WHO MODEL LIST OF ESSENTIAL MEDICINES APPLICATION

1. Summary statement

The fixed-dose combination of isoniazid (INH) 300mg, pyridoxine (Vitamin B6) 25mg, sulfamethoxazole 800mg, and trimethoprim 160mg is proposed for the prevention of tuberculosis, bacterial pneumonia, malaria, and isosporiasis and to reduce mortality and hospitalisations among adults living with HIV/AIDS (ALHIV).

This fixed dose combination is in development. Professor Dan Smith at Purdue University is conducting a feasibility study assessing the FDC’s stability, whether there are significant chemical interactions among its active and inactive ingredients, and whether the final size of this tablet will be conducive to patient administration. His results will be made publicly available in due course. We strive for WHO prequalification and field uptake of this FDC.

According to the procedure for assessing the acceptability of pharmaceuticals for purchase by United Nations agencies, the WHO prequalification programme will consider only those products that are included in the Expressions of Interest (EOI) lists published by WHO. The Global Fund and PEPFAR also require pharmaceuticals that they procure to be approved by a stringent regulatory body, such as the WHO prequalification programme.

In order to be eligible for an EOI list a medicine must meet one of three criteria: (1) listed on the WHO Model List of Essential Medicines; (2) submitted to the Expert Committee for addition to the Model List (and is deemed promising based on public health need, comparative effectiveness, safety, and cost-effectiveness); or (3) recommended in a current WHO treatment guideline. We hope this application provides sufficient evidence to add this fixed dose combination to the HIV/AIDS 10th Invitation for Expression of Interest for HIV medicinal products.

There is also a need for this FDC to be made available to the paediatric population. The dosing of isoniazid is weight based (5mg/kg) while that of cotrimoxazole is age-based (6 months-5 years 240mg, 5-14 years 480mg, ≥ 14 years 960mg). Use of a scored FDC is currently being investigated for this population.
The principal reasons for requesting inclusion of the adult FDC in the WHO Model List of Essential Medicines are as follows:

1. Cotrimoxazole (Sulfamethoxazole 800mg and trimethoprim 160mg) 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. Isoniazid (300mg daily) preventive therapy (IPT) prevents active tuberculosis in HIV-infected persons, which decreases community cases of tuberculosis. Maximizing IPT coverage and adherence will enhance these individual and population benefits.

3. Pyridoxine is recommended in all HIV-infected persons on INH. It may be difficult for countries to procure and distribute pyridoxine with INH. Including it in the FDC ensures all patients on IPT are on concomitant pyridoxine, thereby preventing INH-induced toxicity.

4. Current WHO Guidelines recommend both CPT and IPT as part of the standard package of care available to ALHIV, on the condition that active TB has been excluded. In most settings CPT is recommended indefinitely while IPT is recommended for at least 6 months.

5. The efficacy of CPT and IPT are compromised by lapses in adherence. Lapses in cotrimoxazole adherence may result in cotrimoxazole-resistant bacteria. Lapses in isoniazid adherence results in inadequate sterilization and the potential development of active tuberculosis. The adherence and effectiveness of CPT and IPT will be improved with a one tablet, rather than three tablet, daily regimen.

6. TB programmes are often responsible for procurement and dissemination of isoniazid. This creates constraints prohibiting HIV programmes from disseminating IPT to eligible HIV-infected persons. Because IPT and CPT are interventions for HIV-infected individuals this FDC should be procured, stored, and disseminated by HIV programmes.

7. Cotrimoxazole that does not go through stringent regulatory approval has the potential for under or over concentration of ingredients, contamination, poor quality ingredients, poor stability, and inclusion of other active ingredients. These issues potentiate population resistance to bacteria, decrease effectiveness, increase adverse reactions, waste scarce fiscal and human capital, and increase morbidity and mortality. The FDC of isoniazid, cotrimoxazole, and pyridoxine will be WHO prequalified prior to its uptake, providing a reliable and safe source of isoniazid, cotrimoxazole, and pyridoxine.
Name of the focal point in WHO submitting or supporting the application
Reuben Granich, WHO/HTM/HIV/ATC

Name of the organization(s) consulted and/or supporting the application
Internally developed application

International Nonproprietary Name (INN, generic name) of the medicine
isoniazid/pyridoxine/sulfamethoxazole/trimethoprim

Formulation proposed for inclusion; including adult and paediatric (if appropriate)
Combination tablet comprised of isoniazid 300 mg, pyridoxine 25 mg, sulfamethoxazole 800 mg, and trimethoprim 160 mg for adult patients.

International availability - sources, if possible manufacturers
This FDC is not currently manufactured. Manufacturers of the FDC’s components are below:

<table>
<thead>
<tr>
<th>INN and dosage</th>
<th>Manufacturer and Country</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoniazid 300mg</td>
<td>WHO prequalified: Macleods Pharmaceuticals Limited, India</td>
</tr>
<tr>
<td></td>
<td>Cadila Pharmaceuticals Ltd., India</td>
</tr>
<tr>
<td></td>
<td>Medical Export Group BV, India</td>
</tr>
<tr>
<td></td>
<td>Svizera Europe, India</td>
</tr>
<tr>
<td>Sulfamethoxazole 800mg +</td>
<td>WHO prequalified: Roche Pharmaceuticals, Switzerland</td>
</tr>
<tr>
<td>Trimethoprim 160mg</td>
<td>Cipla Ltd., India</td>
</tr>
<tr>
<td></td>
<td>Instituto Quimioterapico, Peru</td>
</tr>
<tr>
<td>Pyridoxine 25mg</td>
<td>Joint Medical Store, Uganda</td>
</tr>
</tbody>
</table>

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

Information supporting the public health relevance

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).

In 2008, of 9.4 million incident TB cases there were an estimated 1.4 million cases among people living with HIV. These 1.4 million cases resulted in 500,000 deaths (3). This makes TB the most common cause of death in PLHIV, even among those on antiretroviral therapy.
HIV infection increases the risk of TB is 20-37 fold, depending on the severity of the HIV epidemic, and in some countries in Sub-Saharan Africa up to 80% of patients with TB have HIV (3). Of the estimated 33 million people living with HIV, 68% reside in sub-Saharan Africa, a region heavily affected by TB.

Before antiretroviral therapy and *pneumocystis jirovecii* pneumonia (PCP) prophylaxis were given to PLHIV, PCP occurred in 70-80% of patients with AIDS (4). 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 (5). 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% (5). In resource limited settings where exposures to bacteria are different than in industrialised settings, deaths due to malaria, isosporiasis, *mycobacterium tuberculosis*, and bacterial pneumonia are common in HIV infected persons (6,7). Furthermore, current evidence shows that HIV infection increases the risk of malaria and worsens malaria outcomes while malaria infection increases viremia in HIV-infected individuals.

While antiretroviral therapy has reduced mortality due to HIV, additional simple, safe, and effective interventions are needed to prevent malaria, tuberculosis, 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 4 million people on ART are 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 (8). 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.

One of the goals of the Global Plan to Stop TB (2006-2015) was for 1,200,000 people living with HIV to complete IPT in 2006. Sadly, the WHO’s 2009 update to the Report on Global Tuberculosis Control indicated that at the end of 2007, only 48,000 of the 10 million eligible persons living with HIV (0.48%) were receiving IPT.

There is no information available on the number of persons taking pyridoxine.

### 8.3 Target population

Adults living with HIV without active tuberculosis are eligible for isoniazid preventive therapy and cotrimoxazole.

Some country guidelines recommend cotrimoxazole regardless of immune status while others restrict cotrimoxazole to persons with a CD4 ≤ 350 or ≤ 200 cells/µL. IPT is recommended for HIV-infected adults without active TB.
9. Treatment details
The last revision of the WHO guidelines on cotrimoxazole prophylaxis therapy (CPT, 800 mg of sulfamethoxazole and 160 mg of trimethoprim daily) was published in 2006. These guidelines contain the following recommendations for adults (9):

- 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 $\leq 350$ cells/µL
- Continue cotrimoxazole prophylaxis among adults living with HIV indefinitely

Duration of CPT is country specific, and is sometimes discontinued in the event of a severe adverse event or immunological recovery due to ART. In Uganda, CPT is recommended for all HIV positive adults and children for life, and is discontinued only in the event of a severe adverse event (10).

Isoniazid preventive therapy (IPT) includes administration of 300mg of isoniazid daily. The WHO’s 1998 policy statement on IPT recommends IPT for PLHIV, without active TB infection, who are either (11):
1. Tuberculin sensitivity test (TST) positive,
2. living in populations with a high prevalence of TB infection (estimated to be $> 30\%$),
3. health care workers,
4. household contacts of TB patients,
5. prisoners, or
6. miners

*Note for demographics 2-6 IPT is recommended regardless of PPD status

The WHO’s 2004 ‘Interim Policy on collaborative TB-HIV activities’ recommends that HIV programmes provide IPT as part of the package of care for PLHIV when active tuberculosis is safely excluded (12). This recommendation also states that use of antiretroviral drugs does not preclude the use of IPT.

The WHO’s 2009 ‘Priority Interventions for HIV’ document recommends IPT for all PLHIV without an active TB infection (13). In order to rule out an active infection there are several tuberculosis screening algorithms that have been developed for low and middle income countries without access to radiological and/or microbiological methods of confirmation (14-16).

South Africa’s 2010 IPT guidelines recommend isoniazid 300mg daily in all HIV-infected persons without current cough (24 hours or longer), fever, loss of weight, and drenching night sweats (17).

Pyridoxine is recommended in patients on isoniazid as it is a benign intervention which prevents peripheral neuropathy and other isoniazid toxicities. The dosing of pyridoxine when administered with isoniazid preventive therapy for HIV-infected individuals is 25-50mg daily.
<table>
<thead>
<tr>
<th>Source (Year)</th>
<th>Organisation</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Guidelines for Tuberculosis Preventive Therapy Among HIV Infected Individuals (2010)</td>
<td>Ministry of Health, South Africa</td>
<td>Vitamin B6 (pyridoxine) 25 mg per day should be given concomitantly with isoniazid to prevent the occurrence of peripheral neuropathy.</td>
</tr>
<tr>
<td>Prevention and Treatment of Tuberculosis Among Patients Infected with HIV (1998)</td>
<td>CDC</td>
<td>Pyridoxine (vitamin B6) (25–50 mg daily or 50–100 mg twice weekly) should be administered to all HIV-infected patients who are undergoing TB treatment with isoniazid, to reduce the occurrence of isoniazid-induced side effects in the central and peripheral nervous system.</td>
</tr>
</tbody>
</table>

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

10.1 Identification of clinical evidence

10.1.1 Search strategies

**Daily pyridoxine with isoniazid**: The critical outcome of interest was prevention of adverse events due to pyridoxine.


By title: 0 (No articles on the effect of pyridoxine with isoniazid on preventing adverse events)

Recommendations for isoniazid preventive therapy in HIV-infected adults include a recommendation for pyridoxine 25mg daily (2010 South African guidelines, and 1998 CDC guidelines). Of the studies included in the GRADE review for IPT, three used 50mg of pyridoxine daily in both arms of the randomized studies (18-20) while others did not mention use of pyridoxine.

**Cotrimoxazole Prophylaxis Therapy (cotrimoxazole 960mg daily)**: The critical outcomes of interest were efficacies of CPT on improving survival, decreasing hospitalizations, preventing malaria, preventing isosporiasis, adverse events, and preventing bacterial pneumonia. One study was excluded because it only included an analysis on malaria (21).
The GRADE hierarchy considers randomised controlled trials the best source of evidence. Therefore for survival, malaria, bacterial infections, and isosporiasis the randomised controlled trial was used (22). Unfortunately, the randomised study reported only three adverse events in their randomised study. Because this was not consistent with previous estimates of cotrimoxazole toxicity, data from observational cohorts were used for this outcome (23-26). One Cochrane systematic review was identified for CPT in adults with HIV (27). Study summaries and the GRADE table for cotrimoxazole 960mg daily can be found in Annex 1. The data indicate that CPT decreases episodes of malaria, isosporiasis, bacterial pneumonia, hospitalisations, and prolongs life in adults living with HIV. It is also well tolerated with only 1.5% of patients in the four observational studies (23-26) experiencing an adverse event, most of which were mild and transient.

**Isoniazid Preventive Therapy (isoniazid 300mg daily):** The critical outcomes of interest considered were efficacies of IPT in preventing active TB, death, and adverse events. Limits used in this search were: Clinical Trial, Meta-Analysis, Randomized Controlled Trial, Review, Clinical Trial, Phase I, Clinical Trial, Phase II, Clinical Trial, Phase III, Clinical Trial, Phase IV, Comparative Study, Controlled Clinical Trial, Multicenter Study, Adolescent: 13-18 years, Adult: 19-44 years, Middle Aged: 45-64 years, Middle Aged + Aged: 45+ years, Aged: 65+ years, 80 and over: 80+ years.

With respect to our critical outcomes we found 7 randomised studies (18,28-30,19,20,31). Whalen et al. 1997 stratified their analysis by anergy status (where anergy was defined as a 0mm induration in reaction to both TST and candida antigens)(28), these two analyses are listed as two separate studies. A Cochrane review on IPT in HIV-infected individuals was found (32). Since this review was published in January 2010 it was used to guide our review.
of IPT-related data. Study summaries and GRADE tables for isoniazid 300mg daily are found in Annex 2. The randomised studies included in the Cochrane review indicate that IPT decreases the incidence of active tuberculosis by one third. It is also well tolerated with a pooled risk difference of 0.01 (95% CI 0.0007, 0.0193) in the 7 randomised studies. Clinically this means that 1 out of every 100 patients treated with isoniazid will experience a treatment limiting adverse event due to isoniazid.

10.2 Summary of available estimates of comparative effectiveness and safety

Isoniazid 300mg daily: The Cochrane review addressed comparative effectiveness of INH versus other antibiotics in HIV-infected persons (32). A total of eight studies compared INH alone with other regimens, and found that regimens that included combinations of INH, pyrazinamide (PZA), and/or rifampicin (RIF) were as efficacious as INH alone, but were associated with higher rates of treatment-limiting toxicities:

Comparison of different drug regimen efficacy (outcome is an episode of tuberculosis):

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Comparator</th>
<th>RR (95% CI)</th>
<th>Quality of evidence</th>
<th># of studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>INH</td>
<td>RIF+PZA</td>
<td>1.03 (0.75-1.4)</td>
<td>Moderate</td>
<td>6</td>
</tr>
<tr>
<td>INH</td>
<td>INH+RIF</td>
<td>0.97 (0.52-1.83)</td>
<td>Moderate</td>
<td>5</td>
</tr>
<tr>
<td>INH</td>
<td>INH+RIF+PZA</td>
<td>0.60 (0.23-1.57)</td>
<td>Low</td>
<td>2</td>
</tr>
</tbody>
</table>

*The comparison of INH and placebo has been reviewed in depth in Annex 2.

Comparison of different drug regimen safety (outcome is a treatment-limiting adverse event):

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Comparator</th>
<th>RR (95% CI)</th>
<th>Quality of evidence</th>
<th># of studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>INH</td>
<td>Placebo</td>
<td>1.66 (1.09-2.51)</td>
<td>High</td>
<td>6</td>
</tr>
<tr>
<td>INH</td>
<td>INH+RIF</td>
<td>0.79 (0.50-1.23)</td>
<td>Moderate</td>
<td>4</td>
</tr>
<tr>
<td>INH</td>
<td>RIF+PZA</td>
<td>0.63 (0.48-0.84)</td>
<td>Moderate</td>
<td>5</td>
</tr>
<tr>
<td>INH</td>
<td>INH+RIF+PZA</td>
<td>0.10 (0.03-0.33)</td>
<td>Low</td>
<td>2</td>
</tr>
</tbody>
</table>

Cotrimoxazole 960mg daily: 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. 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 (27).

Pyridoxine 25mg daily: No studies assessed the effect of pyridoxine versus placebo on adverse events.

11. Summary of comparative evidence on safety:

11.1 Results of feasibility study

The study assessing the compatibility of this FDC’s active and inactive ingredients, approximate final size of tablet, and stability in different conditions is ongoing.

11.2 Estimate of total patient exposure to date

There are no sources which indicate total exposure to isoniazid, pyridoxine, or sulfamethoxazole-trimethoprim.
11.3 Description of adverse effects/reactions

**ISONIAZID**

A search in MEDLINE yielded a review of INH adverse events published in 2006 (33). Neurological effects of chronic INH treatment include dysarthria, irritability, dysphoria, inability to concentrate, seizures, hallucinosis, psychosis, memory loss, confusion and altered mental status, ototoxicity, optic neuropathy, and other cranial neuropathies. A more common neurological toxicity related to GABA deficiency is peripheral neuropathy. Peripheral neuropathy appears to be dose related and is seen in 0.2-1.2% of patients not on pyridoxine (34,35). The symptoms are reversible after withdrawal of INH. Pyridoxine 25-50mg daily can prevent occurrence of neuropathy and is recommended in high risk groups (i.e. increased age, slow acetylator status, malnutrition, diabetes, renal failure, heavy alcohol intake, pregnancy, and breastfeeding) and in patients taking INH for extended periods of time (greater than six months). With routine monitoring, asymptomatic elevation in liver enzymes was seen in 10 – 22% of patients on INH during the first 4-6 months of therapy (36-40). These elevated liver enzymes usually resolve, despite drug continuation, although around one fifth of these patients may persistently have elevated transaminases, which return to normal only after stopping the medication.

**COTRIMOXAZOLE**

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 (41). Indeed, Walker et al. reported that 3% of participants experienced an adverse event; all were haematological, rash, or hypersensitivity (25). Wateria et al. reported 29 adverse events in 602 participants exposed to CPT (17 were dermatological (itching or rash), 6 were constitutional, 4 were gastrointestinal, 1 had recurrent oral sores, and 1 bruised easily) (26). The only available randomised study in patients without active tuberculosis (22) indicated three treatment limiting adverse events among the 271 participants given CPT (two episodes of grade 2 morbilliform rashes and one episode of grade 3 hepatitis). The incidence and severity of 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.

**PYRIDOXINE**

Doses of more than 2 grams daily for 2-40 months have been associated with sensory neuropathy (42-44). However, since 2 grams is nearly 100 times the dose of 25mg daily provided in this fixed dose combination, sensory neuropathy is not expected with use of this FDC.

11.4 Identification of variation in safety due to health systems and patient factors

Cotrimoxazole and pyridoxine have been used extensively worldwide. No clinically significant differences in safety have been identified due to differences in health systems and patient factors.

INH is metabolised by two pathways. In the direct pathway the enzyme isoniazid hydrolase hydrolyses INH to isonicotinic acid and hydrazine. In the indirect pathway isoniazid is (1) inactivated by the enzyme N-acetyltransferase to acetylisoniazid (2) hydrolysed to isonicotinic acid and monoacetylhydrazine and (3) acetylated to diacetylhydrazine.

Individuals who have higher N-acetyltransferase enzyme activity, known as ‘fast acetylators’, favour use of only the indirect pathway. Individuals with low levels of N-acetyltransferase
activity, known as ‘slow acetylators’, use the direct pathway some for early INH metabolism and then use the indirect pathway. 90% of Orientals are rapid INH acetylators while 45% of black and white populations are rapid acetylators.

Rapid acetylators may be more susceptible to INH liver injury (45), though subsequent studies have suggested that slow acetylation is a risk factor for hepatotoxicity (34,46,47) or that acetylator status had no impact (48-52).

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

Costing for this FDC is currently unavailable. However, using the lowest unit price/day for each of its components, one year of this FDC would cost approximately 10 dollars / year / patient:

<table>
<thead>
<tr>
<th>Source</th>
<th>Unit Price/Day</th>
<th>Source</th>
<th>Unit Price/Day</th>
<th>Source</th>
<th>Unit Price/Day</th>
</tr>
</thead>
<tbody>
<tr>
<td>IMRES (Netherlands)</td>
<td>0.0196</td>
<td>DURBIN (UK)</td>
<td>0.0056</td>
<td>JMS (Uganda)</td>
<td>0.0026</td>
</tr>
<tr>
<td>IDA (Netherlands)</td>
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<td>GDF (India)</td>
<td>0.0064</td>
<td></td>
<td></td>
</tr>
<tr>
<td>JMS (Uganda)</td>
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<td>MISSION (Denmark)</td>
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<tr>
<td>MEG (Netherlands)</td>
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<td>GDF (India)</td>
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<tr>
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<td>0.0305</td>
<td>IDA (Netherlands)</td>
<td>0.0087</td>
<td></td>
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<tr>
<td>MISSION (Denmark)</td>
<td>0.0308</td>
<td>IMRES (Netherlands)</td>
<td>0.0095</td>
<td></td>
<td></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 (53). Yazdanpanah et al. reported that using CPT would cost USD 200 / life-year gained (54). 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.

When treating patients with isoniazid for nine months, regardless of PPD status, Shrestha et al. used a Markov model to estimate a cost-utility of USD 106/quality adjusted life-year gained in Uganda and found that this treatment approach would produce 30 QALY/100 ALHIV. Since USD 1300 is the per capita income in Uganda this is a cost-effective intervention (55). Bell et al. used a Markov model to estimate that six months of isoniazid preventive therapy will save USD 24 per primary or secondary case prevented with IPT (considering medical care and societal costs), will increase life expectancy and quality adjusted life expectancy, and will reduce TB incidence (56).
13. Summary of regulatory status of the medicine (in country of origin, and preferably in other countries as well)
Isoniazid, sulfamethoxazole-trimethoprim, and pyridoxine are off-patent

Isoniazid, sulfamethoxazole, trimethoprim, and pyridoxine are available in the United States Pharmacopoeia.
Isoniazid, sulfamethoxazole, trimethoprim, and pyridoxine are 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. Isoniazid is an antibiotic used for treatment of mycobacterial infections. Pyridoxine, vitamin B6, is a water soluble vitamin.

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.
Isoniazid has good coverage of M. bovis, M. szulgai, M. gordonae, and M. kansasii. It is also used as a second line agent for M. malmoense, M. scrofulaceum, and M. xenopi. Isoniazid is indicated for the treatment of active and latent M. tuberculosis infections.
Pyridoxine is a water soluble B complex vitamin which is obtained by eating meats, whole grain products, vegetables, nuts, and bananas. Pyridoxine deficiency manifests with neurologic symptoms such as somnolence, confusion, dermatitis, anemia, and neuropathy.

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.
The mechanism of isoniazid is not completely understood although it may work by inhibition of mycolic acid synthesis resulting in disruption of the bacterial cell wall. Isoniazid can be bacteriostatic or bactericidal depending on the concentration at site of action and susceptibility.
Isoniazid depletes pyridoxine supplies by binding to pyridoxine. Pyridoxone is required by GABA transaminase and glutamic acid decarboxylase, which both synthesize GABA.
Pyridoxine is converted to active forms of Vitamin B6, pyridoxal phosphate and pyridoxamine phosphate. These forms act as coenzymes in reactions of intermediary metabolism.
Dosage forms: Tablet comprised of Sulfamethoxazole 800mg, Trimethoprim 160mg, Isoniazid 300mg, and Pyridoxine 25mg
**Indications:** Isoniazid is indicated for the prevention of tuberculosis in HIV-infected patients.

Pyridoxine prevents isoniazid-induced neurological toxicities. Sulfamethoxazole-trimethoprim is used to reduce mortality, infections, and hospitalizations in HIV-infected patients. Therefore, this tablet is indicated for HIV-infected persons without active tuberculosis.

**Pharmacokinetics/Pharmacodynamics:** Time until peak concentration: 2 hours (trimethoprim), 4 hours (sulfamethoxazole), 1-2 hours (isoniazid). For isoniazid, plasma concentrations of the drug in rapid isoniazid inactivators are 20-50% of those in slow isoniazid inactivators. Pyridoxine is absorbed from the GI tract with normal serum concentrations of 30-80 ng/mL.

Distribution: Trimethoprim is approximately 44% and sulfamethoxazole is approximately 70% bound to plasma proteins. Isoniazid is not substantially bound to plasma proteins. The volume of distribution for trimethoprim is 100-120 L, while that of sulfamethoxazole is 12-18 L. The forms of pyridoxine in the blood, pyridoxal and pyridoxal phosphate are highly protein bound.

Half life: 11 hours (trimethoprim), 10 hours (sulfamethoxazole), 30-100 minutes (isoniazid, fast acetylators), 2-5 hours (isoniazid, slow acetylators), 15-20 days (pyridoxine). The half life of trimethoprim increases with renal impairment.

Metabolism: Sulfamethoxazole: Biotransformed to inactive compound by N4-acetylation. Isoniazid and pyridoxine are metabolised in the liver.

Excretion: 60% of free trimethoprim excreted in urine, 84.5% of sulfamethoxazole excreted in urine, 75-95% of isoniazid excreted in urine.

**Contraindications:** Isoniazid is contraindicated in patients with acute liver disease or a history of previous isoniazid associated hepatic injury. Isoniazid, sulfamethoxazole, trimethoprim, and pyridoxine 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.
- The US Food and Drug Administration has given isoniazid a black box warning for the possibility of severe and sometimes fatal hepatitis. This typically occurs within the first three months of treatment, but can develop later.
- Caution should be exercised when administering isoniazid to patients with hepatic and/or renal impairment, in daily users of alcohol, and in individuals who inject illicit drugs.
- Hepatotoxicity and peripheral neuropathy (due to pyridoxine deficiency) can occur with administration of isoniazid.
**Toxicity:**

**ISONIAZID:** A search in MEDLINE yielded a review of INH adverse events published in 2006 (24). Neurological effects of chronic INH treatment include dysarthria, irritability, dysphoria, inability to concentrate, seizures, hallucinosis, psychosis, memory loss, confusion and altered mental status, ototoxicity, optic neuropathy, and other cranial neuropathies. A more common neurological toxicity related to GABA deficiency is peripheral neuropathy. Peripheral neuropathy appears to be dose related and is seen in 0.2-1.2% of patients at conventional doses. The symptoms are reversible after withdrawal of INH. Pyridoxine 25-50mg daily can prevent occurrence of neuropathy and is recommended in high risk groups (i.e. increased age, slow acetylator status, malnutrition, diabetes, renal failure, heavy alcohol intake, pregnancy, and breastfeeding) and in patients taking INH for extended periods of time (greater than six months). With routine monitoring, asymptomatic elevation in liver enzymes will be seen in 10 – 22% of patients on INH during the first 4-6 months of therapy (36-40). These elevated liver enzymes usually resolve, despite drug continuation, although around one fifth of these patients may persistently have elevated transaminases, which return to normal only after stopping the medication.

**COTRIMOXAZOLE:** 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 (41). Indeed, Walker et al. reported that 3% of participants experienced an adverse event; all were haematological, rash, or hypersensitivity (25). Watera et al. reported 29 adverse events in 602 participants exposed to CPT (17 were dermatological (itching or rash), 6 were gastrointestinal, 1 had recurrent oral sores, and 1 bruised easily) (26). The only available RCT in patients without active tuberculosis (22) indicated three treatment limiting adverse events among the 271 participants given CPT (two episodes of grade 2 morbilliform rashes and one episode of grade 3 hepatitis). The incidence and severity of 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.

**PYRIDOXINE:** Doses of more than 2 grams daily for 2-40 months have been associated with sensory neuropathy (26) (27) (28). However, since this is nearly 100 times the dose of 25mg daily provided in this fixed dose combination this toxicity is not expected.

**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 the incidence in pregnant women who received 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.

Isoniazid has been reported to induce pulmonary tumors in animals; however, there is no evidence to date to support carcinogenic effects in humans. The American Thoracic Society (ATS), US Centers for Disease Control and Prevention (CDC), and Infectious Diseases Society of America (IDSA) state that isoniazid is considered safe for use in pregnant women, but the risk of hepatitis may be increased in the peripartum period.

Effects of pyridoxine on pregnancy outcomes have not been explored.
Drug Interactions

*Isoniazid:* Isoniazid is an inducer of cytochrome P450 (CYP) 2E1. It inhibits CYPs 1A2, 2A6, 2C9, 2C19, 2D6, 2E1, and 3A4. Since carbamazepine is a CYP 3A4 substrate its concentrations may increase with isoniazid administration, resulting in ataxia, headache, vomiting, blurred vision, drowsiness, and confusion. These symptoms will subside after discontinuation of INH or dose reduction of carbamazepine. Since phenytoin is a 2C19 substrate its concentrations may increase with isoniazid administration, resulting in phenytoin toxicity. Phenytoin toxicity may also arise in slow isoniazid inactivators.

Because isoniazid might have some MAO inhibiting activity, when it is used with selective serotonin reuptake inhibitors patients should be monitored for serotonin syndrome. Isoniazid should be administered at least one hour before aluminium hydroxide because this antacid decreases GI absorption of isoniazid. As a result of probable alterations in dopamine metabolism, patients receiving isoniazid and disulfiram have experienced coordination difficulties and psychotic episodes.

*Cotrimoxazole:* 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%. Given the increased risk of phenytoin toxicity with isoniazid, it is critical to monitor phenytoin levels and adjust the dose as needed with the fixed dose combination of isoniazid, cotrimoxazole, and pyridoxine.

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. Therefore, patients on this fixed dose combination and digoxin should be monitored closely.

*Pyridoxine:* No known drug interactions.
Annex 1: Summary of selected studies for cotrimoxazole
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<th>Author</th>
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<tr>
<td>Anglaert 99</td>
<td>Randomised, double-blind placebo controlled trial. Blocked randomisation (in blocks of four) by independent statistician to assign eligible patients to one of the study regimens. Sequentially numbered sealed packages containing the treatment assigned were prepared by an independent pharmacy.</td>
<td>545 HIV infected persons aged 18 years and over not on ART in Abidjan, Cote d'Ivoire at the community clinic of Yopougon-Anie, 271 given intervention 270 given placebo.</td>
<td>CTX 960mg daily or matching placebo</td>
<td>Mean 9.6 months in CPT arm, 9.3 months in placebo arm</td>
<td>Inclusion: HIV-1 or HIV-2 with WHO stage 2 or 3 infection. Exclusion: WHO stages 1 and 4, current pregnancy or breastfeeding, previous history of sulfa intolerance, Hgb &lt; 7g/dl, PLT &lt; 75<em>10^9/L, absolute neutrophil count &lt; 0.75</em>10^9/L, and renal/hepatic failure</td>
<td>Severe events death or hospital admission. 120 severe events in intervention group. 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% (of 95 on CPT) vs. 45.8% (of 98 on placebo) (HR 0.57, 95% CI 0.43-0.75)</td>
<td>2 on CPT, 20 on placebo HR 0.07 (0.01, 0.56)</td>
<td>2 on CPT, 11 on placebo HR 0.19 (0.04, 0.86)</td>
<td>3 on CPT, 26 on placebo HR 0.16 (0.04, 0.73)</td>
<td>There were three treatment limiting adverse events. Two episodes of grade 2 morbilliform rash and one episode of grade 3 hepatitis for CPT arm. More patients lost to follow up in the placebo group than in the CPT group. Although the difference was not statistically significant.</td>
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<td>Mermin 04</td>
<td>Sequential observational cohort study, six months unexposed to CPT vs. eighteen months exposed to CPT</td>
<td>HIV infected persons in Uganda who were enrolled in HIV treatment and care with The AIDS Support Organization. Median age was 34 years (IQR 28-40)</td>
<td>CTX 960mg daily or none</td>
<td>Median follow up was 154 days (IQR 146-162) without CPT and 535 days with CPT (IQR 471-539)</td>
<td>All HIV infected persons at The AIDS Support Organization were eligible for participation in the study. Those who died before the study started, withdrew, or refused were not included</td>
<td>79 deaths during 545 PY of follow up on CPT and 61 deaths during 232 PY of follow up off CPT (HR 0.54, 95% CI 0.35, 0.84)</td>
<td>Not analysed</td>
<td>Not analysed</td>
<td>Not analysed</td>
<td>Of the 2205 participants in the study 48 had an indeterminate HIV test, 63 had moved or were unreachable, 36 had died, 21 refused HIV testing, and 6 did not follow up for other reasons.</td>
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<tr>
<td>Watera 06</td>
<td>Sequential observational cohort study, mortality and malaria were compared for patients who were off CPT for one year and then on CPT for one year</td>
<td>HIV infected adults attending 2 clinics in Uganda, HIV-1 infected persons willing to attend study clinics whenever all are assessed noninvasively at six monthly visits.</td>
<td>CTX 960mg daily or none</td>
<td>12 months for CPT exposed and for CPT unexposed, 762 person-years follow up on CPT and 701 person-years follow up off CPT</td>
<td>&gt;15 years of age, 936 included in analysis. 1152 patients were on CPT and 219 were excluded for not attending clinic providing 953 for the analysis.</td>
<td>158 deaths during 701 person-years of follow up for patients on CPT. 139 deaths during 762 person-years of follow up for patients on CPT. The adjusted HR for mortality with CPT exposure was 0.76 (95% CI 0.60, 0.96).</td>
<td>Not analysed</td>
<td>Not analysed</td>
<td>Not analysed</td>
<td>21 episodes of malaria during 701 PY on CPT. 7 episodes of malaria during 762 PY on CPT. The adjusted HR for malaria with CPT exposure was 0.31 (95% CI 0.13, 0.72). 29: AE in 602 patients exposed to CPT. 17 were dermatological (itching or rash), 6 were constitutional, 4 were gastrointestinal, 1 had recurrent oral sores, and 1 bruised easily. 1 person was lost to follow up off CPT and six persons were lost to follow up on CPT.</td>
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<tr>
<td>Walker 10</td>
<td>Observational analysis from a randomised study comparing laboratory and clinical monitoring versus clinical monitoring alone</td>
<td>HIV-infected adults who were receiving care at the Medical Research Council (Uganda), the Joint Clinical Research Centre (Uganda), and the University of Harare (Zimbabwe)</td>
<td>CTX 960mg daily or none</td>
<td>8128 PY of follow up on CPT and 6086 PY of follow up off CPT</td>
<td>WHO stage 2-4 HIV-infected adults (≥ 18 years) with CD4 ≤ 200 without previous ART</td>
<td>83 deaths during 8128 PY of follow up on CPT and 105 deaths during 6086 PY of follow up off CPT (OR 0.65, 95% CI 0.50, 0.85)</td>
<td>Not analysed</td>
<td>Not analysed</td>
<td>2362 events total (27 per 100 person-years), OR 0.67 (0.53, 0.88)</td>
<td>22 (7%) adverse events were CTX related (all were hematological, rash, or hypersensitivity) 7% of all participants were lost to follow up. Censoring due to loss of follow up was very low and the effect of this censoring by additional weighting was very small.</td>
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<td>Lowrance 07</td>
<td>Retrospective cohort study of 11 ART clinics that were or were not administering CPT.</td>
<td>HIV-infected Malawians who received HIV care at Malawian clinics</td>
<td>CTX 960mg daily or 480mg twice daily at 5 ART centres, no CPT at 6 ART centres</td>
<td>Six months for both exposure cohorts</td>
<td>Adults ≥ 15 years with WHO stage 3-4 HIV infection or CD4 ≤ 200</td>
<td>57 deaths in 535 persons on CPT, 73 deaths in 406 persons off CPT (RR 0.69, 95% CI 0.43, 0.82)</td>
<td>Not analysed</td>
<td>Not analysed</td>
<td>Not analysed</td>
<td>Of 574 patients who were provided with CPT 22 defaulted and 17 transferred out. Of 478 patients not on CPT 55 defaulted and 21 transferred out.</td>
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</table>
GRADE review for cotrimoxazole

**Author(s):** Amitabh Sutah

**Date:** 2010-06-21

**Question:** Should 960mg of cotrimoxazole be used in HIV-infected persons without active tuberculosis?

**Settings:** Resource-limited

**Bibliography:** Anglaret et al. 1999 (22), Lowrance et al. 2007 (23), Mermin et al. 2004 (24), Walker et al. 2010 (25), Watera et al. 2006 (26)

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<td>Mortality/hospitalisations (follow-up mean 9.55 months)</td>
<td></td>
<td></td>
<td></td>
<td>none</td>
<td>no serious imprecision</td>
<td>no serious limitations</td>
<td>randomised trials</td>
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| | | | | | | | |

| Adverse events (follow-up 6-50 months) | | | | none | no serious imprecision | no serious limitations | observational studies | 4 |

| | | | | | | | | |
| | | | | | | | |

| Malaria (follow-up mean 9.55 months) | | | | strong association | no serious limitations | no serious limitations | randomised trials | 1 |

| | | | | | | | | |
| | | | | | | | |

| Bacterial pneumonia (follow-up mean 9.55 months) | | | | strong association | no serious limitations | no serious limitations | randomised trials | 1 |

| | | | | | | | | |
| | | | | | | | |

| Isosporiasis (follow-up mean 9.55 months) | | | | strong association | no serious limitations | no serious limitations | randomised trials | 1 |

| | | | | | | | | |
| | | | | | | | |

1 Only one randomised trial
2 Because there were 0 adverse events in the control group it was impossible to quantify an accurate RR. An absolute measure of effect, RD, was used in its stead.
3 Wide confidence interval
4 Large effect measure in patients exposed to CTX 960mg daily (i.e. HR <0.5)
Annex 2: Summary of selected studies for isoniazid
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<th>Active TB (suspected, probable, confirmed)</th>
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<td>Pape 1993 (Haiti)</td>
<td>118 individuals randomized using computer generated numbers</td>
<td>Blinding: providers no, participants no, assessors yes. HIV positive patients living in Haiti</td>
<td>1) Pyridoxine 50 mg, daily for 12 months. 2) INH 300mg, plus pyridoxine 50 mg daily for 12 months.</td>
<td>Inclusion criteria: Adults 18 to 65 years, symptom free, newly diagnosed as HIV positive (ELISA confirmed by western blot). Consent - non mentioned. Exclusion Criteria: History of TB, abnormal chest x-ray or liver function tests. Intention to treat analysis</td>
<td>Progression to clinical TB was more rapid in the B6 group than in the INH (p=0.015). Reported 71% TB risk reduction in the entire population and 83% in PPD+ The OR for development of TB with INH prophylaxis was 5.7 in PPD+ and 1.68 in PPD-. Mean duration of follow-up was 36 months.</td>
<td>71% TB risk reduction in the placebo group (5.0%) 22 on placebo (6.8%) 31 on INH (7.8%)</td>
<td>NA</td>
<td>No loss to follow up</td>
<td>Anergy screen included mumps, staphylococcus and candida. The % of PPD+ in the INH plus pyridoxine group was significantly higher than the placebo group (66% vs. 38%).</td>
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<td>Whalen 1997 (Uganda)</td>
<td>2018 individuals randomized in blocks of 6; sequentially numbered, sealed opaque envelopes</td>
<td>Blinding: providers no, participants no, assessors yes. PPD+ adults attending clinics or counselling centres for persons with HIV-1 infection in Kampala.</td>
<td>1) Control (Placebo) 250mg ascorbic acid daily for 6 months. 2) INH 300mg daily for 6 months.</td>
<td>Inclusion criteria: Adults (18 to 50 years) with HIV-1 infection (ELISA test), PPD &gt;=5mm, Karnofsky performance score &gt;50, verbal consent. Exclusion Criteria: Active TB, previous treatment for TB, use of antiviral drugs, anemia, liver or kidney disease, pregnancy test, home &gt;20km from project clinic, advanced HIV disease, serious medical illness not related to HIV. Intention to treat analysis</td>
<td>RR of TB with INH alone was 0.33. When the analysis was restricted to definite, culture-confirmed cases among the PPD+ cohort, the RR of TB with INH was 0.22 (95% CI 0.06 to 0.77). Mean duration of follow-up was 15 months.</td>
<td>There was no significant difference between placebo and each treatment with regard to either the mortality rate or the cumulative proportion of deaths (p-value = 0.2 by the log-rank test)</td>
<td>23 on placebo (5.0%) 60 on INH 60 (11.2%)</td>
<td>No loss to follow up</td>
<td>The long-term results of this study are published in Johnson 01.</td>
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<td>Whalen 1997- anergy (Uganda)</td>
<td>Methods 718 individuals randomized in blocks of 6; sequentially numbered, sealed opaque envelopes</td>
<td>Blinding: providers no, participants no, assessors yes. Anergic adults attending clinics or counselling centres for persons with HIV-1 infection in Kampala.</td>
<td>1) Control (placebo) Ascorbic acid 250mg daily for 6 months. 2) INH 300mg daily for 6 months.</td>
<td>As in Whalen 97 except patients had to be anergic. Anergy was defined as 0mm induration in reaction to both PPD and candida antigens. Intention to treat analysis</td>
<td>The cumulative incidence of tuberculosis was similar in the placebo and INH groups (P 0.68 by the log-rank test) (Fig 1B). The RR of TB in the INH group was 0.83, but the wide CI did not exclude the hypothesis of no difference in incidence rates. The RR of definite TB was 0.75 (95% CI, 0.20 to 2.79). Mean duration of follow-up was 12 months.</td>
<td>There was no significant difference between placebo and each treatment with regard to either the mortality rate or the proportion of deaths</td>
<td>22 on placebo (6.8%) 31 on INH (7.8%) 103 (14%) lost to follow-up</td>
<td>The long-term results of this study are published in Johnson 01.</td>
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<td>Hawken 1997 (Kenya)</td>
<td>684 individuals randomized using computer generated random numbers, permuted blocks of 10</td>
<td>Blinding: providers yes, participants yes, assessors unclear. HIV-1 positive commercial sex workers and patients attending STD clinics in Nairobi.</td>
<td>1) Control (Placebo) daily for 6 months. 2) INH 300mg daily for 6 months.</td>
<td>Inclusion criteria: HIV-1 positive (two ELISA tests), local residents, age 14-65 years. Consent - not mentioned. Exclusion criteria: Past history of TB, current TB suspected, abnormal liver enzymes, life threatening intercurrent illness, pregnant. 98% included in analysis.</td>
<td>25 episodes in INH arm, 23 in placebo arm. TB incidence was 4.29 per 100 PY of observation (95% CI, 2.7–6.33) on INH and 3.86 per 100 PY of observation in the placebo group (95% CI, 2.45–5.79). The adjusted RR for INH versus placebo of 0.92 (95% CI, 0.49–1.71). Median duration of follow-up was 1.83 years.</td>
<td>The mortality rate in INH group was 10.64 per 100 PY of observation (95% CI, 8.29–13.65) and in the placebo group 9.58 per 100 PY of observation (95% CI, 7.39–12.42) giving a crude mortality RR for INH vs placebo of 1.11 (95% CI, 0.77–1.58).</td>
<td>151 (22%) lost to follow-up</td>
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<td>Gordin 1997 (USA)</td>
<td>517 individuals, centralized randomisation, stratified by study unit, permuted blocks</td>
<td>Blinding: providers yes, participants yes, assessors yes.</td>
<td>HIV positive patients attending AIDS research clinics in the US.</td>
<td>1) Control (Placebo) plus pyridoxine 50mg daily for 6 months. 2) INH 300mg plus pyridoxine 50mg daily for 6 months.</td>
<td>Intention to treat analysis</td>
<td>Inclusion criteria: Anergy (PPD less than 5mm induration AND less than 2mm induration to mumps antigen and tetanus toxoid); age &gt;= 13 years; no active TB; written consent. Exclusion Criteria: house hold TB contact in past year, on drugs with activity against TB, acute hepatitis, peripheral neuropathy, history of positive PPD, intolerance to study drug, treatment for &gt;= 1 month with drug active against TB.</td>
<td>Mean duration of follow-up 33.5 months.</td>
<td>Confirmed TB developed in 3 of the 260 patients in INH group and 6/257 patients in the placebo group (rates per 100 patient-years of follow-up, 0.4 and 0.9, respectively; relative risk, 0.48; 95% confidence interval, 0.12 to 1.91; P=0.30). All the cases of TB occurred after 6 months or more after randomization and after study medicine had been discontinued.</td>
<td>129/260 patients on INH died, as compared with 126/257 patients on placebo (RR 0.96; p=0.76).</td>
<td>29 in INH (11.2%) and 30 patients in the placebo group (11.7%) had reportable adverse drug reactions</td>
<td>34 (7%) lost to follow-up</td>
<td>Conducted in 1980s to the early 1990s, when TB control was ineffective in the USA</td>
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<tr>
<td>Mwanga 1998 (Zambia)</td>
<td>1053 individuals assigned using computer generated random method and blocks of 30; serially numbered</td>
<td>Blinding: providers yes, participants yes, assessors yes.</td>
<td>HIV positive patients in Luosha, Zambia.</td>
<td>1) Placebo twice a week for 6 months or 3 months. 2) INH 900 mg, twice a week, for 6 months. 3) Rif+PZA</td>
<td>98% included in analysis</td>
<td>Inclusion criteria: HIV positive (2 positive ELISA tests); over 15 years of age; written consent. Exclusion Criteria: Previous history of treatment of TB; abnormal liver function tests; evidence of TB; pregnant; unable to attend study clinic.</td>
<td>Median duration of follow-up 1.8 years.</td>
<td>The incidence of TB was lower in those subjects on IPT (H and RZ groups combined) compared with those on placebo (rate ratio = 0.60, 95% CI: 0.36–1.01, P = 0.057), as was the incidence of TB/probable TB (rate ratio = 0.60, 95% CI: 0.40–0.89, P = 0.013). The effect of IPT was greater in those with a TST of 5 mm or greater.</td>
<td>29 subjects (3%) were withdrawn from the study because of adverse drug reactions</td>
<td>332 (32%) lost to follow-up</td>
<td>The long-term results of this study are published in the Quigley 01</td>
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<tr>
<td>Fitzgerald 2001 (Haiti)</td>
<td>237 individuals randomized</td>
<td>Blinding: providers yes, participants unclear, assessors unclear.</td>
<td>HIV positive, PPD negative individuals living in Haiti.</td>
<td>1) Control (placebo) plus pyridoxine (vitamin B6): 50 mg daily for 1 year. 2) INH 300 mg per pyridoxine 50 mg daily for 1 year.</td>
<td>Intention to treat analysis</td>
<td>Inclusion criteria: Age &gt;=18 years; HIV symptomfree (CDC category A); PPD &lt;5mm induration; informed consent; negative sputum examination results; homeless and culture; negative chest X-ray, no history of TB. Exclusion Criteria: Positve TB reaction.</td>
<td>Mean duration of follow-up 2.5 years.</td>
<td>4 cases of TB in patients on pyridoxine (1.5 cases/100 PY), 6 cases for patients on isoniazid and pyridoxine (1.9 cases/100 PY). This led to a RR of 1.05 (95% CI 0.36-4.37).</td>
<td>19 patients on isoniazid died (6.0 deaths/100 PY), while 15 patients on pyridoxine died (5.7 deaths/100 PY); RR 1.05 (95% CI 1.00, 3.6-4.37).</td>
<td>NA</td>
<td>54 (23%) lost to follow-up</td>
<td>Notes: All patients were treated for opportunistic infections but none were on ART/91% had +ve reactions to candida + mumps</td>
</tr>
<tr>
<td>Rivero 2003 (Spain)</td>
<td>319 individuals randomized</td>
<td>Blinding: providers no, participants no, assessors unclear.</td>
<td>HIV positive anergy patients attending hospitals in Spain.</td>
<td>1) Control (No treatment) 2) INH 5 mg/kg (max 300 mg) daily for 6 months. 3) Rif+INH 4 Rif+PZA</td>
<td>Intention to treat analysis</td>
<td>Inclusion criteria: Confirmed HIV infection; age 18-65 yrs; anergy (defined as 0mm induration after 48-72 hrs to 3 antigens applied by the Mantoux method; PPD, candida albicans and mumps antigents). Consent: none mentioned. Exclusion Criteria: Presence of active TB; previous treatment or chemoprophylaxis for TB; history of hypersensitivity to study drugs; ALT &gt; 4x normal values; Bilirubin &gt; 2 mg/ml; Creatinine &gt; 2 mg/ml; pregnancy.</td>
<td>Mean duration of follow-up 1.23 years.</td>
<td>11 cases of TB (7 confirmed TB), 3 on INH, 1 on Rif+INH, 1 on Rif+PZA, and 4 on placebo. Median time to TB 14.5 months after treatment completion. INH 3.4 cases/100 PY; Placebo 3.1 cases /100 PY. Mortality in placebo arm was 14.3% while in treatment arm (18/234) was 7.7% (p = 0.08).</td>
<td>34 had treatment interruption because adverse reaction, no significant differences were detected between the groups</td>
<td>17 (5%) lost to follow-up</td>
<td>20</td>
<td></td>
</tr>
</tbody>
</table>
**GRADE review for isoniazid**

**Author(s):** Amitabh Suthar  
**Date:** 2010-07-12

**Question:** Should isoniazid 300mg daily be used in HIV-infected individuals (any PPD) without active tuberculosis?

**Settings:** Resource limited with high TB prevalence (>30% latently infected)


<table>
<thead>
<tr>
<th>No of studies</th>
<th>Design</th>
<th>Limitations</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Other considerations</th>
<th>Summary of findings</th>
</tr>
</thead>
<tbody>
<tr>
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<tr>
<td><strong>Active tuberculosis incidence (probable, possible, or confirmed) (follow-up 1.3 years)</strong></td>
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<tr>
<td>6</td>
<td>randomised trials</td>
<td>no serious limitations</td>
<td>no serious inconsistency</td>
<td>no serious indirectness</td>
<td>no serious imprecision</td>
<td>none</td>
<td>123/1984 (6.2%)</td>
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<td></td>
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<td></td>
<td></td>
<td>20 fewer per 1000 (from 6 fewer to 30 fewer)</td>
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<td></td>
<td>0 fewer per 1000 (from 0 fewer to 0 fewer)</td>
</tr>
<tr>
<td>No of patients</td>
<td>Isoniazid 300mg daily</td>
<td>control</td>
<td>Relative (95% CI)</td>
<td>Absolute</td>
<td>Quality</td>
<td>Importance</td>
<td></td>
</tr>
<tr>
<td>85/2182 (3.9%)</td>
<td>0%</td>
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<tr>
<td><strong>Confirmed tuberculosis (follow-up 1.3 years)</strong></td>
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<tr>
<td>5</td>
<td>randomised trials</td>
<td>no serious limitations</td>
<td>no serious inconsistency</td>
<td>no serious indirectness</td>
<td>no serious imprecision</td>
<td>none</td>
<td>47/1026 (4.6%)</td>
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<td></td>
<td></td>
<td>13 fewer per 1000 (from 2 fewer to 5 more)</td>
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<td></td>
<td></td>
<td>0 fewer per 1000 (from 0 fewer to 0 more)</td>
</tr>
<tr>
<td>No of patients</td>
<td>Isoniazid 300mg daily</td>
<td>control</td>
<td>Relative (95% CI)</td>
<td>Absolute</td>
<td>Quality</td>
<td>Importance</td>
<td></td>
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<tr>
<td>34/1037 (3.3%)</td>
<td>0%</td>
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<tr>
<td><strong>Mortality (any cause) (follow-up 1.3 years)</strong></td>
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<tr>
<td>7</td>
<td>randomised trials</td>
<td>no serious limitations</td>
<td>no serious inconsistency</td>
<td>no serious indirectness</td>
<td>no serious imprecision</td>
<td>none</td>
<td>441/1984 (21.1%)</td>
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<td>11 fewer per 1000 (from 32 fewer to 13 more)</td>
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<td></td>
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<td>0 fewer per 1000 (from 0 fewer to 0 more)</td>
</tr>
<tr>
<td>No of patients</td>
<td>Isoniazid 300mg daily</td>
<td>control</td>
<td>Relative (95% CI)</td>
<td>Absolute</td>
<td>Quality</td>
<td>Importance</td>
<td></td>
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<tr>
<td>427/2162 (19.8%)</td>
<td>0%</td>
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<tr>
<td><strong>Adverse drug reaction leading to treatment interruption (follow-up 1.3 years)</strong></td>
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<tr>
<td>7</td>
<td>randomised trials</td>
<td>no serious limitations</td>
<td>no serious inconsistency</td>
<td>no serious indirectness</td>
<td>no serious imprecision</td>
<td>none</td>
<td>331/1973 (1.8%)</td>
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<td>12 more per 1000 (from 2 more to 27 more)</td>
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<td></td>
<td>0 more per 1000 (from 0 more to 0 more)</td>
</tr>
<tr>
<td>No of patients</td>
<td>Isoniazid 300mg daily</td>
<td>control</td>
<td>Relative (95% CI)</td>
<td>Absolute</td>
<td>Quality</td>
<td>Importance</td>
<td></td>
</tr>
<tr>
<td>55/2026 (2.8%)</td>
<td>0%</td>
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</tr>
</tbody>
</table>

1 Inconsistent direction of effect across studies
Bibliography


