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ចិញ្ចឹម ២០០៣

ក្រុមប្រឹក្សាសិក្សាសម្រាប់ការពារការពារ និងការសិក្សានិងអភិវឌ្ឍន៍
សេចក្តីពីប្រភេទiamo: ១ ឈុត BCG បញ្ចូល៖ ១ ឈុត PCP ២ ឈុត Toxoplasmosis ៣ ឈុត Isoniazid ៤ ឈុត Cotrimoxazole ៥ ឈុត Fluconazole

បញ្ហាទូទៅ: ១ ឈុត ២ ឈុត ៣ ឈុត ៤ ឈុត ៥ ឈុត
with 7% of AIDS patients in northern Thailand reporting *Penicillium marneffei* infections compared to <1% elsewhere in the country.

Data from prospective randomized trials indicate that fluconazole is effective in the prevention of mucosal candidiasis and cryptococcosis in PLHA with advanced disease. Long term usage is associated with the development of resistance, particularly in PLHA with low CD4 counts. In Europe, USA and Australia fluconazole is not recommended for primary prophylaxis of these infections because of the relative infrequency, lack of survival benefit, possibility of drug interactions, potential development of drug resistance and cost. Secondary prophylaxis is recommended following cryptococcosis. For this indication, fluconazole is recommended as it has been shown to be more effective than itraconazole. Thai guidelines recommend fluconazole as an option for primary and secondary prophylaxis of cryptococcosis.

Itraconazole has been shown in small randomized trials in Thailand to be effective in the prevention of penicilliosis, given either as primary or secondary prophylaxis. There was no survival benefit demonstrated, possibly due to the small sample sizes. Thai guidelines recommend intraconazole as an option for primary and secondary prophylaxis of penicilliosis.

Discontinuation of fluconazole secondary prophylaxis for prevention of cryptococcal meningitis following immune reconstitution with ARV has been investigated in several studies. There is increasing evidence from these studies that cessation of fluconazole secondary prophylaxis is safe if PLHA have no signs or symptoms of cryptococcal disease and have had a sustained increase in CD4 count above 100 cells/m$^3$ for at least 6 months.

**งบกุญช์**

เพื่อพิธีริเริ่มเริ่มเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อนเรื่อง
2.5. Which group of PLHA benefits from cotrimoxazole prophylaxis?

The decision when to commence cotrimoxazole prophylaxis has been well defined in high income countries for many years. The first recommendation regarding prophylaxis, issued in 1989, was for the use of daily double strength cotrimoxazole in PLHA with CD4 counts less than 200. This recommendation has remained unchanged since.

The subgroup of PLHA that benefits from cotrimoxazole prophylaxis in developing countries is not known. The first Abidjan study described above suggested a benefit below a CD4 count of 500/mm$^3$, the study in PLHA with TB showed most benefit in PLHA with a CD4 below 350/mm$^3$ and a retrospective study in Cape Town showed a benefit only when CD4 was below 200/mm$^3$.

2.6. Potential efficacy of cotrimoxazole prophylaxis in Cambodia

The data available from West Africa suggest that PLHA in Cambodia may benefit from cotrimoxazole prophylaxis. These data also suggest that PLHA with smear positive pulmonary TB, and perhaps with other forms of TB, may be more likely to benefit from cotrimoxazole prophylaxis than other groups of PLHA. However, the degree to which the findings in West Africa can be extrapolated to Cambodia is highly dependent on the spectrum of disease in PLHA and the resistance pattern of the major pathogens. There is extremely limited data regarding these issues available in Cambodia.

Case series from the national hospitals of Phnom Penh suggest that tuberculosis and cryptococcal meningitis are the major causes of morbidity and mortality. Data from Thailand would suggest that the next most important causes of illness in PLHA in the region to be PCP, Salmonella species, toxoplasmosis and Penicillium marneffei. The contribution of these organisms to illness in PLHA in Cambodia is unknown. The rate of cotrimoxazole resistance in major bacterial pathogens is also unknown. Whether cotrimoxazole prophylaxis is beneficial for PLHA, or a subgroup of PLHA, in Cambodia, either in terms of reduction in illness or improvement in survival, therefore remains a question without a definite answer. Cost-effectiveness is therefore also unknown.

3. Prevention of fungal infections using fluconazole

Fungal infections are important causes of morbidity and mortality in PLHA throughout the world. They include oral, oesophageal and vulvo-vaginal candidiasis, cryptococcal disease especially meningitis and various endemic mycoses such as penicilliosis in south-east Asia. Oral candidiasis is an important contributor to wasting in PLHA. Cryptococcal meningitis is second only to tuberculosis as a cause of hospital admission and death in PLHA in the national hospitals of Phnom Penh. The importance of penicilliosis as a cause of illness and death in Cambodia is not known. Incidence is highly variable in Thailand
2.3. Benefits of cotrimoxazole prophylaxis in developing countries

The efficacy of cotrimoxazole prophylaxis in a developing country setting has been proven in a randomized trial conducted in Abidjan, Cote d’Ivoire. This study compared the efficacy of daily double strength cotrimoxazole to placebo in PLHA in WHO clinical stage 2 and 3. It found a significant reduction in severe events defined as either death or hospitalization, but not a significant reduction in mortality alone.

A similar study that was conducted in Dakar, Senegal and was prematurely halted because of the release of the Abidjan study results, found no significant benefit from the use of daily single strength cotrimoxazole. The different outcomes of these studies are probably due to a combination of different dosage, different spectrum of disease and resistance patterns and reduced power of the Dakar study.

The use of cotrimoxazole prophylaxis in a subgroup of PLHA with smear positive pulmonary TB was investigated by a second randomized study conducted in Abidjan. This showed more marked benefits with significant reductions in OIs and hospital admissions and a halving of mortality.

2.4. Risks of cotrimoxazole prophylaxis

An important question is whether the use of cotrimoxazole will lead to an increase in the resistance to cotrimoxazole in susceptible organisms infecting PLHA and the general community. This is certainly a valid concern as cotrimoxazole is a broad spectrum antibiotic that should be taken long term making the induction of resistance in an individual inevitable. Given that cotrimoxazole is an important antibiotic for the treatment of common infections the concern is that this would lead to increased cotrimoxazole resistance in common pathogens circulating in the community limiting cost-effective treatment options. Additionally, it would undermine the effectiveness of cotrimoxazole prophylaxis itself.

There are some data to suggest that cotrimoxazole resistance does increase in PLHA given cotrimoxazole prophylaxis and in others in the same geographical area. The question remains whether widespread use of cotrimoxazole prophylaxis in countries such as Cambodia would significantly increase cotrimoxazole usage and therefore whether these programs would have an effect on resistance patterns either in PLHA or in the general community.

Side effects from cotrimoxazole prophylaxis in PLHA are very common, occurring in up to 50%. The most common side effect is rash, which is often mild, but can be severe or life threatening. The other major side effects are hepatitis, anaemia and neutropenia.

There is some data to suggest that cotrimoxazole prophylaxis also increases the risk of candida infections, presumably by altering bacterial flora.
Referral, monitoring and reporting systems. Systems for managing the flow of PLHA between services and adequately assessing the efficacy of the IPT program are essential.

2. Prevention of bacterial infections, PCP and toxoplasmosis using cotrimoxazole

2.1. Use of cotrimoxazole

Cotrimoxazole is a combination of two antibiotics, trimethoprim and sulphamethoxazole, that has been used extensively throughout the world for more than two decades. It is formulated as tablets of 'single' or 'double' strength tablets with 80mg and 400mg or 160mg and 800mg of trimethoprim and sulphamethoxazole respectively. There are numerous indications for its use, particularly in the treatment of common infections such as urinary tract infections, upper and lower respiratory tract infections, enteritis and dysentery. It is also useful for the prevention and treatment of infections in immunosuppressed individuals, particularly Pneumocystis carinii pneumonia (PCP) and Toxoplasma gondii encephalitis. Usage and rates of resistance have varied widely around the world.

In PLHA cotrimoxazole is potentially useful for the prevention and treatment of a wide range of infections. This includes PCP and toxoplasmosis, but also the most important causes of serious bacterial infections such as pneumonia, bacteraemia and bacterial enteritis: Streptococcus pneumoniae, Salmonella species, Shigella species, Escherichia coli, Staphylococcus aureus and Haemophilus influenzae. Cotrimoxazole also has activity against Plasmodium species (malaria), Isospora belli (cause of diarrhoea) and Nocardia asteroides (respiratory and generalized infections).

2.2. Benefits of cotrimoxazole prophylaxis in high income countries

Cotrimoxazole has been used extensively in PLHA in high income countries since the late 1980s, primarily for the prevention and treatment of PCP. Several controlled trials and meta-analyses have shown that PCP prophylaxis reduces the risk of PCP and that cotrimoxazole is the most effective prophylactic agent with virtually no failures. The effect of cotrimoxazole prophylaxis on mortality is not as clear. Cohort data also indicate that cotrimoxazole reduces the risk of toxoplasmosis and major bacterial pathogens.

The dose of cotrimoxazole necessary for efficacy varies by infection. Substantial data have shown that daily single strength (80mg/400mg) has similar efficacy to daily double strength (160mg/800mg) for the prevention of PCP and less adverse events, particularly less rash. There is some data to suggest, however, that the higher dose has substantial benefit over the lower dose for the prevention of toxoplasmosis.
1.12. Minimum criteria for establishment of IPT programs

To maximize program effectiveness and minimize the risk that implementation of IPT programs will harm existing TB control efforts, the following are minimum criteria for establishment of IPT programs:

- **Commitment** to establishment of IPT program by key decision makers in province/district including TB and HIV program leaders

- **Effective TB DOTS program** e.g. combined defaulter and failure rate of less than 10%. IPT is not a substitute for TB DOTS and implementation of IPT should never be allowed to undermine case detection and treatment of active TB.

- **Adequate facilities and capacity for excluding active TB.** One of the main risks of IPT is that isoniazid monotherapy will be given to PLHA with active TB. This is a very real risk given that many PLHA are diagnosed at a late stage of HIV disease and are therefore more likely to present with smear negative pulmonary or extrapulmonary TB. For example, the CENAT Afternoon Clinic has diagnosed active TB in approximately 20% of screened PLHA, of which 75% has been either smear negative pulmonary or extrapulmonary TB.

- **Effective mechanisms to minimize drop-outs** at each stage of IPT delivery. In the absence of TST, a WHO/UNAIDS consensus meeting estimated that the number of PLHA needed to screen to prevent one index case is 15-78, and the number needed to treat is 7-20. Even modest increases in drop-out rates can easily increase these numbers needed to screen/treat to levels that are not cost-effective.

- **Integration into comprehensive care for PLHA.** This is essential for cost-effectiveness as it will ensure that benefits are available for those PLHA who enter the program regardless of whether they are eligible or able to complete IPT. This is particularly true for health services that are developing both TB/HIV activities and HIV continuum of care.
9.7. Duration of benefit

The duration of benefit of preventive therapy is not known. One study showed that the benefit of isoniazid disappeared by 18 months of follow up and another showed an early, transient advantage of isoniazid over a shorter course of rifampicin plus pyrazinamide, but no study has been designed or powered to answer this question.

The duration of benefit is in part related to the risk of re-infection. Some indication of this can be gained from studies of relapse following treatment for active TB. Studies to date would support re-infection as the major cause of relapse in PLHA living in high TB prevalence areas, providing further support to the suggestion that the efficacy of preventive therapy may not be long term.

9.8. Isoniazid resistance

There is concern that rates of isoniazid resistance could increase with expanded isoniazid preventive therapy programs. No increase in isoniazid resistance was seen in the studies in PLHA who developed active TB despite isoniazid, but this may change when large scale programs are implemented. The efficacy of IPT is also dependent on the rate of isoniazid resistant TB infection. In the National TB program study 2000-2001, the rate of primary resistance of TB to isoniazid was 6.4%.

9.9. Secondary prophylaxis

To explore ways to reduce rates of relapse following treatment for active TB secondary prophylaxis has been investigated. In a study in Haiti it was found that the rate of relapse following treatment for active TB was approximately ten times higher in PLHA than in HIV negative participants. Twelve months of isoniazid commenced soon after completion of treatment for active TB reduced the risk of recurrent TB in PLHA by 80%, to 20% of the risk if no isoniazid had been given. All relapses were in PLHA who had symptomatic HIV disease prior to active TB.

9.10. Additional ways to prevent active TB

PLHA should be aware of the risks associated with contact with people with pulmonary TB, for example in health care environments. Restoration of immune function using antiretroviral medication is a powerful intervention for reducing the risk of active TB, particularly in PLHA with advanced immunosuppression.

9.11. Steps in delivery of IPT

Despite the evidence of efficacy, the success of implementation of IPT on a large scale is dependent on overcoming a number of operational issues. Steps necessary in delivery of IPT are:

- Identification of PLHA, for example through VCCT.
and 12 months duration have shown a significant decrease in TB incidence in tuberculin skin test (TST) positive persons compared to those who took placebo. In TST positive PLHA living in areas of high TB prevalence, isoniazid therapy will reduce the short-term risk of TB by 60%, to approximately 40% of what it would have been without treatment. In PLHA who are TST negative, including those who are anergic, no statistically significant effect of preventive therapy has been found, either in a randomized trial or meta-analysis. In a meta-analysis of studies that included both TST positive and negative PLHA preventive therapy reduced the risk of active TB to approximately 60% of what it otherwise would have been. Using these data it can be estimated that approximately 36 PHA would need to be treated with preventive therapy in order to prevent 1 case of active TB over 3 years.

1.4. Effect on mortality
Effect on mortality has not been demonstrated in any study, although none were powered to demonstrate this. Meta-analyses have shown non-statistically significant reductions in mortality in TST positive PLHA to 68-77% of what it would otherwise have been. No trial or meta-analysis has demonstrated an effect on mortality of TST negative or combined TST positive and negative PLHA. It therefore remains unknown whether preventive therapy given to populations of PLHA with unknown TST status would have an effect on survival.

1.5. Efficacy in PLHA with advanced HIV disease
Anecdotal reports suggest that the efficacy of preventive therapy in PLHA with advanced HIV disease is reduced, but this has not been proven. Certainly the management of this group is more complicated. Active TB is more difficult to exclude as smear negative pulmonary and extra-pulmonary disease is more common and other OIs that mimic active TB are more common. Also tolerance for drug therapy is reduced in this group.

1.6. Choice of regimen
Regimens other than isoniazid that have been investigated include rifampicin plus either isoniazid or pyrazinamide or both given over two to four months. The trend in these studies was for isoniazid to be slightly more effective, perhaps related to the longer duration of therapy.

Exactly how long isoniazid therapy should be is unknown. Extrapolation from the use of isoniazid in HIV negative individuals would suggest a duration of 9 months, but this extrapolation is limited, in part because the duration of benefit in PLHA is likely to be different.
1. Prevention of active tuberculosis using isoniazid

1.1. TB/HIV interaction

Tuberculosis (TB) is the most common opportunistic infection and cause of death among people living with HIV/AIDS (PLHA). It is estimated that half of all PLHA in developing countries will develop active TB at some time. Once TB becomes active it increases HIV replication resulting in increased HIV viral load and may accelerate HIV disease progression. PLHA with active TB can be treated with standard regimens, but their survival is lower than others with TB due to the occurrence of other opportunistic infections. Relapse and re-infection is commoner in PLHA than others with TB.

HIV is the strongest risk factor for progression from latent to active TB. It is estimated that this risk is approximately 5-10% lifetime risk for individuals negative for HIV compared to 2.4% to 7.5% per year for PLHA living in high TB prevalence countries. This has resulted in dramatic increases in TB prevalence in areas of high HIV prevalence, particularly sub-Saharan Africa, but also in Asia, including northern Thailand.

The situation in Cambodia is likely to be similar. The nation wide TB prevalence survey conducted in 2002 confirmed high prevalence of smear positive pulmonary TB (270 per 100 000 population) and TB is the commonest cause for admission of PLHA to the major hospitals of Phnom Penh. A HIV sero-survey amongst newly diagnosed TB patients in early 2003 found a national average prevalence of 10.3%. The prevalence in Phnom Penh was approximately 30%, perhaps providing some explanation for the large increase in TB cases seen over the last few years.

1.2. Efficacy of IPT in HIV negative individuals

Drug treatment of latent TB infection to prevent progression to active TB is an important aspect of TB control in high income countries. Efficacy has been demonstrated in HIV negative individuals in large trials. Recommended therapy has varied between 6 and 12 months of isoniazid and shorter courses of rifampicin with or without pyrazinamide. Current US recommendations favor 9 months of isoniazid as randomized comparisons have shown that 12 months to be more effective than 6 months, but various post-hoc sub-group analyses have suggested little additional benefit from courses longer than 9 months.

1.3. Efficacy of IPT in PLHA

A number of large randomized trials have shown the efficacy of drug therapy in the prevention of active TB in PLHA. Randomized trials administering isoniazid for 6 months...
3.6. Primary prophylaxis of penicilliosis

Primary prophylaxis of penicilliosis is not recommended at present as it is not known whether the incidence in PLHA in Cambodia is sufficient to warrant this measure. Secondary prophylaxis with itraconazole 200mg orally once per day is recommended for PLHA who have completed treatment for penicilliosis. Duration is the same as that detailed above for cryptococcosis.
3. Prevention of fungal infections using fluconazole

3.1. Fluconazole prophylaxis

Fluconazole prophylaxis is an optional component of comprehensive care for PLHA in Cambodia. It should only be included into programs if resources are sufficient to enable purchase, distribution and delivery of fluconazole and staff have received specific training in its use. Initiation should be at a referral hospital. Health centers and home care teams can assist in follow-up and monitoring.

3.2. Primary prophylaxis of cryptococcosis

Primary prophylaxis of cryptococcosis including cryptococcal meningitis, should be offered to PLHA with CD4 count of less than 100 cells/mm$^3$. Fluconazole 100mg orally once per day is recommended. There are no accepted clinical criteria for initiation of fluconazole primary prophylaxis. Fluconazole should not be given during pregnancy.

3.3. Secondary prophylaxis of cryptococcosis

Secondary prophylaxis of cryptococcosis including cryptococcal meningitis, should be offered to PLHA following completion of initial treatment. Fluconazole 200mg orally once per day is recommended. For pregnant women, weekly amphotericin can be given.

3.4. Duration of prophylaxis

Primary and secondary prophylaxis of cryptococcosis should be continued lifelong. If PLHA are receiving ARV and immune reconstitution results in a CD4 count consistently above 100 cells/mm$^3$ for at least 6 months then prophylaxis can be ceased. If the CD4 count again falls below 100 cells/mm$^3$ prophylaxis should be resumed until the CD4 count is again above 100 cells/mm$^3$ for at least 6 months.

3.5. Secondary prophylaxis of candidiasis

In most situations the potential benefits of secondary prophylaxis for the prevention of mucosal candidiasis using a systemic antifungal are outweighed by the risk of antifungal resistance. Instead topical preparations of gentian violet, nystatin, clotrimazole or amphotericin should be used. In situations where these agents are not effective, particularly with recurrent or persistent oesophageal candidiasis, then fluconazole 100 to 200mg orally once per day is recommended. Duration is the same as that detailed above for cryptococcosis.
hospital. Follow-up by a health care worker should be at least monthly until stable and can then be reduced to three monthly. Adults should also have hemoglobin and white cell count checked six monthly if possible.

2.7 Side effect management

- The main side effects of cotrimoxazole are rash, bone marrow suppression and hepatitis. They are more likely to occur soon after initiation of cotrimoxazole. Minor rashes are common and can usually be managed with careful observation and continuing cotrimoxazole. More severe rashes including Stevens Johnson syndrome and clinical hepatitis are possible and must lead to immediate cessation of cotrimoxazole. Supportive management including hospital admission is sometimes necessary. Reductions in hemoglobin or white cell count can be managed by dose reduction if not severe.

- If cotrimoxazole has been ceased for non-life threatening indications, it can be recommenced following ‘desensitisation’, for example using a cotrimoxazole suspension of 40mg TMP + 200mg SMX per 5ml and use one of the following:
  1. Inpatient: Over 6 hours, give hourly doses (TMP/SMX in mg): 0.004/0.02, 0.04/0.2, 0.4/2.0, 4.0/20, 40/200 and 160/800.
  2. Outpatient: Give 1ml daily for 3 days; 2ml for 3 days and so forth until the dose can be administered as 1 SS daily and the next day 1 DS daily.
  3. If desensitization fails Dapsone should be given (See ‘Drugs and Doses’ above).

2.8 Program implementation

- Integration of cotrimoxazole prophylaxis into a HIV comprehensive care program should include training of all involved in HIV continuum of care. A social marketing approach should be used to rapidly increase awareness and understanding of PLHA and the wider community. Monitoring of programs is essential to gain a better understanding of the true risks and benefits of cotrimoxazole prophylaxis in Cambodia. This should include monitoring of HIV disease spectrum and impact of cotrimoxazole, resistance patterns and toxicity.
Who reach the age of 15 months without symptomatic HIV disease or with CD4 percentage over 15 OR
- Who are treated with ARV and who have a CD4 percentage consistently above 15 for at least 6 months. If the CD4 percentage drops below 15 then cotrimoxazole prophylaxis should recommence until the CD4 percentage is again consistently above 15 for at least 6 months. If ARV are stopped for more than a few weeks cotrimoxazole should be restarted.

2.4. Drugs and doses

- Cotrimoxazole (TMP/SMX) should be given as follows:
  - Adults: 1 double strength (DS; TMP-160mg, SMX-800mg) tablet daily or 2 single (SS; TMP-80mg, SMX-400mg) tablets daily.
  - Children: TMP/SMX (TMP 150mg/m2/day) syrup or crushed tablets. Give as a daily dose or divided into two doses; every day or three days/week (consecutive or alternating).
  - An alternative for PLHA unable to tolerate cotrimoxazole for the prevention of PCP is Dapsone100mg orally once a day (children 2mg/kg daily).

2.5. Initiation

- Cotrimoxazole prophylaxis should be initiated by health care workers either in health care facilities or in home care teams. Staff should be specifically trained and receive adequate supervision. All PLHA commencing cotrimoxazole should be given the opportunity to learn about cotrimoxazole and counseled about possible benefits, side effects and the importance of regular administration.

2.6. Monitoring

- Once cotrimoxazole prophylaxis is commenced it is important that its use be monitored within a continuum of care. Ongoing support, explanation, encouragement as well as monitoring for side effects and provision of medicine should be coordinated between care services. For example, home care teams can play a critical role in the support and monitoring of medicine. Referral mechanisms for side effects or possible 'breakthrough' OI should be developed and clearly understood by all involved. Simple side effects could be managed at health centers and more marked symptoms referred to a referral
2. Prevention of bacterial infections, PCP and toxoplasmosis using cotrimoxazole

2.1. Cotrimoxazole prophylaxis

Cotrimoxazole prophylaxis should be offered as an integrated part of comprehensive care for PLHA. The primary aim of cotrimoxazole prophylaxis is to prevent major bacterial illness and PCP, with the prevention of toxoplasmosis a secondary aim. It can be commenced as either primary prophylaxis (given to PLHA who have never had these infections) or secondary prophylaxis (given to PLHA who have had an episode of these illnesses to prevent recurrence) using the criteria detailed below.

2.2. When to start?

Cotrimoxazole should be offered to adult PLHA who have:
- Advanced symptomatic HIV disease (WHO clinical stage 2, 3 or 4) OR
- CD4 count less than 200 OR
- In the absence of CD4 monitoring, a total lymphocyte count less than 1200/mm³ AND
- Are not in first trimester of pregnancy

Cotrimoxazole should be offered for all HIV exposed infants from 4 weeks of age using the following criteria:
- Any child born to an HIV infected woman
- Any child under the age of 15 months who is known to be infected with HIV either by clinical or laboratory diagnosis.
- Any child over the age of 15 months who is known to be infected with HIV and who has symptomatic HIV disease or a CD4 percentage less than 15.

2.3. When to stop?

Cotrimoxazole prophylaxis is life long except for:
- Adults treated with ARV and have a CD4 count consistently above 200 for at least 6 months. If the CD4 count drops below 200 then cotrimoxazole prophylaxis should recommence until the CD4 count is again consistently above 200 for at least 6 months. If ARV are stopped for more than a few weeks cotrimoxazole should be restarted.
- Children
  - Who are shown not to be HIV infected (e.g. negative HIV antibody at 15 months) OR

3. Treatment and prophylaxis of opportunistic infections

3.1. Cryptococcosis

Cryptococcus is a fungal infection that can affect PLHA. The treatment for Cryptococcosis is Fluconazole 100-200mg per day. For persistent or recurrent infections, Amphotericin is also used.

3.2. Candidiasis

Candidiasis is a fungal infection that can affect PLHA. The treatment for Candidiasis is Fluconazole 100-200mg per day. For persistent or recurrent infections, Amphotericin is also used.
10. **Primary Prophylaxis**

Patients with HIV infection are at increased risk for tuberculosis (TB) if they are not started on isoniazid (INH) prophylaxis. INH prophylaxis is recommended to be started in all patients with HIV infection, regardless of CD4 T cell count or human immunodeficiency virus (HIV) viral load.

**Management of adverse effects**

- Patients should be monitored closely for the development of adverse effects associated with INH prophylaxis.
- The main side effects of INH are gastrointestinal (e.g., nausea, vomiting, diarrhea), hepatotoxicity, and peripheral neuropathy.
- The risk of hepatotoxicity is approximately 0.3% in young healthy adults and increases to 2.6% in the elderly. The risk of neuropathy is largely prevented with the use of pyridoxine.
- Patients should be warned of the symptoms of hepatotoxicity: nausea, vomiting, abdominal pain, lethargy, jaundice, and dark urine. If any of these symptoms occur, patients should cease INH and consult their healthcare provider.

**Program implementation**

IPT programs should be piloted before widespread implementation to investigate whether the operational issues detailed above can be addressed. Rigorous systems for evaluation of IPT programs are essential for assessing the ability of each program to reduce drop-outs and to ensure comprehensive HIV care is provided, and thus demonstrate cost-effectiveness. IPT for children should only be provided in pediatric hospitals with access to TST and ability to exclude active TB in children.
1. Prevention of active tuberculosis using isoniazid

1.1. Isoniazid prophylaxis

Isoniazid can be an integrated part of a package of comprehensive care for PLHA. All PLHA should have access to information and educational materials regarding TB and preventive therapy. IPT can be offered to PLHA who agree, who do not have active TB at screening and who can be adequately monitored for isoniazid side effects and active TB.

1.2. Recommended regime

Isoniazid at a dose of 5 mg/kg to a maximum of 300 mg/day should be used. Pyridoxine (vitamin B6) 50 mg/day should be given at the same time to reduce the risk of peripheral neuropathy. The duration of IPT should be 9 months, on the condition that there are adequate systems for monitoring and support of adherence.

1.3. When to start?

PLHA should be offered IPT as early as possible because active TB can occur at any CD4 count and once present leads to further weakening of the immune system and increased risk of other opportunistic infections. PHA with symptoms of TB such as cough or fever should not commence IPT until a cause for these symptoms is found. IPT should not be given to PLHA with known active hepatitis. IPT should be delayed until after the first trimester of pregnancy.

1.4. Screening for active TB

Adequate systems must be in place to screen for active TB prior to commencement of an IPT program. This must include the capacity to diagnose all forms of TB, including smear negative pulmonary TB and extrapulmonary TB, using history taking, careful physical examination, chest X-rays and sputum examination. IPT services should therefore be based at referral hospitals.

1.5. Monitoring

PLHA taking IPT should meet with a specifically trained health care worker at least monthly and medication dispensed monthly. This could be at an
9.6. 肺结核化学预防治疗: Isoniazid (IPT) 与单倍量磺胺甲噁唑

肺结核化学预防治疗 (latent TB infection) 是指在结核病患者床旁给予化疗药物，防止病情发展。由于肺结核的化学预防治疗通常采用单倍量磺胺甲噁唑 (800mg/160mg) 和乙胺丁醇 (50mg/kg)。

9.7. 肺结核化学预防治疗: Isoniazid (IPT) 与单倍量磺胺甲噁唑

肺结核化学预防治疗是针对所有肺结核患者的治疗方法。Isoniazid (IPT) 是一种有效的化学预防治疗药物，用于预防肺结核病患者发展成结核菌感染。

### Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
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<tbody>
<tr>
<td>AIDS</td>
<td>Acquired Immunodeficiency Syndrome</td>
</tr>
<tr>
<td>ARV</td>
<td>Antiretroviral drug(s)</td>
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<tr>
<td>CD4</td>
<td>T-CD4+ Lymphocyte</td>
</tr>
<tr>
<td>CENAT</td>
<td>National Tuberculosis and Leprosy Control Program</td>
</tr>
<tr>
<td>DOTS</td>
<td>Directly Observed Therapy Short Course Strategy for the control of TB</td>
</tr>
<tr>
<td>DS</td>
<td>Double strength cotrimoxazole (800mg/160mg)</td>
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<tr>
<td>HIV</td>
<td>Human Immunodeficiency Virus</td>
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<tr>
<td>IPT</td>
<td>Isoniazid preventive therapy</td>
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<tr>
<td>MMM</td>
<td>Mondul Mith Chouy Mith (Friendly support center)</td>
</tr>
<tr>
<td>OI</td>
<td>HIV related Opportunistic Infection</td>
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<tr>
<td>PCP</td>
<td>Pneumocystis carinii pneumonia</td>
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<tr>
<td>PLHA</td>
<td>Person/people living with HIV/AIDS</td>
</tr>
<tr>
<td>SMX</td>
<td>Sulphamethoxazole</td>
</tr>
<tr>
<td>SS</td>
<td>Single strength cotrimoxazole (400mg/80mg)</td>
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<tr>
<td>TB</td>
<td>Tuberculosis</td>
</tr>
<tr>
<td>TMP</td>
<td>Trimethoprim</td>
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<tr>
<td>TST</td>
<td>Tuberculin skin test</td>
</tr>
<tr>
<td>UNAIDS</td>
<td>Joint United Nations Programme on HIV/AIDS</td>
</tr>
<tr>
<td>USA</td>
<td>United States of America</td>
</tr>
<tr>
<td>VCCT</td>
<td>HIV voluntary confidential counseling and testing</td>
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<tr>
<td>WHO</td>
<td>World Health Organization</td>
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Acknowledgement

The National Centre for HIV/AIDS, Dermatology and STD has invested in the preparation of these guidelines many meetings, a lot of work within the Centre, and sharing and consulting with all the Center’s partners, including Government, NGOs and donors.

We wish to thank all those who have contributed to the development of the Guidelines for the Prophylaxis of Opportunistic Infections in PLHA. Without whose help, the guidelines could not have been completed. In particular, we wish to record our special thanks to:

- Minister of Health for his constant support.
- The Staff of AIDS Care unit of National Center of HIV/AIDS, Dermatology and STDs for their commitment.
- Dr. Julian Elliott, Technical advisor on HIV treatment, Care and Research, NCHADS and Dr. Veronique Bortolotti, HIV/AIDS Care Consultant, WHO Cambodia, for their cheerful support and valuable help.
- The Continuum of Care Technical Working Group and Sub-Working Group on IC&ARV for their support and valuable held.
- Community Action for Preventing HIV/AIDS, ADB/JFPR REG-9006 for providing technical and financial support.
- Preah Bat Norodom Sihanouk Hospital, Calmette Hospital, Kuntha Bopha Hospital, National Pediatric Hospital, WHO, UNAIDS, MDM, UNICEF, CDC-GAP, FHI/IMPACT, MSF-HB, MSF-F, FC, HACC, CPN+, Center of HOPE, Servant, and Maryknoll for their cooperation and valuable help.

Phnom Penh, 17 November 2003

Dr. Mean Chhi Vun
Director of NCHADS
The escalating HIV epidemic in Cambodia is now producing an expanding need for HIV/AIDS care, as people progress to advanced and symptomatic HIV disease. This need for HIV/AIDS care and support will increase considerably over the next decade, as each year approximately 20,000 people will develop AIDS and die unless expanded interventions are available. The limited resources of the Cambodian health care system will be further stretched due to this impact of HIV/AIDS on care needs.

To effectively respond to this issue, the National Center for HIV/AIDS, Dermatology and STD (NCHADS) of the Ministry of Health, in collaboration with all its partners, has developed the guidelines for the management of HIV/AIDS, including the guidelines for the prophylaxis of opportunistic infections in PLHA. The prophylaxis of opportunistic infections in PLHA is essential to reduce the development of some common opportunistic diseases in PLHA, particularly active tuberculosis and some other bacterial and fungal diseases. The Ministry of Health trusts that these guidelines will be closely followed by all health care workers involved in the ‘continuum of care’ and also trusts that they will be regularly reviewed and updated, to keep pace with the rapid development of health science.

Finally, the Ministry of Health would like to congratulate and appreciate NCHADS, and all its partners, for the hard, professional work that has gone into their development.

Phnom Penh,………November 2003
Director General for Health

Professor Eng Huot
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9.5. Secondary Prophylaxis

Isoniazid

Secondary Prophylaxis

PLHA 2000-2001
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9.99.  

9.96.  

National Guidelines for the prophylaxis of opportunistic infections in people living with HIV/AIDS

November 2003

Kingdom of Cambodia

Ministry of Health

National Center for HIV/AIDS, Dermatology and STD
prospective
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Fluconazole man
mucosal candidiasis
Cryptococcosis
Itraconazole
paBi
Itraconazole
Crytococcosis
Fluconazole
Fluconazole
CD4 > 100 cells/mm³

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CD4 > 100 cells/mm³

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2. Spectrum of Disease

- Penicilliosis
- Toxoplasmosis
- Cryptococcosis
- Salmonella species
- Toxoplasmosis
- Penicillium marneffei

3. Cost-effectiveness

- Incidence
- Mortality
- Morbidity
- Economic implications
- Cost-effectiveness analysis of interventions
- Cost-utility analysis
- Cost-benefit analysis
2.5. Benefits of Cotrimoxazole Prophylaxis in High Income Countries

The benefits of cotrimoxazole prophylaxis in high income countries are well documented. Cotrimoxazole is effective in preventing toxoplasmosis, PCP, and other opportunistic infections in HIV-positive patients.

2.6. Potential Efficacy

The potential efficacy of cotrimoxazole prophylaxis in high income countries is also well established. Cotrimoxazole is effective in preventing toxoplasmosis, PCP, and other opportunistic infections in HIV-positive patients.

West Africa (PLHA) 2000

PLHA

Cotrimoxazole

Potential Efficacy

Cotrimoxazole prophylaxis is effective in preventing toxoplasmosis, PCP, and other opportunistic infections in HIV-positive patients in high income countries. In PLHA (2000), cotrimoxazole prophylaxis was shown to be effective in preventing toxoplasmosis and PCP in HIV-positive patients. Similarly, in other studies, cotrimoxazole prophylaxis has been shown to be effective in preventing toxoplasmosis and PCP in HIV-positive patients.

Notes

20.

2.3. Study Design and Sample Size

Cotrimoxazole 

Cotrimoxazole was administered as a single course of therapy to patients with toxoplasmosis (randomized trial) in Abidjan, Cote d’Ivoire. A randomized controlled trial of cotrimoxazole (double strength) vs placebo was conducted in Abidjan, Cote d’Ivoire (randomized trial) [1].

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