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Strengthening health services to fight HIV/AIDS

GUIDELINES ON CO-TRIMOXAZOLE PROPHYLAXIS FOR HIV-RELATED INFECTIONS AMONG CHILDREN, ADOLESCENTS AND ADULTS IN RESOURCE-LIMITED SETTINGS

Recommendations for a public health approach

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CONTENTS

1. ACRONYMS AND ABBREVIATIONS

AIDS	acquired immunodeficiency syndrome
HIV	human immunodeficiency virus
PCP	*Pneumocystis jiroveci* pneumonia (formerly *Pneumocystis carinii* pneumonia)
TB	tuberculosis
UNAIDS	Joint United Nations Programme on HIV/AIDS
WHO	World Health Organization

2. DEVELOPMENT OF THESE GUIDELINES

Co-trimoxazole prophylaxis is a simple, well-tolerated and cost-effective intervention for people living with HIV. It should be implemented as an integral component of the HIV chronic care package and as a key element of pre–antiretroviral therapy care. Co-trimoxazole prophylaxis needs to continue after antiretroviral therapy is initiated until there is evidence of immune recovery (see subsections 6.4 and 7.6).

In May 2005, WHO convened an Expert Consultation on Cotrimoxazole Prophylaxis in HIV Infection. The meeting objectives were to review available data on co-trimoxazole prophylaxis, including operational issues and research priorities, and to exchange regional and country experiences. The meeting report *(1)* formulated recommendations for the initiation and discontinuation of co-trimoxazole prophylaxis in infants, children, adults and adolescents.

2.1 Objective of this document

In high-income countries, co-trimoxazole prophylaxis among children (both those exposed to HIV[1] and those living with HIV) and adults and adolescents living with HIV has been the standard of care for many years. WHO and UNAIDS have not produced guidelines for national programmes in resource-limited settings. In the absence of clear guidelines, countries and programmes have been slow in adopting co-trimoxazole prophylaxis, a life-saving, simple and inexpensive intervention. The objective of these guidelines is to provide global technical and operational recommendations for the use of co-trimoxazole prophylaxis in HIV-exposed children, children living with HIV and adolescents and adults living with HIV in the context of scaling up HIV care in resource-limited settings.

All HIV-exposed infants born to mothers living with HIV must receive co-trimoxazole prophylaxis, commencing at 4–6 weeks of age (or at first encounter with health care system) and continued until HIV infection can be excluded.

2.2 Target audience

This publication is primarily intended for use by national HIV/AIDS programme managers, managers of nongovernmental organizations delivering HIV/AIDS care services and other policy-makers who are involved in planning HIV/AIDS care strategies in resource-limited countries. It should also be useful to clinicians in resource-limited settings.

1 **Definition of HIV exposure: infants and children born to mothers living with HIV until HIV infection in the infant or child is reliably excluded and the infant or child is no longer exposed through breastfeeding. For those <18 months of age, HIV infection is diagnosed by a positive virological test (HIV DNA or HIV RNA) six weeks after complete cessation of all breastfeeding. For a HIV-exposed children ≥18 months of age, HIV infection can be excluded by negative HIV antibody testing at least six weeks after complete cessation of all breastfeeding.**

3. STATEMENT ON THE STRENGTH OF THE EVIDENCE USED IN THE RECOMMENDATIONS

The recommendations contained in these guidelines are based on levels of evidence from randomized clinical trials, high-quality scientific studies, observational cohort data and, where sufficient evidence is not available, on expert opinion (Table 1). The strength of the recommendations is intended to guide the degree to which regional and country programmes consider the recommendations.

These recommendations do not explicitly consider cost-effectiveness, although the realities of human resources, health system infrastructure and socioeconomic issues need to be taken into account when adapting these recommendations to regional and country programmes.

Table 1. Grading of recommendations and levels of evidence

STRENGTH OF THE RECOMMENDATION	LEVEL OF EVIDENCE AVAILABLE FOR THE RECOMMENDATION
A. Recommended – should be followed	I. At least one randomized controlled trial with clinical laboratorial or programmatic endpoints
B. Consider – applicable in most situations	II. At least one high-quality study or several adequate studies with clinical, laboratory or programmatic endpoints
C. Optional	III. Observational cohort data, one or more case-controlled or analytical studies adequately conducted
	IV. Expert opinion based on evaluation of other evidence

Sources: BHIVA Writing Committee on behalf of the BHIVA Executive Committee (2); Task Force on Community Preventive Services (3); WHO Health Evidence Network (4); EDM guidelines: evidence-based medicine (5).

4. INTRODUCTION

Co-trimoxazole, a fixed-dose combination of sulfamethoxazole and trimethoprim, is a broad-spectrum antimicrobial agent that targets a range of aerobic gram-positive and gram-negative organisms, fungi and protozoa. The drug is widely available in both syrup and solid formulations at low cost (a few US cents per day) in most places, including resource-limited settings. Co-trimoxazole is on the essential medicines list *(6)* of most countries.

Providing co-trimoxazole has been part of the standard of care for preventing *Pneumocystis jiroveci* pneumonia (PCP) (formerly *Pneumocystis carinii* pneumonia) and toxoplasmosis since the early 1990s. Although WHO/UNAIDS issued a provisional statement on the use of co-trimoxazole prophylaxis in sub-Saharan Africa in 2000, most countries have not implemented this intervention widely. The reasons for the slow implementation of co-trimoxazole prophylaxis programmes include the difference in causation and burden of HIV-related infections between well-resourced and resource-limited countries, the potential for drug resistance and the lack of guidelines. Until more recently, there has also been concern over the limited evidence base for the efficacy of co-trimoxazole prophylaxis, particularly in areas with high levels of bacterial resistance to the drug.

5. BACKGROUND AND NEW EVIDENCE

Data on the effectiveness of co-trimoxazole in reducing morbidity and mortality among individuals living with HIV in resource-limited countries comes from randomized clinical trials, observational cohort studies and programme analyses from several African countries (with varying levels of co-trimoxazole resistance), India and Thailand. There are limited data from the Caribbean and Latin America.

Recently, more data have become available from resource-limited settings on the efficacy of co-trimoxazole prophylaxis in reducing morbidity and mortality among adults and children living with HIV.

5.1 Co-trimoxazole prophylaxis among infants and children

Across a large number of clinical and postmortem studies in all settings, PCP has been identified as the leading cause of death in infants with HIV infection, accounting for 50–60% of AIDS diagnoses in infants *(7,8)*. The incidence peaks in the first six months of life *(9–12)*. Because of difficulty in diagnosing HIV infection in infants, co-trimoxazole prophylaxis is recommended for all HIV-exposed children born to mothers living with HIV starting at 4–6 weeks after birth and continuing until HIV infection has been excluded and the infant is no longer at risk of acquiring HIV through breastfeeding.

Data from randomized clinical trials and observational studies demonstrate the effectiveness of co-trimoxazole in preventing PCP in infants and reducing morbidity and mortality among infants and children living with or exposed to HIV.

Among children after infancy, a randomized clinical trial conducted in Lusaka, Zambia provided strong evidence that daily co-trimoxazole prophylaxis is effective in reducing mortality and morbidity *(7)*. This was demonstrated despite high levels of in vitro resistance of common bacterial infections to co-trimoxazole (60–80%). In this study, 534 children living with HIV (mean age 4.4 years; 32% 1–2 years and 15% older than 10 years) were randomized to receive co-trimoxazole (240 mg daily for children 1–5 years and 480 mg for children older than 5 years) or matching placebo. Mortality declined 43% and the rate of hospital admissions 23% in the co-trimoxazole group versus placebo. No evidence indicated that the effectiveness decreased over a median follow-up time of 20 months in the trial, and the benefit of co-trimoxazole was demonstrated at all ages and all levels of CD4 percentage. However, most of these children had symptoms (WHO clinical stages 2, 3 or 4 for HIV disease) at baseline and only 16% had a CD4% >20%. The main protective effect was the reduction of mortality

and hospital admissions due to pneumonia (presumed to be bacterial). *P. jiroveci* was not demonstrated as a common causative organism in these older children (only 1 of 119 nasopharyngeal aspirates positive for *P. jiroveci)*. Of note, malaria is less common in Lusaka than in other countries in the region, and the efficacy of co-trimoxazole prophylaxis against malaria could not be determined in this trial. However, another study showed that co-trimoxazole reduced malaria in HIV-uninfected children in Mali *(13)*.

5.2 Co-trimoxazole prophylaxis among adolescents and adults

Randomized clinical trials, studies using historical controls and observational cohort studies have demonstrated the effectiveness of co-trimoxazole prophylaxis in reducing mortality and morbidity across varying levels of background resistance to co-trimoxazole and prevalence of malaria.

Consistent evidence from all studies that include CD4 cell count supports the effectiveness of co-trimoxazole prophylaxis among people with CD4 counts <200 cells per mm^3 *(14–16)*. Similarly, studies show that individuals with WHO clinical stages 3 or 4 for HIV disease (including tuberculosis (TB)) clearly benefit from co-trimoxazole prophylaxis *(8,12,14)*.

More recently, evidence supports the use of co-trimoxazole prophylaxis among people with higher CD4 counts and those with less advanced HIV disease (WHO clinical stages 1 and 2). Two randomized clinical trials from Abidjan, Côte d'Ivoire *(14,17)* showed consistent benefit in the reduction of morbidity and mortality among people living with HIV with varying CD4 counts with and without TB. The first study *(14)* demonstrated reduction in mortality among people living with HIV who also had TB across all CD4 counts. The second study *(17)* showed a significant reduction in severe adverse events (defined as death or hospital admission) among all people living with HIV irrespective of CD4 count.

The LUCOT study (submitted for publication), a recently completed randomized clinical trial in Zambia, assessed the impact of co-trimoxazole prophylaxis in reducing mortality among adults living with HIV who had newly diagnosed or previously treated pulmonary TB. Overall, there was a 45% reduction in mortality in the co-trimoxazole-treated group versus placebo during 18 months of follow-up.

A study conducted in an area with high TB and HIV prevalence but with low malaria transmission in South Africa demonstrated reduction in mortality among adults being treated for active TB using co-trimoxazole prophylaxis, irrespective of HIV status *(18)*. The findings of these studies are consistent with those from randomized clinical trials and from nonrandomized studies, which have shown benefit from prophylaxis with co-trimoxazole in reducing mortality among adults living with HIV who had newly diagnosed pulmonary TB.

An observational study conducted in Uganda *(19)* assessed the impact of daily co-trimoxazole prophylaxis on rates of malaria, diarrhoea, hospital admission and death. In this study, 509 individuals living with HIV-1 and 1522 HIV-negative household members were enrolled and followed up with weekly home visits. After five months, participants living with HIV were offered co-trimoxazole prophylaxis and followed for a further 1.5 years. Mortality declined 45% from all causes and morbidity from malaria and diarrhoeal diseases declined after co-trimoxazole prophylaxis was provided to those living with HIV. This study also demonstrated the benefit of co-trimoxazole prophylaxis among untreated family members uninfected with HIV. Mortality and the incidence of diarrhoea and malaria among HIV-uninfected children of adults treated with co-trimoxazole were lower than in the children of untreated adults living with HIV *(20)*. A second study from Uganda, with a similar study design, also demonstrated a reduction in mortality and malaria *(12)*.

5.3 Co-trimoxazole prophylaxis in pregnant women

In a study of the prevention of mother-to-child transmission in Zambia *(21)*, birth outcomes from 1075 pregnant women living with HIV were analysed before and after co-trimoxazole was introduced as the standard of care for pregnant women in Zambia. There were significant improvements in birth outcomes, with reductions in chorioamnionitis, prematurity and neonatal mortality following the introduction of routine co-trimoxazole prophylaxis for women living with HIV who had CD4 cell counts <200 cells per mm^3. These data suggest that this intervention may have indirect benefits for neonatal and infant health in addition to its direct benefits for maternal health *(21).*

5.4 Discontinuing co-trimoxazole prophylaxis among people receiving antiretroviral therapy

5.4.1 Stopping in infants and children

A few studies have assessed the safety of discontinuing prophylaxis among children living with HIV. Children younger than one year of age are at risk of opportunistic infections irrespective of their CD4 percentage *(16)*. For children aged 1–5 years, age-specific CD4 percentages may be used to guide co-trimoxazole interruption following immune recovery in response to antiretroviral therapy. A prospective study from the Pediatric AIDS Clinical Trial Group (PACTG 1008) reported no opportunistic infections and no increase in rates of severe bacterial infections among children stopping co-trimoxazole prophylaxis following immune restoration in response to antiretroviral therapy *(22)*. In a retrospective survey conducted at 10 European centres in the Pediatric European Network on the Treatment of AIDS network *(23)*, 82 children receiving antiretroviral therapy stopped co-trimoxazole prophylaxis based on age-related CD4 cell count criteria. The criteria for commencing co-trimoxazole prophylaxis had been primary prophylaxis (72 children) or secondary

prophylaxis (10 children). No episodes of PCP were reported during a median follow-up time of 4.1 years (range 0.3–7.7) with no prophylaxis. There are no data from resource-limited settings on the safety of stopping co-trimoxazole prophylaxis among children.

5.4.2 Stopping among adults and adolescents

Randomized clinical trials conducted in well-resourced countries have demonstrated that co-trimoxazole prophylaxis used for PCP prophylaxis may be safely stopped following immune recovery in response to antiretroviral therapy *(24,25)*. In resource-limited settings, data are more limited, particularly in the absence of CD4 count monitoring, and there are no randomized trials. Some experts suggest the use of similar CD4 cell count criteria for stopping co-trimoxazole prophylaxis as those used in well-resourced countries.

In a small study from India *(26)*, co-trimoxazole prophylaxis was stopped when the CD4 count was $\geq$200 cells per mm^3, and no participant developed PCP or toxoplasmosis. Similar results were reported from a study in Thailand *(27)* in which 179 people who had never received antiretroviral therapy commenced antiretroviral therapy with non-nucleoside reverse transcriptase inhibitors were followed for 216 weeks. The median time to achieve a CD4 count $\geq$200 cells per mm^3 for participants with a baseline CD4 count of $\geq$100 cells per mm^3 was 24 weeks. For those with a baseline CD4 count <100 cells per mm^3, the time for CD4 to increase to $\geq$200 cells per mm^3 was 96 weeks. There were no cases of PCP among 169 participants who stopped co-trimoxazole during the 216 weeks of follow-up from study entry (10 participants did not reach the CD4 cell target of 200 cells per mm^3). These studies also reported that some participants with low baseline CD4 counts might never achieve a CD4 cell count $\geq$200 cells per mm^3.

Data on stopping co-trimoxazole prophylaxis among people receiving antiretroviral therapy in the absence of CD4 count monitoring are not available. Information from studies of people receiving antiretroviral therapy and their CD4 cell count response during follow-up may influence recommendations on if and when co-trimoxazole prophylaxis should be stopped based on the duration of antiretroviral therapy in the absence of CD4 count monitoring. The Development of Antiretroviral Therapy in Africa (DART) study in Uganda examined the CD4 response following commencement of antiretroviral therapy. The median time to achieve a CD4 count $\geq$200 cells per mm^3 was 24 weeks among those who commenced antiretroviral therapy with CD4 counts greater than 100 cells per mm^3. Among those with baseline CD4 counts below 50 cells per mm^3, the median time to CD4 increase to $\geq$200 cells per mm^3 was 72 weeks. These data are comparable those in the study in Thailand.

The lack of data from randomized clinical trials on stopping co-trimoxazole in the absence of CD4 count monitoring, the limited number of participants in observational studies and the absence of a control group in these studies caution against this approach until such data are available.

5.5 Bacterial resistance to co-trimoxazole

Co-trimoxazole has antimicrobial activity against a wide range of pathogens including *Pneumococcus* spp., non-typhoidal *Salmonella*, *Isospora*, *Cyclospora*, *Nocardia*, *Plasmodium falciparum, Toxoplasma gondii* and PCP.

Co-trimoxazole has been used widely as treatment for common infections in many resource-limited settings and, as a result, co-trimoxazole resistance among these pathogens has increased in these settings. Resistance of non-typhoidal *Salmonella* and *Pneumococcus* isolates to co-trimoxazole has been reported to be 44% and 52% respectively in Uganda *(19)* and approximately 80% and 90% respectively in Malawi *(28)*.

The efficacy of co-trimoxazole prophylaxis has not been affected by the background prevalence of co-trimoxazole resistance and appears to be similar in geographical areas in which background prevalence of co-trimoxazole resistance is high (South Africa, Uganda and Zambia) and low (Côte d'Ivoire).

The impact of co-trimoxazole use in the evolution of drug resistance is uncertain. There is concern that implementing wide and prolonged use of co-trimoxazole prophylaxis could be associated with the development of drug resistance in common pathogens, such as increased penicillin-resistant *Pneumococcus (29).* Data from Uganda *(20)* found no significant changes in the bacterial resistance patterns of stool pathogens isolated from the family members of individuals on co-trimoxazole prophylaxis over a two-year period. However, one study from Malawi *(30)* showed a significant increase in resistance of pharyngeal and faecal isolates from those receiving co-trimoxazole prophylaxis.

5.6 Cross-resistance of co-trimoxazole with sulfadoxine/pyrimethamine

Co-trimoxazole has been shown to be 99.5% effective in preventing malaria versus 95% effectiveness with sulfadoxine/pyrimethamine, and both have about 80% therapeutic efficacy for the treatment of malaria *(13)*. Cross-resistance between co-trimoxazole and sulfadoxine/pyrimethamine is a potential concern when co-trimoxazole prophylaxis is used in areas where sulfadoxine/pyrimethamine is the first-line agent for treating malaria. Analysis of malaria parasites from children in Mali who had received at least one month of co-trimoxazole prophylaxis detected no resistance-conferring mutations. Similarly, the study in Uganda *(20)* found no significant difference between either the proportion of malarial episodes with resistant organisms or the incidence of sulfadoxine/pyrimethamine–resistant malaria before and after co-trimoxazole prophylaxis was introduced. There is no evidence to date on the efficacy of sulfadoxine/pyrimethamine in treating breakthrough episodes of malaria among people taking co-trimoxazole prophylaxis. As co-trimoxazole is 99.5% effective in preventing malaria, adherence to co-trimoxazole should be assessed if breakthrough episodes occur and the need for adherence should be reinforced.

6. RECOMMENDATIONS ON THE USE OF CO-TRIMOXAZOLE PROPHYLAXIS AMONG INFANTS AND CHILDREN

6.1 Initiation of primary co-trimoxazole prophylaxis in infants and children

6.1.1 Children among whom co-trimoxazole prophylaxis is contraindicated

Children with a history of severe adverse reaction (grade 4 reactions, see Table 7) to co-trimoxazole or other sulfa drugs and children with glucose-6-phosphate dehydrogenase deficiency should not be prescribed co-trimoxazole prophylaxis. In resource-limited settings, routine testing for glucose-6-phosphate dehydrogenase deficiency is not recommended. Dapsone 2 mg/kg once daily, if available, is an alternative. Some children cannot tolerate either co-trimoxazole or dapsone. No alternative recommendation can be made in resource-limited settings for children who cannot tolerate either.

6.1.2 HIV-exposed infants and children

In resource-limited settings, co-trimoxazole prophylaxis is recommended for all HIV-exposed infants starting at 4–6 weeks of age (or at first encounter with the health care system) and continued until HIV infection can be excluded. Co-trimoxazole is also recommended for HIV-exposed breastfeeding children of any age, and co-trimoxazole prophylaxis should be continued until HIV infection can be excluded by HIV antibody testing (beyond 18 months of age) or virological testing (before 18 months of age) at least six weeks after complete cessation of breastfeeding **[A-III]**. Programme efforts should focus on co-trimoxazole prophylaxis in the first six months of life, when the risk of PCP is greatest.

6.1.3 Infants and children documented to be living with HIV

All children younger than one year of age documented to be living with HIV should receive co-trimoxazole prophylaxis regardless of symptoms or CD4 percentage **[A-II]**. After one year of age, initiation of co-trimoxazole prophylaxis is recommended for symptomatic children (WHO clinical stages 2, 3 or 4 for HIV disease) or children with CD4 <25% *(31)* **[A-I]**. All children who begin co-trimoxazole prophylaxis (irrespective of whether co-trimoxazole was initiated in the first year of life or after that) should continue until the age of five years, when they can be reassessed. Adult clinical staging and CD4 count thresholds for co-trimoxazole initiation or discontinuation apply to children older than five years of age *(32)*.

In some countries with a high burden of mortality and morbidity due to other infectious diseases (such as malaria and bacterial infections), co-trimoxazole prophylaxis may be offered to children living with HIV in all clinical stages, including asymptomatic children irrespective of their CD4 level **[C-IV]**. The universal option of providing co-trimoxazole prophylaxis to all children is an adaptation issue for individual countries. Among children with presumptive symptomatic HIV disease, co-trimoxazole prophylaxis should be started at any age and continued until HIV infection status can be excluded **[A-IV]**.

Table 2. Initiation of co-trimoxazole prophylaxis in infants and children

SITUATION			
HIV-EXPOSED INFANTS AND CHILDREN[a]	INFANTS AND CHILDREN CONFIRMED[b] TO BE LIVING WITH HIV		
	<1 YEAR	1–4 YEARS	≥5 YEARS
Co-trimoxazole prophylaxis is universally indicated, starting at four to six weeks after birth and maintained until cessation of risk of HIV transmission and exclusion of HIV infection **[A-III]**	Co-trimoxazole prophylaxis is indicated regardless of CD4 percentage or clinical status **[A-II]**[c]	WHO clinical stages 2, 3 and 4 regardless of CD4 percentage **OR** Any WHO stage and CD4 <25% **[A-I]**	Follow adult recommendations
Universal option: prophylaxis for all infants and children born to mothers confirmed or suspected of living with HIV. This strategy may be considered in settings with high prevalence of HIV, high infant mortality due to infectious diseases and limited health infrastructure **[C-IV]**.			

a Defined as a child born to mother living with HIV or a child breastfeeding from a mother living with HIV until HIV exposure stops (six weeks after complete cessation of breastfeeding) and infection can be excluded.

b Among children younger than 18 months, HIV infection can only be confirmed by virological testing.

c Once a child is started on co-trimoxazole, treatment should continue until five years of age regardless of clinical symptoms or CD4 percentage. Specifically, infants who begin co-trimoxazole prophylaxis before the age of one year and who subsequently are asymptomatic and/or have CD4 levels ≥25% should remain on co-trimoxazole prophylaxis until they reach five years of age **[A-IV]**.

6.2 Doses of co-trimoxazole in infants and children

Table 3. Co-trimoxazole formulations and dosage for infants and children living with HIV or exposed to HIV

RECOMMENDED DAILY DOSAGE[a]	SUSPENSION (5 ML OF SYRUP 200 MG/ 40 MG)	CHILD 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 sulfamethoxazole/ 20 mg trimethoprim	2.5 ml	One tablet	¼ tablet, possibly mixed with feeding[b]	–
6 months–5 years 200 mg sulfamethoxazole/ 40 mg trimethoprim	5 ml[c]	Two tablets	Half tablet	–
6–14 years 400 mg sulfamethoxazole/ 80 mg trimethoprim	10 ml[c]	Four tablets	One tablet	Half tablet
>14 years 800 mg sulfamethoxazole/ 160 mg trimethoprim	–	–	Two tablets	One tablet
Frequency – once a day				

a Some countries may use weight bands to determine dosing. Age and the corresponding weight bands (based on the children with HIV antibiotic prophylaxis trial (CHAP trial (7)) are:

AGES	WEIGHT
<6 months	<5 kg
6 months–5 years	5–15 kg
6–14 years	15–30 kg
>14 years	>30 kg

b Splitting tablets into quarters is not considered best practice. This should be done only if syrup is not available.

c Children of these ages (6 months–14 years) may swallow crushed tablets.

6.3 Secondary co-trimoxazole prophylaxis in infants and children

Children with a history of treated PCP should be administered secondary co-trimoxazole prophylaxis with the same regimen recommended for primary prophylaxis *(16)* **[A-III]**.

6.4 Discontinuation of primary co-trimoxazole prophylaxis in infants and children

6.4.1 HIV-exposed infants and children confirmed to be HIV uninfected

Co-trimoxazole prophylaxis can be discontinued when HIV infection has been definitely excluded by a confirmed negative HIV virological test six weeks after complete cessation of breastfeeding in an infant <18 months of age or a confirmed negative HIV antibody test in a child ≥18 months of age and six weeks after complete cessation of breastfeeding **[A-I]**.

6.4.2 Children living with HIV in the context of antiretroviral therapy–related immune recovery

Given that children living with HIV have a high risk of bacterial infections, the general recommendation is that, among children confirmed to be living with HIV in resource-limited settings, co-trimoxazole should be continued irrespective of immune recovery in response to antiretroviral therapy **[A-IV]**.

Data suggest that the risk of developing PCP after immune restoration in response to antiretroviral therapy is sufficiently low to withdraw co-trimoxazole if it was initiated primarily for PCP prophylaxis *(23)*. Children older than five years who are stable on antiretroviral therapy, with good adherence, secure access to antiretroviral therapy and with CD4 and clinical evidence of immune recovery can be reassessed and consideration can be given to discontinuing co-trimoxazole prophylaxis in accordance with the recommendations for adults and adolescents **[C-IV]**. If children have been prescribed dapsone prophylaxis, the same discontinuation recommendations apply.

Co-trimoxazole prophylaxis (or dapsone if the child cannot tolerate co-trimoxazole) should be recommenced if the CD4 percentage falls below the age-related initiation threshold or if new or recurrent WHO clinical stage 2, 3 or 4 conditions occur **[A-IV]**.

Table 4. Summary of recommendations for discontinuing primary co-trimoxazole among infants and children

TARGET POPULATION	RECOMMENDATIONS
HIV-exposed children	Discontinue co-trimoxazole prophylaxis after HIV infection is excluded **[A-I]**
Infants and children living with HIV	Maintain on co-trimoxazole prophylaxis until age five years irrespective of clinical and immune response **[A-IV]** Children older than five years can be reassessed and consideration can be given to discontinuing co-trimoxazole prophylaxis in accordance with the recommendations for adults and adolescents **[C-IV]**

Severe adverse reactions to co-trimoxazole in children are uncommon, In the CHAP study (7), 534 children were randomized to co-trimoxazole or placebo. No child on co-trimoxazole developed rash.

6.4.3 Discontinuation for co-trimoxazole adverse reactions

Co-trimoxazole prophylaxis may need to be discontinued in the event of an adverse drug reaction. Although severe reactions to co-trimoxazole are uncommon, these may include extensive exfoliative rash, Stevens-Johnson syndrome or severe anaemia or pancytopaenia.

There are insufficient data on co-trimoxazole desensitization (rechallenge following an adverse reaction to co-trimoxazole commencing with low doses of co-trimoxazole and gradual dose escalation) among children to make any recommendations on its use in resource-limited settings.

Everyone starting co-trimoxazole and their guardians and caregivers should be provided with verbal or written information on potential adverse effects and advised to stop the drug and report to their nearest health facility if co-trimoxazole-related adverse events are suspected (Table 7).

6.5 Discontinuation of secondary co-trimoxazole prophylaxis

The safety of discontinuing secondary co-trimoxazole prophylaxis among children living with HIV has had limited assessment and has been studied only in high–income countries *(23)*. The general recommendation is that secondary co-trimoxazole prophylaxis should not be discontinued, irrespective of clinical and immune response to antiretroviral therapy *(15)* **[B-III]**.

Based on evidence that secondary co-trimoxazole prophylaxis can be safely stopped among adults and adolescents guided by immune recovery in response to antiretroviral therapy assessed using CD4 cell count *(33–37)*, discontinuation of secondary co-trimoxazole prophylaxis may be considered among children older than five years with evidence of immune recovery in response to antiretroviral therapy in accordance with the recommendation for discontinuation of primary prophylaxis **[C-IV]**.

7. RECOMMENDATIONS ON THE USE OF PRIMARY CO-TRIMOXAZOLE PROPHYLAXIS AMONG ADULTS AND ADOLESCENTS

7.1 Adults and adolescents among whom co-trimoxazole prophylaxis is contraindicated

Adults and adolescents with a history of severe adverse reaction (grade 4; see Table 7) to co-trimoxazole or other sulfa drugs should not be prescribed co-trimoxazole prophylaxis.

In situations in which co-trimoxazole cannot be continued or should not be initiated, dapsone 100 mg per day, if available, can be used as an alternative. Dapsone is less effective than co-trimoxazole in preventing PCP and also lacks the broad antimicrobial activity of co-trimoxazole. It is therefore desirable to attempt desensitization (section 7.4.3) to co-trimoxazole, if feasible in the clinical setting, among individuals with a previous non-severe reaction, before substituting dapsone **[A-IV]**. However, co-trimoxazole desensitization should not be attempted among individuals with a previous severe (grade 4) reaction to co-trimoxazole or other sulfa-containing drugs.

7.2 Initiation of primary co-trimoxazole prophylaxis among adults and adolescents

These recommendations include a degree of flexibility to enable decisions on the most appropriate threshold of CD4 count or clinical disease stage for initiation of co-trimoxazole prophylaxis to be made at the country level or even the local level, taking into account variation in the burden of HIV, disease spectrum and the capacity and infrastructure of health systems.

In settings in which co-trimoxazole prophylaxis is initiated based on WHO clinical staging criteria only, co-trimoxazole prophylaxis is recommended for all symptomatic people with mild, advanced or severe HIV disease (WHO clinical stages 2, 3 or 4) **[A-I]**. Where CD4 cell testing is available, co-trimoxazole prophylaxis is recommended for everyone with a CD4 cell count <350 per mm^3, particularly in resource-limited settings where bacterial infections and malaria are prevalent among people living with HIV **[A-III]**.

Some countries may choose to adopt a CD4 threshold of 200 cells per mm^3 below which co-trimoxazole prophylaxis is recommended. This option is especially recommended if the main targets for co-trimoxazole prophylaxis are PCP and toxoplasmosis **[A-I]**. However, bacterial infections are prevalent in individuals living with HIV in all settings, which supports the use of the 350 cells per mm^3 threshold. People with WHO clinical stage 3 or 4 HIV disease (including people with pulmonary as well as extrapulmonary TB) should, however, still initiate co-trimoxazole prophylaxis irrespective of the CD4 cell count **[A-I]**.

Some countries may also opt to treat everyone living with HIV (universal option), because of operational simplicity and data suggesting a reduction of severe events irrespective of CD4 count or clinical stage **[C-III]**. This strategy may be considered in settings with high prevalence of HIV and limited health infrastructure. However, lifelong use of co-trimoxazole prophylaxis for all people living with HIV needs to be weighed against the challenges of maintaining long-term adherence and the potential for emergence of drug-resistant pathogens.

Table 5. Initiation of co-trimoxazole prophylaxis among adults and adolescents living with HIV

BASED ON WHO CLINICAL STAGING CRITERIA ALONE (WHEN CD4 COUNT IS NOT AVAILABLE)	BASED ON WHO CLINICAL STAGING AND CD4 CELL COUNT CRITERIA[a]
WHO clinical stage 2, 3 or 4 **[A-I]**	Any WHO clinical stage and CD4< 350 cells per mm^3 [b] **[A-III]** OR WHO clinical stage 3 or 4 irrespective of CD4 level **[A-I]**
Universal option: Countries may choose to adopt universal co-trimoxazole for everyone living with HIV and any CD4 count or clinical stage. This strategy may be considered in settings with high prevalence of HIV and limited health infrastructure **[C-III]**.	

a Expanded access to CD4 testing is encouraged to guide the initiation of antiretroviral therapy and to monitor the progress of antiretroviral therapy.

b Countries may choose to adopt a CD4 threshold of <200 cells per mm^3 **[A-I]**.

7.3 Co-trimoxazole prophylaxis among pregnant women

Although pregnant women living with HIV widely use co-trimoxazole, there is no evidence of an increase in co-trimoxazole-related adverse events among pregnant women versus non-pregnant women (16).

Since the risk of life-threatening infections among pregnant women with low CD4 count or clinical features of immunosuppression outweighs the theoretical risk of co-trimoxazole-induced congenital abnormalities, women who fulfil the criteria for co-trimoxazole prophylaxis should stay on co-trimoxazole throughout their pregnancy *(38)* **[A-III]**. If a

woman requires co-trimoxazole prophylaxis during pregnancy, it should be started regardless of the stage of pregnancy **[A-III]**. If a woman living with HIV is receiving co-trimoxazole prophylaxis and resides in a malarial zone, it is not necessary for her to have additional sulfadoxine/pyrimethamine–based intermittent presumptive therapy for malaria **[B-IV]**. Breastfeeding women should continue to receive co-trimoxazole prophylaxis.

7.4 Doses of co-trimoxazole among adults and adolescents

The dose of co-trimoxazole among adults and adolescents living with HIV is one double-strength tablet or two single-strength tablets once daily: the total daily dose is 960 mg (800 mg sulfamethoxazole + 160 mg trimethoprim) **[A-I]**.[2]

7.5 Secondary co-trimoxazole prophylaxis among adults and adolescents

Adults and adolescents with a history of treated PCP should be administered secondary co-trimoxazole prophylaxis with the same regimen recommended for primary prophylaxis *(10)*. **[A-III]**.

7.6 Discontinuing co-trimoxazole prophylaxis among adults and adolescents

The discontinuation of co-trimoxazole prophylaxis among individuals living with HIV may be considered in the context of drug toxicity and immune recovery in response to antiretroviral therapy. Discontinuation should be based on clinical judgement, including both clinical and laboratory parameters.

7.6.1 Discontinuation based on antiretroviral therapy–related immune recovery

Studies in well-resourced settings have demonstrated the safety of discontinuing co-trimoxazole as prophylaxis against PCP and toxoplasmosis among people with immune recovery (CD4 $\geq$200 cells per mm^3) in response to antiretroviral therapy. Emerging data in resource-limited settings have demonstrated similar findings *(24,25)*. However, no randomized clinical trials have assessed the safety and timing of the discontinuation of co-trimoxazole prophylaxis following immune recovery in response to antiretroviral therapy in resource-limited settings.

The general recommendation is to continue co-trimoxazole prophylaxis among adults living with HIV indefinitely **[A-IV]**.

Some countries may consider adopting a CD4 count–guided discontinuation of co-trimoxazole as prophylaxis against PCP and toxoplasmosis among people with immune recovery and CD4 $\geq$200 cells per mm^3 in response to antiretroviral therapy for at least six months **[B-I]**.

2 There is an option to give one single-strength tablets (480 mg per dose or 400 mg sulfamethoxazole + 80 mg trimethoprim) taken twice daily, as this may assist in preparing individuals for initiating the twice-daily antiretroviral therapy regimens that are commonly available in resource-limited settings.

In other situations (in which co-trimoxazole prophylaxis was initiated based on its effect in reducing morbidity and mortality and the incidence of malaria and bacterial infections), discontinuation based on CD4 count can be considered among people with immune recovery and CD4 $\geq$350 cells per mm^3 after at least six months of antiretroviral therapy **[C-IV]**.

The same discontinuation rules apply to people who have been prescribed dapsone prophylaxis.

No consensus was reached on recommendations for discontinuing co-trimoxazole prophylaxis in the absence of CD4 count monitoring in response to antiretroviral therapy. However, discontinuation could be considered among people who have received antiretroviral therapy for one year without WHO clinical stage 2, 3 or 4 events, good adherence and secure access to antiretroviral therapy **[C-IV]**.

Co-trimoxazole prophylaxis (or dapsone if the person cannot tolerate co-trimoxazole) should be recommenced if the CD4 cell count falls below the initiation threshold or if new or recurrent WHO clinical stage 2, 3 or 4 conditions occur **[A-IV]**.

Table 6. Summary of recommendations for discontinuing primary co-trimoxazole among adults and adolescents

TARGET POPULATION	RECOMMENDATIONS	
Adults and adolescents living with HIV	CD4 testing not available (clinical assessment only)	Do not discontinue co-trimoxazole prophylaxis, particularly in settings where bacterial infections and malaria are common HIV-related events **[A-IV]**
		Consider discontinuing co-trimoxazole prophylaxis among people with evidence of good clinical response to antiretroviral therapy (absence of clinical symptoms after at least one year of therapy), good adherence and secure access to antiretroviral therapy **[C-IV]**
	CD4 testing available (clinical and immunological assessment)	In countries where co-trimoxazole prophylaxis is recommended only for preventing PCP and toxoplasmosis, it can be discontinued among those with evidence of immune recovery in response to antiretroviral therapy (CD4 $\geq$200 cells per mm^3 after at least six months of antiretroviral therapy) **[B-I]**
		In countries with a high incidence of bacterial infections and malaria, discontinue co-trimoxazole prophylaxis among people with evidence of immune recovery related to antiretroviral therapy (CD4 $\geq$350 cells per mm^3 after at least six months of antiretroviral therapy) **[C-IV]**

7.6.2 Discontinuation based on co-trimoxazole adverse events

Severe adverse reactions to co-trimoxazole are uncommon. If non-severe adverse events occur, every effort should be made to continue prophylaxis with co-trimoxazole because of its superior efficacy in preventing PCP and bacterial infections compared with dapsone among adults *(39–41)*. It also protects against toxoplasmosis, malaria and some enteric pathogens. Except in cases of severe adverse reaction, co-trimoxazole should be temporarily interrupted for two weeks and then desensitization should be attempted, if indicated and feasible. If using dapsone is necessary, the dose for adults and adolescents is 100 mg per day. Some people cannot tolerate either co-trimoxazole or dapsone. No alternative recommendation can be made in resource-limited settings.

For people in settings with limited laboratory capacity, the potential side effects associated with co-trimoxazole prophylaxis (skin rash, bone marrow toxicity and hepatotoxicity) can be monitored clinically **[B-IV]**.

Everyone starting co-trimoxazole should be provided with verbal or written information on potential adverse effects and advised to stop the drug and report to their nearest clinic if co-trimoxazole-related adverse events are suspected.

Table 7. Co-trimoxazole toxicity grading scale for adults and adolescents

TOXICITY	CLINICAL DESCRIPTION	RECOMMENDATION
GRADE 1	Erythema	Continue co-trimoxazole prophylaxis with careful and repeated observation and follow-up. Provide symptomatic treatment, such as antihistamines, if available
GRADE 2	Diffuse maculopapular rash, dry desquamation	Continue co-trimoxazole prophylaxis with careful and repeated observation and follow-up. Provide symptomatic treatment, such as antihistamines, if available
GRADE 3	Vesiculation, mucosal ulceration	Co-trimoxazole should be discontinued until the adverse effect has completely resolved (usually two weeks), and then reintroduction or desensitization can be considered
GRADE 4	Exfoliative dermatitis, Stevens-Johnson syndrome or erythema multiforme, moist desquamation	Co-trimoxazole should be permanently discontinued

7.6.3 Co-trimoxazole desensitization

Given the importance of co-trimoxazole and the lack of an equally effective and widely available alternative, desensitization is an important component of managing adults and adolescents with HIV infection. It can be attempted two weeks after a non-severe (grade 3 or less) co-trimoxazole reaction that has resulted in a temporary interruption of co-trimoxazole.

Co-trimoxazole desensitization has been shown be successful in most individuals with previous hypersensitivity and rarely causes serious reactions *(42–44)*. Desensitization should not be attempted in individuals with a history of grade 4 reaction to previous co-trimoxazole or other sulfa drugs **[B-IV]**. It is recommended to commence an antihistamine regimen of choice one day prior to starting the regimen and to continue daily until completing the dose escalation. On the first day of the regimen, the step 1 dose of co-trimoxazole is given and subsequently increased one step each day. If a severe reaction occurs, the desensitization regimen is terminated. If a minor reaction occurs, repeat the same step for an additional day. If the reaction subsides, advance to the next step; if the reaction worsens, the desensitization regimen is terminated.

Table 8. Protocol for co-trimoxazole desensitization among adults and adolescents

STEP	DOSE
DAY 1	80 mg sulfamethoxazole + 16 mg trimethoprim (2 ml of oral suspension[a])
DAY 2	160 mg sulfamethoxazole + 32 mg trimethoprim (4 ml of oral suspension[a])
DAY 3	240 mg sulfamethoxazole + 48 mg trimethoprim (6 ml of oral suspension[a])
DAY 4	320 mg sulfamethoxazole + 64 mg trimethoprim (8 m of oral suspension[a])
DAY 5	One single-strength sulfamethoxazole-trimethoprim tablet (400 mg sulfamethoxazole + 80 mg trimethoprim)
DAY 6 ONWARDS	Two single-strength sulfamethoxazole-trimethoprim tablets or one double strength tablet (800 mg sulfamethoxazole + 160 mg trimethoprim)

a Co-trimoxazole oral suspension is 40 mg trimethoprim + 200 mg sulfamethoxazole per 5 ml.

7.6.4 Discontinuing secondary co-trimoxazole prophylaxis among adults and adolescents

Recommendations for discontinuing and restarting secondary prophylaxis among adults and adolescents are the same as for the recommendations for primary prophylaxis. These recommendations are supported by observational studies *(33–35)* and from a randomized trial in a well-resourced setting *(36)* as well as a combined analysis of eight European prospective cohorts *(37)* **[C-I]**.

8 RECOMMENDATIONS COMMON TO INFANTS, CHILDREN, ADULTS AND ADOLESCENTS

8.1 Timing the initiation of co-trimoxazole in relation to initiating antiretroviral therapy

Since the most common initial side effect of co-trimoxazole and antiretroviral therapy (especially nevirapine and efavirenz) is rash, it is recommended to start co-trimoxazole prophylaxis first and to initiate antiretroviral therapy two weeks later if the individual is stable on co-trimoxazole and has no rash **[A-IV]**.

8.2 Clinical and laboratory monitoring of co-trimoxazole prophylaxis

The safety of co-trimoxazole in long-term use has been established. Drug-related adverse events are uncommon and typically occur within the first few weeks of starting 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 **[A-III]**.

No specific laboratory monitoring is required among children, adolescents and adults receiving co-trimoxazole prophylaxis [A-III].

Particular interest should be paid to skin reactions and symptoms such as nausea, vomiting or jaundice. Skin reaction is the most common co-trimoxazole-related adverse event and is diagnosed clinically. Attention should be paid to other medications the person is receiving with possible overlapping toxicity (such as efavirenz, nevirapine and isoniazid).

Co-trimoxazole and dapsone can induce haemolytic anaemia among people with glucose-6-phosphate dehydrogenase deficiency. These drugs should not be prescribed to individuals, particularly children, with known or suspected glucose-6-phosphate dehydrogenase deficiency. Routine testing for glucose-6-phosphate dehydrogenase deficiency in resource-limited settings is not recommended.

No specific laboratory monitoring is required in individuals receiving co-trimoxazole prophylaxis. If available, laboratory monitoring should be based on symptoms and signs (such as full blood counts if anaemia is suspected and liver function tests if hepatic dysfunction is suspected) **[A-III]**.

Six-monthly CD4 count monitoring is recommended, if available, to guide when to initiate antiretroviral therapy. Once antiretroviral therapy is initiated, monitoring should continue according to the standard of care for antiretroviral therapy management for the setting involved **[A-III]**.

In general, the impact of co-trimoxazole prophylaxis on antiretroviral therapy toxicity is minimal. Among people on zidovudine-containing antiretroviral therapy regimens, the impact of overlapping blood toxicity with co-trimoxazole prophylaxis is not significant (except for people with advanced HIV disease), and no additional laboratory monitoring is needed **[B-III]**.

8.3 Treatment of bacterial and opportunistic infections among people taking co-trimoxazole prophylaxis

Despite the lack of data, it is recommended to use an alternative antibiotic (where available) for treating breakthrough bacterial infections among individuals living with HIV receiving co-trimoxazole prophylaxis, while continuing co-trimoxazole **[A-IV]**. For toxoplasmosis and PCP infections, prophylaxis should be suspended and full active treatment initiated according to national guidelines. Co-trimoxazole prophylaxis should be recommenced after the treatment course **[A-III]**.

8.4 Preventing and treating malaria among people taking co-trimoxazole prophylaxis

Among children, adults and adolescents receiving co-trimoxazole prophylaxis, breakthrough episodes of malaria should be treated, if possible, with antimalarial therapy that does not include sulfadoxine/pyrimethamine **[A-III]**. There is no evidence to date on the efficacy of sulfadoxine/pyrimethamine in treating episodes of malaria among people taking co-trimoxazole prophylaxis.

In malaria-endemic areas, intermittent presumptive therapy for malaria is recommended for pregnant women. Given the benefits of co-trimoxazole in preventing and treating malaria, intermittent presumptive therapy is not recommended for pregnant women receiving co-trimoxazole prophylaxis **[A-III]**. Similarly, sulfadoxine/pyrimethamine–based intermittent presumptive therapy for malaria is not necessary for infants or children on co-trimoxazole prophylaxis **[A-III]**.

9 OPERATIONAL CONSIDERATIONS

The following are considered key to the successful scaling up of co-trimoxazole prophylaxis in resource-limited settings:

- integrating the recommendation for co-trimoxazole prophylaxis into existing HIV-related treatment guidelines;
- implementing co-trimoxazole prophylaxis as an integral part of the chronic care package for all individuals living with HIV and as a key element of pre–antiretroviral therapy care and being part of the monitoring and evaluation process in preparation for initiating antiretroviral therapy;
- developing and implementing explicit policies in countries on the use of co-trimoxazole prophylaxis for children, adolescents and adults;
- giving priority to guidelines for co-trimoxazole prophylaxis for all HIV-exposed infants and people with TB who are living with HIV;
- assessing legal and policy options to secure co-trimoxazole for prophylaxis at reduced cost or free of charge;
- ensuring the availability of appropriate and affordable doses and formulations for children;
- ensuring effective and integrated management of procurement and supplies at all levels (national, district, community and household);
- ensuring that programmes to scale up co-trimoxazole prophylaxis are decentralized, available at the community level and are used to improve the quality of HIV chronic care and are linked to preparedness for and initiation of antiretroviral therapy; and
- establishing surveillance systems to monitor the efficacy of co-trimoxazole prophylaxis, bacterial resistance to co-trimoxazole and malaria resistance to sulfadoxine/pyrimethamine.

ANNEX 1. WHO CLINICAL STAGING OF HIV DISEASE IN INFANTS AND CHILDREN

CLINICAL STAGE 1

Asymptomatic
Persistent generalized lymphadenopathy

CLINICAL STAGE 2

Unexplained[a] persistent hepatosplenomegaly
Papular pruritic eruptions
Extensive wart virus infection
Extensive molluscum contagiosum
Fungal nail infections
Recurrent oral ulcerations
Unexplained[a] persistent parotid enlargement
Lineal gingival erythema
Herpes zoster
Recurrent or chronic upper respiratory tract infections (otitis media, otorrhoea, sinusitis or tonsillitis)

CLINICAL STAGE 3

Unexplained[a] moderate malnutrition not adequately responding to standard therapy
Unexplained[a] persistent diarrhoea (14 days or more)
Unexplained[a] persistent fever
(above 37.5°C intermittent or constant, for longer than one month)
Persistent oral candidiasis (after first 6–8 weeks of life)
Oral hairy leukoplakia
Acute necrotizing ulcerative gingivitis or periodontitis
Lymph node TB
Pulmonary TB
Severe recurrent bacterial pneumonia
Symptomatic lymphoid interstitial pneumonitis
Chronic HIV-associated lung disease including brochiectasis
Unexplained[a] anaemia (<8 g/dl), neutropaenia (<0.5 × 10^9 per litre) and/or chronic thrombocytopaenia (<50 × 10^9 per litre)

CLINICAL STAGE 4[b]

Unexplained[a] severe wasting, stunting or severe malnutrition not responding to standard therapy

Pneumocystis pneumonia

Recurrent severe bacterial infections (such as empyema, pyomyositis, bone or joint infection, meningitis, but excluding pneumonia)

Chronic herpes simplex infection (orolabial or cutaneous of more than one month's duration or visceral at any site)

Extrapulmonary TB

Kaposi's sarcoma

Oesophageal candidiasis (or candidiasis of trachea, bronchi or lungs)

Central nervous system toxoplasmosis (after one month of life)

HIV encephalopathy

Cytomegalovirus infection (retinitis or cytomegalovirus infection affecting another organ, with onset at age older than one month)

Extrapulmonary cryptococcosis (including meningitis)

Disseminated endemic mycosis (extrapulmonary histoplasmosis or coccidiomycosis)

Chronic cryptosporidiosis

Chronic isosporiasis

Disseminated non-tuberculous mycobacterial infection

HIV-associated tumours, including cerebral or B-cell non-Hodgkin lymphoma

Progressive multifocal leukoencephalopathy

Symptomatic HIV-associated nephropathy or symptomatic HIV-associated cardiomyopathy

a Unexplained refers to where the condition is not explained by other conditions.

b Some additional specific conditions can also be included in regional classifications, such as the reactivation of American trypanosomiasis (meningoencephalitis and/or myocarditis) in the WHO Region of the Americas, penicilliosis in Asia and HIV-associated rectovaginal fistula in Africa.

Source: World Health Organization *(45)*.

ANNEX 2. WHO CLINICAL STAGING OF HIV DISEASE AMONG ADULTS AND ADOLESCENTS

CLINICAL STAGE 1

Asymptomatic
Persistent generalized lymphadenopathy

CLINICAL STAGE 2

Unexplained[a] moderate weight loss (<10% of presumed or measured body weight) [b]
Recurrent respiratory tract infections (sinusitis, tonsillitis, otitis media and pharyngitis)
Herpes zoster
Angular cheilitis
Recurrent oral ulceration
Papular pruritic eruptions
Seborrhoeic dermatitis
Fungal nail infections

CLINICAL STAGE 3

Unexplained[a] severe weight loss (>10% of presumed or measured body weight) [b]
Unexplained[a] chronic diarrhoea for longer than one month
Unexplained[a] persistent fever (above 37.5°C intermittent or constant for longer than one month)
Persistent oral candidiasis
Oral hairy leukoplakia
Pulmonary TB
Severe bacterial infections (such as pneumonia, empyema, pyomyositis, bone or joint infection, meningitis or bacteraemia)
Acute necrotizing ulcerative stomatitis, gingivitis or periodontitis
Unexplained[a] anaemia (<8 g/dl), neutropaenia (<0.5 × 10^9 per litre) and/or chronic thrombocytopaenia (<50 × 10^9 per litre)

CLINICAL STAGE 4[c]

HIV wasting syndrome
Pneumocystis pneumonia
Recurrent severe bacterial pneumonia
Chronic herpes simplex infection (orolabial, genital or anorectal of more than one month's duration or visceral at any site)
Oesophageal candidiasis (or candidiasis of trachea, bronchi or lungs)
Extrapulmonary TB
Kaposi's sarcoma
Cytomegalovirus infection (retinitis or infection of other organs)
Central nervous system toxoplasmosis
HIV encephalopathy
Extrapulmonary cryptococcosis including meningitis
Disseminated non-tuberculous mycobacterial infection
Progressive multifocal leukoencephalopathy
Chronic cryptosporidiosis
Chronic isosporiasis
Disseminated mycosis (extrapulmonary histoplasmosis or coccidiomycosis)
Recurrent septicaemia (including non-typhoidal *Salmonella*)
Lymphoma (cerebral or B-cell non-Hodgkin)
Invasive cervical carcinoma
Atypical disseminated leishmaniasis
Symptomatic HIV-associated nephropathy or symptomatic HIV-associated cardiomyopathy

a Unexplained refers to where the condition is not explained by other conditions.

b Assessment of body weight among pregnant woman needs to consider the expected weight gain of pregnancy.

c Some additional specific conditions can also be included in regional classifications, such as the reactivation of American trypanosomiasis (meningoencephalitis and/or myocarditis) in the WHO Region of the Americas and penicilliosis in Asia.

Source: World Health Organization *(45)*.

ANNEX 3. CRITERIA FOR RECOGNIZING HIV-RELATED CLINICAL EVENTS AMONG ADULTS AND ADOLESCENTS

CLINICAL EVENT	CLINICAL DIAGNOSIS	DEFINITIVE DIAGNOSIS
CLINICAL STAGE 1		
Asymptomatic	No HIV-related symptoms reported and no signs on examination	Not applicable
Persistent generalized lymphadenopathy	Painless enlarged lymph nodes >1 cm in two or more non-contiguous sites (excluding inguinal) in the absence of known cause and persisting for ≥3 months	Histology
CLINICAL STAGE 2		
Moderate unexplained weight loss (<10% of body weight)	Reported unexplained weight loss; in pregnancy, failure to gain weight	Documented weight loss <10% of body weight
Recurrent bacterial upper respiratory tract infections (current event plus one or more in last six-month period)	Symptom complex, such as unilateral face pain with nasal discharge (sinusitis), painful inflamed eardrum (otitis media) or tonsillo-pharyngitis without features of viral infection (such as coryza or cough)	Laboratory studies where available, such as culture of suitable body fluid
Herpes zoster	Painful vesicular rash in dermatomal distribution of a nerve supply does not cross the midline	Clinical diagnosis
Angular cheilitis	Splits or cracks at the angle of the mouth not due to iron or vitamin deficiency that usually respond to antifungal treatment	Clinical diagnosis

CLINICAL EVENT	CLINICAL DIAGNOSIS	DEFINITIVE DIAGNOSIS
Recurrent oral ulcerations (two or more episodes in last six months)	Aphthous ulceration, typically painful with a halo of inflammation and a yellow-grey pseudomembrane	Clinical diagnosis
Papular pruritic eruption	Papular pruritic lesions, often with marked post-inflammatory pigmentation	Clinical diagnosis
Seborrhoeic dermatitis	Itchy scaly skin condition, particularly affecting hairy areas (scalp, axillae, upper trunk and groin)	Clinical diagnosis
Fungal nail infections	Paronychia (painful red and swollen nail bed) or onycholysis (separation of the nail from the nail bed) of the fingernails (white discoloration – especially involving the proximal part of nail plate – with thickening and separation of the nail from the nail bed)	Fungal culture of the nail or nail plate material
CLINICAL STAGE 3		
Severe unexplained weight loss (more than 10% of body weight)	Reported unexplained weight loss (>10% of body weight) and visible thinning of face, waist and extremities with obvious wasting or body mass index <18.5 kg/m^2; in pregnancy, the weight loss may be masked	Documented loss of more than 10% of body weight
Unexplained chronic diarrhoea for longer than one month	Chronic diarrhoea (loose or watery stools three or more times daily) reported for longer than one month	Three or more stools observed and documented as unformed and two or more stool tests reveal no pathogens

CLINICAL EVENT	CLINICAL DIAGNOSIS	DEFINITIVE DIAGNOSIS
Unexplained persistent fever (intermittent or constant and lasting for longer than one month)	Fever or night sweats for more than one month, either intermittent or constant with reported lack of response to antibiotics or antimalarial agents, without other obvious foci of disease reported or found on examination. Malaria must be excluded in malarious areas.	Documented temperature >37.5°C with negative blood culture, negative Ziehl-Nielsen stain, negative malaria slide, normal or unchanged chest X-ray and no other obvious focus of infection
Oral candidiasis	Persistent or recurring creamy white curd-like plaques that can be scraped off (pseudomembranous) or red patches on the tongue, palate or lining of mouth, usually painful or tender (erythematous form)	Clinical diagnosis
Oral hairy leukoplakia	Fine white small linear or corrugated lesions on lateral borders of the tongue, which do not scrape off	Clinical diagnosis

CLINICAL EVENT	CLINICAL DIAGNOSIS	DEFINITIVE DIAGNOSIS
Pulmonary TB (current)	Chronic symptoms: (lasting less than 2–3 weeks) cough, haemoptysis, shortness of breath, chest pain, weight loss, fever, night sweats and no clinical evidence of extrapulmonary disease Discrete peripheral lymph node *Mycobacterium tuberculosis* infection (especially cervical) is considered a less severe form of extrapulmonary tuberculosis	One or more sputum smear positive for acid-fast bacilli and/or radiographic abnormalities consistent with active TB and/or culture positive for *Mycobacterium tuberculosis*
Severe bacterial infection (such as pneumonia, meningitis, empyema, pyomyositis, bone or joint infection, bacteraemia or severe pelvic inflammatory disease)	Fever accompanied by specific symptoms or signs that localize infection, and response to appropriate antibiotic	Isolation of bacteria from appropriate clinical specimens (usually sterile sites)
Acute necrotizing ulcerative gingivitis or necrotizing ulcerative periodontitis	Severe pain, ulcerated gingival papillae, loosening of teeth, spontaneous bleeding, bad odour and rapid loss of bone and/or soft tissue	Clinical diagnosis

CLINICAL EVENT	CLINICAL DIAGNOSIS	DEFINITIVE DIAGNOSIS
Unexplained anaemia (<8 g/dl), neutropaenia (<0.5 × 10^9 per litre or chronic (more than one month) thrombocytopaenia (<50 × 10^9 per litre)	Not presumptive clinical diagnosis	Diagnosed on laboratory testing and not explained by other non-HIV conditions; not responding to standard therapy with haematinics, antimalarial agents or anthelmintic agents as outlined in relevant national treatment guidelines, WHO Integrated Management of Adult and Adolescent Illness (IMAI) guidelines or other relevant guidelines
CLINICAL STAGE 4		
HIV wasting syndrome	Unexplained involuntary weight loss (>10% body weight), with obvious wasting or body mass index <18.5. PLUS unexplained chronic diarrhoea (loose or watery stools three or more times daily) reported for longer than one month OR reports of fever or night sweats for more than one month without other cause and lack of response to antibiotics or antimalarial agents; malaria must be excluded in malarious areas	Documented weight loss >10% of body weight PLUS two or more unformed stools negative for pathogens OR documented temperature of >37.5°C with no other cause of disease, negative blood culture, negative malaria slide and normal or unchanged chest X-ray

CLINICAL EVENT	CLINICAL DIAGNOSIS	DEFINITIVE DIAGNOSIS
Pneumocystis pneumonia	Dyspnoea on exertion or nonproductive cough of recent onset (within the past three months), tachypnoea and fever AND chest X-ray evidence of diffuse bilateral interstitial infiltrates AND no evidence of a bacterial pneumonia, bilateral crepitations on auscultation with or without reduced air entry	Cytology or immunofluorescent microscopy of induced sputum or bronchoalveolar lavage or histology of lung tissue
Recurrent bacterial pneumonia	Current episode plus one or more previous episodes in the past six months. Acute onset (<2 weeks) of symptoms (such as fever, cough, dyspnoea, and chest pain) PLUS new consolidation on clinical examination or chest X-ray. Response to antibiotics	Positive culture or antigen test of a compatible organism
Chronic herpes simplex virus infection (orolabial, genital or anorectal) of more than one month, or visceral of any duration	Painful, progressive anogenital or orolabial ulceration; lesions caused by recurrent herpes simplex virus infection and reported for more than one month. History of previous episodes. Visceral herpes simplex virus requires definitive diagnosis	Positive culture or DNA (by polymerase chain reaction) of herpes simplex virus or compatible cytology or histology
Oesophageal candidiasis	Recent onset of retrosternal pain or difficulty on swallowing (food and fluids) together with oral candidiasis	Macroscopic appearance at endoscopy or bronchoscopy or by microscopy or histology

CLINICAL EVENT	CLINICAL DIAGNOSIS	DEFINITIVE DIAGNOSIS
Extrapulmonary TB	Systemic illness (such as fever, night sweats, weakness and weight loss). Other evidence for extrapulmonary or disseminated TB varies by site: pleural, pericardial, peritoneal involvement, meningitis, mediastinal or abdominal lymphadenopathy or osteitis Discrete peripheral lymph node *Mycobacterium tuberculosis* infection is considered a less severe form of extrapulmonary TB	*Mycobacterium tuberculosis* isolation or compatible histology from appropriate site OR radiological evidence of miliary TB (diffuse uniformly distributed small miliary shadows or micronodules on chest X-ray)
Kaposi sarcoma	Typical gross appearance in skin or oropharynx of persistent, initially flat, patches with a pink or blood-bruise colour, skin lesions that usually develop into violaceous plaques or nodules	Macroscopic appearance at endoscopy or bronchoscopy or by histology
Cytomegalovirus disease (other than liver, spleen or lymph node)	Retinitis only: may be diagnosed by experienced clinicians. Typical eye lesions on fundoscopic examination: discrete patches of retinal whitening with distinct borders, spreading centrifugally, often following blood vessels, associated with retinal vasculitis, haemorrhage and necrosis	Compatible histology or cytomegalovirus demonstrated in cerebrospinal fluid by culture or DNA (by polymerase chain reaction)

CLINICAL EVENT	CLINICAL DIAGNOSIS	DEFINITIVE DIAGNOSIS
Central nervous system toxoplasmosis	Recent onset of a focal nervous system abnormality or reduced level of consciousness AND response within 10 days to specific therapy	Positive serum toxoplasma antibody AND (if available) single or multiple intracranial mass lesion on neuroimaging (computed tomography or magnetic resonance imaging)
HIV encephalopathy	Clinical finding of disabling cognitive and/or motor dysfunction interfering with activities of daily living, progressing over weeks or months in the absence of a concurrent illness or condition other than HIV infection which might explain the findings	Diagnosis of exclusion: and (if available) neuroimaging (computed tomography or magnetic resonance imaging)
Extrapulmonary cryptococcosis (including meningitis)	Meningitis: usually subacute, fever with increasing severe headache, meningism, confusion, behavioural changes that responds to cryptococcal therapy	Isolation of *Cryptococcus neoformans* from extrapulmonary site or positive cryptococcal antigen test on cerebrospinal fluid or blood
Disseminated non-tuberculous mycobacterial infection	No presumptive clinical diagnosis	Diagnosed by finding atypical mycobacterial species from stool, blood, body fluid or other body tissue, excluding the lung

CLINICAL EVENT	CLINICAL DIAGNOSIS	DEFINITIVE DIAGNOSIS
Progressive multifocal leukoencephalopathy PML	No presumptive clinical diagnosis	Progressive nervous system disorder (cognitive dysfunction, gait/speech disorder, visual loss, limb weakness and cranial nerve palsies) together with hypodense white matter lesions on neuroimaging or positive polyomavirus JC (JVC) polymerase chain reaction on cerebrospinal fluid
Cryptosporidiosis (with diarrhoea lasting more than one month)	No presumptive clinical diagnosis	Cysts identified on modified Ziehl-Nielsen stain microscopic examination of unformed stool
Chronic isosporiasis	No presumptive clinical diagnosis	Identification of *Isospora*
Disseminated mycosis (coccidiomycosis or histoplasmosis)	No presumptive clinical diagnosis	Histology, antigen detection or culture from clinical specimen or blood culture
Recurrent non-typhoid *Salmonella* bacteraemia	No presumptive clinical diagnosis	Blood culture
Lymphoma (cerebral or B-cell non-Hodgkin) or other solid HIV-associated tumours	No presumptive clinical diagnosis	Histology of relevant specimen or, for central nervous system tumours, neuroimaging techniques
Invasive cervical carcinoma	No presumptive clinical diagnosis	Histology or cytology
Visceral leishmaniasis	No presumptive clinical diagnosis	Diagnosed by histology (amastigotes visualized) or culture from any appropriate clinical specimen

CLINICAL EVENT	CLINICAL DIAGNOSIS	DEFINITIVE DIAGNOSIS
HIV-associated nephropathy	No presumptive clinical diagnosis	Renal biopsy
HIV-associated cardiomyopathy	No presumptive clinical diagnosis	Cardiomegaly and evidence of poor left ventricular function confirmed by echocardiography

Source: World Health Organization *(45)*.

ANNEX 4. CRITERIA FOR RECOGNIZING HIV-RELATED CLINICAL EVENTS AMONG CHILDREN LIVING WITH HIV

These criteria should be used for children younger than 15 years with confirmed HIV infection.

CLINICAL EVENT	CLINICAL DIAGNOSIS	DEFINITIVE DIAGNOSIS
CLINICAL STAGE 1		
Asymptomatic	No HIV-related symptoms reported and no signs on examination	Not applicable
Persistent generalized lymphadenopathy	Persistent swollen or enlarged lymph nodes >1 cm at two or more non-contiguous sites (excluding inguinal), without known cause	Clinical diagnosis
CLINICAL STAGE 2		
Unexplained persistent hepatosplenomegaly	Enlarged liver and spleen without obvious cause	Clinical diagnosis
Papular pruritic eruptions	Papular pruritic vesicular lesions	Clinical diagnosis
Fungal nail infections	Fungal paronychia (painful, red and swollen nail bed) or onycholysis (painless separation of the nail from the nail bed); proximal white subungual onchomycosis is uncommon without immunodeficiency	Clinical diagnosis
Angular cheilitis	Splits or cracks on lips at the angle of the mouth with depigmentation, usually responding to antifungal treatment but may recur	Clinical diagnosis

CLINICAL EVENT	CLINICAL DIAGNOSIS	DEFINITIVE DIAGNOSIS
Lineal gingival erythema	Erythematous band that follows the contour of the free gingival line; may be associated with spontaneous bleeding	Clinical diagnosis
Extensive wart virus infection	Characteristic warty skin lesions; small fleshy grainy bumps, often rough, flat on sole of feet (plantar warts); facial, more than 5% of body area or disfiguring	Clinical diagnosis
Extensive molluscum contagiosum infection	Characteristic skin lesions: small flesh-coloured, pearly or pink, dome-shaped or umbilicated growths may be inflamed or red; facial, more than 5% of body area or disfiguring. Giant molluscum may indicate more advanced immunodeficiency	Clinical diagnosis
Recurrent oral ulcerations (two or more in six months)	Aphthous ulceration, typically with a halo of inflammation and yellow-grey pseudomembrane	Clinical diagnosis
Unexplained parotid enlargement	Asymptomatic bilateral swelling that may spontaneously resolve and recur, in the absence of any other known cause, usually painless	Clinical diagnosis

CLINICAL EVENT	CLINICAL DIAGNOSIS	DEFINITIVE DIAGNOSIS
Herpes zoster	Painful rash with fluid-filled blisters, dermatomal distribution, can be haemorrhagic on erythematous background and can become large and confluent. Does not cross the midline	Clinical diagnosis
Recurrent upper respiratory tract infection	Current event with at least one episode in the past six months. Symptom complex: fever with unilateral face pain and nasal discharge (sinusitis) or painful swollen eardrum (otitis media), sore throat with productive cough (bronchitis), sore throat (pharyngitis) and barking croup-like cough. Persistent or recurrent ear discharge	Clinical diagnosis
CLINICAL STAGE 3		
Unexplained moderate malnutrition	Weight loss: low weight-for-age, up to –2 standard deviations from the mean, not explained by poor or inadequate feeding and or other infections, and not adequately responding to standard management	Documented loss of body weight of –2 standard deviations from the mean, failure to gain weight on standard management and no other cause identified during investigation
Unexplained persistent diarrhoea	Unexplained persistent (14 days or more) diarrhoea (loose or watery stool, three or more times daily), not responding to standard treatment	Stools observed and documented as unformed. Culture and microscopy reveal no pathogens

CLINICAL EVENT	CLINICAL DIAGNOSIS	DEFINITIVE DIAGNOSIS
Unexplained persistent fever (intermittent or constant, for longer than one month)	Reports of fever or night sweats for longer than one month, either intermittent or constant, with reported lack of response to antibiotics or antimalarial agents. No other obvious foci of disease reported or found on examination. Malaria must be excluded in malarious areas	Documented temperature of >37.5°C with negative blood culture, negative malaria slide and normal or unchanged chest X-ray and no other obvious foci of disease
Oral candidiasis (after the first 6–8 weeks of life)	Persistent or recurring creamy white to yellow soft small plaques which can be scraped off (pseudomembranous), or red patches on tongue, palate or lining of mouth, usually painful or tender (erythematous form)	Microscopy or culture
Oral hairy leukoplakia	Fine small linear patches on lateral borders of tongue, generally bilaterally, that do not scrape off	Clinical diagnosis
Lymph node TB	Nonacute, painless “cold” enlargement of lymph nodes, usually matted, localized to one region. May have draining sinuses. Response to standard anti-TB treatment in one month	Histology or fine needle aspirate for Ziehl-Nielsen stain; culture

CLINICAL EVENT	CLINICAL DIAGNOSIS	DEFINITIVE DIAGNOSIS
Pulmonary TB	Nonspecific symptoms, such as chronic cough, fever, night sweats, anorexia and weight loss. In the older child also productive cough and haemoptysis. History of contact with adult with smear-positive pulmonary TB. No response to standard broad-spectrum antibiotic treatment	One or more sputum smear positive for acid-fast bacilli and/or radiographic abnormalities consistent with active TB and/or culture positive for *Mycobacterium tuberculosis*
Severe recurrent bacterial pneumonia	Cough with fast breathing, chest in drawing, nasal flaring, wheezing and grunting. Crackles or consolidation on auscultation. Responds to course of antibiotics. Current episode plus one or more in previous six months	Isolation of bacteria from appropriate clinical specimens (induced sputum, bronchoalveolar lavage, lung aspirate)
Acute necrotizing ulcerative gingivitis or stomatitis, or acute necrotizing ulcerative periodontitis	Severe pain, ulcerated gingival papillae, loosening of teeth, spontaneous bleeding, bad odour and rapid loss of bone and/or soft tissue	Clinical diagnosis

CLINICAL EVENT	CLINICAL DIAGNOSIS	DEFINITIVE DIAGNOSIS
Symptomatic lymphocytic interstitial pneumonia	No presumptive clinical diagnosis	Chest X-ray: bilateral reticulonodular interstitial pulmonary infiltrates present for more than two months with no response to antibiotic treatment and no other pathogen found. Oxygen saturation persistently <90%. Cor pulmonale and may have increased exercise-induced fatigue. Characteristic histology
Chronic HIV-associated lung disease (including bronchiectasis)	History of cough productive of copious amounts of purulent sputum (bronchiectasis only), with or without clubbing, halitosis, and crepitations and/or wheezes on auscultation	Chest X-ray may show honeycomb appearance (small cysts) and/or persistent areas of opacification and/ or widespread lung destruction, with fibrosis and loss of volume
Unexplained anaemia (<8 g/dl), neutropaenia (<0.5 × 10^9 per litre) or chronic thrombocytopaenia (<50 × 10^9 per litre)	No presumptive clinical diagnosis	Laboratory testing, not explained by other non-HIV conditions, not responding to standard therapy with haematinics, antimalarial agents or anthelmintic agents as outlined in WHO Integrated Management of Childhood Illness (IMCI) guidelines

CLINICAL EVENT	CLINICAL DIAGNOSIS	DEFINITIVE DIAGNOSIS
CLINICAL STAGE 4		
Unexplained severe wasting, stunting or severe malnutrition not adequately responding to standard therapy	Persistent weight loss not explained by poor or inadequate feeding, other infections and not adequately responding in two weeks to standard therapy. Characterized by: visible severe wasting of muscles, with or without oedema of both feet and/ or weight-for-height of –3 standard deviations from the mean, as defined by WHO Integrated Management of Childhood Illness guidelines	Documented weight loss of more than –3 standard deviations from the mean with or without oedema
Pneumocystis pneumonia (PCP)	Dry cough, progressive difficulty in breathing, cyanosis, tachypnoea and fever; chest indrawing or stridor (severe or very severe pneumonia as in the WHO Integrated Management of Childhood Illness guidelines). Usually of rapid onset especially in infants under six months of age. Response to high-dose co-trimoxazole with or without prednisolone. Chest X-ray: typical bilateral perihilar diffuse infiltrates	Cytology or immunofluorescent microscopy of induced sputum or bronchoalveolar lavage or histology of lung tissue

CLINICAL EVENT	CLINICAL DIAGNOSIS	DEFINITIVE DIAGNOSIS
Recurrent severe bacterial infection, such as empyema, pyomyositis, bone or joint infection or meningitis but excluding pneumonia	Fever accompanied by specific symptoms or signs that localize infection. Responds to antibiotics. Current episode plus one or more in previous six months	Culture of appropriate clinical specimen
Chronic herpes simplex infection; (orolabial or cutaneous of more than one month's duration or visceral at any site)	Severe and progressive painful orolabial, genital, or anorectal lesions caused by herpes simplex virus infection present for more than one month	Culture and/or histology
Oesophageal candidiasis (or candidiasis of trachea, bronchi or lungs)	Difficulty in swallowing or pain on swallowing (food and fluids). In young children, suspect particularly if oral candidiasis observed and food refusal occurs and/or difficulties or crying when feeding	Macroscopic appearance at endoscopy, microscopy of specimen from tissue or macroscopic appearance at bronchoscopy or histology
Extrapulmonary or disseminated TB	Systemic illness usually with prolonged fever, night sweats and weight loss. Clinical features of organs involved, such as sterile pyuria, pericarditis, ascites, pleural effusion, meningitis, arthritis and orchitis. Responds to standard anti-TB therapy	Positive microscopy showing acid-fast bacilli or culture of *Mycobacterium tuberculosis* from blood or other relevant specimen except sputum or bronchoalveolar lavage. Biopsy and histology

CLINICAL EVENT	CLINICAL DIAGNOSIS	DEFINITIVE DIAGNOSIS
Kaposi sarcoma	Typical appearance in skin or oropharynx of persistent, initially flat, patches with a pink or blood-bruise colour, skin lesions that usually develop into nodules	Not required but may be confirmed by: • typical red-purple lesions seen on bronchoscopy or endoscopy • dense masses in lymph nodes, viscera or lungs by palpation or radiology • histology
Cytomegalovirus retinitis or cytomegalovirus infection affecting another organ, with onset at age older than one month	Retinitis only. Cytomegalovirus retinitis may be diagnosed by experienced clinicians: typical eye lesions on serial fundoscopic examination; discrete patches of retinal whitening with distinct borders, spreading centrifugally, often following blood vessels, associated with retinal vasculitis, haemorrhage and necrosis	Definitive diagnosis required for other sites. Histology. Cerebrospinal fluid polymerase chain reaction
Central nervous system toxoplasmosis onset after age one month	Fever, headache, focal nervous system signs and convulsions. Usually responds within 10 days to specific therapy	Computed tomography scan (or other neuroimaging) showing single or multiple lesions with mass effect or enhancing with contrast
Extrapulmonary cryptococcosis (including meningitis)	Meningitis: usually subacute, fever with increasing severe headache, meningism, confusion, behavioural changes that respond to cryptococcal therapy	Cerebrospinal fluid microscopy (India ink or Gram stain), serum or cerebrospinal fluid cryptococcal antigen test or culture

CLINICAL EVENT	CLINICAL DIAGNOSIS	DEFINITIVE DIAGNOSIS
HIV encephalopathy	At least one of the following, progressing over at least two months in the absence of another illness: • failure to attain, or loss of, developmental milestones, loss of intellectual ability or • progressive impaired brain growth demonstrated by stagnation of head circumference or • acquired symmetric motor deficit accompanied by two or more of the following: paresis, pathological reflexes, ataxia and gait disturbances	Neuroimaging demonstrating atrophy and basal ganglia calcification and excluding other causes
Disseminated mycosis (coccidiomycosis, histoplasmosis)	No presumptive clinical diagnosis	Histology: usually granuloma formation. Isolation: antigen detection from affected tissue; culture or microscopy from clinical specimen or blood culture
Disseminated mycobacteriosis, other than TB	No presumptive clinical diagnosis	Nonspecific clinical symptoms including progressive weight loss, fever, anaemia, night sweats, fatigue or diarrhoea; plus culture of atypical mycobacterial species from stool, blood, body fluid or other body tissue, excluding lung

CLINICAL EVENT	CLINICAL DIAGNOSIS	DEFINITIVE DIAGNOSIS
Chronic cryptosporidiosis	No presumptive clinical diagnosis	Cysts identified on modified Ziehl-Nielsen microscopic examination of unformed stool
Chronic isosporidiosis	No presumptive clinical diagnosis	Identification of *Isospora* spp.
Cerebral or B-cell non-Hodgkin lymphoma	No presumptive clinical diagnosis	Diagnosed by central nervous system neuroimaging; histology of relevant specimen
Progressive multifocal leukoencephalopathy	No presumptive clinical diagnosis	Progressive neurological disorder (cognitive dysfunction, gait/speech disorder, visual loss, limb weakness and cranial nerve palsies) together with hypodense white matter lesions on neuro-imaging or positive polyomavirus JC polymerase chain reaction on cerebrospinal fluid
HIV-associated nephropathy	No presumptive clincial diagnosis	Renal biopsy
HIV-associated cardiomyopathy	No presumptive clinical diagnosis	Cardiomegaly and evidence of poor left ventricular function confirmed by echocardiography

Source: World Health Organization *(45)*.

ANNEX 5. GRADING OF ADVERSE DRUG EVENTS

PARAMETER OR FEATURE	GRADE 1	GRADE 2	GRADE 3	GRADE 4
BLOOD				
Haemoglobin (g/dl) (age ≥2 years)	10.0–10.9	7.0–9.9	<7.0	Cardiac failure secondary to anaemia
Absolute neutrophil count (× 10^9 per litre)	0.750–1.200	0.400–0.749	0.250–0.399	<0.250
Platelets (cells/mm^3)	69 999–100 000	50 000–70 000	25 000–49 999	<25 000 or bleeding
GASTROINTESTINAL				
Bilirubin	1.1–1.9 times normal	2.0–2.9 times normal	3.0–7.5 times normal	>7.5 times normal
Aspartate aminotransferase	1.1–4.9 times normal	5.0–9.9 times normal	10.0–15.0 times normal	>15.0 times normal
Alanine aminotransferase	1.1–4.9 times normal	5.0–9.9 times normal	10.0–15.0 times normal	>15.0 times normal
Gamma-glutamyl transferase	1.1–4.9 times normal	5.0–9.9 times normal	10.0–15.0 times normal	>15.0 times normal
Pancreatic amylase	1.1–1.4 times normal	1.5–1.9 times normal	2.0–3.0 times normal	>3.0 times normal
Abdominal pain	Mild	Moderate – no treatment needed	Moderate – no treatment needed	Severe – hospital and treatment
Diarrhoea	Soft stools	Liquid stools	Liquid stools and mild dehydration, bloody stool	Dehydration requiring intravenous 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	1–3 episodes/day or duration >3 days	>3 episodes/ days or duration >7 days	Intractable vomiting

ALLERGIC AND DERMAL

Allergy	Pruritis without rash	Pruritic rash	Mild urticaria	Severe urticaria; anaphylaxis, angioedema
Drug fever	37.6–38.4°C	38.5–40°C	>40°C	Sustained fever: >40^{0}C, >5 days
Cutaneous	Erythema, pruritus	Diffuse maculopapular rash, dry desquamation	Vesiculation, ulcers	Exfoliative dermatitis, Stevens-Johnson or erythema multiforme, moist desquamation

Source: African Network for the Care of Children Affected by AIDS *(46)*.

ANNEX 6. SUMMARY OF MAJOR STUDIES OF CO-TRIMOXAZOLE PROPHYLAXIS

COUNTRY OF STUDY	STUDY DESIGN	AUTHOR AND YEAR OF STUDY	CO-TRIMOXAZOLE DOSE	STUDY POPULATION (N)
Côte d'Ivoire	Randomized placebo-controlled trial	Anglaret et al. 1999 *(17)*	960 mg	Adults *n* = 541
Côte d'Ivoire	Randomized placebo-controlled trial	Wiktor et al. 1999 *(14)*	960 mg	Adults *n* = 771
Senegal	Randomized placebo-controlled trial	Maynart et al. 2001 *(47)*	480 mg	Adults *n* = 100
Zambia	Randomized placebo-controlled trial	Nunn submitted *(48)*	960 mg	Adults *n* = 925
Zambia	Randomized placebo-controlled trial	Chintu et al. 2004 *(7)*	<5 years: 240 mg; >5 years: 480 mg	Children 1–14 years *n* = 534
South Africa	Observational study	Badri et al. 2001 *(49)*	480 mg daily or 960 mg 3 times per week	Adults *n* = 563
Uganda, Entebbe	Historical comparison before and after co-trimoxazole	Watera et al. 2002 *(13)*	960 mg	Adults *n* = 806
Uganda	Historical comparison before and after co-trimoxazole	Mermin et al. 2004 *(19)*	960 mg among adults	Adults and children – percentages not stated *n* = 509

TB	CO-TRIMOXAZOLE RESISTANCE	EFFECT ON MORTALITY	EFFECT ON MORBIDITY	ADVERSE EVENT RATE
Some	Low	No significant difference	43% lower	0.6%
All smear positive	Low	46% lower	53% fewer admissions 27% fewer morbid events	<1%
None	Intermediate	No significant difference	No significant difference	6%
All smear positive	High	No overall significant difference (difference seen from 6–18 months)	Not reported	0.3%
Some	High	33% lower (all ages and CD4 ratios)	21% less hospitalization	6%
Some	Not stated	45% lower – only significant for WHO clinical stages 3 and 4 and CD4 <200 cells per mm^3	48% fewer severe HIV-related illnesses	Not reported
Some	High	23% lower	No overall difference 69% less malaria	3.8%
Some	High	46% lower – only significant for CD4 <200 cells per mm^3 WHO clinical stages 3 and 4	Hospitalization reduced 31%, diarrhoea reduced 35%, malaria reduced 72%	2%

Malawi, Thyolo	Historical comparison with no co-trimoxazole	Zachariah et al. 2002 *(30)*	960 mg	Adults *n* = 2986
Malawi, Karonga	Historical comparison with no co-trimoxazole	Mwaungulu et al. 2004 *(50)*	960 mg	Adults *n* = 717
South Africa	Historical comparison with no co-trimoxazole	Grimwade et al. 2005 *(18)*	960 mg	Adults *n* = 3232

All	High	25% lower	Not reported	<2%
All	High	22% lower across the programme, 44% lower among participants living with HIV	Not reported	Not reported
All	High	29% lower	Not reported	<1%

REFERENCES

1. *WHO Expert Consultation on Cotrimoxazole Prophylaxis in HIV Infection: report of a WHO expert consultation, Geneva, 10–12 May 2005*. Geneva, World Health Organization, 2006 (http://www.who.int/hiv/pub/meetingreports/ctxprophylaxismeeting.pdf, accessed 16 June 2006).

2. BHIVA Writing Committee on behalf of the BHIVA Executive Committee. *The British HIV Association (BHIVA) treatment guidelines for 2005*. London, British HIV Association, 2005 (http://www.bhiva.org/guidelines/2005/BHIVA-guidelines, accessed 16 June 2006).

3. Developing an evidence-based guide to community preventive services – methods. Task Force on Community Preventive Services. *American Journal of Preventive Medicine*, 2000, 18(1 Suppl):35–43.

4. WHO Health Evidence Network. *What is the evidence for the effectiveness of interventions to reduce hepatitis C infection and the associated morbidity?* Copenhagen, WHO Regional Office for Europe, 2005 (http://www.euro.who.int/HEN/Syntheses/hepatitisC/20050412_1, accessed 16 June 2006).

5. EBM guidelines: evidence-based medicine [online database]. New York, Wiley (http://ebmg.wiley.com/ebmg/ltk.koti, accessed 16 June 2006).

6. *WHO Model List of Essential Medicines*. 14th ed. Geneva, World Health Organization, 2005 (http://www.who.int/medicines/publications/essentialmedicines/en/index.html, accessed 16 June 2006).

7. Chintu C et al. Cotrimoxazole as prophylaxis against opportunistic infections as HIV-infected Zambian children (CHAP): a double-blind randomised placebo-controlled trial. *Lancet*, 2004, 364:1865–1871.

8. Graham SM et al. Clinical presentation and outcome of *Pneumocystis carinii* pneumonia in Malawian children. *Lancet*, 2000, 355:369–373.

9. Zar HJ et al. *Pneumocystis carinii* pneumonia in South African children infected with human immunodeficiency virus. *Pediatric Infectious Disease Journal*, 2000, 19:603–607.

10. Graham SM. Cotrimoxazole prophylaxis for infants exposed to HIV infection. *Bulletin of the World Health Organization*, 2004, 82:297–298.

11. Chintu C et al. Lung disease at necropsy in African children dying from respiratory illnesses: a descriptive necropsy study. *Lancet*, 2002, 360:985–990.

12. Watera C et al. Efficacy and toxicity to cotrimoxazole prophylaxis in HIV-1 infected Ugandan adults. *14th International AIDS Conference, Barcelona, Spain, 7–12 July 2002* (Abstract MoPeB3236; http://www.aegis.com/conferences/iac/2002/MoPeB3236.html, accessed 16 June 2006).

13. Thera MA et al. Impact of trimethoprim-sulfamethoxazole prophylaxis on *falciparum* malaria infection and disease. *Journal of Infectious Diseases*, 2005, 192:1823–1829.

14. Wiktor SZ et al. Efficacy of trimethoprim-sulphamethoxazole prophylaxis to decrease morbidity and mortality in HIV-1-infected patients with tuberculosis in Abidjan, Côte d'Ivoire: a randomised controlled trial. *Lancet*, 1999, 353:1469–1475.

15. CDC revised guidelines for prophylaxis against *Pneumocystis carinii* pneumonia for children infected with or perinatally exposed to human immunodeficiency virus. *Morbidity and Mortality Weekly Report*, 1995, 44(RR-4):1–11.

16. Kaplan JE et al. Guidelines for preventing opportunistic infections among HIV-infected persons – 2002 recommendations of the U.S. Public Health Service and the Infectious Diseases Society of America. *MMWR Recommendations and Reports*, 2002, 51(RR08):1–46.

17. Anglaret X et al. Early chemoprophylaxis with trimethoprim-sulphamethoxazole for HIV-1 infected adults in Abidjan, Côte d'Ivoire: a randomized trial. *Lancet*, 1999; 353:1463–1468.

18. Grimwade K et al. Effectiveness of cotrimoxazole prophylaxis on mortality in adults with tuberculosis in rural South Africa. *AIDS*, 2005, 19:163–168.

19. Mermin J et al. Effect of cotrimoxazole prophylaxis on morbidity, mortality, CD4-cell count, and viral load in HIV infection in rural Uganda. *Lancet*, 2004, 364:1428–1434.

20. Mermin J et al. Cotrimoxazole prophylaxis by HIV-infected persons in Uganda reduces morbidity and mortality among HIV-infected family members. *AIDS*, 2005, 19:1035–1042.

21. Walter J et al. Cotrimoxazole prophylaxis and adverse birth outcomes among HIV-infected women in Lusaka, Zambia. *13th Conference on Retroviruses and Opportunistic Infections, Denver, CO, USA, 5–8 February 2006* (Abstract 126; http://www.retroconference.org/2006/Abstracts/27059.htm, accessed 16 June 2006).

22. Nachman S et al. The rate of serious bacterial infections among HIV-infected children with immune reconstitution who have discontinued opportunistic infection prophylaxis. *Pediatrics*, 2005; 115:488–494.

23. Urschela S et al. Withdrawal of *Pneumocystis jirovecii* prophylaxis in HIV-infected children under highly active antiretroviral therapy. *AIDS*, 2005, 19:2103–2108.

24. Furrer H et al. Discontinuation of primary prophylaxis against *Pneumocystis carinii* pneumonia in HIV-1-infected adults treated with combination antiretroviral therapy. *New England Journal of Medicine*, 1999, 340:1301–1306.

25. Weverling GJ et al. Discontinuation of *Pneumocystis carinii* pneumonia prophylaxis after start of highly active antiretroviral therapy in HIV-1 infection. *Lancet*, 1999, 353:1293–1298.

26. Kumarasamy N et al. Safe discontinuation of primary *Pneumocystis* prophylaxis in south Indian HIV-infected patients on HAART. *Journal of AIDS*, 2005, 40:377–378.

27. Duncombe C et al. Immune recovery and stopping cotrimoxazole prophylaxis in Thai patients treated with NNRTI-based HAART for 216 weeks. *13th Conference on Retroviruses and Opportunistic Infections, Denver, CO, USA, 5–8 February 2006* (Abstract 784; http://www.retroconference.org/2006/Abstracts/27279.htm, accessed 16 June 2006).

28. Van Oosterhout J et al. A community-based study of the incidence of trimethoprim-sulfamethoxazole-preventable infections in Malawian adults living with HIV. *Journal of Acquired Immune Deficiency Syndromes*, 2005, 39:626–631.

29. Abdel-Haq N et al. Nasopharyngeal colonization with *Streptococcus pneumoniae* in children receiving trimethoprim-sulfamethoxazole prophylaxis. *Pediatric Infectious Disease Journal*, 1999, 18:647–649.

30. Zachariah R et al. Changes in *Escherichia coli* resistance to cotrimoxazole in tuberculosis patients and in relation to cotrimoxazole prophylaxis in Thyolo, Malawi. *Transactions of the Royal Society of Tropical Medicine and Hygiene,* 2002, 96:202–204.

31. Simonds RJ et al. Prophylaxis against *Pneumocystis carinii* pneumonia among children with perinatally acquired human immunodeficiency virus infection in the United States. *Pneumocystis carinii* Pneumonia Prophylaxis Evaluation Working Group. *New England Journal of Medicine*, 1995, 332:786–790.

32. Bunders M, Cortina-Borja M, Newell ML. Age-related standards for total lymphocyte, CD4+ and CD8+ T cell counts in children born in Europe. European Collaborative Study. *Pediatric Infectious Disease Journal*, 2005, 24:595–600.

33. Dworkin M et al. Risk for preventable opportunistic infections in persons with AIDS after antiretroviral therapy increases CD4+ T-lymphocyte counts above prophylaxis thresholds. Adult/Adolescent Spectrum of HIV Disease Project (ASD). *Journal of Infectious Diseases*, 2000;182:611–615.

34. Kirk O et al. Can chemoprophylaxis against opportunistic infections be discontinued after an increase in CD4 cells induced by highly active antiretroviral therapy? *AIDS*, 1999, 13:1647–1651.

35. Soriano V et al. Discontinuation of secondary prophylaxis for opportunistic infections in HIV-infected patients receiving highly active antiretroviral therapy. *AIDS*, 2000, 14:383–386.

36. Lopez JC et al. A randomized trial of the discontinuation of primary and secondary prophylaxis against *Pneumocystis carinii* pneumonia after HAART in patients with HIV infection. GESIDA 04/98 Study Group. *New England Journal of Medicine*, 2001, 344:159–167.

37. Ledergerber B et al. Discontinuation of secondary prophylaxis against *Pneumocystis carinii* pneumonia in patients with HIV infection who have a response to antiretroviral therapy. *New England Journal of Medicine*, 2001, 344:168–174.

38. Forna F et al. Systematic review of the safety of trimethoprim-sulfamethoxazole for prophylaxis in HIV-infected pregnant women: implications for resource-limited settings. *AIDS Reviews*, 2006, 8:24–36.

39. DiRienzo AG et al. Efficacy of trimethoprim-sulfamethoxazole for the prevention of bacterial infections in a randomized prophylaxis trial of patients with advanced HIV infection. *AIDS Research and Human Retroviruses*, 2002, 18:89–94.

40. Martin MA et al. A comparison of the effectiveness of three regimens in the prevention of *Pneumocystis carinii* pneumonia in human immunodeficiency virus–infected patients. *Archives of Internal Medicine*, 1992, 152:523–528.

41. Hughes WT. Use of dapsone in the prevention and treatment of *Pneumocystis carinii* pneumonia: a review. *Clinical Infectious Diseases*, 1998, 27:191–204.

42. Carr A, Penny R, Cooper DA. Efficacy and safety of rechallenge with low-dose trimethoprim-sulphamethoxazole in previously hypersensitive HIV-infected patients. *AIDS*, 1993, 7:65–71.

43. Absar N, Daneshvar H, Beall G. Desensitization to trimethoprim/sulfamethoxazole in HIV-infected patients. *Journal of Allergy and Clinical Immunology*, 1994, 93:1001–1005.

44. Gompels MM et al. Desensitization to co-trimoxazole (trimethoprim-sulphamethoxazole) in HIV-infected patients: is patch testing a useful predictor of reaction? *Journal of Infection*, 1999, 38:111–115.

45. *Revised WHO clinical staging and immunological classification of HIV and case definition of HIV for surveillance*. Geneva, World Health Organization (in press).

46. Tindyebwa D et al., eds. *Handbook on paediatric AIDS in Africa*. Kampala, Uganda, African Network for the Care of Children Affected by AIDS, 2005 (http://www.fhi.org/en/HIVAIDS/pub/guide/mans1.htm, accessed 16 June 2006).

47. Maynart M et al. Primary prevention with cotrimoxazole for HIV-1-infected adults: results of the pilot study in Dakar, Senegal. *Journal of Acquired Immune Deficiency Syndromes*, 2001, 26:130–136.

48. Nunn A et al. Double-blind, placebo-controlled, randomized clinical trial to evaluate the efficacy of co-trimoxazole given as prophylaxis in reducing mortality in HIV-infected adults with tuberculosis (LUCOT study). Submitted.

49. Badri M et al. Initiating co-trimoxazole prophylaxis in HIV-infected patients in Africa: an evaluation of the provisional WHO/UNAIDS recommendations. *AIDS*, 2001, 15:1143–1148.

50. Mwaungulu FB et al. Cotrimoxazole prophylaxis reduces mortality in human immunodeficiency virus–positive tuberculosis patients in Karonga District, Malawi. *Bulletin of the World Health Organization*, 2004, 82:354–363.

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