

DRAFT POLICY GUIDELINES FOR COTRIMOXAZOLE PROPHYLAXIS IN UGANDA

Introduction

Uganda was one of the first sub-Saharan countries to be affected by the Human Immunodeficiency Virus (HIV) epidemic. The first two AIDS cases were reported in 1982. Since the mid-1990s, there has been a downward trend in HIV prevalence; however, despite declining trends, the burden of HIV/AIDS disease is high with considerable morbidity and mortality. AIDS is currently the leading cause of death among people aged 15 – 49 years (Ministry of Health of the Republic of Uganda, Annual Performance Report 2002). Approximately 50% of hospitalized patients and 60% of patients with tuberculosis are infected with HIV, and an estimated 1,000,000 Ugandans are living with HIV/AIDS.

HIV/AIDS Care and Support -The National Strategic Framework for Care

In response to the epidemic, the Government has developed and implemented a number of plans regarding HIV/AIDS, most notably the National Strategic Framework for HIV/AIDS Activities in Uganda 2000/1 – 2005/6 and the National Strategic Framework for Expansion of HIV/AIDS Care and Support in Uganda 2001/2 - 2005/6. The goals of the National Strategic Framework for Expansion of HIV/AIDS Care and Support are to reduce morbidity, disability and mortality due to HIV/AIDS, and to improve the quality of lives of HIV-infected people.

Care is an indispensable component of the response to the HIV/AIDS epidemic and the Ministry of Health considers it a priority area of intervention. Investing in the care and support of people living with HIV/AIDS will:

- Complement and enhance prevention activities
- Prolong and improve quality of life
- Maintain the working capacity of the people infected with HIV
- Decrease the social impact of AIDS
- Prevent the secondary spread of infectious diseases like tuberculosis

The Framework was designed in the context of Comprehensive HIV/AIDS care and support and focuses on 3 major components:

- a) Counseling for HIV infection including Voluntary Counseling and Testing (VCT)
- b) Prevention of Mother-To-Child-Transmission (PMTCT)
- c) Clinical management including:
 - i. Prophylaxis against opportunistic infections
 - ii. Treatment of opportunistic infections
 - iii. Antiretroviral therapy
 - iv. Palliative care
 - v. Paediatric AIDS Care

The framework also takes into consideration the existing programs and the National Minimum Health Care Package as articulated in the Health Sector Strategic Plan and National Health Policy documents. Programs providing HIV/AIDS care should be guided by this framework.

Within this context, it is critical that persons living with HIV/AIDS in Uganda have access to effective care. There is a need to expand the use of simple, effective interventions for all persons with HIV/AIDS and access to antiretroviral medication for those who are clinically eligible. One effective, inexpensive intervention is cotrimoxazole (trimethoprim-sulfamethoxazole or Septrin™) prophylaxis.

Cotrimoxazole is a broad-spectrum antibiotic with activity against bacteria and some parasites. Single-strength tablets contain 80 mg trimethoprim and 400 mg sulfamethoxazole, and double strength tablets contain 160mg trimethoprim and 800mg sulfamethoxazole. Each teaspoonful (5 ml) of pediatric suspension contains 40 mg trimethoprim and 200 mg sulfamethoxazole.

Justification for Cotrimoxazole prophylaxis

Cotrimoxazole prophylaxis is standard of care for persons with HIV/AIDS in USA and Europe and is increasingly being used in Africa. Evidence from trials on cotrimoxazole prophylaxis conducted in Africa, including Cote d'Ivoire, South Africa, Malawi, Zambia, and Uganda show reductions in mortality between 25% and 46%, and a beneficial effect of cotrimoxazole in reducing morbidity, even in areas with high bacterial resistance.¹⁻⁸ Cotrimoxazole prophylaxis has also been found to decrease the frequency of clinic visits and hospitalizations, and improve weight.^{1, 6, 9} The beneficial effects of Cotrimoxazole prophylaxis have been found to be similar in both early and advanced HIV disease.^{6, 8, 10}

In colder climates, the primary benefit of cotrimoxazole prophylaxis has been in the reduction of the incidence of *Pneumocystis jiroveci* (formerly *Pneumocystis carinii*) pneumonia, although it has been shown to decrease rates of bacterial pneumonia, toxoplasmosis, and other infections. Studies in Africa have shown a primary effect of cotrimoxazole prophylaxis on the incidence of all cause mortality, malaria, non-typhoidal salmonellosis, *Pneumocystis jiroveci* pneumonia, and diarrhea.¹⁻⁷ In addition, recent studies in Uganda and Zambia showed a beneficial effect of cotrimoxazole prophylaxis on CD4 cell count and HIV viral load.^{6, 8}

Opportunities for providing cotrimoxazole prophylaxis in Uganda

Cotrimoxazole is a safe, inexpensive, and readily available antimicrobial agent, with substantive evidence that it extends and improves quality of life. Daily prophylaxis costs between 15,000 and 25,000 Ug Shs per person per year. It is widely available throughout the country and requires no laboratory monitoring.

Evidence from studies conducted in Africa indicates that cotrimoxazole prophylaxis has few adverse reactions and high levels of adherence.^{3, 6, 7, 11} Its efficacy does not appear to decrease over the 1-2 year follow-up periods in studies. Additionally, the number of persons with HIV that need to be given prophylaxis for a beneficial effect (number-needed-to-treat) is very low: 8 persons per year of life saved, 1 person per case of diarrhea prevented, and 2 persons per case of malaria prevented.⁶ This suggests it is one of the most cost-effective health interventions for persons with HIV. In addition, reductions in morbidity, and the beneficial effects of cotrimoxazole prophylaxis on CD4 cell counts and HIV viral loads, have been observed regardless of CD4 cell count, thus obviating the need for laboratory testing before initiating prophylaxis.³⁻⁷

Cotrimoxazole prophylaxis should therefore be a health priority and part of the standard of care for persons with HIV in Uganda. With additional resources in the country from the Multi-country HIV/AIDS Program (MAP), the Global Fund against AIDS, Tuberculosis and Malaria (GFATM), and bilateral partners, Uganda is in a position to provide cotrimoxazole prophylaxis to all eligible patients. Regional and district hospitals in Uganda have qualified staff. Training and recruitment of staff has increased in recent times to try and match demand. Uganda's decentralized system of service delivery provides an opportunity for effective provision of care.

Current Practice in Africa

The use of cotrimoxazole for the prevention of opportunistic infections in adults and children with HIV/AIDS in Africa has been recommended in provisional guidelines developed from a conference convened by the Joint United Nations Program on HIV/AIDS (UNAIDS) and the World Health Organization in April 2000.¹² WHO/UNAIDS recommends Cotrimoxazole use for prophylaxis in adults and children living with HIV/AIDS in Africa as part of a minimum package of care.¹² The recommendation states cotrimoxazole prophylaxis should be provided to adults and children living with HIV/AIDS in Africa with symptomatic HIV disease (Stage 2, 3 or 4 of the provisional WHO classification of HIV), or asymptomatic individuals with a CD4 count ≤ 500 cells/ μ L or total lymphocyte count equivalent.¹² However only a few African countries, including Cote d'Ivoire and South Africa have made it national policy. More recent data from Africa, including Uganda, shows that Cotrimoxazole prophylaxis reduces morbidity and has beneficial effects on immune function in persons with HIV regardless of CD4 cell count.^{6,8}

POLICY STATEMENTS

Cotrimoxazole prophylaxis should be given to all HIV-infected adults and children in Uganda regardless of whether they are on antiretroviral therapy (ART) or not. In addition, cotrimoxazole prophylaxis is indicated for all children born to HIV-infected mothers, unless testing has shown they do not have HIV.

All persons testing HIV positive should receive counseling and education about cotrimoxazole prophylaxis and be assessed for allergy to cotrimoxazole. This should be done at units providing HIV/AIDS care and support. Counseling and testing centres can also provide this information in their counseling sessions and refer all persons with HIV to appropriate HIV/AIDS care and support units. It is also recommended that all patients attending HIV/AIDS care clinics be assessed for and offered cotrimoxazole prophylaxis.

Cotrimoxazole prophylaxis is indicated for all HIV exposed children (children born to HIV infected mothers) from 4-6 weeks of age (whether or not part of a prevention of mother-to-child transmission [PMTCT] programme), until HIV infection has been definitively ruled out AND the mother is no longer breastfeeding.

Any child identified as HIV-infected regardless of any clinical signs or symptoms suggestive HIV, age or CD4 count.

Recommended regimens:

Adults:

- Two single strength tablets of cotrimoxazole (2 x 80mg Trimethoprim/400 mg sulfamethoxazole) or one double strength tablet (1 x 160mg Trimethoprim/800 mg sulfamethoxazole) daily for life.

Children: ¹³

Recommended dosage for children is 4 mg/kg trimethoprim and 20 mg/kg sulfamethoxazole once daily.

- Cotrimoxazole syrup should be administered once a day; Syrup use is recommended in very young children up to 10-12 kg; 5ml of cotrimoxazole paediatric suspension contains 40mg Trimethoprim/200 mg sulfamethoxazole. If syrup is unavailable, crushed tablets may be used and depending on availability; one may switch from syrup to tablet to ensure uninterrupted medication.
- Once tablets can be taken; (a single strength tablet provides Sulfamethoxazole 400 mg and trimethoprim 80 mg).
 - ≤10kg: half of a single strength adult tablet.
 - 10-25kg: one whole single strength adult tablet.
 - >25kg: two single strength adult tablets.
- Adjust dosages according to body weight rather than body surface area doses

Recommendations for pregnant mothers

Cotrimoxazole prophylaxis is recommended for all HIV positive pregnant women, after the first trimester. HIV positive pregnant women eligible for cotrimoxazole prophylaxis or already receiving daily cotrimoxazole should not be given Sulfadoxine-Pyrimethamine prophylaxis as MOH recommended intermittent preventive treatment for malaria; cotrimoxazole is sufficient and has been proven to have prophylactic effect on malaria as well as other opportunistic infections, and is sufficient in this case.

Recommendations for malaria prophylaxis in HIV infected individuals

HIV positive persons with advanced immuno-suppression are at an increased risk of developing malaria especially severe forms of malaria. For those who require malaria prophylaxis, including pregnant women, and are eligible for cotrimoxazole prophylaxis, or already on daily cotrimoxazole there is no need to take additional drugs for malaria prophylaxis.

Antiretroviral therapy and Cotrimoxazole prophylaxis

The Ministry of Health ART policy recommendation for initiation of antiretroviral therapy (ART) is clearly inclusive of the eligibility for cotrimoxazole prophylaxis, which

also complements ART benefits and should be provided to all people on ART. For persons in ART programs, cotrimoxazole prophylaxis should be initiated first while screening and preparing them for ARVs.

Discontinuing Cotrimoxazole prophylaxis

Cotrimoxazole prophylaxis should ideally be given to adults and children with HIV infection for life because of its beneficial effects on the immune function in persons with HIV regardless of CD4 cell count.^{6, 8} However, the benefit of cotrimoxazole prophylaxis for adults and children on ART in Africa whose CD4 cell counts are >200 cells/ μ L and CD4%>15 respectively has not been evaluated. Until more information is available, the decision to discontinue cotrimoxazole prophylaxis in this group should be made on an individual basis by the provider.

Cotrimoxazole prophylaxis can be discontinued in an HIV exposed child ONLY once HIV infection has confidently been excluded;

- For a non-breastfeeding child <18 months of age this is by negative DNA or RNA virological HIV testing
- For a breastfed HIV exposed child < 18months – negative virological testing is only reliable if conducted 6 weeks after cessation of breastfeeding,
- For a breastfed HIV-exposed child >18 months - negative HIV antibody testing 3 months after stopping breastfeeding

Toxicity

Cotrimoxazole prophylaxis should not be given to anybody with a known severe allergy or hypersensitivity reaction to either of its components (sulphur-containing drugs or trimethoprim).

Adverse effects are rare; studies in Africa show they occur in less than 5% of persons per year, although the potential for cotrimoxazole to cause severe reactions exists. Eighty percent of documented adverse effects seen are skin reactions, 3% are Stevens-Johnson syndrome, and rarely bone marrow suppression, anaemia, neutropenia, and jaundice.^{3, 6-8, 11, 14} Prior to initiating the prophylaxis, both the provider and client should be aware of the possibility to adverse reactions and what to do in the event of occurrence.

Criteria for withdrawal of cotrimoxazole prophylaxis

In both adults and children prophylaxis should be stopped in the event of severe cutaneous reactions such as a fixed drug reaction or Stevens-Johnson syndrome.

Desensitization

For patients who have an adverse reaction that is non-mucocutaneous and not life threatening, reinstatement of cotrimoxazole should be strongly considered after the adverse reaction has resolved. Patients who have experienced adverse reactions may better tolerate reintroduction of cotrimoxazole with a gradual increase in dose (desensitization)

as per published regimens, which gradually increase the dose over a 2-4 week period, or reintroduction of cotrimoxazole at a reduced frequency. More than 70% of patients can tolerate such reinstating of therapy. This procedure should only be conducted under the supervision of a qualified medical doctor. Persons who experience Stevens-Johnson reactions should not be desensitized.

Alternate drugs to use in case of hypersensitivity to Cotrimoxazole

There is no substitute for cotrimoxazole prophylaxis; no single drug is currently known to provide a similar range of protection against morbidity or mortality at such an affordable cost. However there are some alternative regimens for specific conditions.

- Dapsone can be used as an alternative prophylactic agent against *Pneumocystis jiroveci* (formerly *Pneumocystis carinii*) pneumonia. When given with pyrimethamine, it also offers protection against toxoplasmosis.
- Sulphadoxine/pyrimethamine offers some preventive activity against *Pneumocystis jiroveci* (formerly *Pneumocystis carinii*) pneumonia and toxoplasmosis
- Pentamidine can be used to prevent *Pneumocystis jiroveci* (formerly *Pneumocystis carinii*) pneumonia, however it is expensive, not easy to implement and not as effective as cotrimoxazole.

Follow-up

Regular follow-up of clients should be individualized, but a reasonable approach might be monthly for the first 2 months and every 3 months thereafter. At each visit the patient should be monitored for adherence and adverse reactions. Follow-up visits should be synchronized with those for comprehensive HIV/AIDS care including ART.

Issues of Cotrimoxazole resistance

Despite high bacterial resistance to cotrimoxazole in Uganda, cotrimoxazole prophylaxis has been effective in reducing morbidity and mortality. Long-term cotrimoxazole prophylaxis by persons with HIV was not associated with increased antimicrobial resistance among diarrheal pathogens infecting HIV-negative family members. In Uganda, it is estimated that 5% of the adult population <50 years old, and many fewer children, have HIV infection. Thus, even if every person with HIV begins cotrimoxazole prophylaxis, <2% of the population would be taking prophylaxis on a daily basis. It is unlikely that this would have a major effect on rates of bacterial or parasitic resistance to cotrimoxazole or sulfadoxine-pyrimethamine, compared with the use of these drugs for treatment. However, with a 50% reduction in morbidity and mortality, cotrimoxazole prophylaxis could have a profound effect on the health and longevity of persons living with HIV in Uganda.

Education and Training

All stakeholders including public and private health care providers should advocate for the use of Cotrimoxazole prophylaxis. Patients, care givers and communities should be

made aware that regular cotrimoxazole prophylaxis will prevent infections that are more common in HIV infection and improve the quality of life for persons with HIV/AIDS. Cotrimoxazole prophylaxis, however is not a cure for HIV and does not replace the need for antiretroviral therapy.

Health care providers at all levels should receive education and training in provision of cotrimoxazole prophylaxis. They should be educated about how to counsel clients and care-givers, including the benefits of prophylaxis, eligibility, adherence, and possible adverse reactions.

Essential Drug List

Cotrimoxazole is included as an antibiotic on the Essential Drugs List of Uganda 2001 for treatment purposes. There is need to include this additional important use of cotrimoxazole for prophylaxis among persons with HIV/AIDS

Table 1 Studies of cotrimoxazole prophylaxis among persons with HIV in Africa

Country	Authors	Study design	Participants	Inclusion criteria	Adverse events per year	Results: Reduction in
South Africa ²	Badri, et al,	Observational cohort	609 (adults)	WHO stages 2-4 or CD4 count <500	Not reported	Mortality ↓ 44% Morbidity ↓ 48% WHO stage 2: no benefit
Cote d'Ivoire ¹⁵	Anglaret et al.	Randomized trial	541 (adults)	WHO stages 2-3	0.6%	Severe event ↓28% NS
Cote d'Ivoire ¹	Wiktor, et al	Randomized trial	771 (adults)	TB and WHO stages 3-4	Not reported	Mortality ↓46% Hospitalizations ↓ 43%
Senegal ¹¹	Maynard, et al.	Randomized trial	100 (adults)	WHO stage 1-4 and CD4 < 400	4%	Mortality ↓16% NS Morbidity ↓NS Stopped prematurely
Zambia ⁵	Mulenga, et al. (abstract)	Randomized trial	540 (children 1-14 years)	HIV-positive	Skin rash =0.3% Anemias =5.7% neutropenias =3%	Mortality ↓ 43% Admissions ↓20%
Zambia ⁸	Chintu, et al.	Randomized trial	541	Symptomatic HIV-infected children 1-14 years	Similar in intervention and control groups	Mortality ↓ 43% Hospitalizations ↓ 23%
Malawi ³	Zachariah, et al.	Cohort	1986 (adults)	TB and all CD4 counts	< 2%	Mortality ↓ 25%
Malawi ⁴	Mwaungulu, et al.	Cohort	717 (adults)	TB and all CD4 counts	Not reported	Mortality ↓ 28%
Uganda ⁶	Mermin, et al.	Prospective cohort	509 (adults and children)	All HIV positives	2%	Mortality ↓ 46% Hospitalizations ↓31% Diarrhea ↓35% Malaria ↓ 72%
Uganda ⁷	Watera, et al. (Abstract)	Cohort	806 (adults)	All HIV positives	3%	Mortality ↓ 33% Malaria ↓ 69%

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