P.O. Box 38597, Pinelands, Cape Town, South Africa, 7430
Email: afa@afadm.co.za
Website: www.aidforaids.co.za

Tel: 0800 227 700 or +27 (0)21 466 1700
Fax: 0800 600 773 or +27 (0)21 466 1744

Healthcare Professional Newsletter

March 2019 – Issue 49

Tuberculosis Preventive Therapy for Adults

The Aid for AIDS programme endorses the new, simplified national guidelines on isoniazid preventive therapy (IPT) issued in the 2018 Standard Treatment Guidelines and Essential Medicines List, Primary Healthcare Level Care (http://www.health.gov.za/index.php/standard-treatment-guidelines-and-essential-medicines-list/category/285-phc). The new guidelines recommend isoniazid 300 mg daily together with pyridoxine (vitamin B6) 25 mg daily for 12 months. IPT should be started with ART or added to those on ART who have not yet received IPT. There is no need to test for latent TB infection (either tuberculin skin tests or interferon-gamma release assays (like QuantiFERON-TB gold test).

The rationale for these simplified guidelines is from a South African trial,[1] which showed that IPT for 12 months given to patients on ART, or starting ART, reduced the risk of TB by about a third and was well tolerated. The benefit of IPT in patients on ART was seen irrespective of tuberculin skin test (TST) status, which is unlike findings of studies done in the pre-ART era.

Before commencing IPT, active tuberculosis should always be excluded. Further investigations to exclude TB must be done if any of the following symptoms are present (note that a screening chest x-ray is not required before initiating IPT):

- Current cough
- Fever
- Weight loss
- Drenching night sweats

If any of the above symptoms are present, a sputum should be sent for GeneXpert MTB/RIF – if this is negative and symptoms persist a second sputum sample should be sent for mycobacterial culture. IPT should be deferred until these results are known and the symptoms have resolved.

Unfortunately, a recent trial of IPT in pregnant women on ART, the TB APPRISE study,[2] showed that IPT resulted in worse pregnancy outcomes with no benefit. Therefore, IPT should not be started in pregnancy, except for pregnant women with CD4 counts <100 cells/µL, who are at high risk of death from tuberculosis. The new national guidelines recommend doing sputum for GeneXpert MTB/RIF assay even if they are asymptomatic, following a large South African study showing that symptoms were not good predictors of TB in pregnant HIV-positive women.[3]

Patients must be followed up regularly whilst on IPT and asked specifically about symptoms of hepatotoxicity (nausea, vomiting, right upper quadrant pain, and jaundice). If these symptoms occur, examine for jaundice and urgently check ALT. If significant hepatotoxicity (defined as ALT >5 times upper limit of normal (ULN) or >3 times ULN with symptoms or jaundice) occurs discontinue IPT immediately. Pyridoxine should be given concurrently to reduce the risk of peripheral neuropathy.

Contributors:
Prof. Gary Maartens
Prof. Graeme Meintjes

This newsletter has been edited by:
Liezl Dunn

References:
1. Rangaka MX, et al. Isoniazid plus antiretroviral therapy to prevent tuberculosis: a randomised double-blind, placebo-controlled trial. Lancet. 2014;384:682-90.
2. Gupta A et al. TB APPRISE: Phase IV Randomized Double-blind Placebo-controlled Trial to Evaluate the Safety of Immediate (Antepartum-initiated) vs. Deferred (Postpartum-initiated) Isoniazid Preventive Therapy among HIV-infected Women in High TB Incidence Settings IMPAACT P1078 Conference of Retroviruses and Opportunistic Infections, Boston 2018.
3. Hoffmann CJ, et al. High prevalence of pulmonary tuberculosis but low sensitivity of symptom screening among HIV-infected pregnant women in South Africa. PLoS One. 2013 Apr 17;8(4):e62211.

Undetectable = Untransmittable (U=U)

Several recent studies have evaluated the risk of HIV transmission in serodiscordant couples in whom the HIV-positive partner has an undetectable viral load and the couple is having condomless sex. These studies all had similar designs: couples were prospectively followed and condomless sexual acts recorded, the HIV viral load regularly measured and HIV testing in the HIV-negative partner regularly conducted. The number of linked transmissions during periods of time when the viral load was suppressed could then be calculated. The studies are briefly summarised in the table below:

Study	Study population	Couple years follow-up	Number of condomless sexual acts	Linked transmissions during periods when viral load undetectable
PARTNER 1	888 couples in Europe (62% heterosexual and 38% MSM)	1,238	58,000	0
PARTNER 2	783 MSM couples in Europe	1,596	76,991	0
Opposites Attract	343 MSM couples in Australia, Brazil and Thailand	588	16,800	0

Cumulatively there were over 150,000 condomless sexual acts across these studies with zero linked transmissions documented. What these findings mean, in the words of Dr Tony Fauci (Director of the National Institute of Allergy and Infectious Diseases at the NIH), is that for onward sexual transmission from an HIV-positive person with a suppressed viral load "from a practical standpoint, the risk is zero". The US Center for Disease Control and Prevention (CDC) has also supported the public health message that with a suppressed viral load there is no risk of sexual transmission. It is important to note that this cannot be extrapolated to vertical transmission or transmission via shared needles.

Based on this data, Aid for AIDS advises that a serodiscordant couple can be counselled and advised that if the HIV-positive partner has been on ART for longer than 6 months, has had a viral load suppressed on the two most recent measurements and provided ART adherence is maintained that condoms are not required to prevent sexual transmission. Pre-exposure prophylaxis is also not required for the HIV-negative partner under these circumstances, but frequent viral load monitoring (3-4 monthly) should be done. Condoms may still be required for prevention of pregnancy and obviously any condomless sexual encounter outside the couple carries a potential risk of HIV and/or acquisition of other sexually transmitted infections.

References:
1. Rodger AJ, et al. Sexual Activity Without Condoms and Risk of HIV Transmission in Serodifferent Couples When the HIV-Positive Partner Is Using Suppressive Antiretroviral Therapy. JAMA. 2016 Jul 12;316(2):171-81.
2. Rodger A, et al. Risk of HIV transmission through condomless sex in MSM couples with suppressive ART: the PARTNER2 Study extended results in gay men. AIDS 2018: 22nd International AIDS Conference, Amsterdam, Netherlands, July 23-27, 2018. Abstract WEAX0104LB.
3. Bavinton BR, et al. Viral suppression and HIV transmission in serodiscordant male couples: an international, prospective, observational, cohort study. Lancet HIV. 2018 Aug;5(8):e438-e447.

Important drug-drug interactions with dolutegravir

Interacting drug	Effect of co-administration	Recommendation
Metformin	↑metformin	Maximum metformin dose 500 mg 12 hourly
Polyvalent cations (Mg, Fe, Ca, Al, Zn) e.g. antacids, sucralfate, supplements	↓dolutegravir	Take dolutegravir either 2 hours before or 6 hours after
Anticonvulsants: **Carbamazepine** **Phenobarbital** **Phenytoin** **Valproate***	↓dolutegravir	Avoid co-administration if possible (lamotrigine, levetiracetam, and topiramate can be used) or double dolutegravir dose to 50 mg 12 hourly
Rifampicin	↓dolutegravir	Avoid co-administration if possible (rifabutin 300 mg daily can be used) or double dolutegravir dose to 50 mg 12 hourly
Efavirenz	↓dolutegravir	Avoid co-administration if possible (rilpivirine can be used) or double dolutegravir dose to 50 mg 12 hourly
Nevirapine	↓dolutegravir	Avoid co-administration if possible (rilpivirine can be used) or double dolutegravir dose to 50 mg 12 hourly

*There is a report of an interaction with valproate resulting in a substantial reduction of dolutegravir trough concentrations. The mechanism is unknown & this report needs confirmation. Double dose dolutegravir should only be considered if there are no other options to replace valproate.

Reference:

1. Palazzo A, et al. Lower dolutegravir plasma concentrations in HIV-positive patients receiving valproic acid. J Antimicrob Chemother 2018; 73: 826–827.