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REVIEW ARTICLE

Latent Tuberculosis Treatment in People Living with HIV/AIDS in Algeria, Time to Act: A Review

***Ouyahia Amel*[1*], *Rais Mounira, PhD*[2], *Gasmi Abdelkader, PhD*[2], *Kouicem Aya Tinhinane*[3], *Kouicem Mohamed Safir*[4] *and Lacheheb Abdelmadjid*[5]**

[1]*Professor Infectious Diseases, Faculty of Medicine, Chief of Unit HIV AIDS STDI Teaching Hospital, Ferhat Abbas Sétif University 1, Algeria*

[2]*Infectious Diseases, Faculty of Medicine, Teaching Hospital, Ferhat Abbas Sétif University 1, Algeria*

[3]*Faculty of Medicine, Interne in Teaching Hospital, Ferhat Abbas Sétif University 1, Algeria*

[4]*Master Biotechnology and Health High school of Biotechnology Constantine, Algeria*

[5]*Professor Infectious Diseases, Chief of Department of Infectious Diseases Teaching Hospital, Ferhat Abbas Sétif University 1, Algeria*

***Corresponding authors:** *Ouyahia Amel, Professor Infectious Diseases, Faculty of Medicine, Chief of Unit HIV AIDS STDI Teaching Hospital, Ferhat Abbas Sétif University 1, Bp 589 19000, Setif, Algeria, Tel/Fax: +213540280852*

Abstract

In 2017, World Health Organization (WHO) estimates that 920000 of People living with HIV/AIDS (PLWHA) developed tuberculosis disease worldwide, which is the number one infectious killer of PLWHA. To the end of 2019 there are an estimated 13000 PLWHA in Algeria, the estimated rate of the killing couple HIV-tuberculosis in 2018 was 14.7% (276 cases) [1].

Once acquired latent tuberculosis infection (LTBI), PLWHA developed active TB disease at a higher rate than HIV negative [2]. Although tuberculosis is a prevented disease by screening for and treating LTBI , fewer than 1 million HIV infected patients, with an estimated 30 million eligible, received this primary prophylaxis; we do not know for instance what are the percentages of LTBI among PLWHA in Algeria . While access to ART has increased in Algeria, treatment of LTBI among PLWHA is unfortunately inexistent.

We aimed in this review article to report the current situation of management of LTBI in Algeria, highlight the net gain of such treatment in PLWHA and make a summary of the pros and cons of different regimens and current international guidelines for treating LTBI among PLWHA, to develop a decision aid allowing the integration of the suitable strategy for Algeria. Data available at the official websites of WHO, and from the Algerian Ministry of Health, were consulted, and search engines PubMed® and Google Scholar® were used.

Keywords

Latent tuberculosis infection, Primary prophylaxis, Algeria, People living with HIV/AIDS

Introduction

Tuberculosis (TB) is a dreaded infectious disease and one of the major global public health problems. Worldwide, approximately 1000 PLWHA die from tuberculosis each day, including many who are receiving antiretroviral therapy [3].

Infected individuals are classified as either having latent tuberculosis infection (LTBI), or active TB disease. World Health Organization (WHO) guidelines define LTBI as state of persistent immune response to stimulation by *M. tuberculosis* antigens without evidence of clinically manifested active TB.

TB is one of the main public health issues in Algeria, it has become a health priority since 1962 with a free-of-charge diagnostics and complete treatment which permit it to join the group of countries with moderate prevalence since the 1980s.

Tuberculosis reactivation rates can be substantially

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reduced by up to 90%, if LTBI patients take preventative therapy [4], prevention studies among PLWHA began in the early 1990s in the era before ART.

Despite high-quality evidence supporting the efficacy of preventive therapy for tuberculosis in PLWHA and recommendations from the WHO and others experts, Its Implementation has been hampered by low adherence worldwide. In 2017, fewer than 1 million PLWHA received preventive treatment, with an estimated 30 million eligible; in Algeria such primary prevention is inexistant.

In this review article we present a summary of different regimens and current international guidelines for treating LTBI among PLWHA to along with innovations in the field of TB-preventive therapy and suggest possible improvements in our national guideline.

Tools of LTBI Diagnosis

The two currently available methods for the diag-

Table 1: Tuberculosis preventive therapy regimens.

Regimens	Dose /Kg (number of pills)
6/9 - month daily Isoniazid monotherapy (6 H, 9 H)	Age >= 10 years: 5 mg/kg/day Age < 10 years: 7-15 mg/kg/day
4 - month daily rifampicin (4R)	Age >= 10 years: 10 mg/kg/day Age < 10 years: 10-20 mg/kg/day; range,.
3 - month daily rifampicin/Isoniazid (3HR)	Isoniazid: Age >= 10 years: 5 mg/kg/day Age < 10 years: 7-15 mg/kg/day Rifampicin: Age >= 10 years: 10 mg/kg/day Age < 10 years: 10-20 mg/kg/day
3 - month Rifapentine/Isoniazid weekly (3HP) (12 doses)	Age 2-14 years Isoniazid, 100 mg 10-15 kg (3) 16-23 kg (5) 24-30 kg (6) 31-34 kg (7) > 34 kg (7) Rifapentine, 150 mg 10-15 kg (2) 16-23 kg (3) 24-30 kg (4) 31-34 kg (5) > 34 kg (5)
	Age >14 years Isoniazid, 300 mg 30-35 kg (3) 36-45 kg (3) 46-55 kg (3) 56-70 kg (3) > 70 kg (3) Rifapentine, 150 mg 30-35 kg (6) 36-45 kg (6) 46-55 kg (6) 56-70 kg (6) > 70 kg (6)
One month daily (1HP) 1 - month Rifapentine/Isoniazid (28 doses)	Age ≥ 13 years (regardless of weight band) Isoniazid, 300 mg/day Rifapentine, 600 mg/day

nosis of LTBI are the tuberculin skin test (TST) and the interferon gamma release assay (IGRA). Since there is no gold standard, there are considerable differences in screening guidelines between countries (Table 1).

The *in vivo* TST remains the most widely used due to its low cost; *it consists of* the intradermal injection of purified protein derivative *containing* more than 200 antigens that are also shared by other mycobacteria, leading to a delayed-type hypersensitivity response causing at 48-72 a cutaneous induration at the site of injection. In PLWHA, a reaction greater than 5 mm is considered positive. False-positive TST can occur following exposure to other non-tuberculous mycobacteria and immunization with bacillus Calmette-Guerin (BCG) [5], its sensitivity is reduced with progressing immunodeficiency in PLWHA [6].

The *in vitro* IGRA measures the production of interferon-gamma by immune cells in response to *M. tuberculosis* antigen stimulation; its specificity is superior to the TST as it utilizes antigens found only in *M. tuberculosis*, thereby eliminating cross-reactivity with non tuberculous mycobacteria and the BCG vaccine. Unfortunately, IGRA testing is expensive and not widely available in low- and middle-income countries.

What is the Benefit of LTBI Treatment?

PLWHA are 15-22 times more likely to develop active TB than people without HIV; HIV infection by compromising cell-mediated immunity is an important risk factor for the reactivation of LTBI to active TB disease. The risk of TB disease due to reactivation of latent infection for persons with untreated HIV is approximately 3-16% per year [2]. Even it is both preventable and treatable disease, TB is the leading cause of death among PLWHA, approximately 300,000 PLWHA infection died from TB in 2018 [7].

Antiretroviral therapy (ART) and TB-preventive therapy (TPT) are both effective interventions to prevent active TB disease in PLWHA.

The immunological efficacy of ART has been associated with a reduction in the incidence of coinfection HIV-TB of > 80% especially in symptomatic patients and those with advanced immune suppression [8].

The utility of TPT was demonstrated more than 60 years ago, when Isoniazid preventive therapy (IPT) was used to reduce the risk of TB among Alaskan villages, household contacts, and persons living in mental health facilities [9]. IPT reduces, among PLWHA, both of TB incidence and mortality by up to 37%, regardless of CD4 cell count or antiretroviral therapy [10,11]. In combination with ART, TPT reduces the risk of TB disease among PLWHA by 76% [12].

Some studies in Africa have evaluated the duration of protective effect of some regimens in HIV-infected individuals, in Uganda this duration was for only 1 year after receiving 6 months of INH with positive skin tests.

And for 3 years after a 3-month regimen of INH, rifampicin, and pyrazinamide, or 3 months of INH and rifampicin [13]. In Zambia, the protective effect was approximately 2.5 years after 6 months of INH or 3 months of rifampicin plus pyrazinamide) [14].

The Methods to Treat LTBI

Four main antimicrobial regimens are currently available for LTBI treatment: Isoniazid monotherapy (INH), Rifampicin monotherapy (R), Rifampicin or Rifapentine in combination with Isoniazid (RH), (HP) (Table 2).

Pyrazinamide and either Rifampicin or Rifabutin for 2 months leads to fatal hepatitis and shouldn't be used in LTBI treatment [15].

INH inhibits the synthesis of mycolic acids, which are essential components of the mycobacterial cell wall, primarily acting on cells which are rapidly dividing. It is recommended as a first-line option in treating LTBI since the 1965 American Thoracic Society guidelines especially in high risk individuals [16].

For several decades, Isoniazid-preventive therapy (IPT) has been the most recommended regimen for the treatment of LTBI in people with HIV infection. IPT is advantageous due to the considerable clinical experience and low cost, it reduces the risk for developing TB disease and death in PLWHA regardless of CD4 count and whether they are on ART or not [10,17].

The combined use of ART and INH preventive treatment is additive in reducing active TB disease incidence among HIV-positive individuals.

INH is formulated as 100 mg and 300 mg tablets, optimal duration of Isoniazid monotherapy regimen vary from 6 to 9 and 12 months; clinical efficacy of 9H regimen is similar to 12 months and superior to 6 H regimen, which has been documented to achieve better completion rates but a protective efficacy of only 67% or 69% [18,19].

INH does not interact with CYP450 system, thus, is not prone to cross-reactions with the CYP450 substrates, and can be safely co-administered with any antiretroviral regimen without dose adjustment.

The Achilles' heel of IPT is the long duration resulting in low rates of prescription and poor completion rates by patients and above all the risk of fatal hepatotoxicity [20,21].

The risk of hepatotoxicity increases with age and alcohol consumption and preexisting liver conditions; liver enzymes typically increase in the first 3 months of treatment then, through the process of hepatic adaptation, return to normal despite continued therapy [22]; if the serum aminotransferase level increases to greater than five times the upper limit of normal without symptoms or greater than three times the upper limit

Table 2: Available guidelines on the management of LTBI in People living with HIV/AIDS (PLWHA)

Guidelines	**Whom to treat** **(Active disease must be excluded before initiating preventive treatment in all guidelines)**	**Regimens (dose cf Table 1)**
WHO consolidated guidelines on tuberculosis Module 1: Prevention Tuberculosis preventive treatment [39]	Adults and adolescents living with HIV: On antiretroviral treatment, to pregnant women and to those who have previously been treated for TB Infants aged < 12 months: In contact with a person with TB. Children aged ≥ 12 months: If they live in a setting with high TB transmission, regardless of contact with TB.	Preferred - 6 or 9 month INH - or a 3-month regimen of weekly Rifapentine plus Isoniazid - or a 3 RH daily alternatives - 1-month regimen of daily Rifapentine plus Isoniazid - or 4- month of daily rifampicin In settings with high TB transmission and an unknown or a positive LTBI test: 36 months of daily INH
BHIVA guidelines for the management of TB in adults living with HIV [40]	- Positive IGRA - If first and repeat IGRAs are either indeterminate or borderline, the clinician should use clinical judgement testing for, and treatment of, LTBI for all HIV-positive individuals who are close contacts of people with infectious TB, against testing for LTBI in individuals who have been treated for active TB.	6 -month of Isoniazid plus pyridoxine; or 3 -month of Isoniazid plus rifampicin plus pyridoxine.
EACS 2019 [41]	TST > 5 mm or positive IGRA or close contacts to persons with sputum smear positive tuberculosis.	- 6-9 month (9-month duration in high-prevalent TB countries) daily Isoniazid: 5 mg/kg (max 300 mg) + pyridoxine 25 mg Or - 4- month daily Rifampicin: 600 mg po or rifabutin po, Or - 3- month daily RH: Rifampicin 600 mg po or rifabutin po : - without PIs, EFV, RPV: 5 mg/kg (usual dose 300 mg) - with PIs 150 mg qd - with EFV 450 -600 mg qd - with TAF or EVG/c Not recommended + Isoniazid 5 mg/kg/day (max 300 mg) + pyridoxine (Vit B6) 25 mg/day Or - 3 -month rifampicin 600 mg x 2/week po + Isoniazid 900 mg x 2/week po + pyridoxine (300 mg x 1/ week po Or - 3 -month/ weekly Rifapentine 900 mg + Isoniazid 900 mg - 1-month daily Rifapentine 450 mg (< 45 kg) or 600 mg (> 45 kg) + Isoniazid 300 mg + pyridoxine 25 mg

Guidelines for the Prevention and Treatment of Opportunistic Infections in Adults and Adolescents with HIV [22]	Positive screening test for LTBI, with no evidence of active TB, and no prior treatment for active TB or LTBI *or* Close contact with a person with infectious TB, with no evidence of active TB, regardless of screening test results.	Preferred Therapy: 9 -month - Isoniazid 300 mg PO daily + pyridoxine 25-50 mg PO daily Alternative: - 12 weeks/once weekly Rifapentine (32.1-49.9kg: 750 mg > 50 kg: 900 mg) + Isoniazid 15 mg/kg (900 mg maximum) + pyridoxine 50 mg. Rifapentine is only recommended for patients receiving an Efavirenz- or Raltegravir-based ART regimen. - 4 month daily Rifampicin Adults: 10 mg/kg Children: 15-20 mg/kg Maximum dose: 600 mg
Prise en charge médicale des personnes vivant avec le VIH Infections chez l'adulte : prophylaxies et traitements curatifs (juillet 2018) (France) [42]	Positive IGRA	9 - month daily Isoniazid (4-5 mg/kg) + vit B6 (250 mg) or 3 -month daily Isoniazid (4-5 mg/kg) + vit B6 (250 mg) + Rifampicin (10 mg/kg)
Manuel de la lutte antituberculeuse A l'usage des personnels médicaux (Algeria) [36]	Not recommended	None
Guide national de prise en charge thérapeutique de l'infection à VIH 2017 (Algeria) [37]	Not recommended Primary prophylaxis is NOT indicated for HIV-infected patients	None

of normal with symptoms, chemoprophylaxis should be stopped [22].

Peripheral neuropathy, is another common toxicity, which can largely be prevented via supplementation with pyridoxine at a dose of 25 to 50 mg/day.

Isoniazid has not been found to be associated with congenital anomalies, even if it is given early in pregnancy, making 6-9 months of daily Isoniazid the recommended treatment for pregnant women at risk of developing TB.

Rifampicin (RMP) is a rifamycin which is bactericidal against *Mycobacterium tuberculosis* by disrupting protein synthesis in both actively replicating mycobacteria and dormant what makes it ideal candidates for treatment of LTBI; it is formulated as 150 mg and 300 mg capsules.

A daily 3 or 4-month course of Rifampicin monotherapy regimen (3R) or (4R) is a safe, effective, more low cost regimen and showed better compliance with less hepatotoxicity compared with 9H [23,24].

The potential disadvantages of Rifampicin is the fact of being a strong inducer of most CYP450 isoforms that hasten elimination of drugs also substrates of CYP450 enzymes, such as protease inhibitors (PIs) and some Non-nucleoside reverse transcriptase inhibitors (NNRTIs) [25].

There is a good virologic efficacy and clinical outcomes with co-administration of standard Efavirenz dosing (600 mg) and RMP, likewise when given at reduced doses (400 mg) the plasma exposures are within efficacy ranges.

However, combination of RMP with Nevirapine, Rilpivirine, Etravirine, or Doravirine leads to sub-therapeutic concentrations and an increased virological failure in patients starting antiretroviral treatment.

Co-administration of PIs with RMP reduces PIs systemic concentration to less than 75% lowering treatment efficacy. In this case PIs plasma concentrations could be boosted by either super-boosting by administering PI with higher dose of Ritonavir (RTV) or doubling the dose of both the PI and RTV, with however the risk of an increased hepatotoxicity.

Although most Nucleos(t)ide reverse transcriptase

inhibitors (NRTI) are compatible with Rifampicin containing LTBI regimens, Tenofovir alafenamide (TAF) and Rifampicin results in decreased plasma exposure of TAF.

Additionally, in PLWHA with low CD4+ lymphocyte counts, the risk for asymptomatic active TB increases, and if it is inadvertently treated with Rifampicin monotherapy it will lead to widespread rifampicin resistance [26].

Some congenital anomalies, such as hydrocephalus, anencephaly, and limb defects, have been reported with the use of Rifampicin.

Rifampicin in Combination with Isoniazid (RH)

Similar TB prevention efficacy rates have been reported for 3 or 4 month Isoniazid-Rifampicin combination (3 RH) or (4 RH) compared with standard Isoniazid monotherapy [27].

Hepatotoxicity risk might be greater with the two drugs given together than with either drug given alone [28].

Rifapentine in Combination with Isoniazid (HP)

Rifapentine (RPT) is a rifamycin derivative, with greater potency against MTB and a half-life which is four to five-times longer than Rifampicin [29]. It has similar mechanism of action and emergence of resistance compared with Rifampicin and activity to treat other mycobacteria such as *Mycobacterium avium*.

RPT is formulated as 150 mg 2ts; it is used in combination with Isoniazid for the treatment of LTBI with shorter regimens in an intermittent fashion.

Rifapentine plus Isoniazid once weekly for 12 weeks (3HP) in PLWHA is as effective as 6 to 9 months of daily IPT, better tolerated, less hepatoxicity and higher completion rates.

Although Rifapentine is 85% as potent CYP450 enzyme system inducer as rifampicin. It can be co-administered without significant drug interactions with Efavirenz (EFV), Raltegravir (RAL), and Dolutegravir (DTG)-based ART regimens and without dose adjustment [30-33].

The potential disadvantages of the 3HP regimen for adults is its high cost-effective, take numerous pills simultaneously on one day per week, 10 tablets are necessary including 900 mg Rifapentine (6 × 150 mg tablets) with 900 mg Isoniazid (3 × 300 mg tablets) along with pyridoxine.

Ultrashort regimen 1 month of daily Rifapentine plus Isoniazid (1HP) is noninferior to daily 9 months Isoniazid in PLWHA adults and adolescents with lower incidence of adverse events, fewer treatment interruptions ever reported in a preventive therapy trial [34]. Cases of hepatotoxicity and peripheral neuropathy were unusual in the 1-month group (2% of recipients), and no hypersensitivity reactions were reported.

What is the Situation in Algeria?

According to the WHO, Algeria, is a country with intermediate TB burden and low HIV incidence; The incidence of tuberculosis was reported at 55/100,000 in 2017 which corresponds to 22,780 cases.

The first case of AIDS in Algeria was reported in 1985, at the end of 2019, there were 13,000 reported PLWHA, corresponding to a prevalence of approximately 0.1%. In 2018 the estimated rate of TB- HIV coinfection was 14.7% [1].

The government has actively participated in the fight against TB and HIV; the priorities for TB control program are free-of-charge of mandatory BCG vaccination at birth, diagnostic and specific treatment.

All PLWHA are eligible for antiretroviral therapy (ART) irrespective of CD4 count; in 2018 the estimated rate of receiving ART was 91.2% (12759) [1], diagnosis and treatment are free of charge through the government as part of its national aids control program.

World Health Organization declares that one third of people worldwide is infected with LTBI which is the main source for active TB disease; unfortunately the information about how much people among PLWHA are infected with LTBI In Algeria, is scarce.

Despite the evidence of the efficacy of preventive therapy for tuberculosis and recommendations from multiples guidelines (Table 2) the use of such intervention worldwide has been low [35].

In Algeria, Two guidelines are available, national tuberculosis control [36] and therapeutic management of PLWHA [37], the first one [36] allows the administration of preventive treatment to Children ≤ 5-years-old, close contact with active pulmonary TB cases and showing a positive response to the TST, and patients > 5-years-old close contact with active pulmonary TB cases, showing a positive response to the TST, only if they become symptomatic.

Both guidelines [36,37] don't offer any strategy for treating LTBI in PLWHA; obligatory screening for TB is performed on all PLWHA at the initial assessment for The purpose of ruling out active TB.

Since LTBI is a non-contagious, asymptomatic condition that may never progress into active disease, is there a need to introduce this primary prophylaxis in our guidelines?

It is of utmost importance to decide whether the potential benefit of LTBI treatment outweighs its risks and should or not, taking place in our national guidelines.

Given the high risk of progression of latent infection into active TB disease in PLWHA [2] which is classified among the leading infectious causes of morbidity and mortality worldwide, we can't argue with the necessity of the treatment of LTBI, which should be an integral

part of the policies that govern the programmatic management of LTBI in PLWHA in our country. There are two main points to discuss, the first one is about the option to adopt, screening for tuberculosis disease then treating only positive PLWHA, after excluding active tuberculosis, as in the majority of guidelines or offering LTBI treatment to all PLWHA with an unknown or positive TST result, moreover, even with negative LTBI testing as in WHO guidelines [35].

There is no gold standard for detecting *Mycobacterium tuberculosis* infection neither *ex vivo* interferon-γ release assays (IGRA) nor tuberculin skin test (TST) can distinguish between latent and active TB in PLWHA, the tests can also be negative due to T-cell anergy in patients with low CD4 counts. However, specificity of the IGRA is superior to the TST as it utilizes antigens found only in *M. tuberculosis*, thereby eliminating cross-reactivity with non tuberculosis mycobacteria and the BCG vaccine [38] unfortunately IGRAs testing aren't available in Algeria.

The second important point is the choice of the most suitable regimen, in fact, implementation of preventive therapy of tuberculosis is plagued by several problems; the first one is the exclusion of active TB which is a "sine qua non" of TB preventive therapy to ensure that no person with active TB starts mono- or dual therapy resulting in a Hight risk of development of drug resistant tuberculosis but stills a challenge in PLWHA.

According to WHO, the absence TB-related symptoms and chest X-ray abnormality has the highest negative predictive value for ruling out TB, but this can't be reliable since tuberculosis in HIV has atypical clinical presentation with normal or atypical chest X-ray, skin test anergy and sputum smear-negative.

Furthermore, the choice of the most appropriate treatment regimen should be based on the evidence around efficacy, safety, acceptability, costs, and risk of fostering drug resistance during treatment.

Safety is extremely important in this context as all infected people are asymptomatic, and only few of those would develop active TB even in the absence of treatment. By choosing the regimens it must be taken into account the risk of adverse drug reactions especially fatal hepatotoxicity and interaction with ART; based on safety considerations, Pyrazinamide containing regimens are no longer recommended.

Short or ultra short course treatment based on rifampicin or Rifapentine containing regimen are effective, safe, with a lower risk of hepatotoxicity, and have a higher completion rates than longer 6 to 9 months of Isoniazid monotherapy.

Summary

LTBI treatment in PLWHA is an effective strategy for TB control. Algerian experts should act on LTBI management and protect PLWHA in order to achieve the global goals of the end TB Strategy. Nevertheless, innovative work is needed to develop guidelines on LTBI management suitable for our country with a favorable trade-off between benefits and harms of treatment.

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