WHO MODEL LIST OF ESSENTIAL MEDICINES APPLICATION

21st January 2013

1. Summary statement

The fixed-dose combination of isoniazid (INH) 300mg, pyridoxine (Vitamin B6) 25 mg, sulfamethoxazole 800mg, and trimethoprim 160mg is proposed. It will prevent tuberculosis, bacterial pneumonia, malaria, and isosporiasis; and reduce mortality and hospitalisations among adults and children living with HIV/AIDS (PLHIV). This formulation is not yet commercially available, but is currently being manufactured.

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. WHO has listed this fixed-dose combination of isoniazid, pyridoxine, sulfamethoxazole, and trimethoprim in the 10th Invitation for Expression of Interest for HIV medicinal products, and we therefore now propose its consideration for inclusion on the Essential Medicines list. The principal reasons for requesting inclusion of a FDC (in adults and children) in the WHO Model List of Essential Medicines are as follows:

1. Current WHO Guidelines recommend both cotrimoxazole preventive therapy (CPT) and isoniazid preventive therapy (IPT) as part of the standard package of care available to PLHIV, 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 and for a longer duration for specific groups populations, settings or where evidence results in changing the balance of risk-benefit.[1]

2. 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.

3. 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.

4. 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.

5. Several large trials have found fixed dose combinations improve compliance, particularly in individuals with chronic conditions. [2, 3]

6. 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.

7. TB programmes are often responsible for procurement and distribution 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.

8. IPT uptake lags behind CPT uptake. Combining this drug may help to improve isoniazid uptake.

9. A fixed dose combination will reduce the pill-burden in PLHIV who are concomitantly taking multiple medications for treatment of HIV.

10. 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.

2. Name of the focal point in WHO submitting or supporting the application
Lisa J. Nelson, WHO/HTM/HIV/TAC

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

4. International Non-proprietary Name (INN, generic name) of the medicine
isoniazid/pyridoxine/sulfamethoxazole/trimethoprim

5. 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. This formulation can be provided in ½ or ¼ tablet for children.

6. International availability - sources, if possible manufacturers

This FDC is currently being manufactured by CIPLA for use in a clinical trial involving adults and children. The REALITY Trial (Reduction of Early MortaLITY in HIV-infected adults and children starting antiretroviral therapy), sponsored by MRC, aims to recruit 1800 adults, adolescents and children in Uganda, Zimbabwe, Malawi, and Kenya to look at strategies to reduce early mortality. Better prevention of opportunistic infections is one strategy being investigated. Study recruitment will begin in early 2013. A summary of the trial is available at: http://www.ctu.mrc.ac.uk/research_areas/study_details.aspx?s=270.

A recent update from CIPLA, (email correspondence from Viraj Metha, Medical Services 9/1/2013), states that the product is at a preliminary stage. One batch has been manufactured for scale up, and further regulatory studies are planned.

Manufacturers of the FDC's components are below:

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

7. 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)

8. Information supporting the public health relevance

8.1 Epidemiological information on disease burden

HIV infection increases the risk of TB 20-37 fold, depending on the severity of the HIV epidemic,[4] and in some countries in Sub-Saharan Africa up to 77% of new patients with TB have HIV.[5]

In 2011 there were 34.0 million people living with HIV/AIDS(PLHIV) Globally: [6]

- 2.5 million were new infections
- 95% of the 34. million were in low and middle income countries
- 79% reside in sub-Saharan Africa, a region heavily affected by TB.
- 3.44 million(only 10%) were screened for TB
- 1.1 million people with active TB were HIV positive, of these 1.1 million cases 430,000 resulted in death. This makes TB the most common cause of death in PLHIV, even among those on antiretroviral therapy.]
- 2.3 million PLHIV were therefore eligible for IPT
- It is estimated that 0.45million people were prescribed IPT in 2011 [5]
- 79% of HIV positive TB patients were on CPT [3]

Before antiretroviral therapy and *Pneumocystis jirovecii* pneumonia (PCP) prophylaxis were given to PLHIV, PCP occurred in 70-80% of patients with AIDS.[7] Among those with significant immunosuppression, approximately 20-40% dies. The majority of PCP cases occur in patients who are unaware of their HIV infection or not receiving HIV care regularly.[8] 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 and other pathogens are different than in industrialised settings, deaths due to malaria, isosporiasis, *mycobacterium tuberculosis,* and bacterial pneumonia are common in HIV infected persons.[9, 10] 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 of the FDC is on-going as part of a clinical trial (see above);however, estimations of current usage of its components are as follows**:**

The WHO does not routinely collect statistics on the PLHIV without active TB who are also taking cotrimoxazole. The majority of the 8 million people on ART are eligible for cotrimoxazole. According to the most recent Global TB Report, 79% (410,000) of patients with TB and HIV received CPT in 2011. [5]

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. 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 nationwide implementation. 51% of responding countries had a national IPT policy, with 28% indicating nationwide implementation.[11]

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. According to the most recent Global TB Report, 3.2 million people were reported to have been screened for TB among 29 countries reporting, only 450,000 persons were receiving IPT, including 373,000 in South Africa alone. This represents a small proportion of PLHIV who would potentially have been eligible for the FDC cotrimoxazole/isoniazid/pyridoxine.

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

Target populations: In general the target population for this FDC is PLHIV in whom active TB has been excluded.. More specific populations are detailed in the table below,

Isoniazid, cotrimoxazole and pyridoxine remain on the EML as separate components and should be given in instances where these drugs are not required at the same time. The inadvertent administration of the combined formulation where only one component is primarily recommended would not however be harmful, since both IPT and CPT are conditionally recommended as lifelong medications for PLHIV in high burden settings. In fact, recent studies have found that the efficacy of IPT in preventing TB is reduced when it is stopped.[12, 13] In addition although some countries recommend stopping CPT when PLHIV commence ART and have a CD4 of > 200 cells, Campbell et al found that continuing CPT while on ART and CD4>200 was associated with reduced incidences of malaria and diarrhoea.[14]. A systematic review found that CPT given while taking ART significantly improved mortality and morbidity in PLHIV on ART[15] The case for co-administration of CPT and IPT beyond 6 months and for PLHIV with CD4 counts >350 cells and/or on ART is also supported in a memorandum from Dr Charles Gilks [16]

<table>
<tr><th>Target Population (Resource limited settings)</th><th>CPT Guidelines 2006[17]</th><th>IPT Guidelines 2011[1]</th><th>Conditions for extended use</th><th>FDC suitable</th></tr>
<tr><td>Children over 1 year with HIV in whom TB excluded with symptom-based screening</td><td>CPT for symptomatic children or children with CD4 <25% should continue until the age of five years, when they can be reassessed.</td><td>IPT for children with HIV over 1 who are unlikely to have active TB on symptom-based screening receive six months of IPT</td><td rowspan="2">In countries with a high burden of mortality and morbidity due to malaria and bacterial infections), CPT may be offered to children with HIV in all clinical stages, including asymptomatic children irrespective of their CD4 level[17]</td><td>6 months FDC then single dose cotrimoxazole</td></tr>
<tr><td>Children > 5yrs</td><td>Adult clinical staging and CD4 count thresholds for CPT initiation or discontinuation apply to children older than five years of age</td><td></td><td>6 months FDC then single dose cotrimoxazole.</td></tr>
<tr><td>Adults and adolescents living with HIV in whom active TB has been excluded using a clinical algorithm</td><td>The general recommendation is to continue CPT among adults living with HIV indefinitely</td><td>Adults and adolescents living with HIV unlikely to have active TB based on clinical screening should be offered IPT for at least 36 months in high burden settings.</td><td>in settings with high prevalence of HIV and limited health infrastructure, countries may offer CPT to everyone living with HIV (universal option), because of operational simplicity and data suggesting a reduction of severe events irrespective of CD4 count or clinical stage</td><td>FDC for at least 36 months or indefinitely</td></tr>
<tr><td colspan="5">Pyridoxine is recommended for all PLHIV taking Isoniazid</td></tr>
</table>

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:[17] 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

These guidelines are scheduled to be updated in 2013.

At present, the duration of CPT varies by country-specific guidelines, and is sometimes discontinued in the event of immunological recovery due to ART. CPT should always be discontinued in the event of a severe hypersensitivity reaction. 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.

Isoniazid preventive therapy (IPT) includes administration of 300mg of isoniazid daily for adults and 10mg/kg for children (range 7-15mg/kg; maximum 300mg).
In 2011, WHO released the revised "Guidelines for intensified tuberculosis case-finding and isoniazid preventive therapy for people living with HIV in resource-constrained settings". [1] Key recommendations of these guidelines which relate to IPT and which followed the GRADE process are

-Adults and adolescents living with HIV should be screened with a clinical algorithm and those who do not report any one of: current cough, fever, weight loss or night sweats are unlikely to have active TB and should be offered IPT if they have unknown or positive skin test
(Strong recommendation, moderate quality evidence)

-Children living with HIV who have any one of poor weight gain, fever, current cough or contact history with a TB case may have TB and should be evaluated for TB and other conditions. If the evaluation shows no TB, children should be offered IPT regardless of their age. (Strong recommendation, low quality evidence)

-Children over 12 months of age who are living with HIV and who are unlikely to have active TB on symptom based screening and have no contact with a TB case should receive 6 months of INH preventive therapy (10mg/kg)
(Strong recommendation, moderate quality evidence)

-Children less than 12 months of age, only those children who have contact with a TB case and who are evaluated for TB (using investigations) should receive 6 months IPT if the evaluation shows no TB disease
(Strong recommendation, low quality evidence)

These guidelines also provide clinical algorithms to screen all PLHIV through intensified TB case finding.

The WHO's 2012 "Policy on collaborative TB-HIV activities: guidelines for national programmes and other stakeholders" recommends that HIV programmes provide IPT as part of the package of care for PLHIV when active tuberculosis is safely excluded.[18] This recommendation also states that use of antiretroviral drugs does not preclude the use of IPT. 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 adults and adolescents ranges between 10-50mg daily:

For children, the dosing of isoniazid is weight based (10mg/kg, range 7-15mg/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. Supplemental pyridoxine (5–10 mg/day) is recommended in children treated for TB that are HIV-infected or severely malnourished.[19]

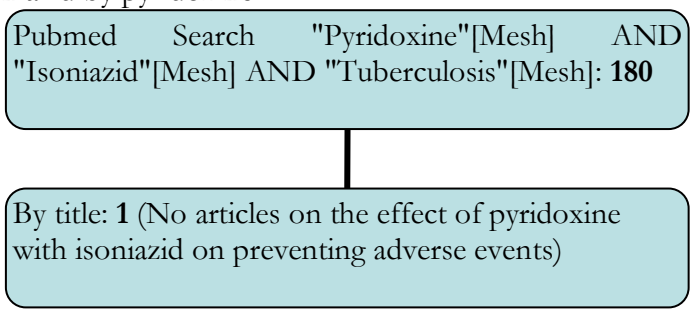
Guidelines for isoniazid preventive therapy in HIV-infected adults		
Source (Year)	**Organisation**	**Recommendation**
Guidelines for Tuberculosis Preventive Therapy Among HIV Infected Individuals (2010)	Ministry of Health, South Africa	Vitamin B6 (pyridoxine) 25 mg per day should be given concomitantly with isoniazid to prevent the occurrence of peripheral neuropathy.
Guidelines for Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents Recommendations from CDC, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America 2009	CDC	Pyridoxine (vitamin B6) (10–50 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.
Treatment of Tuberculosis Guidelines (2010)	WHO	Isoniazid-induced peripheral neuropathy may be prevented in patients with HIV infection, alcohol dependency, malnutrition, diabetes, chronic liver disease, renal failure. By treatment with pyridoxine, 10 mg/day along with their anti-TB drugs. (Other guidelines recommend 25 mg/day (7).)

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

10.1 Identification of clinical evidence

10.1.1 Search strategies

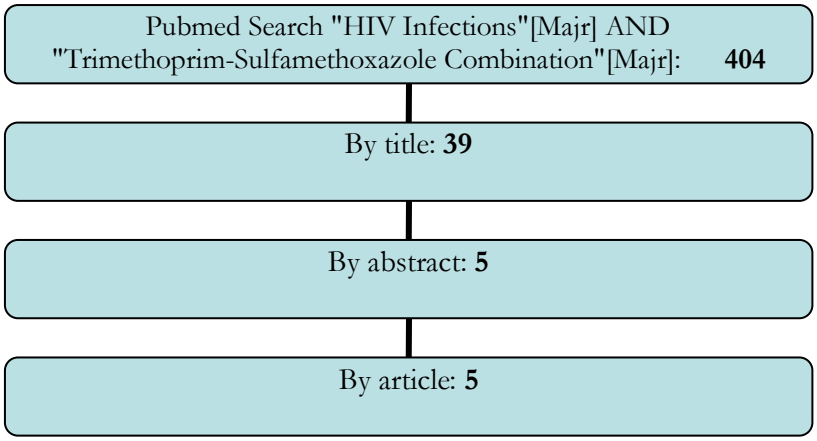
Daily pyridoxine with isoniazid: The critical outcome of interest was prevention of adverse events due to isoniazid by pyridoxine.



One systematic review [19] was found. This explored impact of antiretroviral treatment and TB-HIV co-infection. From cross-sectional reports, 2–12% of patients treated with low or standard dosages of 3–5 mg/kg/day develop peripheral neuropathy (PN) symptom, this figure has been found to increase fourfold in PLHIV. Although there no recent trials (post 1980) were found which specifically examined the effects of pyridoxine in HIV patients, recent trials evaluating IPT and which have used pyridoxine prophylaxis have reported low incidences of PN. For example 2/683 in [20], and 0.21% in the Thibela TB trial among miners in South Africa.[21]

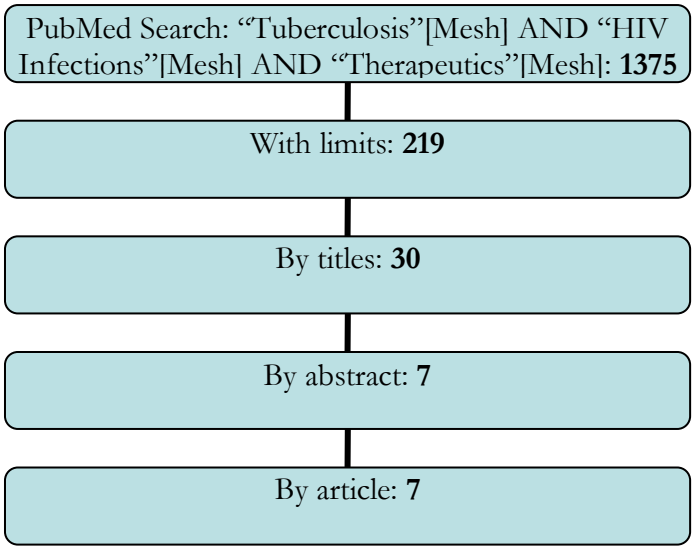
Recommendations for isoniazid preventive therapy in HIV-infected adults include a recommendation for pyridoxine ranging from 10-50mg daily as noted in the table Of the studies included in the GRADE review for IPT, three used 50mg of pyridoxine daily in both arms of the randomized studies[22-24] while 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 [25].



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.[26] 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.[27-29] One Cochrane systematic review was identified for CPT in adults with HIV.[30] 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 experiencing an adverse event, most of which were mild and transient.[20-22] The above search was repeated and limited to between 2009 and 2012. A systematic review and meta-analysis and one operational research study supported evidence of reduced mortality and morbidity [15, 31]. A cohort study reported a 36% reduction in mortality for patients with on cART and CD4>350 cells.[32]. An RCT study of ARV naïve children on CPT found that they had slower weight and height reduction, and a greater increase in haemoglobin than those on placebo.[33] A systematic review of CPT and bacterial resistance showed that this drug protect against the development of bacterial resistance to other bacterial drugs.[34]

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. [22, 35-37]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),[35] these two analyses are listed as two separate studies.

A Cochrane review on IPT in HIV-infected individuals was found .[38] 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.

A modified search was repeated for articles published after January 2010: ("isoniazid"[MeSH Terms] OR "isoniazid"[All Fields]) AND (("tuberculosis"[MeSH Terms] OR "tuberculosis"[All Fields]) AND ("prevention and control"[Subheading] OR ("prevention"[All Fields] AND "control"[All Fields]) OR "prevention and control"[All Fields] OR "prevention"[All Fields])) AND ("hiv"[MeSH Terms] OR "hiv"[All Fields]) AND ("2008/01/12"[PDat] : "2013/01/09"[PDat]). One RCT was found. This showed the efficacy of 36 months' IPT over 6 months IPT in reducing TB incidence.[40] One study reported no increase in hepatic toxicity in children receiving IPT and ART. Another study found the incidence of drug resistance TB in miners who developed TB subsequent to IPT to be similar to the background incidence of drug resistance.[12, 13, 20, 39-46] Further analysis of the IPT in South African miners study showed that the risk of adverse events, particularly hepatoxicty was very low (0.07%,) and was associated with alcohol consumption. (0.03% if no alcohol was consumed [41].

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.[38] 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):

Intervention	Comparator	RR (95% Cl)	Quality of evidence	# of studies
INH	RIF+PZA	1.03 (0.75-1.4)	Moderate	6
INH	INH+RIF	0.97 (0.52-1.83)	Moderate	5
INH	INH+RIF+PZA	0.60 (0.23-1.57)	Low	2

*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):

Intervention	Comparator	RR (95% Cl)	Quality of evidence	# of studies
INH	Placebo	1.66 (1.09-2.51)	High	6
INH	INH+RIF	0.79 (0.50-1.23)	Moderate	4
INH	RIF+PZA	0.63 (0.48-0.84)	Moderate	5
INH	INH+RIF+PZA	0.10 (0.03-0.33)	Low	2

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 [30]A repeat search found one study which revealed that In HIV-infected pregnant women, daily CTX was associated with reduced malaria parasitemia and anaemia compared with SP-IPTp[47]

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 has been completed It concluded that adequate separation of the individual components with HPLC testing and that there were no stability or chemical compatibility issues. Bioavailability should not therefore be a problem. Furthermore, Cotrifazid, a fixed combination of rifampicin 112.5 mg, sulfamethoxazole 200 mg + trimethoprim 40 mg, and isoniazid 75 mg cotrimoxazole isoniazid rifampicin and administered 2 bd for the prevention of malaria had not been found to have any bioavailability problems or specific adverse reactions.[48]

11.2 Estimate of total patient exposure to date

There are no sources which indicate total exposure to isoniazid, pyridoxine, or sulfamethoxazole-trimethoprim. However, concomitant use of cotrimoxazole, isoniazid and pyridoxine (as well as other TB drugs and ART) is recommended in the WHO guidelines: "New TB patients living with HIV should receive a TB regimen containing 6 months of rifampicin (2 months of isoniazid, rifampicin, pyrazinamide and ethambutol followed by 4 months of rifampicin and isoniazid, 2HRZE/4RH) on a daily schedule; and should be started on ART…."[18](p22)
"Routine cotrimoxazole preventive therapy should be administered in all HIV-infected patients with active TB disease regardless of CD4 counts (strong recommendation, high quality of evidence)"[18](p28)

In 2011, 79% of the 562,026 HIV positive TB patients were on CPT. As they were persons with TB disease, they would not take IPT but rather a TB treatment regimen which contains isoniazid.

In 2011 there were an estimated 2.3 million people living with HIV who did not have TB and who might be eligible for CPT and IPT or the FDC if it were available.

11.3 Description of adverse effects/reactions

ISONIAZID

A search in MEDLINE yielded a review of INH adverse events published in 2006.[49] 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.[50, 51] 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. HIV, 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.[52-55] 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.[29] Watera 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, 56] The only available randomised study in patients without active tuberculosis [26] 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.[57] 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

[58, 59]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 [58], though subsequent studies have suggested that slow acetylation is a risk factor for hepatotoxicity [50, 60, 61] or that acetylator status had no impact).[62-64]

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:

Cotrimoxazole 960mg		Isoniazid 300mg		Pyridoxine 25mg	
Source	Unit Price/Day	Source	Unit Price/Day	Source	Unit Price/Day
IMRES (Netherlands)	0.0196	DURBIN (UK)	0.0056	JMS (Uganda)	0.0026
IDA (Netherlands)	0.0216	GDF (India)	0.0064		
JMS (Uganda)	0.0224	MISSION (Denmark)	0.0085		
MEG (Netherlands)	0.0226	GDF (India)	0.0087		
MEDS (Kenya)	0.0305	IDA (Netherlands)	0.0087		
MISSION (Denmark)	0.0308	IMRES (Netherlands)	0.0095		

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)[65]. 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.[66] 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.[67]

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

14. Availability of pharmacopoeial standards (British Pharmacopoeia, International Pharmacopoeia, United States Pharmacopoeia)
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).

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 jerovicii, 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 ().21] 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)47-50.] 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. Indeed, Walker et al. reported that 3% of participants experienced an adverse event; all were haematological, rash, or hypersensitivity (25).¨22] Watera 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)).51] 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).51,52,53] 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 atazia, 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 hypogylcemic 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.

Sulfonadmides 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

Author	Methods/ design	Population	Intervention	Follow-up	Participants	Death and illness episodes	Bacterial pneumonia	Isosporiasis	Malaria	Adverse events	Loss to follow up
Anglaret 99 (Cote d'Ivoire)	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.	545 HIV infected persons aged 18 years and over not on ART in Abidjan, Cote d'Ivoire at the community clinic of Yopougon-Attie. 271 given intervention 270 given placebo.	CTX 960mg daily or matching placebo	Mean 9.6 months in CPT arm, 9.5 months in placebo arm	Inclusion: HIV-1 or HIV-1/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 < 7g/dL, PLT < 75*10^9/L, absolute neutrophil count < 0.75*10^9/L, and renal/hepatic failure	Severe event: 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)	2 on CPT, 20 on placebo HR 0.07 (0.01, 0.56)	2 on CPT, 11 on placebo HR 0.19 (0.04, 0.86)	3 on CPT, 26 on placebo HR 0.16 (0.04, 0.73)	There were three treatment limiting adverse events. Two episodes of grade 2 morbilliform rashes 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
Mermin 04 (Uganda)	Sequential observational cohort study, six months unexposed to CPT vs. eighteeen months exposed to CPT	HIV infected persons in Uganda who were enroled in HIV treatment and care with The AIDS Support Organization. Median age was 34 years (IQR 28-40)	CTX 960mg daily or none	Median follow up was 154 days (IQR 146-162) without CPT and 535 days with CPT (IQR 471-539)	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	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)	Not analysed	Not analysed	54 during 454 PY of follow up on CPT and 116 during 183 PY of follow up off CPT IRR 0.28 (0.19, 0.40)	Nine of 423 participants had adverse reactions associated with CTX, of which three were mucocutaenous	Of the 2205 particpants in the study 48 had an indeterminndate HIV test, 63 had moved or were unreachable, 36 had died, 21 refused HIV testing, and 6 did not follow up for other reasons
Watera 06 (Uganda)	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	HIV infected adults attending 2 clinics in Uganda. HIV-1 infected persons willing to attend study clinics whenever ill are assessed routinely at six monthly visits.	CTX 960mg daily or none	12 months for CPT exposed and for CPT unexposed. 762 person-years follow up on CPT and 701 person-years follow up off CPT	> 15 years of age. 936 included in analysis. 1152 patients were on CPT and 219 were excluded for not attending clinic providing 933 for the analysis.	158 deaths during 701 person-years of follow up for patients off 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).	Not analysed	Not analysed	23 episodes of malaria during 701 PY off 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.
Walker 10 (Uganda/Zimbabwe)	Observational analysis from a randomised study comparing laboratory and clinical monitoring versus clinical monitoring alone	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)	CTX 960mg daily or none	8128 PY of follow up on CPT and 6086 PY of follow up off CPT	WHO stage 2-4 HIV-infected adults (≥ 18 years) with CD4 ≤ 200 without previous ART	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)	Not analysed	Not analysed	2362 events total (27 per 100 person-years). OR 0.74 (0.63, 0.88)	22 (3%) adverse events were CTX related (all were haematological, 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.
Lowrance 07 (Malawi)	Retrospective cohort study of 11 ART clinics that were or were not administering CPT.	HIV-infected Malawians who received HIV care at Malawian clinics	CTX 960mg daily or 480mg twice daily at 5 ART centres, no CPT at 6 ART centres	Six months for both exposure cohorts	Adults ≥ 15 years with WHO stage 3-4 HIV infection or CD4 ≤ 200	57 deaths in 535 persons on CPT, 73 deaths in 406 persons off CPT (RR 0.59, 95% CI 0.43, 0.82)	Not analysed	Not analysed	Not analysed	10 patients on CPT stopped treatment	Of 574 patients who were provided with CPT 22 defaulted and 17 transferred out. Of 478 patients not on CPT 51 defaulted and 21 transferred out.

GRADE review for cotrimoxazole

Author(s): Amitabh Suthar **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)

Quality assessment							Summary of findings					Importance
							No of patients		Effect		Quality	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	960mg of cotrimoxazole	control	Relative (95% CI)	Absolute		
Mortality/hospitilisations (follow-up mean 9.55 months)												
1	randomised trials	no serious limitations	serious[1]	no serious indirectness	no serious imprecision	none	120/271 (44.3%)	198/270 (73.3%)	HR 0.57 (0.43 to 0.75)	204 fewer per 1000 (from 104 fewer to 300 fewer)	⊕⊕⊕O MODERATE	CRITICAL
								0%		0 fewer per 1000 (from 0 fewer to 0 fewer)		
Adverse events (follow-up 6-60 months)												
4	observational studies	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	70/4739 (1.5%)	0/2985 (0%)	RD 0.0148 (0.0113 to 0.018) [2]	0 fewer per 1000 (from 0 fewer to 0 fewer)	⊕⊕OO LOW	IMPORTANT
								0%		0 fewer per 1000 (from 0 fewer to 0 fewer)		
Malaria (follow-up mean 9.55 months)												
1	randomised trials	no serious limitations	serious[1]	no serious indirectness	serious[3]	strong association[4]	3/271 (1.1%)	26/270 (9.6%)	HR 0.16 (0.04 to 0.73)	80 fewer per 1000 (from 25 fewer to 92 fewer)	⊕⊕⊕O MODERATE	IMPORTANT
								0%		0 fewer per 1000 (from 0 fewer to 0 fewer)		
Bacterial pneumonia (follow-up mean 9.55 months)												
1	randomised trials	no serious limitations	serious[1]	no serious indirectness	serious[3]	strong association[4]	2/271 (0.7%)	20/270 (7.4%)	HR 0.07 (0.01 to 0.56)	69 fewer per 1000 (from 32 fewer to 73 fewer)	⊕⊕⊕O MODERATE	IMPORTANT
								0%		0 fewer per 1000 (from 0 fewer to 0 fewer)		
Isosporiasis (follow-up mean 9.55 months)												
1	randomised trials	no serious limitations	serious[1]	no serious indirectness	serious[3]	strong association[4]	2/271 (0.7%)	11/270 (4.1%)	HR 0.19 (0.04 to 0.86)	33 fewer per 1000 (from 6 fewer to 39 fewer)	⊕⊕⊕O MODERATE	IMPORTANT
								0%		0 fewer per 1000 (from 0 fewer to 0 fewer)		

[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

Author	Methods/design	Blinding	Population	Intervention	Analysis	Participants (%)	Follow-up	Active TB (suspected, probable, confirmed)	Mortality	Adverse Events	Loss to follow up	Comments
Pape 1993 (Haiti)	118 individuals randomized using computer generated numbers	Blinding: providers no, participants no, assessors yes.	HIV positive patients living in Haiti	1) Pyridoxine 50 mg, daily for 12 months. 2) INH 300mg plus pyridoxine 50 mg daily for 12 months.	Intention to treat analysis	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.	Mean duration of follow-up was 36 months	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-	Long rank 3.95 (p=0.054)OR for reaching the endpoint without INH was 3.75 (0.95-14.8)	NA	No loss to follow up	Anergy screen included mumps, tricophyton and candida. The % of PPD+ in the INH plus pyridoxine group was significantly higher than the placebo group (66% vs. 38%).
Whalen 1997 (Uganda)	2018 individuals randomized in blocks of 6; sequentially numbered, sealed opaque envelopes	Blinding: providers no, participants no, assessors yes.	PPD+ adults attending clinics or counselling centres for persons with HIV-1 infection in Kampala.	1) Control (Placebo) 250mg ascorbic acid daily for 6 months.2) INH 300mg daily for 6 months.	Intention to treat analysis	Inclusion criteria: Adults (18 to 50 years) with HIV-1 infection (ELISA test), PPD >=5mm, Karnofsky performance score >50, verbal consent. Exclusion Criteria: Active TB, previous treatment for TB, use of antiviral drugs, anaemia, liver or kidney disease, pregnancy test, home >20km from project clinic, advanced HIV disease, serious medical illness not related to HIV.	Mean duration of follow-up was 15 months	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).	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)	23 on placebo (5.0%) 60 on INH 60 (11.2%)	No loss to follow up	The long-term resultsof this study are published in Johnson 01.
Whalen 1997-anergy (Uganda)	Methods 718 individuals randomized in blocks of 6. Sequentially numbered, sealed opaque envelopes	Blinding: providers no, participants no, assessors yes.	Anergic adults attending clinics or counselling centres for persons with HIV-1 infection in Kampala.	1) Control (placebo) Ascorbic acid 250mg daily for 6 months.2) INH 300mg, daily for 6 months.	Intention to treat analysis	As in Whalen 97 except patients had to be anergic. Anergy was defined as 0mm induration in reaction to both PPD and candida antigens.	Mean duration of follow-up was 12 months.	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)	There was no significant difference between placebo and each treatment with regard to either the mortality rate or the proportion of deaths	22 on placebo (6.8%) 31 on INH (7.8%)	103 (14%) lost to follow-up	The long-term results of this study are published in Johnson 01.
Hawken 1997 (Kenya)	684 individuals randomized using computer generated random numbers, permuted blocks of 10	Blinding: providers yes, participants yes, assessors unclear.	HIV-1 positive commercial sex workers and patients attending STD clinics in Nairobi.	1) Control (Placebo) daily for 6 months.2) INH 300mg daily for 6months.	98% included in analysis	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.	Median duration of follow-up was 1.83 years.	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).	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).	There were 4.75 adverse drug reactions per 100 PY (95% CI, 3.10–6.96) on INH and 3.37 per 100 PY (95% CI,2.03–5.26) on placebo (RR, 1.41; 95% CI, 0.78–2.54). Drugs were stopped because of an adverse drug reaction in 11 persons in the INH group and five in the placebo group.	151 (22%) lost to follow-up	

Author	Methods/design	Blinding	Population	Intervention	Analysis	Participants (%)	Follow-up	Active TB (suspected, probable, confirmed)	Mortality	Adverse Events	Loss to follow up	Comments
Gordin 1997 (USA)	517 individuals, centralized randomisation, stratified by study unit, permuted blocks	Blinding: providers yes, participants yes, assessors yes.	HIV positive patients attending AIDS research clinics in the US.	1) Control (Placebo) plus pyridoxine 50mg daily for 6months.2) INH 300mg plus pyridoxine 50mg daily for 6months.	Intention to treat analysis	Inclusion criteria: Anergic (PPD less than 5mm induration AND less than 2mm induration to mumps antigen and tetanus toxoid); age >= 13+ years; no active TB; written consent. Exclusion Criteria: household TB contact in past year, on drugs withactivity against TB, acute hepatitis, peripheral neuropathy, history of positive PPD, intolerance to studydrug, treatment for >= 1 month with drug active against TB.	Mean duration of follow-up 33.5 months.	Confirmed TB developed in 3 of the 260 patients in INH group and 6/257 patients in the placebo group (rates per 100 patientyears of follow-up, 0.4 and 0.9, respectively; relative risk, 0.48; 95 percent confidence interval, 0.12 to 1.91; P=0.30).All the cases of TB occurred after 6 months or nore after randomization and after study drug had been discontinued.	129/ 260 patients on INH died, as compared with 126/ 257 patients on placebo (RR 0.96; P= 0.76)	29 in INH (11.2%) and 30 patients in the placebo group (11.7%) had reportable adverse drug reactions	34 (7%) lost to follow-up	Conducted in 1980s to the early 1990s, when TB control was ineffective in the USA
Mwinga 1998 (Zambia)	1053 individuals assigned using computer generated random method and blocks of 30; serially numbered	Blinding: providers yes participants yes, assessors yes.	HIV positive patients in Lusaka, Zambia.	1) Placebo twice a week for 6 months or 3 months.2) INH 900 mg, twice a week, for 6 months. 3) RIF+PZA	98% included in analysis	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.	Median duration of follow-up 1.8 years.	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 = .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.	There was no difference in mortality rates	29 subjects (3%) were withdrawn from the study because of adverse drug reactions	332 (32%) lost to follow-up	The long-term results of this study are published in the Quigley 01
Fitzgerald 2001 (Haiti)	237 individuals randomized	Blinding: providers unclear, participants unclear, assessors unclear.	HIV positive, PPD negative individuals living in Haiti.	1) Control (placebo) plus pyridoxine (vitamin B6): 50 mg daily for 1 year.2) INH 300 mg plus pyridoxine 50 mg daily for 1 year.	Intention to treat analysis.	Inclusion criteria: Age >18 years; HIV symptomfree (CDC category A); PPD < 5mm induration; informed consent; negative sputum examination results bysmear and culture; negative chest x-ray; no history of TB. Exclusion Criteria: Pos sputum examination results by smear and culture; a history of TB; pregnant.	Mean duration of follow up 2.5 years.	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 1.26 (95% CI 0.36-4.37)	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 1.26, 0.36-4.37)	NA	54 (23%) lost to follow-up	Notes All patients were treated for opportunistic infections but none were on ART.91% had +ve reactions to candida + mumps
Rivero 2003 (Spain)	319 individuals randomized	Blinding: providers no, participants no, assessors unclear.	HIV positive anergy patients attending hospitals in Spain.	1) Control (No treatment).2) INH 5 mg/kg (max 300 mg) daily for 6 months. 3) RIF+INH 4) RIF+PZA	Intention to treat analysis.	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 antigens). Consent: none mentioned. Exclusion Criteria: Presence of active TB; previous treatment or chemoprohylaxis for TB; history of hypersensitivity to study drugs; ALT > 4x normal values; Bilirubin > 2 mg/ml; Creatinine > 2 mg/ml; pregnancy.	Mean duration of follow-up 1.23 years.	11 cases of TB (7 confirmed TB): 3 on INH, 3 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).	34 had treatment interruption because adverse reaction, no significant differences were detected between the groups	17 (5%) lost to follow-up	

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)

Bibliography: Pape et al. 1993 (18), Whalen et al. 1997 (28), Hawken et al. 1997 (29), Mwinga et al. 1998 (30), Fitzgerald et al. 2001 (19), Gordin et al. 1997 (20), Rivero et al. 2003 (31), Whalen et al. 1997 – anergy (28)

Quality assessment							Summary of findings					Importance
							No of patients		Effect		Quality	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	isoniaizid 300mg daily	control	Relative (95% CI)	Absolute		
Active tuberculosis incidence (probable, possible, or confirmed) (follow-up 1-3 years)												
8	randomised trials	no serious limitations	serious[1]	no serious indirectness	no serious imprecision	none	85/2152 (3.9%)	123/1984 (6.2%) 0%	RR 0.67 (0.51 to 0.87)	20 fewer per 1000 (from 8 fewer to 30 fewer) 0 fewer per 1000 (from 0 fewer to 0 fewer)	⊕⊕⊕O MODERATE	CRITICAL
Confirmed tuberculosis (follow-up 1-3 years)												
5	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	34/1037 (3.3%)	47/1026 (4.6%) 0%	RR 0.72 (0.47 to 1.11)	13 fewer per 1000 (from 24 fewer to 5 more) 0 fewer per 1000 (from 0 fewer to 0 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Mortality (any cause) (follow-up 1-3 years)												
7	randomised trials	no serious limitations	serious[1]	no serious indirectness	no serious imprecision	none	427/2152 (19.8%)	419/1984 (21.1%) 0%	RR 0.95 (0.85 to 1.06)	11 fewer per 1000 (from 32 fewer to 13 more) 0 fewer per 1000 (from 0 fewer to 0 more)	⊕⊕⊕O MODERATE	CRITICAL
Adverse drug reaction leading to treatment interruption (follow-up 1-3 years)												
7	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	56/2026 (2.8%)	33/1873 (1.8%) 0%	RR 1.66 (1.09 to 2.51)	12 more per 1000 (from 2 more to 27 more) 0 more per 1000 (from 0 more to 0 more)	⊕⊕⊕⊕ HIGH	CRITICAL

[1] Inconsistent direction of effect across studies

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