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WHO EXPERT CONSULTATION ON COTRIMOXAZOLE PROPHYLAXIS IN HIV INFECTION

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Contents

Acronyms and abbreviations

AIDS	Acquired Immunodeficiency Syndrome
ARV	Antiretroviral
ART	Antiretroviral therapy
CHAP	Children with HIV antibiotic prophylaxis trial (CHAP Trial)
CTX	Cotrimoxazole
DART	Development of Antiretroviral Therapy in Africa (DART Trial)
HAART	Highly active antiretroviral therapy
HIV	Human immunodeficiency virus
Hb	Haemoglobin
HQ	Headquarters
IMAI	Integrated Management of Adult/Adolescent Illness
IMCI	Integrated Management of Childhood Illness
IPT	Intermittent preventive treatment
MDR	Multidrug resistance
MTCT	Mother-to-child transmission
NTS	Non-typhoidal salmonella
OI	Opportunistic infections
PCP	*Pneumocystis jiroveci* pneumonia (formerly *Pneumocystis carinni* pneumonia)
PLWHA	People living with HIV/AIDS
RCT	Randomized clinical trial
SP	Sulfadoxine-pyrimethamine
SMX	Sulfamethoxazole
TB	Tuberculosis
TMP	Trimethoprim
UNICEF	United Nations Children's Fund
UNAIDS	Joint United Nations Programme on AIDS
VCT	Voluntary counselling and testing
WBC	White blood cells
WHO	World Health Organization
ZDV	Zidovudine

1. Introduction

Cotrimoxazole (CTX), also known as Sulfamethoxazole-Trimethoprim (SMX-TMP), is a broad-spectrum antimicrobial agent that targets a variety of aerobic Gram-positive and Gram-negative organisms and protozoa. The drug is widely available in both syrup and solid formulations at low cost in most places, including resource-limited settings.

Provision of CTX as primary or secondary prophylaxis for prevention of *Pneumocystis jiroveci* pneumonia (PCP) (formerly *Pneumocystis carinii* pneumonia) and toxoplasmosis has been part of the standard care in the management of HIV-infected individuals in developed countries since the early 1990s. Though provisional WHO/UNAIDS guidelines for CTX have been in place since the year 2000, most countries have not implemented this intervention widely. Some of the concerns related to the slow implementation of CTX include the difference in etiology and burden of common opportunistic infections between developed and resource-poor countries, the potential for drug resistance, pill burden and the lack of guidelines for duration of therapy. There has also been concern over the limited evidence base on CTX prophylaxis. To date, more effort has gone toward scaling up the provision of antiretroviral therapy (ART), whose efficacy is undisputed, than toward implementing CTX prophylaxis.

Over the past few years, more data from resource-limited settings have become available on the feasibility and the positive impact of CTX prophylaxis on morbidity and mortality among adults and children infected with HIV. CTX has been shown to be effective in preventing bacterial infections and malaria, despite the existence of variable levels of resistance to CTX. In addition, with the scaling up of highly active antiretroviral therapy (HAART) in resource-poor settings, there is the possibility that immune reconstitution secondary to HAART may provide opportunities for discontinuing CTX.

This meeting was organized by WHO/HIV/HQ to review current developments in the use of CTX prophylaxis and to formulate recommendations for CTX prophylaxis in adults and children in resource-limited settings.

2. Meeting objectives

- Review available data on CTX prophylaxis;
- Exchange regional and country experiences;
- Revise the recommendations for CTX prophylaxis in HIV-infected adults and children;
- Consider research priorities;
- Develop simple guidance on when to initiate and discontinue CTX prophylaxis in HIV-infected adults and children for use in programmes scaling up access to HIV care and treatment.

3. Expected outcomes

Global technical and operational recommendations for a comprehensive use of CTX prophylaxis in HIV-infected patients in the context of HAART scale-up in resource-limited settings.

4. Summary of presentations and discussions

The participants discussed research findings in plenary sessions and worked in smaller groups to develop specific recommendations in the following major areas:

- Starting CTX prophylaxis in adults and children;
- Discontinuing CTX in adults and children;
- Using CTX in special situations;
- Making operational recommendations: implementation, policy framework and operational research.

The following summarizes the discussions from these sessions.

4.1 New evidence for cotrimoxazole prophylaxis effectiveness in HIV-infected patients

Adults

Presentations were made that reviewed data on the effectiveness of CTX in reducing morbidity and mortality among HIV-infected patients in resource-limited countries. Data were shown from randomized clinical trials (RCTs), observational cohort studies and programme analyses in several African countries (with varying levels of CTX resistance), India and Thailand. There is a notable paucity of evidence from the Caribbean and Latin America. A further weakness is the lack of specific data on the etiology of morbidity and mortality events in almost all studies presented during the meeting.

Numerous studies have documented the value of CTX in prevention of PCP, toxoplasmosis and bacterial infections. Data were presented from a study conducted in a high tuberculosis (TB) and HIV-prevalence area but with low malaria transmission in South Africa, showing reduction in mortality in adults on treatment for active tuberculosis using CTX prophylaxis, irrespective of HIV status (*1*). There was extensive discussion over whether CTX should be offered to all individuals within high-risk populations with high levels of HIV infection (such as patients on treatment for active tuberculosis) without HIV testing and counselling where it is unavailable. The meeting reached a consensus agreement that this would be acceptable as an interim arrangement. However, it was stated that this should not detract from efforts to ensure that all TB patients in high HIV prevalence settings are routinely offered HIV testing and counselling.

The LUCOT study, a recently completed RCT from Zambia, suggested that despite being safe and well tolerated, the effect of CTX waned with time, probably due to falling adherence levels. There is no evidence of benefit in patients who had completed their anti-tuberculosis treatment prior to starting the study. The findings of this study, in a setting of high levels of resistance, are consistent with those from non-randomized studies, which have shown benefit from prophylaxis with CTX in reducing mortality in HIV-infected adults with newly diagnosed pulmonary tuberculosis.

A study conducted in Uganda reported a reduction in mortality from all causes and in morbidity from malaria and diarrhoeal diseases in a community before and after CTX prophylaxis was provided to those with HIV infection. The study also suggested a slower decline of CD4 count during the use of CTX. However, this effect has never been described elsewhere, and some experts have suggested that this may be part of natural disease progression and a survivorship effect given the "before and after" nature of the study (*2*). A second intervention from Uganda, with a similar study design but within a different community also demonstrated a reduction in mortality and malaria but did not demonstrate a similar effect on CD4 counts, with an increasing rate of decline in CD4 count in those with higher baseline CD4 counts and a slowing decline rate in those with lower baseline counts (*3*). Discussion focused on the need to further analyse the two studies and the need for more work in this area.

The study conducted in Uganda also demonstrated the benefit of CTX prophylaxis in untreated, HIV-negative family members. Mortality among HIV-negative children under age 10 of adults treated with CTX was lower than in those children of untreated HIV-infected adults, with reductions in diarrhoea and malaria (*4*). Only a percentage of this reduction could be attributed to the decreased mortality of parents, a recognized risk for child mortality that suggests a potential and important additional effect of CTX.

Taken together, these studies show the effectiveness of CTX across varying levels of background resistance to CTX and prevalence of malaria.

Children

Data on the effectiveness of CTX prophylaxis are particularly scarce regarding infants, due to the complexity of early diagnosis of HIV infection in infants under 15–18 months of age and the limited use of CTX prophylaxis in managing paediatric HIV in many resource-limited settings. This is despite the clear data from resource-limited and well-resourced settings that PCP contributes to significant morbidity and mortality in HIV-infected children, particularly under one year of age (*5, 6*). A cumulative report from the United States of America (*15*) among children aged <13 years showed that PCP contributed to 34% of the opportunistic infection and remained the most common opportunistic infection in HIV-infected children. In South Africa, in 1999 and 2002, PCP in HIV-infected children (under one year) contributed to 10% and 49% respectively of hospital admissions and 47% and 28% mortality respectively (*7*). A similar study from Malawi reported that 25% and 63% of hospital admissions and mortality respectively were due to PCP infection while a study from Thailand showed that PCP contributed to 35% of hospital admissions and 44% mortality among HIV-infected children admitted with pneumonia (*6, 8*). In Zambia, a postmortem study documented PCP as the predominant (50%) cause of mortality in HIV-infected infants under the age of six months (*9*). There was consensus that these findings emphasize the need for early administration of CTX prophylaxis in infants in all settings for the maximum benefit of preventing mortality.

Beyond the age of one year, results from resource-limited settings indicate that bacteria are the predominant cause of pneumonia, leading to significant morbidity and mortality in children with HIV infection. Unfortunately, despite these data, there is limited use of CTX prophylaxis in children.

A randomized clinical trial using CTX prophylaxis in 541 HIV-infected children (age 1-14 years) from Zambia—the CHAP trial—showed significantly reduced hospital admission and mortality rates over a substantial period of time (43% reduction over 19 months) compared to the placebo group. This was the case despite high levels of *in vitro* resistance of common bacterial pathogens to CTX (60-80%) (*5*). The effect was recognized across all ages and CD4 percentages. This study was terminated early due to the statistically significant benefit of CTX in reducing mortality compared to a placebo. PCP was not identified as a cause of respiratory deaths in these older children.

Data were presented from a study in Côte d'Ivoire, which followed a cohort of children treated with CTX prophylaxis based on CD4 threshold or clinical symptoms or both. Apart from problems with adherence, particularly among those co-infected with TB, the study demonstrated that CTX prophylaxis is a feasible strategy. The country has moved to rolling out CTX prophylaxis for children along with scaling up ART.

4.2 Criteria for starting cotrimoxazole prophylaxis

Adults

Consistent evidence supports the effectiveness of primary CTX prophylaxis in those with CD4 counts <200 cells per mm^3 from all studies that provide data on CD4 counts (2, *11, 12*). Similarly, studies show that those with World Health Organization (WHO) stages 3 or 4 clearly benefit from CTX prophylaxis as well as all studies with TB-HIV coinfected patients (*2, 10, 11*). Some presentations provided evidence to support the use of CTX prophylaxis with higher CD4 counts or less advanced disease, (i.e. WHO clinical stages 1 and 2). However, the original RCTs from Abidjan differ somewhat in their findings. This may, in part, be due to the difference in outcome measures. One study showed a significant reduction in severe events (defined as death or hospital admission) in all participants irrespective of CD4 count (*10*). However, the other demonstrated some reduction in mortality across all CD4 counts but this only achieved significance in those with CD4 counts below 350 cells per mm^3 (*11*). The ability to define the effects of CTX in various CD4 strata is often limited by the small number of participants in studies. It remains to be seen whether meta-analysis of the studies would be possible to better define the effect.

There is extensive evidence from high-income settings for the use of a CD4 threshold of <200 cells per mm^3 for starting CTX for the prevention of PCP and toxoplasmosis (*12*). On the other hand, clear benefits were shown in the Ugandan study in the incidence of diarrhoeal illness and malarial episodes throughout all CD4 strata (*2*).

In settings with limited access to CD4 cell counts, all patients with advanced and severe HIV disease (WHO stages 3 and 4) should receive CTX prophylaxis. Despite the lack of definitive data on the effect of prophylaxis on those in WHO stage 2, a strong case was made on an operational basis to include them in prophylaxis provision. Claims were made about ease of provision and motivational reasons to provide CTX for all people with HIV infection regardless of CD4 cell count or stage of disease. There are also some clinical and cost-effective arguments since one study demonstrated reduction of early severe morbidity (*10*). However, provision of CTX prophylaxis to all infected people and the impact this might have on adherence are two challenges that must be considered. Consensus was not reached and it was suggested that this should be left as a possible option for individual countries to consider during adaptation of their national guidelines. There was agreement that the recommendations must include a degree of flexibility to enable the most appropriate decisions to be made at country or even local level, taking into account variations in the burden of HIV, disease spectrum as well as capacity and infrastructure of health systems.

During the discussions, it was felt that countries might be able to use the knowledge of those common diseases that can be prevented in their setting with CTX prophylaxis and at what stage of HIV disease these illnesses tend to occur in reaching a decision on which threshold of CD4 or stage they should use for initiation of CTX prophylaxis.

Children

As with adults, there is a growing body of evidence on the benefit of CTX prophylaxis in infants with HIV (*5, 12, 13*).

Studies confirm that there is a much higher risk of PCP among HIV-infected children <12 months of age (peak at 3-6 months) in all settings (*15, 16*). This age group is also problematic because definitive diagnosis of HIV infection requires the use of tests for viral detection, which are not available in most resource-poor settings. Therefore, infants often die of PCP before being recognized as having confirmed HIV infection. For this reason, in well-resourced countries, CTX prophylaxis is provided to all HIV-exposed infants until HIV infection can be excluded (*16*). Thus, the meeting recommended CTX prophylaxis for all HIV-exposed infants under age 18 months starting at 4–6 weeks of age or when first seen and continued until HIV infection can be excluded. CTX was also recommended for a breastfeeding child of any age, continued until HIV infection

can be excluded following cessation of breastfeeding, with testing performed six weeks or more after breastfeeding was stopped.

After the age of one year, CTX prophylaxis use can be guided by the CD4 level. However, unlike adults, absolute CD4 count is high in infants and decreases with age to reach adult values at approximately six years (*17, 18*). Therefore, adult CD4 count thresholds are not applicable to younger children; CD4 percentage is more stable and may be more useful to predict risk in children between one and five years of age. After five years of age, adult thresholds may apply.

The review of experience from well-resourced countries (United States) noted that all HIV-exposed infants receive CTX prophylaxis until HIV infection is excluded or until age 12 months (*16*). The need for subsequent prophylaxis is based on age-specific CD4 count (or CD4 <15%):

- <500/mm3 if 1–5 years
- <200/mm3 if ≥5 years.

In this situation, CTX is provided based on the CDC immunologic category (Category 3) of the child and the follow-up consists of periodic determination of CD4 level.

The study from Côte d'Ivoire demonstrated the benefit of CTX for children offered CTX based on their CD4 level (CD4< 25%). However, the study from Zambia demonstrated the benefit of CTX across all levels of CD4 percentage (*5*). It was therefore agreed that CTX should be offered to asymptomatic (WHO Stage 1) children <5 years of age with CD4 <25% and all symptomatic (WHO Stage 2, 3 or 4) children older than 12 months, regardless of CD4 percentage or count. It was also agreed that for children older than five years of age the corresponding adult CD4 threshold should be applied. It was emphasized that children with documented HIV infection should get CTX prophylaxis for the first 12 months of life, regardless of CD4 percentage, due to the high risk of PCP and lack of predictive value of CD4 in that age group.

It was argued that in some countries with a high burden of mortality and morbidity due to infectious diseases (e.g. malaria, bacterial infections), CTX should be offered to HIV-infected children in all clinical stages, including asymptomatic children despite their CD4 level. While consensus was not reached, this option is further strengthened by the findings of the Ugandan study, where children under the age of 10 were nearly two thirds less likely to die if a family member was receiving CTX (*4*). The option of providing CTX to all children was considered as an adaptation issue for individual countries. It was also suggested that in circumstances where HIV testing is not available, CTX prophylaxis should be recommended for children identified clinically as symptomatic HIV cases (identified using IMCI or IMAI algorithm). Again, consensus was not reached and efforts should continue to obtain confirmation of HIV exposure or infection status or both.

4.3 Adverse reactions to cotrimoxazole

The potential adverse reactions to CTX include skin rash, haematological reactions, namely neutropaenia anaemia and liver toxicity. The available studies and data from programmes in low- and middle-income settings report low rates of adverse reactions. There was some suggestion that additional haematological adverse effects could be detected with availability of laboratory monitoring.

Studies from resource-poor settings have, to date, documented fewer side effects in adults and in children as well. The most commonly observed adverse reaction among 540 children enrolled in the CHAP study was mild, moderate rash, with no report of serious or life-threatening rash (grade 3 or 4) (*5*).

4.4 Monitoring of CTX prophylaxis

In settings where monitoring HIV infection (including those on ART) consists of routine laboratory tests carried out as part of HIV care or work-up for ART, such as CD4 counts, white blood cell (WBC) count and haemoglobin level checks, this monitoring should continue with CTX prophylaxis and no additional laboratory monitoring should be required for CTX prophylaxis alone. Apart from this no formal additional laboratory monitoring should be required for CTX alone. It was agreed that individuals entering a prophylaxis programme should be provided with information on how to recognize common CTX reactions such as jaundice and rash and what to do should they occur. Clinical monitoring of individuals should be performed by health staff at the site of CTX provision at three monthly intervals, followed by laboratory investigations or referral, as required.

4.5 Discontinuation of cotrimoxazole prophylaxis on ART

Adults

The issue of whether to continue CTX in patients on ART who have experienced immune restoration is coming to the fore. If CTX is well tolerated and the patient is on ART, uncertainty exists about whether it is necessary to continue CTX prophylaxis for an unlimited period; or if and when it can be safely be discontinued. Advantages to discontinuation may include reduced risk of drug interactions, and decrease in pill burden. However, stopping prematurely may increase the risk of severe morbidity or mortality.

It has been well established that effective ART results in immune restoration and a marked decrease in mortality and morbidity. In high-resource countries, where the main effect of CTX prophylaxis is to prevent PCP and toxoplasmosis, several studies have shown that CTX discontinuation is safe and feasible in such patients. Since the risk of both PCP and toxoplasmosis is increased with CD4 counts of less than 200 cells per mm^3 (*19*), an individual could be considered for discontinuation of CTX who has fulfilled two criteria. First, he or she has responded and is well and adherent to ART and second, he or she has at least two CD4 counts obtained at least three months apart that are >200 cells per mm^3, and in the absence of clinical events. There is evidence from both India and Thailand supporting the safety of discontinuing CTX prophylaxis under these circumstances (20). In settings where the only concerns are that of preventing PCP and toxoplasmosis this practice can be recommended. Insufficient data exist on the safety of discontinuing CTX in the absence of CD4 counts, using clinical criteria alone. However, these studies had a limited number of participants and the safety of such a strategy in resource-limited settings awaits larger studies.

In addition, few studies have assessed the impact of CTX discontinuation on incidence of bacterial infections, particularly in resource-limited settings where bacterial infections are a predominant cause of HIV-associated morbidity and mortality. No data exist with or without the use of CD4 cell count monitoring on the safety of discontinuing CTX once ART-induced immune restoration has been determined in these settings. As a result, no formal recommendations were made on discontinuation of CTX.

Insufficient data exist on the safety of discontinuing CTX in the absence of CD4 counts, using clinical criteria alone. In these situations, the lack of CD4 monitoring hampers the ability to identify thresholds at which CTX needs to be reinitiated. Failure to recognize clinically if the CD4 count falls could lead to episodes of PCP, toxoplasmosis or other opportunistic infections. Since some individuals may wish to stop CTX as their conditions improve after starting ART, advice might need to be provided about the safety of stopping CTX. In order to determine if the time to

CD4 restoration could be anticipated in settings without availability of CD4 cell counts, data were reviewed from the Development of Antiretroviral Therapy in Africa (DART) study in Uganda from initiation of ART to increase in CD4 cell count. The median time to a CD4 count >200 cells per mm^3 was 24 weeks among those who commenced ART with CD4 counts greater than 100 cells per mm^3. In those whose baseline CD4 counts were below 50 cells per mm^3, at the time of ART initiation, the median time to CD4 recovery (>200 cells per mm^3) was 72 weeks. The data suggested that some patients with low CD4 may never achieve CD4 cell count above 200/ cells per mm^3. These data indicate a longer time to immune reconstitution than anticipated and make it more difficult to estimate a suitable period to reach adequate immunity in settings where no CD4 monitoring is available.

When CD4 counts are available to guide discontinuation of CTX and clinicians or individuals wish to consider discontinuation, the level that should be achieved prior to stopping prophylaxis should be higher than the threshold used to initiate CTX. Additional clinical factors should be considered, including adherence to HAART, drug availability and supply, and time free from clinical events.

With respect to the use of CTX in pregnancy; since the risk of life-threatening infection in a pregnant woman with a low CD4 count (<200 cells/mm^3) or clinical symptoms of immunosuppression (WHO stages 2, 3 or 4) outweighs the theoretical risk of congenital abnormalities, women who require CTX and become pregnant should continue CTX prophylaxis throughout pregnancy.

Children

There are very limited data on children with regard to when to discontinue CTX prophylaxis in the context of ART. A study involving multiple sites in the United States suggests that prophylaxis can be withdrawn safely for HIV-infected children >2 years of age who demonstrate sustained recovery of CD4 count while receiving ART, based on no increase in bacterial infections observed in the children following discontinuation of CTX prophylaxis. Furthermore, no cases of PCP occurred in these children (*21*). Several studies from other well-resourced countries have suggested similar criteria to that of adults for discontinuation of CTX in HIV-infected children.

It was recognized that with the main concern of the potential for rapid decline of CD4 in children and the limited capacity to measure CD4 counts in resource-limited settings, it may be essential to obtain more information to determine the criteria for discontinuation of CTX in children. The meeting agreed that it is not possible to make recommendations on discontinuation of CTX in HIV-infected children for resource-limited settings at this time. However, it was suggested that for some countries where ART is well in place and CD4 cell monitoring is available, the option of discontinuing CTX could be considered in clinically asymptomatic children who have received HAART for at least two years and who have confirmed CD4 >25% for children aged one to four years (two tests performed at least three months apart) or >adult threshold for children >5 years old; if CD4 falls below the threshold, CTX should be reinstated. It was also agreed that in the absence of CD4 monitoring availability, CTX should not be discontinued.

4. 6 Bacterial resistance to cotrimoxazole

The benefits of CTX prophylaxis in HIV-infected individuals include the prevention of bacterial infections (*Pneumococcus,* non-typhoidal Salmonella (NTS)), diarrhoeal disease (*Isospora, Cyclospora*), *Plasmodium falciparum* malaria, toxoplasmosis and PCP. CTX has been used widely as treatment for common infections in many resource-poor settings and, as a result, in these areas CTX resistance among these pathogens has increased. Several of the studies that assessed the efficacy of CTX prophylaxis demonstrated its value despite high rates of background CTX resistance in bacterial pathogens in those settings. Resistance of non-typhoidal Salmonella (NTS)

and *Pneumococcus* has been reported as 44% and 52% respectively in Uganda (*2*) and as high as 85% in Malawi (*22*) for both. It is also recognized that despite the high rates of resistance, treatment failure is uncommon in the case of pneumonia.

One study from Malawi showed significant increase in resistance of pharyngeal and faecal isolates from those receiving CTX prophylaxis (*23*). Some reassuring data from Uganda found no significant changes in the bacterial resistance patterns of stool pathogens isolated from the family members of individuals on CTX prophylaxis over a two-year period (*4*). However, there is concern that the implementation of wide and prolonged use of CTX prophylaxis could be associated with the development of multi-drug resistance (MDR) in common pathogens, such as increased penicillin-resistant pneumococcus (*24*).

The panel discussed the need for sentinel surveillance to monitor the incidence of resistance among invasive and carried organisms as an element of any CTX prophylaxis programme. However, it remains unclear as to what methods should be used to best monitor such resistance. While the resistance pattern of carriage isolates may reflect that of invasive isolates (*25*) it is thought that it might be preferable to monitor resistance patterns of invasive isolates.

Despite the lack of data on the subject, the panel members advised the use of an alternative antibiotic (where available) for the treatment of breakthrough bacterial or diarrhoeal infections in HIV-infected individuals receiving CTX prophylaxis, while continuing CTX. In the case of toxoplasmosis and PCP infections where the standard of care for treatment of such events is the use of high-dose CTX, prophylaxis should be suspended in those settings in favour of a full-treatment dose.

4.7 Cross-resistance of cotrimoxazole with sulfadoxine pyrimethamine (SP)

CTX has been shown to be 99.5% effective in preventing malaria compared to an efficacy of 95% with SP, and both have around 80% therapeutic efficacy for treatment of malaria (*26*). Pyrimethamine and trimethoprim act by inhibition of parasite dihydrofolate reductase (DHFR) while sulfadoxine and sulfamethoxazole both inhibit parasite dihydropteroate synthetase (DHPS). Cross-resistance between each regimen has been demonstrated *in vitro* via the development of mutations in the genes coding for the targeted enzymes. Because of this, cross-resistance between CTX and SP, *P. falciparum* with anti-folate resistance is a potential concern when CTX prophylaxis is used in areas where SP is the first-line treatment for malaria. However, clinical failure only occurs following the accumulation of all of the five possible mutations. Analysis of malaria parasites from children in Mali who had received at least one month of CTX prophylaxis detected no resistance-conferring mutations (*26*). The investigators concluded that, at present, there is no clinical evidence for long-term CTX selecting for these anti-folate mutations. Similarly, there was no significant difference between either the proportion of malarial episodes with resistant mutants or the incidence of SP resistant malaria before and after the introduction of CTX prophylaxis in the Ugandan study (*4*). It is important to note that the study from Mali utilized isolates from patients with limited duration of exposure to CTX and the study from Uganda included assessment of a limited number of malaria episodes. Further studies are needed to confirm these findings.

There is no evidence yet on SP efficacy for treatment of episodes of malaria in persons taking CTX prophylaxis but it was believed to make clinical sense to use, where possible, a non-antifolate-based antimalarial to treat breakthrough episodes of malaria for those on CTX prophylaxis. The panel members concurred with the need for monitoring SP resistance in *P. falciparum* in the context of CTX prophylaxis implementation. In malaria-endemic areas, IPT is recommended for pregnant women. Given the benefits of CTX in prevention and treatment of malaria, the consensus view was that HIV-infected pregnant woman receive no additional benefit from SP-based IPT and

this was not, therefore, recommended. Infants or children on CTX prophylaxis are also unlikely to benefit from the addition of SP-based IPT for malaria.

4.8 Cost-effectiveness of cotrimozaxole prophylaxis

Three presentations from Côte d'Ivoire, South Africa and Uganda examined the cost-effectiveness of CTX prophylaxis. Despite using different models, varying assumptions and outcome measures, all three concluded that CTX was cost effective.

In the study from South Africa where 78% of TB patients are co-infected with HIV, CTX prophylaxis offered to all TB patients was found to be cost-effective compared to other HIV interventions such as the prevention of mother-to-child HIV transmission (PMTCT). The authors concluded that CTX is inexpensive and does not generate extra burden to the health service. The cost per life saved at six months was US$ 187.05. Similarly, the Côte d'Ivoire study, based on a model using data from the randomized placebo-controlled trial in that setting, offered an economic case for the recommendation to provide CTX in early HIV-infection (WHO stage $\geq$2) (*27*). The study from Uganda also demonstrated a cost saving with the use of CTX. The investigators demonstrated that it was highly cost effective, generating savings to the health-care system. The use of screening algorithms to identify individuals with advanced HIV disease may result in higher programme costs and less favourable cost-effectiveness. These findings support policies for wide-scale implementation of CTX prophylaxis to all HIV-infected persons. However, while cost-effectiveness analysis and simplicity may make a case for universal administration of CTX to all HIV-positive adults, long-term adherence may be a problem.

5. Technical recommendations for cotrimoxazole prophylaxis in adults and children

The following recommendations are based on the available evidence and expert opinion on the use of CTX prophylaxis in HIV-infected adults. They contain a number of options to be considered by the policy-makers for each setting in which they are used. Local factors such as HIV seroprevalence, burden and spectrum of opportunistic infections and capacity and development of health systems should inform the decisions on local adaptation.

5.1 Starting cotrimoxazole prophylaxis in HIV-infected adults

- When CD4 is not available, the use of CTX prophylaxis in resource-limited settings is recommended for advanced and severe HIV disease (WHO stages 3 and 4) and can be considered in mild HIV disease (WHO stage 2).

- When CD4 is available, it is more informative to identify when to start CTX prophylaxis, especially in asymptomatic patients (WHO stage 1) according to CD4 cell value. There is a clear consensus that CTX prophylaxis is recommended for all HIV-infected patients with CD4 < 200/mm^3 in all settings. However, there is some evidence from limited-resource settings that people with higher CD4 cell values can also receive some benefit. In addition, some flexibility in the CD4 threshold can be considered according to country-specific context, HIV epidemiologic pattern, differences in OI/co-infections spectrum, resistance risk as well as the potential impact of extra benefits over mortality and morbidity that CTX can apparently promote in some situations. Thus, when CD4 is available, the following recommendations can be considered:

    - In all settings, particularly where prevention of PCP and toxoplasmosis are the major targets, the recommended CD4 threshold to start CTX prophylaxis is 200/mm^3.

- In settings where bacterial infections and malaria are prevalent, some studies suggest that a threshold of 350/mm^3 is more adequate.
- Some expert opinions considered a recommendation for CTX prophylaxis in patients with CD4 < 500/mm^3 considering operational simplicity, cost-effectiveness analysis and some data on the effectiveness of CTX in reducing severe morbidity at early stages.

- Since limited data suggest reduction of severe events irrespective of CD4 count or clinical stage and because of operational simplicity, some countries can opt to treat all HIV individuals. This strategy can be considered in settings with high prevalence of HIV and limited health infrastructure, which can find implementing the WHO staging system to start CTX prophylaxis difficult. However, lifelong use of CTX prophylaxis for all persons infected with HIV must be weighed against potential challenges of long-term adherence to such advice; the practicality of such a recommendation and the potential for emergence of drug-resistant pathogens. There was no consensus on this approach.

Table 1
Starting CTX prophylaxis in HIV-infected adults

	WHO clinical stage	Recommendations		Comments
ASYMPTOMATIC HIV DISEASE	1	If CD4 is not available	CTX prophylaxis **generally not recommended**	The majority of experts suggest that it is not appropriate to start CTX in asymptomatic HIV+ individuals without evidence of immunodeficiency due to limited evidence of clinical benefit and concerns about toxicity and long-term adherence. The operational simplicity of universal CTX, irrespective of CD4 or clinical stage suggest this could be a suitable option in settings with high prevalence of HIV and limited health infrastructure.
		If CD4 is available	CTX prophylaxis **recommended guided by CD4 cell count** selection of a specific CD4 threshold (200, 350 or 500) should be decided at country level, considering HIV prevalence, OI burden/ spectrum of preventable diseases & health system capacity	**if selected CD4 threshold is 200/mm^3** Randomized trials in industrialized and limited-resource settings consistently demonstrated evidence of effectiveness to prevent PCP and toxoplasmosis, particularly where these opportunistic infections are the major targets for CTX prophylaxis. **if selected CD4 threshold is 350/mm^3** Some randomized studies in resource-limited settings shown significant reduction in morbidity and mortality. Can be recommended in settings where bacterial infections and malaria are prevalent in HIV-infected population. **if selected CD4 threshold is 500/mm^3** Limited randomized and non-randomized clinical studies suggest low rates of severe events, and may provide operational simplicity. However, experts are concerned about toxicity and long-term adherence in asymptomatic adults. Should be considered only in countries with high HIV prevalence, limited health infrastructure and high rates of diarrhoeal disease and malaria.
SYMPTOMATIC HIV DISEASE	2	CTX prophylaxis **considered** irrespective of CD4 cell count		No clear evidence on the impact on mortality from randomized trials, but expert opinion suggests CTX prophylaxis can be considered. This is based upon operational simplicity, impact on early severe morbidity and cost-effectiveness modelling from some high HIV prevalence settings. Long-term adherence to CTX may be a problem.
	3 or 4	CTX prophylaxis **recommended** irrespective of CD4 cell count		Randomized trials demonstrate evidence of effectiveness, demonstrated impact on mortality and morbidity.

5.2 Starting cotrimoxazole prophylaxis in HIV-infected children

- In HIV-exposed infants, CTX prophylaxis is universally indicated, starting at four to six weeks after birth and maintained until exclusion of HIV infection.

- In HIV-infected infants aged < 12 months, CTX prophylaxis is indicated regardless of CD4 or clinical status.

- The use of CTX prophylaxis is recommended in all children with mild, advanced or severe HIV disease (Stages 2, 3 or 4) aged between one and four years. When CD4 is available, its use can be extended to asymptomatic patients (WHO Stage 1) if CD4 cell count is < 25%.

- Children > 5 years old should start or continue CTX prophylaxis with similar clinical and/or laboratory criteria adopted for adults.

- In children with presumptive symptomatic HIV disease, CTX prophylaxis should be started at any age and maintained until HIV infection status is clarified.

Table 2

Starting CTX prophylaxis in HIV-infected/exposed children

Situation	Age	Recommendations		
HIV-exposed infant[1]	4-6 weeks of age (or when first recognized)	Use CTX Prophylaxis **regardless of CD4** and discontinue only if HIV infection excluded and no longer exposed.		
HIV-infected infant[2]	< 12 months	Use CTX prophylaxis **regardless of CD4 or clinical status.**		
	≥ 12 months to 4 years	If CD4 not available	Use CTX prophylaxis **regardless of clinical status**[3]**.**	
		If CD4 is available	Asymptomatic HIV disease (WHO Stage 1)	Use CTX prophylaxis **guided by CD4 cell count**[4]
			Mild, advanced or severe HIV disease (WHO stages 2, 3 or 4)	Use CTX prophylaxis **regardless of CD4 cell count.**
	≥ 5 years	Use CTX prophylaxis **as recommended for adults**.		
Presumptive severe HIV disease	Use CTX Prophylaxis **regardless of CD4**.			

(1) Defined as a child born to an HIV-infected mother or child breastfeeding from an HIV-infected mother, **and extends until HIV exposure stops and infection can be definitively excluded.**

(2) In children under 18 months HIV infection can only be confirmed by virological testing.

(3) Where CD4 is not available, most experts recommend CTX prophylaxis for all HIV-infected children under 5 years irrespective of CD4 or clinical stage. This may be particularly important in settings with high burden of child mortality and morbidity due to infectious diseases (e.g. bacterial infections), limited access to HIV testing and poor health infrastructure and may facilitate easier programmatic implementation.

(4) If CD4 is available, most experts recommend starting or continuing CTX prophylaxis in HIV-infected children aged 1-4 years if CD4 < 25%.

5.3 Recommended dosage of CTX for prophylaxis in HIV-infected adults and children

- In HIV-infected adults the recommended dosage of cotrimoxazole is 960 mg per day (800 mg of sulphamethoxazole /160 mg of trimethoprim). This can be given in one dose (as a double strength tablet) once daily or as two single-strength tablets taken once or twice daily as a divided dose.
- In HIV-exposed or -infected children, the following table with recommended daily dosage should be adopted accordingly with interval ages:

Table 3

Cotrimoxazole (SMX/TMP) formulation & dosage for HIV-infected/exposed children

Recommended daily dosage	Suspension (5 ml syrup 200 mg /40 mg)	Paediatric tablet (100 mg/20 mg)	Single strength adult tablet (400 mg/ 80 mg)	Double strength adult tablet (800 mg/ 160 mg)
< 6 months 100 mg SMX /20 mg TMP	2.5 ml	One tablet	¼ tablet, possibly mixed with feeding	----
6 months – 5 years 200 mg SMX /40 mg TMP	5 ml	Two tablets	Half tablet	----
> 6 – 14 years 400 mg SMX /80 mg TMP	10 ml	Four tablets	One tablet	Half tablet
> 15 years 800 mg SMX/ 160 mg TMP	----	----	Two tablets	One tablet
Frequency - once a day				

5.4 Clinical and laboratory monitoring of CTX prophylaxis:

- Clinical monitoring should be carried out regularly, ideally at a minimum of three monthly intervals, with individuals encouraged to report adverse symptoms as soon as they are noted. Particular interest should be paid to skin reactions, symptoms such as fatigue, breathlessness or sore throat that may be related to haematological events and nausea, vomiting or jaundice. Adverse effects are most common within the first few weeks of starting prophylaxis. Extra vigilance is required during this time to detect such events clinically and patients should be advised accordingly. Attention should be paid to other medications that the patient is receiving with possible overlapping toxicity (e.g. zidovudine (ZDV) or isoniazid).

- Where laboratory monitoring is ongoing for HIV care and for initiation of ART, blood counts and liver function tests may be used to detect adverse effects of CTX. Once ART is initiated, monitoring should continue as standard for ART management for the setting involved.

5.5 Discontinuation of cotrimoxazole prophylaxis:

The discontinuation of CTX prophylaxis in HIV-infected individuals has been considered in the context of drug toxicity, pregnancy and immune restoration promoted by ART response. In these situations, discontinuation should be based on clinical judgment, considering the clinical and laboratory parameters as well as the adherence profile or if severe adverse reactions occur.

Discontinuation in the context of cotrimoxazole toxicity:

- In patients in settings with limited laboratory capacity, the potential side effects associated with CTX prophylaxis (skin rash, bone marrow toxicity and hepatotoxicity) can be monitored on a clinical basis, using a symptomatic approach.

- In patients on ZDV-containing ART regimens, the impact of potential overlapping of haematological toxicity associated with CTX prophylaxis is not significant and no additional laboratory tool or change in the usual monitoring frequency of haematological parameters (Hb or WBC) adopted for ART care is needed. Clinical monitoring is recommended to detect potential side effects.

- Individuals with a history of severe reactions to sulpha drugs should not be started on CTX prophylaxis. In these settings, particularly in patients with severe HIV disease (i.e. WHO stage 4 disease or CD4< 200/mm^3), Dapsone in a dose of 100mg per day (in adults) or 2mg/kg once daily (in children) can be used as an alternative. Dapsone is less effective in the prevention of PCP and also lacks the broad antibacterial activity of CTX. Therefore, it may be desirable to attempt desensitization to CTX, if feasible, before substituting Dapsone (see Annex 5).

- All those starting CTX as well as their guardians and caregivers, should be provided with verbal or written information on potential adverse effects and on what to do should they occur (stop the drug and report to their nearest clinic).
    - **Grade 1 or 2 events.** Attempts can be made to continue treatment with careful and repeated observation and treatment of symptoms, where available (antihistamines, antiemetics).
    - **Grade 3 events**. CTX should be discontinued until the adverse event has resolved and reintroduction can be considered using a desensitization schedule. For a sample schedule see Annex 5
    - **Grade 4 events**. CTX should be permanently discontinued.

Table 4

Discontinuation of CTX prophylaxis in HIV infected adults and children

Situation		Recommendations
Toxicity(1)	Grade 1 or 2	Continue CTX prophylaxis with careful and repeated observation and follow up symptomatic treatment where available.
	Grade 3	CTX should be discontinued until the adverse effect has completely resolved at which point reintroduction can be considered using desensitization or reduced-dose schedule.
	Grade 4	CTX should be permanently discontinued.

(1) All those starting CTX should be provided with verbal and written information on potential adverse effects and on what to do should they occur (stop the drug and report to the nearest clinic).

For definitions of event grades see Annex 4.

Discontinuation in the context of pregnancy:

- Since the risk of life-threatening infection in a pregnant woman with low CD4 count or clinical features of immunosuppression outweighs the theoretical risk of congenital abnormalities, women who fulfil the criteria for CTX prophylaxis should stay on CTX throughout the pregnancy. Should a woman be found to require CTX prophylaxis during pregnancy, it should be started regardless of the stage of pregnancy.

- If an HIV-infected woman is on CTX prophylaxis and resides in a malarial zone, it is not necessary for her to have additional SP-based IPT.

Discontinuation in the context of ART-related immune restoration:

- The safety of CTX prophylaxis discontinuation has yet to be proven in some situations: several studies have shown safety in a context where the major objective of CTX use is to prevent PCP and toxoplasmosis. However, there are insufficient data at present to issue

recommendations on discontinuing CTX following immune reconstitution on ART in resource-limited settings and in countries where bacterial infections and malaria are common HIV-related problems.

- According to expert opinion, in several situations, discontinuing CTX can be considered in the context of ART-related immune restoration that is documented with sustained increases in CD4 cell counts when believed to be desirable or necessary to ensure continued use and adherence to ART.

- In adult patients receiving ART and with evidence of immune restoration, the use of immunologic parameters (i.e. CD4 cell count) should be utilized in determining appropriateness of CTX discontinuation. Although specific CD4 thresholds were not established for discontinuing CTX prophylaxis, the expert opinion recommended that the same value adopted to start should be considered in the decision about when to stop CTX prophylaxis. The following criteria are a suggested approach in the context of immune restoration following ART:
    - Use of ART for a minimum of one year;
    - CD4 count exceeding that used for a threshold for initiation of CTX in that setting, on at least two occasions obtained a minimum of three months apart;
    - Evidence of good adherence and continued access to ART;
    - A minimum of six months free from WHO Stage 2, 3 or 4 events;
    - Reinitiate CTX prophylaxis if CD4 cell count falls below starting threshold.

- In adult patients on ART and with sustained clinical response, but without access to CD4 cell counts, similarly no data are available to advise on whether and when CTX prophylaxis should be discontinued. The need is to balance adherence/pill burden with potential benefit. Conservatively, it was recognized by an expert panel that the minimum requirements for stopping CTX prophylaxis were:
    - at least one year on ART;
    - at least 6–12 months symptom-free (i.e. without WHO stage 2, 3 or 4 events).

- In children, there is also insufficient evidence to recommend discontinuation of CTX prophylaxis safely. Some experts recommend the use of a similar approach indicated in adults, but considering the specific age-related CD4 thresholds. The following criteria are a suggested approach in the context of immune restoration following ART in children:
    - Child should have been on ART for at least 6–12 months;
    - Two CD4 tests at least three months apart. The CD4 per cent or absolute count between the two tests should be stable and above the threshold adopted for starting CTX prophylaxis; (CD4 > 25% if aged 1–4 yrs or >adult threshold for children ≥ 5 yrs);
    - Evidence of good adherence and safe access to drug supply;
    - Six months or more free from WHO Stage 2, 3 or 4 events;
    - Reinitiate CTX if CD4 falls below threshold again.

Table 5

Discontinuation of CTX prophylaxis in HIV-infected adults and children

Situation			Recommendations
Immune restoration with ART [1]	In adults	If CD4 is not available	Continue CTX prophylaxis. There is insufficient evidence to safely recommend discontinuation of CTX prophylaxis solely guided in clinical parameters[2].
		If CD4 is available	Can discontinue CTX prophylaxis in those with CD4 cell count above the threshold for starting CTX on at least 2 occasions, 3 months apart, have been on ART, for at least one year, have evidence of good adherence, there is access to secure drug supply, and have had six months or more with no WHO stage 2, 3 or 4 events.
	In children	If CD4 is not available	Continue CTX prophylaxis. There is insufficient evidence to safely recommend discontinuation of CTX prophylaxis guided by clinical parameters.
		If CD4 is available	Continue CTX prophylaxis. There is insufficient evidence to safely recommend discontinuation of CTX prophylaxis guided by CD4 parameters[3].

(1) The safety of CTX prophylaxis discontinuation has yet to be proven in most situations, but several studies have shown safety where the major objective of CTX use is to prevent PCP and toxoplasmosis. According to expert opinion, discontinuation can be considered in the context of HAART associated immune reconstitution when it is felt desirable or necessary to ensure continued adherence to ART.

(2) Some experts suggest that discontinuation maybe safe in patients who have been on ART for at least one year, have evidence of good adherence, access to secure drug supply, and have had six months or more with no events associated with WHO stages 2, 3 or 4.

(3) Some experts suggest that discontinuation may be safe if CD4 remains above the threshold adopted for starting CTX prophylaxis (CD4 > 25% if aged 1-4 years or > adult threshold for children ≥ 5 years), on at least 2 occasions, 3 months apart, and have been on ART, for at least 6-12 months, have evidence of good adherence, access to secure drug supply, and have had 6 months or more with no WHO stages 2, 3 or 4 events.

6. Operational issues

Operational recommendations

- Governments should ensure sustainable and quality supply of sulpha drugs at all levels, including paediatric drug formulations;
- Medication should be supplied using the existing distribution system and integrated with related services;
- All stakeholders, including the private sector, should be encouraged to participate in the scaling up of CTX prophylaxis;
- Cotrimoxazole should be offered ideally at no cost or free at the point of delivery.

Policy and programme linkages

- Engage policy-makers and implementers in designating responsibilities for decision-making in national programmes;
- Enhance decentralization of intervention to increase access;
- Ensure integration of CTX prophylaxis into nationwide programmes (e.g. PMTCT, TB, IMCI, IMAI);
- Encourage and use people living with HIV/AIDS (PLWHA) and nongovernmental organizations (NGOs) to create awareness and demand for prophylaxis.

Training and education

- Orientation and training using updated guidelines should be given for health-care providers;
- Appropriate messages should be developed to increase awareness of communities and should include information that CTX prophylaxis does not replace ART but is part of the care for HIV infection, both pre-ART and for at least initial ART;
- Advocacy for greater use and access to CTX is required at all levels, particularly for infants and children.

Monitoring and evaluation

- Countries should be encouraged and supported to collect baseline data for future evaluation of scaling up access to CTX for adults and children;
- Indicators need to be developed to support information-gathering at various levels;
- Surveillance systems need to be established for clinical effect of CTX, bacterial resistance to CTX and malaria resistance to SP;
- CTX-related adverse events need to be documented.

7. Research priorities

The following are considered priority areas for research to enhance successful implementation of CTX prophylaxis:

- How best to sequence CTX with other treatments – ART, TB treatment;
- Treatment of breakthrough infections while on CTX;
- Efficacy of CTX with higher CD4 counts and asymptomatic individuals – to cover mortality, morbidity and effect on disease progression;
- Factors affecting adherence and impact on health-related behaviours with the type and model of care;Criteria for interruption and reinstitution of CTX prophylaxis in the context of ART;
- Simplified methods to increase early diagnosis of HIV infection in children;
- Impact of CTX on malaria and bacterial resistance carriage, implications for future treatment;
- Role of integrated child survival approaches, including IMCI pre- and post-HAART care and support;
- Benefits for HIV-uninfected children and at household level where an individual is receiving CTX prophylaxis;
- Impact of CTX prophylaxis in the context of malnutrition;
- Consequences of long-term use (10–15 years) of CTX.

8. Summary of programmatic recommendations for scaling up cotrimoxazole prophylaxis in HIV-exposed and -infected children and adults

The panel of experts confirmed that CTX prophylaxis is an affordable, safe, easy and simple intervention that should be scaled up as part of standard care for HIV-exposed and infected children and adults. The following recommendations were made:

To national programmes

- Develop and implement explicit policy on use of CTX for adults and children;
- Ensure legal/policies in place to secure reduced cost or free CTX;
- Examine and document operational issues in scaling up CTX prophylaxis in the context of improving access to HAART;
- Intensify efforts to establish linkages between entry points for CTX prophylaxis (PMTCT, VCT, IMCI, IMAI, TB clinics, etc.);
- Intensify efforts to identify at-risk children early through building capacity for laboratory investigations and expanding testing coverage at immunization and well baby clinic to avoid missed opportunities;
- Examine obstacles to testing for adults and children and document success stories to improve coverage.

To WHO & UNICEF

- Develop clear and consistent messages about the need and value of CTX prophylaxis intervention for adults and children infected with HIV;
- Advocate for improved access to affordable and reliable age-appropriate HIV tests for different levels of health delivery sites;
- Develop targets and tools for monitoring and evaluation.

WHO

- Disseminate guidelines and relevant documents for effective utilization in implementation;
- Provide technical assistance for implementation of CTX prophylaxis;
- Encourage and support research for the identified issues to improve and develop evidence-based practice in resource-poor settings.

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Annex 1

Meeting agenda

DAY 1 (May 10)

8:30–9:00	Registration
9:00–9:30	Introduction of the meeting, objectives and expected outcomes - Dr Jim Kim - Director, WHO/HIV Department - Dr Charles Gilks - TPS Coordinator, WHO/HIV Department
9:30–10:30	Plenary session 1: New and recent evidence on CTX use in adults - I - Kate Grimwade - United Kingdom - N Kumarasamy - India - Jonathon Mermin - Uganda
10:30–10:45	- Coffee break
10:45–12:00	Plenary session 2: New and recent evidence on CTX use in adults - II - Chifumbe Chintu - Zambia - Chris Duncombe - Thailand - Rehab Chimzizi - Malawi
12:00–13:15	Plenary session 3: New and recent evidence on CTX use in children - Diane Gibb - United Kingdom - Lynne Mofenson - United States - Anaky Marie-France - Côte D'Ivoire
13:15–14:15	Lunch break
14.15–15.45	Working groups: Starting CTX Prophylaxis in children and adults
15:45–16:15	Coffee break
16:15–17:15	Working groups: Starting CTX Prophylaxis in children and adults
17:15–17:45	Progress report of working groups
18:00–19:30	Welcome reception

DAY 2 (May 11)

09:00–10:30	Plenary session 4: Discontinuation of CTX in patients using HAART - Wafaa El-Sadr - United States - Paula Munderi - Uganda - Maria Grazia Lain - Italy
10:30–10:45	Coffee break
10:45–12:15	Plenary session 5: Special considerations of CTX prophylaxis - Christopher Plowe - United States - Stephen Graham - Malawi - Christine Watera - Uganda
12:15–13:15	Lunch break

13:15–15:00	Working groups: Clinical recommendations: CTX discontinuation and use in special situations
15:00–15:15	Coffee break
15:45–16:45	Working groups: Clinical recommendations: CTX discontinuation and use in special situations
16:45–17:45	Working group presentations: Summary recommendations for CTX prophylaxis (Starting, discontinuation and use in special situations)
17:45–18:15	Discussion and conclusions of Day 2

DAY 3 (May 12)

9:00–10:30	Plenary session 6: operational considerations & cost effectiveness - Yazdan Yazdanpanah - France - Antonieta Medina Lara - United Kingdom - Christian Pitter - Uganda
10:30–11:00	Coffee break
11:00–12:30	Working groups: operational recommendations: implementation, policy issues and operational research
12:30–13.30	Lunch break
13:30–14:30	Working group presentations: operational recommendations: implementation, policy issues and operational research
14:30–15:00	Discussion
15:00–15:15	Next steps
15:15–15:30	Conclusions and closing

Annex 2

List of participants

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Annex 3

Revised WHO classification of HIV disease in children according to clinical and immunologic categories

1) WHO clinical classification of established HIV infection

HIV-associated symptomatology	WHO clinical stage
Asymptomatic	1
Mild symptoms	2
Advanced symptoms	3
Severe/very advanced symptoms	4

2) WHO proposed immunological classification of established HIV infection

HIV-associated immunodeficiency	Age-related CD4 values			
	< 11 mo (%)	**12–35 mo (%)**	**36–59 mo (%)**	**≥ 5 yrs (mm/3)**
None/not significant	> 35	> 30	> 25	> 500
Mild	30−35	25−30	20−25	350−499
Advanced	25−30	20−25	15−20	200−349
Severe /very advanced	<25	<20	<15	<200 *or* <15%

Annex 4

Grades of adverse drug events

Parameter/feature	Grade 1	Grade 2	Grade 3	Grade 4
Haematology				
Haemoglobin (g/dL) (age ≥2 yrs)	10-10.9	7.0-9.9	<7.0	Cardiac failure secondary to anaemia
Abs neutrophil count (x109/L)	0.750-1.200	0.400-0.749	0.250-0.399	<0.250
Platelets (cells/mm^3)	-	50 000–70 000	25 000–49 999	<25,000 or bleeding
Gastrointestinal				
Bilirubin	1.1-1.9XN	2.0-2.9XN	3.0-7.5XN	>7.5XN
AST	1.1-4.9XN	5.0-9.9XN	10.0-15.0XN	>15.0XN
ALT	1.1-4.9XN	5.0-9.9XN	10.0-15.0XN	>15.0XN
γGT	1.1-4.9XN	5.0-9.9XN	10.0-15.0XN	>15.0XN
Pancreatic Amylase	1.1.-1.4XN	1.5-1.9XN	2.0-3.0XN	>3.0XN
Abdominal pain	Mild	Moderate - no Rx needed	Moderate - no Rx needed	Severe - hospital and Rx
Diarrhoea	Soft stools	Liquid stools	Liquid stools and mild dehydration, bloody stool	Dehydration requiring IV therapy or hypotensive shock
Nausea	Mild	Moderate decreased oral intake	Severe, little oral intake	Unable to ingest food or fluid for >24 hours
Vomiting	<1 episode/day	1-23 episodes/day or duration >3 days	>3 episodes/days or duration >7 days	Intractable vomiting
Allergic/dermatological				
Allergy	Pruritis without rash	Pruritic rash	Mild urticaria	Severe urticaria; anaphylaxis, angioedema
Drug fever	-	38.5-40^0 C	>40^0 C	Sustained fever: >40^0 C, >5 days
Cutaneous	-	Diffuse maculopapular rash, dry desquamation	Vesiculation, ulcers	Exfoliative dermatitis, Stevens-Johnson or Erythema multiforme, moist desquamation

Source: adapted from African Network for the Care of Children Affected by AIDS. *Handbook on Paediatric AIDS in Africa*, 2005.

Annex 5

Cotrimoxazole (SMZ+TMP) desensitization protocol

Gradually increasing dosages of TMP-SMX oral suspension (40mg TMP + 200 mg SMX per 5 mL) are administered as follows:

Step 1	80 mg SMX + 16 mg TMP (2 mL oral suspension)
Step 2	160 mg SMX + 32 mg TMP (4 mL oral suspension)
Step 3	240 mg SMX + 48 mg TMP (6 mL oral suspension)
Step 4	320 mg SMX + 64 mg TMP (8 mL oral suspension)
Step 5 (and daily thereafter)	1 single-strength SMX-TMP tab (400 mg SMX + 80 mg TMP)

Patients start an antihistamine regimen of choice one day prior to starting the regimen and continue daily until completing the dose escalation.

On the first day of the regimen, patients receive the Step 1 dose of SMX-TMP and subsequently advance a step each day. If a severe reaction occurs, the desensitization regimen is terminated. If a patient experiences a minor reaction, the patient may remain on the same step for an additional day. If the reaction subsides, the patient may advance to the next step; if the reaction worsens, the patient should not advance and the desensitization regimen is terminated. Thus, patients could achieve advancement to the full prophylactic dosage of SMX-TMP in as few as five days or in as many as nine days if each step of the escalation requires two days.

Note: In the study investigating this regimen, patients were eligible for desensitization if they were at least six months removed from their treatment-limiting reactions to TMP-SMX.[2]

[2] Leoung GS. Trimethoprim-sulfamethoxazole (TMP-SMZ) dose escalation versus direct rechallenge for Pneumocystis Carinii pneumonia prophylaxis in human immunodeficiency virus-infected patients with previous adverse reaction to TMP-SMZ, *Journal of Infectious Diseases*, 2001, 184:992-7.

Annex 6 Summary information of major studies on CTX prophylaxis in HIV-infected patients

Country of study	Study design	Author and year of study	CTX dose	Study population (N)	TB	CTX resistance	Effect on mortality	Effect on morbidity	Adverse event rate
Côte d'Ivoire	RPCT	Anglaret 1999	960mg	Adults N=541	Some	Low	No significant difference	↓43%	0.6%
Côte d'Ivoire	RPCT	Wiktor 1999	960mg	Adults N=771	All smear positive	Low	↓46%	↓53% admissions ↓27% morbid events	<1%
Senegal	RPCT	Maynart 2000	480mg	Adults N=100	None	Intermediate	No significant difference	No significant difference	6%
Zambia	RPCT	Nunn 2005	960mg	Adults N=925	All smear positive	High	No overall significant difference (difference seen from 6-18 months)	Not reported	0.3%
Zambia	RPCT	Chintu 2005	<5yrs -240mg >5yrs -480mg	Children 1-14yrs N=534	Some	High	↓33% (all ages and CD4 ratios)	↓21% hospitalization	6%
South Africa, Cape Town	OB	Badri 2001	480mg daily or 960mg 3x/week	Adults N=563	Some	Not stated (known to be high from other SA data)	↓45%- only significant WHO stages 3-4 CD4<200	↓48% severe HIV-related illnesses	Not reported
Uganda, Entebbe	HC before and after CTX	Watera 2002	960mg	Adults N=806	Some	High	↓23%	No overall difference ↓69% malaria	3.8%
Uganda	HC before and after CTX	Mermin 2004	960mg in adults	Adults and children - % not stated N=509	Some	High	↓46% - only significant CD4<200 WHO stage 3-4	↓hospitalization 31%, ↓diarrhoea 35%, ↓malaria 72%	2%
Malawi, Thyolo	HC with no CTX	Zachariah 2003	960mg	Adults N=2986	All	High	↓25%	Not reported	<2%
Malawi, Karonga	HC with no CTX	Mwaungulu 2004	960mg	Adults N=717	All	High	↓22% across programme, ↓44% HIV infected participants	Not reported	Not reported
South Africa, Hlabisa	HC with no CTX	Grimwade 2005	960mg	Adults N=3232 Irrespective of HIV status	All	High	↓29%	Not reported	<1%

RPCT: Randomized placebo controlled trial; OB: Observational study;, HC: Historical control study