WHO MODEL LIST OF ESSENTIAL MEDICINES APPLICATION

1. Summary statement
   Inclusion of the tablet formulation of sulfamethoxazole 800mg and trimethoprim 160mg (cotrimoxazole 960mg) is proposed to reduce mortality and hospitalisations among adults living with HIV/AIDS (ALHIV).

   The principal reasons for requesting this inclusion are as follows:

   1. Cotrimoxazole (Sulfamethoxazole 800mg and trimethoprim 160 mg) prophylaxis therapy (CPT) prevents *pneumocystis jirovecii* pneumonia (PCP), cerebral toxoplasmosis, bacterial pneumonia, diarrhoea, *isospora belli*, malaria, and other infections in ALHIV. This has led to a significant mortality benefit in clinical trials in low and high income countries.

   2. WHO Guidelines recommend CPT as part of the standard package of care available to ALHIV.

   3. In most settings CPT is recommended indefinitely.

   4. The effectiveness of CPT is compromised by lapses in adherence, resulting in cotrimoxazole-resistant bacteria.

   5. Adherence and effectiveness of CPT will be improved with wider availability of this tablet.

2. Name of the focal point in WHO submitting or supporting the application
   Reuben Granich, WHO/HTM/HIV/ATC

3. Name of the organization(s) consulted and/or supporting the application
   Not applicable

4. International Nonproprietary Name (INN, generic name) of the medicine
   sulfamethoxazole/trimethoprim

5. Formulation proposed for inclusion; including adult and paediatric (if appropriate)
   Combination tablet comprised of sulfamethoxazole 800 mg, and trimethoprim 160 mg for adult patients.
6. International availability - sources, if possible manufacturers

<table>
<thead>
<tr>
<th>INN and dosage</th>
<th>Manufacturer and Country</th>
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</thead>
<tbody>
<tr>
<td>Sulfamethoxazole 800mg +</td>
<td>WHO prequalified: Roche Pharmaceuticals, Switzerland</td>
</tr>
<tr>
<td>Trimethoprim 160mg</td>
<td>Cipla Ltd., India</td>
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<tr>
<td></td>
<td>Instituto Quimioterapico, Peru</td>
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</table>

7. Whether listing is requested as an individual medicine or as an example of a therapeutic group
This strength is proposed for the ‘Other Antibiotics’ category (6.2.2)

8. Information supporting the public health relevance

8.1 Epidemiological information on disease burden
As of December 2008, 95% of the world’s 33.4 million people living with HIV/AIDS (PLHIV) were in low and middle income countries (1). In 2008 there were 2.7 million new HIV infections, two million AIDS-related deaths, and 5.5 million people needing antiretroviral therapy (1) (2).

Before antiretroviral therapy and pneumocystis jirovecii pneumonia (PCP) prophylaxis were given to PLHIV, PCP occurred in 70-80% of patients with AIDS (3). Among those with significant immunosuppression, approximately 20-40% die. The majority of PCP cases occur in patients who are unaware of their HIV infection or not receiving HIV care regularly (4). For patients with advanced immunosuppression who were seropositive for T. gondii and not receiving prophylaxis with drugs active against T. gondii, the 12 month incidence of toxoplasmosis was 33% (4). In resource limited settings where exposures to bacteria are different than industrialized settings, deaths due to malaria, isosporiasis, mycobacterium tuberculosis, and bacterial pneumonia are common in HIV infected persons (5,6). Indeed, current evidence shows that HIV infection increases the risk of malaria and worsens malaria outcomes (7) while malaria infection increases viraemia in HIV-infected individuals (8).

While antiretroviral therapy has reduced mortality due to HIV, additional simple, safe, and effective interventions are needed to prevent malaria, bacterial infections, and improve survival among HIV-infected persons.

8.2 Assessment of current use
The WHO does not collect statistics on the 33 million PLHIV who are also taking cotrimoxazole. The majority of the 5 million people on ART are also eligible for cotrimoxazole.

In 2008, the WHO sent out a survey on CPT and IPT policy and implementation to 69 countries with a high burden of TB-HIV (9). 41 countries responded to the survey, representing 82% of the global HIV burden and 85% of the global HIV/TB burden. 93% of these countries had a national CPT policy, and 66% had nation wide
implementation. 51% of responding countries had a national IPT policy, with 28% indicating nation wide implementation.

8.3 Target population
Some country guidelines recommend cotrimoxazole in HIV-infected individuals regardless of immune status while others restrict cotrimoxazole to persons with a CD4 ≤ 350 cells/µL or ≤ 200 cells/µL.

9. Treatment details (dosage regimen, duration; reference to existing WHO and other clinical guidelines; need for special diagnostic or treatment facilities and skills)
The last revision of WHO guidelines on cotrimoxazole prophylaxis therapy (CPT, 800 mg of sulfamethoxazole and 160 mg of trimethoprim daily) were published in 2006. These guidelines contain the following recommendations for adults (10):

- In countries with a high prevalence of HIV and limited health infrastructure, CPT should be initiated in all patients, regardless of CD4 count or WHO clinical stage.
- For countries who initiate CPT based on WHO clinical stage, CPT should be initiated in ALHIV stages 2-4.
- For countries who initiate CPT based on CD4 count, CPT should be initiated in ALHIV with a CD4 ≤ 350 cells/µL.
- Continue cotrimoxazole prophylaxis among adults living with HIV indefinite
  o Duration of CPT is country specific, and is sometimes discontinued in the event of a severe adverse event or immunological recovery due to ART.
  o In Uganda, cotrimoxazole prophylaxis therapy is recommended for all HIV positive adults and children for life, and is discontinued only in the event of a severe adverse event (11).

10. Summary of comparative effectiveness in a variety of clinical settings:
10.1 Identification of clinical evidence

10.1.1 Search strategies

A Pubmed Search "HIV Infections"[Majr] AND "Trimethoprim-Sulfamethoxazole Combination"[Majr]: 404

By title: 39

By abstract: 11

By article: 3

The critical outcomes of interest were improving survival and decreasing hospitalisations.

The GRADE hierarchy considers randomised controlled trials the best source of evidence. Therefore the three randomised controlled trials were used (12-14), while the other eight identified observational studies were excluded. One Cochrane systematic review was identified for CPT in adults with HIV (15). Study summaries and the GRADE table for cotrimoxazole 960mg daily can be found in Annex 1. The data indicate
that CPT decreases hospitalisations and prolongs life in adults living with HIV. It is also well tolerated with only 3.9% of patients in the three randomised studies (16-19) experiencing a cotrimoxazole-induced adverse event.

10.2 Summary of available estimates of comparative effectiveness
Unfortunately, our search did not yield studies comparing the effect of cotrimoxazole to other antibiotics on survival in persons living with HIV in resource limited settings.

11. Summary of comparative evidence on safety:
11.1 Estimate of total patient exposure to date
There are no sources which indicate total exposure to cotrimoxazole.

11.2 Description of adverse effects/reactions
The most frequent adverse effects of cotrimoxazole are adverse GI effects (nausea, vomiting, anorexia) and sensitivity skin reactions (e.g., rash, urticaria), each reportedly occurring in about 3.5% of patients (20). The incidence and severity of these adverse reactions are generally dose related, and adverse reactions may occasionally be obviated by a reduction in dosage. Hypersensitivity and hematologic reactions are the most serious adverse effects of cotrimoxazole, reportedly occurring in less than 0.5% of patients.

11.4 Identification of variation in safety due to health systems and patient factors
Cotrimoxazole has been used extensively worldwide. No clinically significant differences in safety have been identified due to differences in health systems and patient factors.

11.5 Summary of comparative safety against comparators
Cotrimoxazole: When analysing the ‘adverse events’ outcome the CPT Cochrane review found that there was no significant difference (N=1405, RR 1.28, 95% CI 0.47 – 3.51) compared to placebo (15). In the GRADE table (Annex 1) treatment-limiting adverse events were more likely in patients on CPT (RR 1.89, 1.31-2.72). Using an absolute measure of effect indicates that 36 in 1000 patients would experience a treatment-limiting adverse event due to cotrimoxazole.

12. Summary of available data on comparative cost and cost-effectiveness within the pharmacological class or therapeutic group*:
12.1 Range of costs of the proposed medicine

<table>
<thead>
<tr>
<th>Cotrimoxazole 960mg tablet</th>
<th>Source</th>
<th>Unit Price/Day</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>IMRES (Netherlands)</td>
<td>0.0196</td>
</tr>
<tr>
<td></td>
<td>IDA (Netherlands)</td>
<td>0.0216</td>
</tr>
<tr>
<td></td>
<td>JMS (Uganda)</td>
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<td></td>
<td>MEG (Netherlands)</td>
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</tr>
<tr>
<td></td>
<td>MEDS (Kenya)</td>
<td>0.0305</td>
</tr>
<tr>
<td></td>
<td>MISSION (Denmark)</td>
<td>0.0308</td>
</tr>
</tbody>
</table>

The table above was modified from http://erc.msh.org/dmpguide/pdf/DrugPriceGuide_2008_en.pdf. The listed sources (e.g. IMRES) are pharmaceutical suppliers. Costs are priced in USD.
12.2 Comparative cost-effectiveness presented as range of cost per routine outcome (e.g. cost per case, cost per cure, cost per month of treatment, cost per case prevented, cost per clinical event prevented, or, if possible and relevant, cost per quality-adjusted life year gained)

Health economists suggest that a life-saving intervention that costs between two to three times the gross national product (GNP) per year-of-life saved represents a reasonable expenditure (21). Yazdanpanah et al. reported that using CPT would cost USD 200 / life-year gained (22). This analysis was performed in Cote d’Ivoire, where the per capita GDP is USD 1700, making this a cost-effective intervention. Given the vast majority of African countries have a GDP above USD 200 this cost-effectiveness research can also be generalised to other countries.

13. Summary of regulatory status of the medicine (in country of origin, and preferably in other countries as well)

sulfamethoxazole-trimethoprim is off-patent


Sulfamethoxazole-trimethoprim is available in the United States Pharmacopoeia.

Sulfamethoxazole-trimethoprim is available in the International Pharmacopoeia.

15. Proposed (new/adapted) text for the WHO Model Formulary

*Note the AHFS Drug Information book was used as a reference for this section (32).

Description: Sulfamethoxazole and trimethoprim are synthetic folate-antagnoist antibiotics.

Spectrum of activity: Cotrimoxazole has good activity against gram positive and negative organisms, including *Pneumocystis jirovecii*, *Stenotrophomonas maltophilia*, *Nocardia*, *S. pneumoniae* (some resistance), *Staphylococcus aureus/epidermidis/pyogenes*, *Streptococcus viridians*, *E coli*, *T. gondii*, *Proteus spp.*, *Enterobacter spp.*, *Salmonella*, *Shigella*, *Klebsiella*, *Yersinia*, and enteric gram negative rods.

Mechanism of action: Sulfamethoxazole interferes with bacterial folic acid synthesis and growth via inhibition of dihydrofolic acid formation from para-aminobenzoic acid. Trimethoprim blocks the production of tetrahydrofolic acid by inhibiting the enzyme dihydrofolate reductase. Therefore, these two antibiotics work synergistically against many bacteria by inhibiting two consecutive steps of bacteria growth.

Dosage forms: Tablet comprised of Sulfamethoxazole 800mg and Trimethoprim 160mg

Indications: Sulfamethoxazole-trimethoprim is used to reduce mortality, infections, and hospitalizations in HIV-infected patients.

Pharmacokinetics/Pharmacodynamics: Time until peak concentration: 2 hours (trimethoprim), 4 hours (sulfamethoxazole).

Distribution: Trimethoprim is approximately 44% and sulfamethoxazole is approximately 70% bound to plasma proteins. The volume of distribution for trimethoprim is 100-120 L while that of sulfamethoxazole is 12-18 L.
Half life: 11 hours (trimethoprim) and 10 hours (sulfamethoxazole). The half life of trimethoprim increases with renal impairment.

Metabolism: Sulfamethoxazole: Biotransformed to inactive compound by N4-acetylation.

Excretion: 60% of free trimethoprim excreted in urine, 84.5% of sulfamethoxazole excreted in urine.

**Contraindications:** Sulfamethoxazole and trimethoprim are contraindicated in patients with known hypersensitivity to any of these active ingredients

**Precautions:**
- Caution should be exercised when giving cotrimoxazole to patients with G6PD deficiency.
- Gastrointestinal distolerance, rash (which can progress to Stephens-Johnson syndrome), thrombocytopenia, leucopenia, hepatitis, and hyperkalemia can occur with administration of cotrimoxazole.

**Toxicity:**
The most frequent adverse effects of cotrimoxazole are adverse GI effects (nausea, vomiting, anorexia) and sensitivity skin reactions (e.g., rash, urticaria), each reportedly occurring in about 3.5% of patients (25). The incidence and severity of these adverse reactions are generally dose related, and adverse reactions may occasionally be obviated by a reduction in dosage. Hypersensitivity and hematologic reactions are the most serious adverse effects of cotrimoxazole, reportedly occurring in less than 0.5% of patients.

**Pregnancy:** Although there are no adequate and controlled studies to date in humans, studies in pregnant women suggest that the incidence of congenital abnormalities in those who received cotrimoxazole was similar to that in those who received a placebo; there were no abnormalities in 10 children whose mothers had received the drug during the first trimester. In one report, there were no congenital abnormalities in 35 children whose mothers had received cotrimoxazole at the time of conception or shortly thereafter. Reproduction studies in rats using oral trimethoprim (as cotrimoxazole) dosages up to 70 mg/kg daily have not revealed evidence of impaired fertility.

**Drug Interactions**
Megoblastic anemia has been reported in patients receiving cotrimoxazole and pyrimethamine dosages exceeding 25mg weekly. Cotrimoxazole may decrease the efficacy of tricyclic antidepressants.

Sulfonamides increase the effect of oral hypoglycemic agents, so close monitoring of these patients is suggested. Cotrimoxazole also inhibits the metabolism of phenytoin. Administration of cotrimoxazole and phenytoin may increase the half life by as much as 39% and decrease the metabolic clearance by as much as 27%.

Sulfonadimides may also displace methotrexate from plasma protein binding sites, resulting in increased free methotrexate concentrations. Nephrotoxicity has been reported in renal transport recipients who were receiving cotrimoxazole and cyclosporine.

Administration of cotrimoxazole and digoxin may also result in increased digoxin levels, which has been reported in geriatric patients.
Annex 1: Summary of selected studies for cotrimoxazole

<table>
<thead>
<tr>
<th>Author</th>
<th>Methods/design</th>
<th>Population</th>
<th>Intervention</th>
<th>Participants</th>
<th>Follow-up</th>
<th>Number of deaths and hospitalisations avoided</th>
<th>Infection: HIV-1 or HIV-2 ( \geq 2 ) or other infection</th>
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<th>Bacteriological response</th>
<th>Isotretinoin</th>
<th>Adverse events</th>
<th>Notes</th>
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<tbody>
<tr>
<td>Anglaret 99</td>
<td>Randomised, double-blind placebo controlled trial</td>
<td>Patients who had symptoms suggestive of Pneumonia or malaria, aged ( \geq 18 ) years and over not receiving treatment at the community chest clinic of Yopougon-Attie.</td>
<td>CTX: 500mg/day or matching placebo</td>
<td>Mean ( n=18 ) months in CPT arm, 9.5 months in placebo arm</td>
<td>120 severe events in intervention group vs 198 in placebo group. 84 participants experienced at least one event with intervention compared to 124 in placebo. Probability of remaining free of severe events after twelve months was 63.7%(0.85) on CPT vs. 48.3%(0.68) on placebo. HR(0.57, 95% CI 0.43-0.75)</td>
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GRADE review for cotrimoxazole

**Author(s):** Amitabh Suthar  
**Date:** 2010-07-26  
**Question:** Should 960mg of cotrimoxazole be used in HIV-infected persons?  
**Settings:** Resource-limited  
**Bibliography:** Anglaret et al. 1999 (14), Wiktor et al. (12), Nunn et al. (13)

<table>
<thead>
<tr>
<th>Quality assessment</th>
<th>Summary of findings</th>
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<tbody>
<tr>
<td><strong>No of patients</strong></td>
<td><strong>960mg of cotrimoxazole</strong></td>
</tr>
<tr>
<td><strong>Deaths/hospitalisations (follow-up 0.46 months)</strong></td>
<td></td>
</tr>
<tr>
<td>No. of studies</td>
<td>Design</td>
</tr>
<tr>
<td><strong>Adverse drug reaction leading to treatment interruption (follow-up 0.46 months)</strong></td>
<td></td>
</tr>
<tr>
<td>No. of studies</td>
<td>Design</td>
</tr>
</tbody>
</table>
Bibliography


