

The prophylaxis of opportunistic infections in HIV-infected adults

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HIGHLIGHTS

- When should prophylaxis for opportunistic infections be initiated?
- For which opportunistic infections are prophylactic therapy available?
- What is the appropriate choice of drugs?

INTRODUCTION

Ultimately the profound immune suppression resulting from Human Immunodeficiency virus (HIV) infection renders patients vulnerable to opportunistic infections (OIs). Patients are vulnerable to some of the OIs even at relatively preserved CD4 counts. Other OIs are associated with very low CD4 counts. Primary prophylaxis is initiated at a stage when the patient is at risk of the particular infection. Secondary prophylaxis (also called maintenance therapy) is initiated after appropriate treatment of the acute OI, since relapses of some infections are common as long as the patient is severely immune suppressed.

Table I summarises the prophylactic regimens that are either generally recommended or can be considered for specific patients. The dosages given in the table are for adults.

The timely use of highly active antiretroviral therapy (HAART) with concomitant reconstitution of the immune system is the most effective way to prevent opportunistic infections. Unfortunately many patients are only diagnosed with HIV once

they are severely immune compromised and need prophylactic therapy until immune reconstitution takes place. Other patients have such profound damage to the immune system that very little immune reconstitution takes place after initiation of HAART and the prophylaxis of OIs needs to be continued indefinitely.

CO-TRIMOXAZOLE PROPHYLAXIS

Indications

Co-trimoxazole prophylaxis has become part of standard care for HIV worldwide. It is used for the prevention of *Pneumocystis jirovecii* pneumonia (PCP), also previously known as *Pneumocystis carinii*. This infection is usually associated with a CD4 count below 100 cells/L.¹ The risk of PCP without prophylaxis is 60-70% per year in those patients with previous PCP and 40-50% in those without previous PCP, but a CD4 count below 100 cells/L. PCP prophylaxis reduces the risk of PCP nine-fold. Patients who get PCP while on prophylaxis have a lower mortality rate.²

As additional benefit, co-

trimoxazole prophylaxis decreases the incidence of toxoplasmosis and some bacterial infections targeting the urinary tract, respiratory tract or skin. Toxoplasmosis is usually associated with a CD4 count below 100 cells/L. Some bacterial organisms covered by co-trimoxazole include *H. influenzae*, *S. pneumoniae*, gram-negative bacilli, *Salmonella sp.*, methicillin-sensitive *S. aureus*, *Legionella* and *Nocardia*.

Indications for initiating co-trimoxazole prophylaxis are summarised in **Table II**. Primary co-trimoxazole prophylaxis should be initiated when the CD4 count decreases to below 200 cells/L. Where facilities for CD4 count monitoring are not available, an absolute lymphocyte count $< 1.25 \times 10^9/L$ can be used. When no laboratory monitoring of HIV is available, primary co-trimoxazole prophylaxis should be initiated in patients with World Health Organization (WHO) Stage 3 or 4 disease. Stage 3 disease includes pulmonary tuberculosis (TB), prolonged fever and oral candidiasis. Stage 4 disease is Acquired Immune Deficiency Syndrome (AIDS).

Table I: Prophylaxis for common opportunistic infections found in HIV-positive patients.

Infection	Indications	Primary Prophylaxis	Secondary prophylaxis	Treatment	Duration
Tuberculosis	PPD > 5 mm or tuberculosis contact Active tuberculosis must be excluded Not treated for tuberculosis in past two years	Recommended	Not recommended	INH 300 mg daily po & pyridoxine 25-75 mg/day Alternative: Rifampicin 600 mg daily & PZA 15-20 mg/kg daily for 2 months	6 months
<i>Mycoplasma avium complex (MAC)</i>	CD4 < 50 or previous infection	Recommended	Recommended	Clarithromycin 500 mg bd po or azithromycin 1200 mg/week	Lifelong or till CD4 >100 on HAART
<i>Pneumocystis jiroveci pneumonia (PCP)</i>	CD4 < 200 Previous PCP infection	Recommended	Recommended	Co-trimoxazole one D/S or one S/S dly po Alternative: Dapsone 100 mg po dly	Lifelong or till CD4 >200 on HAART
Toxoplasmosis	CD4 < 100 & positive IgG serology	Recommended	Recommended	Co-trimoxazole one D/S or two S/S dly po	Lifelong or till CD4 >200 on HAART
Cryptococcal meningitis	Previous cryptococcal meningitis	Not recommended	Recommended	Fluconazole 200 mg po dly (occasionally up to 400 mg dly)	Lifelong or till CD4 >200 on HAART
Vaccines					
Influenza	All patients, but poor response with CD4 <200	Recommended	Not recommended	Influenza vaccine 0.5 ml IMI	Yearly
Hepatitis B	Negative anti-HBc or anti-HBs screening	Recommended	Not recommended	Recombivax HB10 µg IMI x3	Once
Pneumococcal	Presently controversial	Not recommended	Not recommended	Pneumovax 0.5 ml IMI	Unknown

[D/S = double strength 960 mg; HAART = highly active antiretroviral therapy; PPD = purified protein derivative; PZA = pyrazinamide; S/S = single strength 480 mg]

Secondary prophylaxis (maintenance therapy) should be initiated directly after the three-week treatment of the acute PCP or three-month treatment for acute toxoplasma infection has been completed.

Both primary and secondary prophylaxis for PCP and toxoplasmosis continue lifelong or until the CD4 count is sustained above 200 cells/L for more than three months while on HAART.³⁻⁶ Prophylaxis should be restarted should the CD4 count fall again below 200 cells/L.

Co-trimoxazole prophylaxis doses in adults

Possible regimens include:

- 960 mg/day (2 single strength tablets or 1 double strength tablet)
- 480 mg/day
- 480 mg/day Monday to Friday
- 960 mg three days/week (2 single strength tablets or 1 double strength tablet)

The lower doses are usually better tolerated by the patients. All the regimens are equally effective as prophylaxis for PCP, but the lower doses are not effective against toxoplasma and bacterial infections.

Co-trimoxazole intolerance

Side-effects due to co-trimoxazole are frequent in HIV-positive individuals. A maculopapular rash is the most common. However, many of the patients developing itching or a maculopapular rash can continue with co-trimoxazole under antihistamine cover.

Patients with a history of an adverse reaction to co-trimoxazole can either be rechallenged or desensitised. Rechallenge can be done with a single dosage of 480 mg and observation for a few hours. However, patients who had a skin rash with systemic symptoms (e.g. fever) or mucocutaneous involvement (oral

or urogenital) should not be rechallenged. Patients with a history of allergy and/or skin reaction to co-trimoxazole can, in most cases, be desensitised safely. This should be done under antihistamine cover in hospital for at least 24 hours prior to initiation of treatment. A simple desensitisation regimen is suggested in **Table III**.⁷

Alternatives to co-trimoxazole prophylaxis

Dapsone 100 mg/day is as effective as co-trimoxazole as prophylaxis against PCP, but offers no proven protection against toxoplasma and bacterial infections.

Table II: Indications for use of co-trimoxazole prophylaxis in HIV-infected individuals.

Laboratory	Clinical
CD4 count < 200 cells/mL Absolute lymphocyte count < 1.25 x10 ⁹ /L	WHO stage 3 or 4 Previous episode of PCP

Table III: Co-trimoxazole desensitisation regimen.

Day 1	1.25 ml syrup daily (240 mg/5 ml)
Day 2	1.25 ml syrup bd (240 mg/5 ml)
Day 3	1.25 ml syrup tds (240 mg/5 ml)
Day 4	2.5 ml syrup bd (240 mg/5 ml)
Day 5	2.5 ml syrup tds (240 mg/5 ml)
Day 6	480 mg tablet once daily

TB PROPHYLAXIS

M. tuberculosis is the most common cause of morbidity and mortality associated with HIV in Sub-Saharan Africa.

The most effective way of preventing TB infection in an HIV-positive individual is to control HIV in the general population through an effective TB treatment programme.

An effective TB programme will ensure high cure rates of TB through DOTS (directly observed treatment, short course).

An acute TB infection may be due to the flare-up of a dormant infection or to a reinfection with the organism.

The incidence of active TB is substantially increased by HIV co-infection. The risk of active TB for HIV-positive individuals with a positive tuberculin skin test is approximately 10% per annum.⁸ The incidence of active TB in those with a positive tuberculin skin test is magnified 7-8-fold by HIV co-infection.⁹ It also appears that TB accelerates the rate of HIV progression.¹⁰

Indications

HIV-positive individuals in Sub-Saharan Africa are at significant risk of TB even at relatively preserved CD4 counts. Thus preventative therapy should be offered irrespective of the CD4 count. With the use of TB prophylaxis, the reduction of TB incidence amongst HIV-positive individuals with a positive tuberculin skin test is 60%.¹¹ However, other categories of patients can also be offered prophylactic therapy.

Indications for the use of TB prophylaxis include:⁸

- Positive PPD (>5 mm)
- TB contact
- Staying in high risk dormitory conditions (e.g. mines, prisons)
- Active TB excluded
- No TB treatment in past 2 years

Since drug resistance can occur if a patient with active TB is given a single antituberculosis drug, it is essential to exclude active TB before initiating prophylaxis. Signs or symptoms that

could fit in with TB (e.g. weight loss, fever, night sweats, coughing) should actively be sought and fully investigated. In any patient with respiratory symptoms, a chest X-ray should be done and sputum samples sent for TB microscopy and culture.

A prerequisite for TB prophylaxis is patient compliance. Without that, drug resistance might emerge. Compliance with 6 months of TB prophylaxis might predict a patient's future compliance with antiretrovirals.

Patients should only be supplied with one month of preventative therapy at a time and monitored for symptoms and signs of active TB or side-effects such as peripheral neuropathy and liver toxicity. It is not necessary to do routine liver functions, unless the patient has underlying liver disease.

Patients with a history of active alcohol abuse or liver disease should not be offered TB prophylaxis, because of possible hepatotoxicity due to antituberculostatics.

Current data seem to suggest that the benefit of TB prophylaxis is lost 18 months after completing therapy.^{12,13}

Regimen

The preferred regimen for primary prophylaxis is isoniazid (INH) 5 mg/kg/day (maximum 300 mg/day) plus pyridoxine 50 mg/day for 6 months. Although 9 months of preventative therapy is prescribed in the northern hemisphere, in southern Africa 6 months of preventative therapy is regarded as sufficient and also easier for patient compliance.

An alternative regimen is isoniazid and rifampicin as a combination pill for three months.¹¹ TB differs from other OIs with regard to secondary prophylaxis. Short course (6-9 months) treatment of the acute infection need not be followed by secondary prophylaxis.

FLUCONAZOLE PROPHYLAXIS

Indication

Fluconazole at 200 mg/day is used for secondary prophylaxis of cryptococcus meningitis after treatment of

the acute infection. This continues lifelong or until sufficient immune reconstitution has taken place. Although international data¹⁴ suggest that prophylaxis in patients on HAART may be discontinued at a CD4 count of 100 cells/L, it might be safer to continue until the CD4 count is above 200 cells/L since no data exist for our patient population.

Primary prophylaxis does not form part of any southern African guidelines, but can be considered for selected patients.

INFLUENZA VACCINE

Influenza is more severe and prolonged in HIV-infected individuals.¹⁵⁻

¹⁶ Thus HIV-infected individuals form a prime target group for influenza vaccine.¹⁷ Influenza vaccine should be administered annually, preferably March to May, due to the antigenic shift in strains from year to year. Influenza vaccines currently used are inactive subunits or split-product vaccines and are safe to use. CD4 cells govern the humoral response (IgG and IgA) stimulated by the vaccination. In HIV-positive individuals with CD4 counts less than 200 cells/L, the antigenic response tends to be poor.¹⁸

A transient increase in viral load can occur. Thus viral load monitoring should not be done within two weeks of vaccination.¹⁹ This, however, does not have any clinical implications.

HEPATITIS B-VACCINE

Hepatitis B vaccine can be administered to patients who are anti-HBs and antiHBe antibody negative. It is given as 3 doses intramuscularly, spaced over a period of 6 months.

PNEUMOCOCCAL VACCINE

The risk of invasive pneumococcal infection is 50-100 times higher in HIV-positive individuals than in the general population.²⁰ The use of the 23-polyvalent pneumococcal vaccine was until recently recommended as standard care in the Western world, but a review of available data found no evidence of efficacy in the target population.²¹ One large clinical trial in Uganda showed increased risk of

pneumococcal disease in vaccine recipients and also a higher mortality rate.²² Thus pneumococcal vaccine is currently not recommended for HIV-positive individuals.

M. AVIUM COMPLEX (MAC) PROPHYLAXIS

The 2002 UPSHDS/IDSA Guidelines for the Prevention of Opportunistic Infections in Persons with Human Immunodeficiency Virus²³ strongly recommends a macrolide (clarithromycin 500 mg bd or azithromycin 1200 mg weekly) as primary prophylaxis against MAC disease when the CD4 count is less than 50 cells/L. MAC prophylaxis does not form part of any southern African guideline. This is an as yet unobtainable goal in sub-Saharan Africa, since these drugs are financially out of reach for most of the population.

Should primary prophylaxis be instituted, it can be discontinued once the CD4 count is above 100 cells/L for more than 3 months.^{24,25} However, in patients on HAART, MAC maintenance treatment can be discontinued after one year, provided that the patient remains asymptomatic, the CD4 count is above 100 cells/L for more than 3-6 months and bone marrow and blood cultures are negative.²⁶

See CPD Questionnaire p.49

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