the PLHIV .Despite the positive treatment outcome of 3HP to PLHIV little is known on the effectiveness of this regimen in adolescent and adult PLHIV in Tanzania . The results from this review provides insight understanding the existing gap on the effectiveness of 3HP to adolescent and adult \PLHIV, hence help Ministry-Health to modify the existing guideline for treatment Also this results will help health care practitioners to know how long 3HP become effective to adolescent and adult PLHIV hence prescribe the patient accordingly. Moreover, the research will play great role in the completion of my studies since it is one of the college requirements.

3.0. RESEARCH METHODOLOGY

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3.1Study design

This was the systematic-review study design whereby all data were collected from the previous conducted studies. The primary source of the data was published papers dissertation reports, journal, books and approved guidelines Open Gray Database to reveal the unpublished articles and reports to ensure that the necessary information is found for the review

3.2 Data base search and search strategy

During this review the thorough search of Embase, Medline, PubMed, EBSCO, Cochrane database and ClinicalTrial.gov, Google Scholar, clinicalTrials.gov, International Clinical Trials Registry, were used as the search strategies. All the data sources selected were those includes thee information of the latent TB infections for the PLHIV who was the age of the 10 years old and above. Boolean operators (AND, OR, NOT) were used to identify relevant information available on the topic of the project. Truncation and wildcards were also used to widen the search and to ensure that relevant information is not missed. The Gray Literature Search were used to collected the information produced from the unpublished sources such as reports, working papers, policy and guiltiness.

3.2.Data collection methods and procedures

A systematic review was done by the evaluation of the available literatures focusing on what has been done on treatment effectiveness and outcomes six-monthly (6H) ,nine monthly (9H), regimen compared with three months (3HP) regimen. The screening of the published papers, reports and dissertation were through carefully reading of the tittles and abstracts. A total of 16 published papers, 5 dissertation reports and 5 gray literatures were carefully refined to obtain the relevant information.

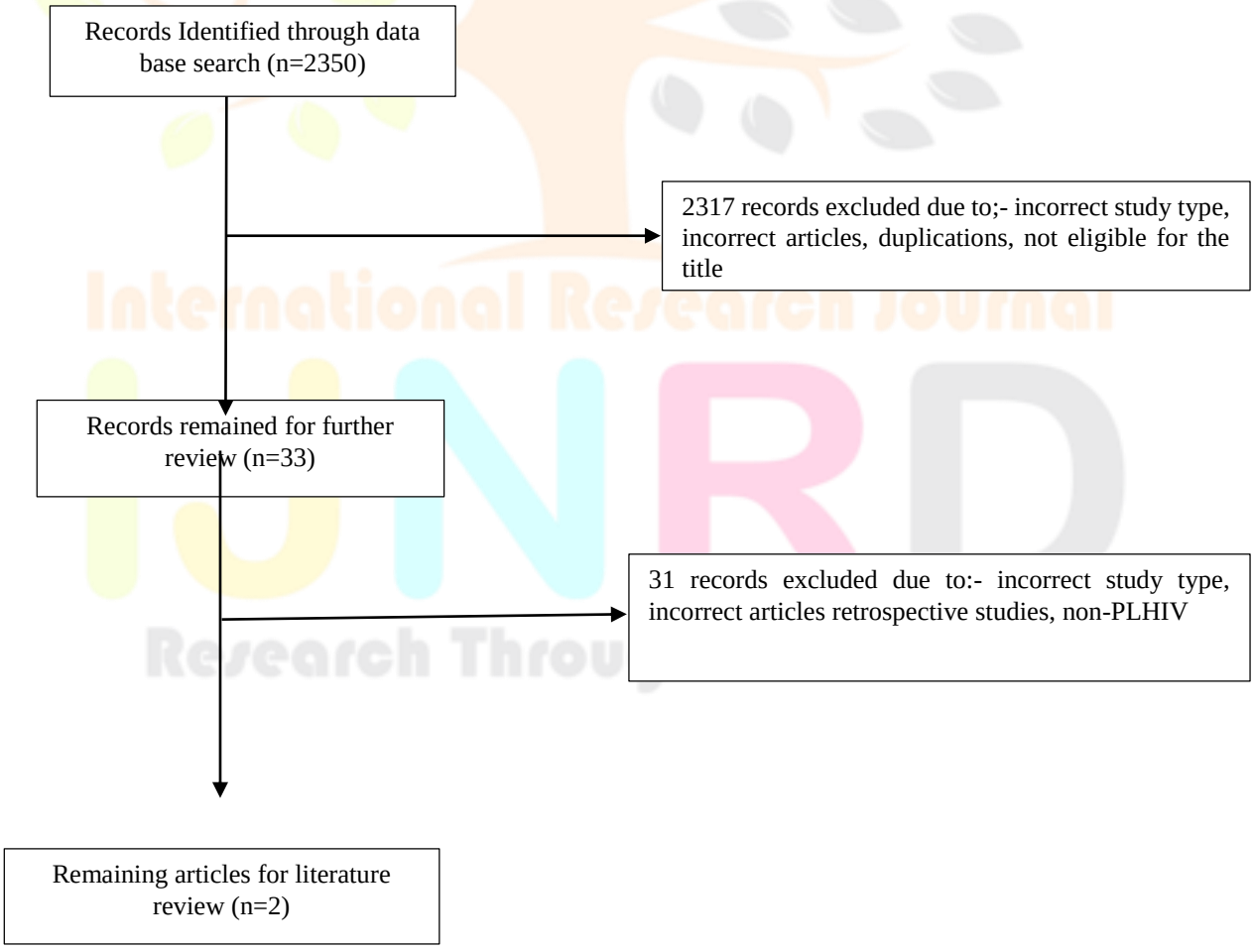

Figure 1. The PRISMA flow chart for identification and selection of publications for the literature review.

3.3. Data analysis and interpretation

Data collected were coded, summarized and entered in SPSS version 26.0 for data cleaning, analysis and interpretations. Tables were used to interpret the characteristics of the selected studies and papers and the effective of the 3HP on the treatment of the LTBI. Logistic regression were used to make comparison of the 3HP regimen with 6HP and 9HP.

3.4. Ethical Issues

The permission to conduct this systematic-review was obtained from the University of South Wales Research ethical committee. Permission to use the data from the data base were sought from the relevant authors and institutions.

4.0. RESULTS AND DISCUSSION

4.1. Characteristics of the selected studies

A total of 16 published papers, 5 dissertation reports and 5 gray literatures were screened 4 studies were selected for data collection. The document was categorized in the authors name, years and outcome of the study See table 1 below:

Table 1. Characteristics of the included studies

1st author (year)	Study country	Study design	Number of participants	Age	ART use	Intervention	Follow up period	Primary and secondary endpoints
Martinso, N, et al, 2011	South Africa	Open-label randomized trial	1150	Median age 30.4	not on ART	3HP, 3HR, 6H continuous H	4years in 3HP, 4.1 years in RH, 3.9 in continuous H, 3.9 years in 6H	Primary outcome = Tuberculosis free survival Secondary end point = Adherence rate to treatment
Sterling, T, et al, 2016	US, Canada, Brazil, Spain and Hong Kong, Peru	Open-label randomized trial	399	>12yrs median age years =36	Both on ART and not On ART For 3HP 33%, 9H 30% p	3HP, 9H	33 Months	Primary outcome = Tuberculosis free survival Secondary end point = completion rate to treatment
Semitala, F et al, 2021	Kampala-Uganda	Randomized controlled trial	479	>18 years, mean 41.9 years	On ART	3HP compared under DOT,SAT	78.4 days	Primary end point =Treatment completion rate, secondary end point development of serious adverse events.
Churchyard, G, et al, 2021	South Africa, Ethiopia Mozambique.	Randomized controlled trial	4027	Median age 41 Years	On ART	3HP, 6H	24 months	Primary end point= Development of TB cases Secondary end point treatment completion

.4. Effectiveness of 3HP

The review observed that 3HP had slightly higher rates of TB compared to the comparator (Isonized) in one study by Martinson, et al. (IRR 1.05, 95% CI 0.56-1.97, p= 0.87) and lower rates were observed in other study by Sterling et al, 2016 (IRR 1.1, 95% CI 0.2-5.4) P= 0.13 but, the difference in TB cases that developed between 3HP and the comparator in both studies were not statistically significant (p >0.05). The studies in both groups between 3HP and Ionized showed protective effect against development of active TB. Also among these studies, one study assessed the death rates among the 3HP and the comparator (6H) where 3HP group had relatively lower rates of deaths though the difference were not statistically significant (IRR 0.66, 95 CI,0.33-1.26) p = 0.18. Table 2 and 3 below summarizes the rates of TB confirmed among the selected studies

Table 2: Rates of TB confirmed cases

AUTHOR, YEAR	TB incidence rates per 100 person-years				Incidence rate ratio(95% CI)	P value
	3HP	6H	9H	Overall		
Martinson N, el al, 2011	2	1.9		1.9	1.05(0.56-1.970	0.87
Sterling, T, et al 2016	1.01		3.5		1.1(0.2-5.4)	0.13

Table3: Death rates

Author, year	Death rates per 100 person-years		overall death rates	Incidence rate ratio(95% CI)	P value
	3HP	6H			
Martinson N, el al, 2011	1.4	2.1	1.6	0.66, (0.33-1.26)	0.18

5.0. DISCUSSION

In this review of randomized controlled trials conducted to PLHIV two studies demonstrated the effectiveness of 3HP, the study conducted in South Africa by Martnson, N, et al, 2011 and that of Sterling, T, et al, 2016 conducted in US, Brazil, Spain, Hong Kong, and Peru, these studies found 3HP to be effective in the treatment of LTBI by preventing the microbiologically and clinically confirmed TB cases and statistically significant in preventing all cause mortalities as 3HP was non inferior to Isoniazid. The rates of TB disease among the study groups were lower compared to a population with PLHIV that had no any intervention of reducing TB infection, where in Africa the annual risk for TB is estimated to be between 5-10% (Akolo C, et al, 2010). Putting together the two studies (Martinson N, et al 2011) and (Sterling T, et al, 2016) there appear to be minimal difference in rates of reported rates of confirmed TB among the comparison groups that used 3HP and those who used 6H or 9H, this difference was statistically not significant indicating the non-inferiority of 3HP to 6/9H but the rates of TB that were confirmed in the group that used 3HP are significantly lower compared to the incidences described in PLHIVs with no any intervention in the study settings. Despite the lower rates of TB described by the use of 3HP in all studies, in one study the rates of TB in 3HP group were slightly higher than that in the Isoniazid monotherapy group, this could be due to the confounding effect to the results by TB incidence in the setting due to the risk of re-infection as the study was conducted in South Africa which is the setting with higher TB rates (762 per 100,000 persons), also the longer follow-up periods could have reduced the effectiveness of 3HP

The overall estimations in this review also showed that, the prevention of all cause-mortalities were better described by 3HP as compared to 6H where there were 17 deaths (incidence rate of 1.4) in the 3HP group and 25 deaths (incidence rate of 2.1) in the comparison group that used 6H with the incidence rate difference of 0.7 which is statistically significant, this meant and indicated that the 3HP is more effective and can be a better option when targeting reducing the mortalities of PLHIV related to TB disease. The reason as to why 3HP has the greater effect of reducing all-cause mortalities is not well stated by the studies, but this could be due the sterilizing effect of Rifapentine (arifamycin) in the group that used 3HP (Mitchison D, 2004) (Rosenthal I, et al, 2012) and the synergistic effect in the combination therapy of 3HP provide more effect in clearing the dormant MTB bacilli in the granulomas reducing the all cause mortalities (MOH,2020), these results are similar to the results in the network meta-analysis study conducted by Yanes-Lane M, et al, 2021 that also showed decreased rates of death in the groups that used rifamycins (Rifapentine and Rifampicin) drugs. The direct effects of rifapentine in the combination therapy and the synergistic effects could have the confounding effects to the results. However, more studies need to be conducted to have a greater generalizability.

6.0. CONCLUSION AND RECOMMENDATION

This study review evaluated the effectiveness of 3HP in treating LTBI in adolescent and adults PLHIV. The findings of this study found that 3HP is effective in treating LTBI and thereby effective in preventing Tuberculosis and all cause mortalities, the dosage effective in treating

The review recommend on research needs to be conducted on evaluating the effectiveness of 3HP in the treatment of LTBI in adolescents and adults PLHIV as only two studies were found in this study review also on determining the protection duration that is attained after successful completion of 3HP treatment to PLHIV so that ministries can decide if there is a need for a repeated dose or not. LTBI treatment should be scaled up to all at risk populations and not only to PLHIV and children under five years of bacteriological TB contacts.

DISCLOSURE

The authors declare no competing interest

AUTHORS CONTRIBUTION

All the authors discussed the results and contributed to the critical review of the final manuscript. They have also read and approved the final manuscript

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