COTRIMOXAZOLE PREVENTIVE THERAPY FOR HIV-POSITIVE PERSONS IN MALAWI

New and recent evidence (see references 1-12) shows that cotrimoxazole (CTX) preventive therapy is associated with a 25-46% reduction in mortality in sub-Saharan Africa, even in areas with high bacterial resistance to the antibiotic. CTX preventive therapy also decreases the frequency of clinic visits and hospitalisations, improves weight and reverses the decline in CD4-lymphocyte counts and the rise in HIV viral loads. Efficacy seems to be maintained over the 1-2 year follow-up periods of the studies. CTX preventive therapy in Africa has few adverse reactions and there are high levels of adherence. In summary, CTX is a safe, cheap and readily available anti-microbial agent, which can extend and improve the quality of life.

There is therefore unanimous agreement to modify the current recommendations for CTX preventive therapy in Malawi. It is also agreed that these be regarded as "Interim" as the evidence-based for some of the recommendations is scarce or absent.

CTX should be used for preventive therapy in adults and children living with HIV/AIDS in Malawi as part of a minimum package of care and that this intervention is provided to adults and children free of charge.

In Adults:

CTX should be offered to the following HIV-positive adults (aged 13 years and above):

- All persons with symptomatic HIV disease (Stage II, III and IV)
- All persons who have a CD4-lymphocyte count of 500/ mm^3 or less, regardless of symptoms
- Pregnant women after the first trimester who are symptomatic or have a CD4-lymphocyte count < 500/ mm^3

Note: In adults there is not enough evidence to recommend CTX to HIV-positive adults who are asymptomatic (ie Stage I). However, if the evidence is forthcoming in the future then this recommendation will be re-examined. It was also felt that the threshold of CD4-count of 500cells/mm^3 may be too high, but it is agreed to stick with this threshold as it is similar to that recommended by WHO. Again, if evidence is forthcoming in the future that this threshold is too high, the recommendation will be re-examined.

In Children:

CTX should be offered to children in the following circumstances:

- Any child, aged 6 weeks or above, born to an HIV-positive woman irrespective of whether the woman received antiretroviral therapy in pregnancy
- Any child, 6 weeks or more, who is HIV-positive regardless of symptoms

Note: All HIV-positive children should be offered CTX because they have higher viral loads than adults, progress faster to AIDS and to death compared with adults and at present do not have the same opportunities to access antiretroviral therapy as adults.

Operational Issues:

Drug Regimens and individual patient supply:

Adults:

One single-strength tablet of CTX (480mg) is taken twice a day, one tablet in the morning and evening. Drugs are supplied to patients for 3 months at a time.

Children:

For children aged less than 5 years, half a tablet (240mg) is taken once a day.
This medication is taken from six weeks of age.

For children aged 5 years or more, one tablet (480mg) is taken once a day

Contra-indications:
Known allergy to CTX for adults and children
First trimester of pregnancy for adult women

Duration of therapy:

Adults:
CTX prophylaxis should be lifelong. If antiretroviral therapy is started , then CTX should be continued. CTX should be **discontinued** in the event of severe cutaneous reactions, renal or hepatic toxicity or severe haematological toxicity

Children:
In HIV-exposed infants (ie children born to HIV-positive women) CTX should be taken until HIV infection can be confidently excluded. At 18 months of age and provided the child has stopped breast-feeding, the child should have an HIV test. If the child continues to breast feed after 18 months, CTX is continued until 3 months after breast-feeding has stopped and the child is then offered an HIV test. In both situations, if the HIV test is positive, then the child continues on CTX indefinitely. If the HIV test is negative, then the child discontinues CTX.

HIV-positive children take CTX life-long. If antiretroviral therapy is started, then CTX should be continued. CTX should be **discontinued** in the event of severe cutaneous reactions, renal or hepatic toxicity or severe haematological toxicity

Note: There is no evidence in adults or children to show the added benefit or not of CTX when combined with ARV therapy. This is an area of uncertainty, which requires both clinical and operational research. Such research conducted in Malawi, either through clinical trials or operational research, is highly encouraged.

Recruitment:

Adults:
The entry point to CTX preventive therapy is through Counselling and HIV testing. Once a client is known to be HIV-positive, he/she is referred for clinical staging if there are symptoms. Once staged by a clinician as being in Stage II, III or IV, the client will be given a prescription of CTX to take to the pharmacy in order to collect drugs for 3 months provided there are no contraindications. Follow-up will be undertaken usually in the general OPD unless health care facilities have the resources to staff and run HIV care / support / and follow-up clinics (see below).

Children:
HIV-exposed infants. Children, aged six weeks or above, who are born to HIV-infected mothers (usually through the PMTCT programme) will be given a prescription of CTX for their mothers to take to the pharmacy in order to collect drugs for 3 months provided there are no contraindications.

HIV-positive children. Children will be identified HIV-positive through under-five clinics, the general out-patient department and through high risk areas such as nutritional rehabilitation units. HIV-positive children, aged 6 weeks or above, will be given a prescription of CTX for their mothers to take to the pharmacy in order to collect drugs for 3 months provided there are no contraindications.

Follow-up, monitoring and evaluation:
Supplies of CTX preventive therapy will be given to last for 3 months. Every three months the patient (adult or child) will be reviewed by a clinician in the OPD, the HIV care and

support clinic, the under-five clinic or other setting, following which the next supply of drugs will be collected at the pharmacy. Each clinic visit will be documented in the health passport.

The pharmacy will keep the vital register for CTX preventive therapy. Patients will be given a unique CTX registration number, and this number plus name, age and sex will be entered into the register. The patient's registration number will be written into the health passport. If the patient has no health passport, then the CTX number will be written on a card. The register will have a row for each patient, and each row divided into several columns. When a patient comes to collect CTX, the appropriate column will be ticked off with the date to indicate that the drugs have been given. Thus, the monitoring of the number of patients (adults and children) starting CTX and the number who continue on CTX will be carried out through regular checks on the CTX register in health facility pharmacies.

Drug Supply:

CTX will be supplied through existing drug systems. In the Global Fund Proposal for year 3, 4 and 5, a budget line has been created for CTX. In the third year the budget line is for 100,000 tins of CTX (containing 1000 tablets per tin), which would provide almost 140,000 persons on CTX for one year. This budget line increases in the next two years to cater for an increased number of persons on CTX. Tins of CTX will be procured through the Global Fund, supplied to Central Medical Stores and distributed in standard manner to peripheral facilities.

Adults will receive 180 tablets of CTX 480mg every three months. Procurement of tins with this quantity would facilitate drug dispensing and drug monitoring, and enquiries will be made about feasibility.

Training and Education:

Health care providers will need to be briefed on the new policy, and this will be incorporated into the ARV-HIV related diseases management module that is currently taught to clinicians and nurses in the country. The policy should also be incorporated into other ongoing training courses such as Integrated Management of Childhood Illness (IMCI). Teachers at the various training institutions in Malawi for nurses, clinical officers and medical doctors should be made aware of the policy revision so that it is incorporated into the curriculum for undergraduate teaching of the management of HIV-related illness.

Pharmacy technicians will need to be briefed on how to monitor CTX use and how to fill in the drug registers. This training should be organised by the HIV Unit.

Implementation:

There will be a phased scale-up of CTX preventive therapy, with 6-12 district or mission hospitals implementing the service for 6 months, and being assessed before expanding to other sites.

Research:

These policy recommendations are regarded as "Interim" as the evidence base for some of them are scarce or absent. In particular, research is encouraged into the value of CTX :- a) in conjunction with ARV therapy; b) given to un-infected children born to HIV-positive mothers as a large percentage of children born to such mothers will in fact be HIV-negative.

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