



# SUPPORTING 3HP ADHERENCE

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## Acronyms and Abbreviations

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<b>CDC</b>	Center for Disease Control USA
<b>DDI</b>	Drug-drug interaction
<b>DOT</b>	Directly observed therapy
<b>HIV</b>	Human immunodeficiency virus
<b>INH or H</b>	Isoniazid
<b>IPT</b>	Isoniazid preventive treatment
<b>PLHIV</b>	Person/people living with human immunodeficiency virus
<b>RPT or P</b>	Rifapentine
<b>SAT</b>	Self-administered therapy
<b>TPT</b>	Tuberculosis preventive treatment
<b>WHO</b>	World health organisation
<b>3HP</b>	3 month regimen of weekly isoniazid and rifapentine

## 1. What is Tuberculosis (TB) Preventive Treatment (TPT)?

TB preventive treatment prevents TB from developing in persons who have TB infection. Not everyone exposed to TB will get TB disease immediately. Some will go on to develop latent TB infection (LTBI), a state in which the TB does not cause active disease but can be reactivated with time or if there is immune suppression due to HIV or other conditions. TPT uses some of the same drugs that are used to treat TB, but typically only one or two drugs instead of four and sometimes for a shorter period. There have been concerns that using the same drugs in persons with latent TB infection and active TB disease would create drug-resistant strains of TB that would later become active and more difficult to treat.

## 2. What is 3HP?

3HP is a short-course TB Preventive Treatment (TPT) regimen which is endorsed by the World Health Organisation (WHO)<sup>1</sup>. It combines high dose isoniazid and high dose rifapentine once a week, every week for three months. Randomised controlled trials have shown no significant difference in the incidence of active TB between participants given 3HP and 6 or 9 months of isoniazid. 3HP is associated with significantly lower hepatotoxicity and higher rates of treatment completion than INH<sup>1,2,3,4</sup>.

## 3. Why can 3HP be self-administered?

Both the PREVENT TB study<sup>5</sup> and the South African "Soweto trial"<sup>6</sup> compared 3HP by directly observed treatment to (DOT) to INH by self-administered treatment (SAT). To address the question of 3HP administration by DOT compared to SAT, the iAdhere study was conducted in outpatient clinics in Hong Kong, South Africa, Spain, and the USA (77% of participants were from the USA) from 2012–2014. This study randomised 1,002 adults to receive 3HP with either DOT, self-administered therapy (SAT) without any reminders, or SAT with weekly text message reminders. Treatment completion in the DOT group (87.2%) was higher than in either SAT group (74.0% without reminders; 76.4% with reminders). When the analysis was restricted to participants in the USA only, 'SAT no reminder' was non-inferior to DOT with a completion of 85.4% for DOT vs. 77.9% SAT no reminder vs. 76.7% for SAT with reminders). The authors recommended that strategies to improve adherence to 3HP under routine conditions be evaluated<sup>7</sup>.

The iAdhere study did not recruit HIV-positive individuals who were taking or about to commence ART. The 3HP-SAT regimen has not been studied in randomized controlled trials in persons aged <18 years.

Primarily as a result of this study, the CDC moved from a recommendation of 3HP administration by DOT to recommend DOT or SAT in persons aged ≥2 years<sup>8</sup>.

A systematic review conducted for the WHO 2015 LTBI guidelines provided heterogeneous results for interventions to improve treatment adherence and completion, and the evidence was considered inconclusive. The WHO guidelines for treatment of drug-susceptible active TB propose several interventions to support adherence could be applied to treatment of TPT<sup>9</sup>.

**The World Health Organization supports the notion that all TPT options can be self-administered**

**Interventions to ensure adherence and treatment completion should be tailored to the specific needs of risk groups and the local context, however, concerns about adherence should not be a barrier to providing TPT<sup>10</sup>.**

## 4. Adherence support

Adherence is a complex behaviour that is influenced by the many factors such as patient motivation, family environment, the patient's trust in the health provider, the complexity of the drug regimen, patient and family factors, and the patient-provider relationship.

Effective patient-centred strategies and patient education may incorporate the following components:

- Ensure confidentiality and obtain their commitment to complete treatment before initiating 3HP
- Ensure that the patient understands TPT and provide materials available in patient's and/or care giver's primary language and at the appropriate literacy level
- Include patient's family and/or caregivers in health education whenever possible. Children often move between households; it may be helpful to include additional facility members/care givers in adherence support
- Reinforce supportive educational messages at each visit
- Give clear instructions regarding side effects and when to report them to a health care provider
- Allow opportunities for questions and answers
- Develop an adherence plan with support of a healthcare worker that specifically focuses on weekly vs daily adherence strategies

### 4.1 Supporting messaging that can be used to improve adherence and treatment completion

#### 4.1.1 Explaining rationale for treatment

- A patient's acceptance of TPT is often influenced by the initial approach of the clinic staff; this includes administration staff, counsellors, nurses, doctors and pharmacists
- Providers should communicate the **benefits** of treatment:
  - Treating TB infection will prevent TB disease from occurring later. TB disease can lead to a long period of illness and can also lead to death. **Completing TPT can reduce the risk of TB disease by 90%**
  - This is particularly important for people who have the following conditions and are at higher risk of developing TB disease:
    - People with recent TB infection
    - Certain medical conditions that lower immunity including HIV and diabetes
    - Those taking medication that may lower their immunity e.g. steroids
- Treating TB infection now only requires one or two drugs for a shorter time, whereas TB disease initially requires four drugs and can take much longer to cure

#### 4.1.2 Explaining risks associated with LTBI treatment

The risk of side effects from the regimen they are taking should be explained to patients, as well as their likelihood of occurring. Red/orange discoloration of urine and other body fluids while taking 3HP is normal and completely harmless. Some side effects that can be experienced are flu-like symptoms, liver injury or a rash

- Patients should be alert to the following symptoms:
  - Weakness, fatigue, loss of appetite, persistent nausea (early symptoms of hepatotoxicity)
  - Flu-like, or other acute symptoms appearing shortly after taking a dose of 3HP
  - Rash that started after starting 3HP

If patients experience any of the above symptoms or a change in their health situation they should contact a healthcare provider for advice and only continue taking 3HP if advised to do so by a healthcare provider

### **TB disease can develop during 3HP treatment**

- While every effort was made to exclude active TB through a symptom screen prior to starting TB treatment, patients should be vigilant as they can still develop TB
- If they start having a cough, unexplained weight loss, fever and night sweats, they should immediately let the provider know

### **Pregnancy can occur during 3HP treatment**

- Women of child bearing age should be counselled to use barrier methods of contraception while using 3HP
- If pregnancy occurs during 3HP treatment, 3HP should be discontinued immediately and can be restarted after delivery.

## **4.2 Strategies to improve adherence and treatment completion**

To improve the chances of adherence and regimen completion, the following need to be taken into consideration when providing guidance:

- Explore and unpack what the patient knows about TB
- The support from a family member and/or a treatment buddy
- The importance of taking the course on the same day every week - the exact timing does not matter but it is easier if the same time is kept each week
- The importance of completing the full 12 week course to be protected from TB
- Taking all medication together at once and not dividing the dose over a few hours or a few days. Pills can be separated if the whole dose can be taken within 30 minutes
- Use reminders to help take medication weekly vs daily e.g. weekly events
- Caution on an overreliance on a TV show that may be rescheduled, moved to a different time slot or other socioeconomic factors like electricity outages
- Religious meeting e.g. Church on Sunday
- Electronic reminders on cell phones

## **4.3 Potential barriers to adherence**

Many variables affect a patient's adherence to the recommended treatment regimen, episodes of non-adherence should be recognized and addressed as soon as possible. The following need to be considered as potential barriers for adults:

- Clinic opening hours conflict with patient's schedule
- Competing priorities prevent patients from attending e.g. work, school, caring for children or elderly
- Long waiting times at clinics
- Cost of clinic visits (transport, time, loss of work)
- Incorrect or insufficient information about:
  - TB infection
  - 3HP regimen
  - TB disease
- Real or perceived stigma related to TB infection treatment and/or TB disease
- Health beliefs and practices

- Treatment-related
  - Co-existing medical conditions
  - Side effects
  - Difficulty remembering weekly dose
  - Religious practices e.g. fasting
  - Use of unregulated medicines, supplements and alcohol might interfere with adherence or with the effectiveness of the drugs

#### 4.4 Options that can be used for supporting adherence

- Identification of treatment supporter e.g. family member, neighbour, colleague
- Use of directly observed therapy for patients whose treatment has been interrupted or who often miss appointments for medication refills
- Incentives which are small rewards that encourage or motivate patients may be considered, depending on acceptability within the country context/availability of funds. Examples of incentives include airtime/grocery store coupons/food parcels or supplements. While these are commonly used, their link to improved adherence has not been clearly demonstrated<sup>11</sup>
- Enablers such as reimbursing transport, phone calls, make it easier to keep appointments and may be used depending on acceptability within the country context/availability of staff resources and funds
- Developing an adherence plan with the patient and discussing it at each visit. Such a plan could include information such as:
  - Motivators for the client to want to be TB free
  - Taking 3HP with food to reduce nausea and vomiting
  - Using patient and family routines and their variations to assist in identifying the best time to take the medicines

### 5. Special considerations for adherence in children

Infants and children are dependent on caregivers for medication administration, and therefore the barriers faced by these adult caregivers can contribute to missing doses in children. The considerations laid out above would apply to caregivers of children and infants on 3HP.

#### 5.1 Potential barriers for children:

- The absence of child friendly formulations makes medication more difficult to administer and may put off some caregivers and increase child refusal of crushed pills
- Caregiver – provider trust: if the caregiver is invested in the outcome then the adherence of the child will be improved
- Family Factors:
  - Not having an appropriate caregiver or set of caregivers. Because young children are often moved around different family members' homes, involvement of multiple caregivers (grandparents, father's family, etc) may be necessary
  - Caregivers lack of knowledge
  - Age and developmental stage at which children can take more responsibility for taking their own medications while still being supervised by an adult
  - Changes in routine for the family or child (school vacations for example) that disrupts administration schedule

## 5.2 Strategies for managing and enhancing adherence in children:

- Explain and emphasize to care-giver and child why they must take the full course of treatment
- Note risk factors for poor adherence such as distance/transport; orphan (especially if mother has died) or primary care-giver unwell
- Provide adolescents with education and adherence support directly especially if living with HIV
- For young children refusing medicine:
  - Change food type to better mask the taste. Solids with medicines in the centre or crushed with an easy to swallow food are options to mixing in water.
  - Provide a treat as a reward
  - If a child vomits within 30 minutes of a dose, a new dose should be given to the child by the family. Practically this means families are given an extra dose every month
  - Make sure that families understand that providing extra doses will not be viewed negatively to improve the likelihood that they give a second dose if the first one is vomited.
- Prepare an adherence plan with the caregiver and ask that it be shared with other caregivers.
- Review the adherence plan at each encounter especially if there is a new caregiver present.
- Review the knowledge and barriers at each visit. Examples of questions to be asked:
  - Who is the primary caregiver? parent grandparent auntie/uncle other child
  - Does the child sometimes sleep in other family members' home?
  - Is the caregiver aware that the treatment is daily (isoniazid, 3HR) or once weekly (3HP) for 3 months?
  - Is the caregiver aware of dose/pill number at each time?
  - Is the caregiver counselled regarding the need for adherence?
  - Is the caregiver counselled regarding side effects and what to return for?
  - Is the caregiver counselled on post medication vomiting (re-dosing)?

## 6. Processes to support patient retention

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Patients on 3HP should have monthly visits scheduled at which treatment will also be dispensed.

At each visit:

- Ask patients about their adherence as well as strategies they are using to assist with adherence, to show that you are not only interested in them adhering but also in helping them to adhere
  - Discuss how many weekly doses were missed and how this can be avoided in the future
- Patients should also return their used blister packs, all remaining pills, and a pill count should be done
- Adherence counselling should be done as appropriate
  - Discuss any identified barrier and propose joint solutions
  - Use motivational interviewing techniques to improve adherence<sup>12</sup> (how do you feel when you've missed a dose? How do you want to change that?)
- Adverse events and TB symptoms should be specifically asked about (refer to the technical brief on adverse events, [www.impaact4tb.org/library/](http://www.impaact4tb.org/library/))
- Detailed contact information should be checked against the clinic records, including one verified cell phone number and the number of a close contact person

- There should also be a monitoring system in place as part of clinic routine. This should flag any person who misses a visit and include a follow up process. This process should include a call within one week of missing a monthly clinic visit to collect treatment. On this call, the following should be discussed:
  - Ask for side effects/TB symptoms/pregnancy
  - Advise on taking medication if appropriate (patient still has meds/no side effects or TB symptoms)
  - Reschedule clinic appointment as soon as possible if patient is agreeable
- If patient wishes to discontinue treatment, record as “discontinued at patient’s request” (with reason if possible)

## 7. Management of missed doses

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- Adherence to weekly doses
    - Encourage a weekly routine of taking medications i.e. Sunday. If a patient misses Sunday, they can take 3HP within 3 days and go back to their normal Sunday routine
    - If they miss a dose for more than 3 days there are two options: They can skip this dose and go back to their original chosen day i.e. Sunday and continue until all 12 doses have been taken
- OR**
- Start the new schedule on the day they remembered to take the dose i.e. Schedule was a Sunday and only remembered Thursday, they now start a once weekly Thursday routine and forget about Sundays
  - The 12 week course should be completed within 16 weeks which provides some leeway for missed doses
  - 11 doses in 16 weeks can also be counted as sufficient, although not ideal

## 8. Provide accurate and appealing information to clients

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- Patients need accurate and sufficient information presented to them in ways that they can understand, relate and find attractive
- A 3HP patient centered flip chart has therefore been developed to guide a facilitator, such as a counselor or community health worker, in providing this accurate and accessible information; **you can access the tool here** ([www.impact4tb.org/library/](http://www.impact4tb.org/library/))

## 9. Example of an Adherence plan

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### 1. TB background

- Ask the client what they know about TB infection, TB disease and TB treatment
  - Give information where necessary e.g. correcting a myth or wrong information about TB
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### 2. Establish client's motivation to start treatment

- What motivates them to stay healthy
  - Find out if the client is ready to start treatment, if not ready then the clinician should advise
  - What is their take on disclosure?
  - If they are willing discuss who they would like to disclose to
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### 3. Role of medication

- Explain the role of treatment
  - Discuss how treatment is supposed to be taken (See 3HP counselling flipchart, for graph)
  - Ensure the client understand possible side-effects and what should happened if they experience any of them
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### 4. Client's lifestyle

- The discussion should be based on:
    - Keeping alcohol consumption low
    - Traditional and/or over the counter medications as there may be possible drug interactions
  - Assist the client to choose a day of the week, based on their lifestyle, when they would like to take their medication e.g. every Sunday
  - Discuss reminder devices/strategies to help them remember when to take the medication i.e. cellphone alarm, weekly routine or ritual etc.
  - Preferably chose more than 1 strategy or reminder system
  - Discuss each device's/strategies' advantages and disadvantages
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### 5. Agree on a tracing/support option if needed

- Ask which mode of tracing the client would prefer:
    - Telephone call
    - Home visit
    - DOTS
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### 6. Ongoing support

- Reassure the client that you have an open-door policy for clients to come back at any time if they have any challenges

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