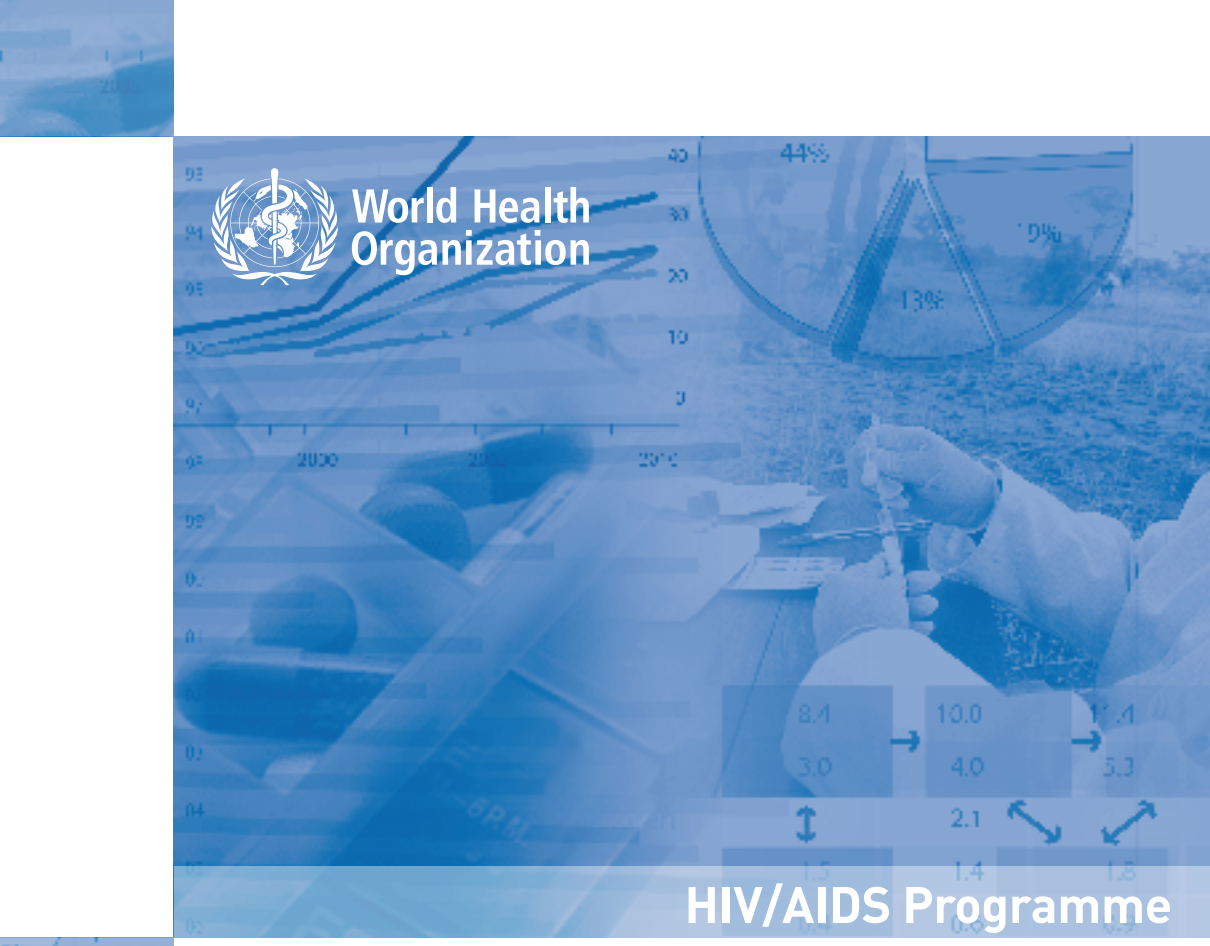

World Health Organization

HIV/AIDS Programme

Strengthening health services to fight HIV/AIDS

ESSENTIAL PREVENTION AND CARE INTERVENTIONS FOR ADULTS AND ADOLESCENTS LIVING WITH HIV IN RESOURCE-LIMITED SETTINGS

WHO Library Cataloguing-in-Publication Data

Essential prevention and care interventions for adults and adolescents living with HIV in resource-limited settings / coordinated by Kevin O'Reilly.

1.HIV infections - prevention and control. 2.HIV infections - therapy. 3.HIV infections - complications. 4.Developing countries. I.World Health Organization. II.Boothroyd, Jim.

ISBN 978 92 4 159670 1 (NLM classification: WC 503.5)

Printed in

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Acknowledgements

The work was coordinated by Kevin O'Reilly, Department of HIV/AIDS, World Health Organization, with the assistance and support of many others. Jim Boothroyd edited this guidance.

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ACRONYMS AND ABBREVIATIONS

3TC	lamivudine
AIDS	acquired immunodeficiency syndrome
Anti HBc	antibodies to hepatitis-B core antigen
Anti HBs	antibodies to hepatitis-B surface antigen
ARV	antiretroviral
ART	antiretroviral therapy
AZT	azidothymidine
BMI	body-mass index
CTX	co-trimoxazole
EPI	Expanded Programme on Immunization
HBV	hepatitis-B virus
HIV	human immunodeficiency virus
IMAI	Integrated Management of Adolescent and Adult Illness
IPT	intermittent preventive treatment
IPTp	intermittent preventive treatment in pregnancy
IRS	indoor residual spraying
ITNs	insecticide-treated mosquito nets
MDR	multidrug resistant
NNRTI	non-nucleoside reverse transcriptase inhibitor
NRTI	nucleoside reverse transcriptase inhibitor
NSP	needle-syringe programme
NVP	nevirapine
OI	opportunistic infection
OST	opioid substitution therapy
PCP	*Pneumocystis jiroveci* pneumonia (formerly *Pneumocystis carinii*)
PI	protease inhibitor
PLHIV	people living with HIV
PMTCT	prevention of mother-to-child transmission of HIV
PPV	pneumococcal polysaccharide vaccine
RCT	randomized clinical trial
RDA	recommended daily allowance
RTI	reproductive tract infection
SP	sulfadoxine-pyrimethamine
SMX	sulfamethoxazole
STI	sexually transmitted infection
TB	tuberculosis
UNAIDS	Joint United Nations Programme on HIV/AIDS
UNFPA	United Nations Population Fund
VCT	voluntary counselling and testing
WHO	World Health Organization
ZDV	zidovudine

EXECUTIVE SUMMARY

People living with HIV in resource limited settings should have access to essential interventions to prevent illness and HIV transmission. Under Universal Access, agreed to by the G8, efforts to scale up all prevention interventions, to promote provider-initiated HIV testing and counselling services and to integrate these into the care and treatment of people with HIV are underway. Expansion of HIV testing and counselling will greatly increase the number of people with HIV who are aware of their HIV status and can benefit from comprehensive HIV-related prevention, care, and treatment services. All people with HIV for whom ART is clinically indicated should have access to it. But people with HIV for whom ART is not clinically indicated should also benefit from basic HIV prevention and care, including a core set of effective interventions that are simple, relatively inexpensive, can improve the quality of life, prevent further transmission of HIV, and for some interventions, delay progression of HIV disease and prevent mortality. Defining, implementing, and promoting access to a set of effective HIV prevention and care interventions, in addition to ART, through health facilities, and at the community level through outreach, are critical to achieving universal access.

This document is the result of an effort to review the evidence and develop recommendations for interventions to reduce illness associated with HIV infection and prevent HIV transmission. It follows on an expert panel convened in June 2006. This review meeting used a standardized rating system and a structured guidance development process. Recommendations were formulated covering thirteen areas of intervention seen as low cost and of particular importance for people living with HIV. These areas are:

- psychosocial counselling and support;
- disclosure, partner notification and testing and counselling;
- co-trimoxazole prophylaxis;
- tuberculosis (TB);
- preventing fungal infections;
- sexually transmitted and other reproductive tract infections;
- preventing malaria;
- selected vaccine preventable diseases (hepatitis-B, pneumococcal, influenza vaccine, and yellow fever vaccines);
- nutrition;
- family planning;
- preventing mother-to-child transmission of HIV;
- needle-syringe programmes and opioid substitution therapy; and
- water, sanitation and hygiene.

While not all interventions will be needed or equally important in all countries, depending on local and national epidemiology, it is hoped that those most useful will be adopted, adapted as needed and provided to people living with HIV. Once ART is begun, the utility of many of these interventions will not decrease and they should be maintained throughout the treatment course as well.

1. BACKGROUND AND RATIONALE

WHO and UNAIDS, in line with commitments made by the United Nations General Assembly and G8 nations, are working towards the goal of universal access to comprehensive HIV prevention, treatment, care and support for people living with HIV by 2010. This requires a massive and unprecedented scale-up of public health infrastructure and strengthening of health services worldwide. It is estimated that at the end of 2007, 33.2 million people were living with HIV, 95% of whom were in developing countries.[1] Progress has been achieved over a short period of time in supporting antiretroviral therapy (ART) for more than two million persons in low- and middle-income countries.[2] To date, however, estimates based on surveys conducted in sub Saharan Africa indicate that only 12 to 25% of people living with HIV know their status.[2] Thus many people with HIV are not receiving even basic HIV-related services and at the end of 2006 approximately 72% of those who require ART were not receiving it.[2] Coverage of all interventions for HIV prevention has remained low and although the impact of prevention is beginning to be seen in more countries, the number of new infections remains unacceptably high.

To achieve universal access, efforts to scale up all prevention interventions, provider-initiated HIV testing and counselling services[3] and integration of these into the care and treatment of people with HIV must be accelerated.[4,5] Expansion of HIV testing and counselling will greatly increase the number of people with HIV who are aware of their HIV status and can benefit from comprehensive HIV-related prevention, care, and treatment services.

All people with HIV for whom ART is clinically indicated should have access to it. Increasing ART coverage is a key goal of many countries. But people with HIV should also benefit from basic HIV prevention and care, including a core set of effective interventions that are simple, relatively inexpensive, can improve the quality of life, prevent further transmission of HIV, and for some interventions, delay progression of HIV disease and prevent mortality. Voluntary testing and counselling, for example, has been shown to reduce the likelihood that people living with HIV will transmit the infection to their sex partners [6] while the distribution of sterile needles and syringes has been shown to be highly effective in reducing transmission from injecting drug users living with HIV to their uninfected needle-sharing partners.[7] Interventions to prevent mother-to-child transmission, including family planning to prevent unintended pregnancies in women living with HIV, are also highly effective.[8] A key component of basic HIV care is provision of co-trimoxazole (CTX), as recommended by 2006 WHO guidelines[9]. Studies have consistently demonstrated the effectiveness of CTX in reducing morbidity and mortality among people living with HIV in resource-limited settings.[10,11] There is also a growing body of evidence indicating the effectiveness of other interventions that prevent illness in people with HIV—for example, use of insecticide-treated mosquito nets for malaria prevention, measures to ensure safe drinking water and improve nutrition, and isoniazid prophylaxis—which have come to be considered part of basic HIV care in some resource-limited settings.[2,12] Defining, implementing, and promoting access to a set of effective HIV prevention and care interventions, in addition to ART, through health facilities, and at the community level through outreach, are critical to achieving universal access.[2] To review the evidence and develop recommendations for interventions to reduce illness associated with HIV infection and prevent HIV transmission, WHO convened an expert panel in June 2006, that used a standardized rating system and a structured guidance development process.

These WHO recommendations outline evidence-based interventions that, in addition to or prior to the initiation of ART, promote health, reduce the risk of HIV transmission to others, and address diseases that most impact the quality and duration of life of adults and adolescents with HIV. The recommended interventions focus on prevention of initial illness or episodes of opportunistic infections (OIs) and malignancies rather than treatment or prevention of recurrence. Although most interventions considered in this guidance are delivered by staff in health-care facilities, some are best delivered in households, such as point-of-use interventions to improve water safety. Guidance is provided for interventions that fall into two groups: 1) those that prevent transmission of HIV infection through sex, injecting drug use and from mother to infant; and 2) those that prevent opportunistic illnesses. In the first group, guidance is provided for interventions that can be implemented by health-care providers to substantially reduce HIV transmission to others, including screening for HIV-related risk behaviours, support for safer sexual and drug-use behaviours, condom promotion and provision, partner notification and beneficial disclosure, identification and treatment of sexually transmitted infections (STIs), HIV testing and counselling for partners and family members, and provision of psychosocial support and family planning services. In the second group, guidance is provided for interventions to prevent a range of common opportunistic infections, including malaria, tuberculosis, bacterial diseases, and selected fungal infections and to promote health with safe water, nutritional support and vaccination. In developing the recommendations for this second focus, consideration was given to the level of immunosuppression or clinical stage at which the opportunistic disease or illness is most likely to occur, the incidence of disease, the severity or impact of disease among HIV-infected populations and, for chemoprophylaxis interventions, efficacy, drug toxicities, drug interactions, and drug resistance.

These interventions should be considered as a part of an essential package of services for people living with HIV, which can be adapted according to countries' burdens of disease, epidemiology, and infrastructure capacity.[2] Some interventions, however, are strongly recommended in all settings. Recommendations from previously published co-trimoxazole prophylaxis[9], nutrition[13,14] and PMTCT guidelines[15] have been incorporated into this guidance to provide a comprehensive set of recommendations. Where relevant recommendations exist for these interventions within other WHO guidance documents, efforts were made to cross reference these and ensure consistency. These recommendations complement the ART guidelines[16] and together provide core components of an integrated set of prevention, care, and treatment services.

Implementation of the HIV prevention and care services outlined in these recommendations may assist in building sustainable infrastructure that can enhance the delivery of services for other diseases and help establish models for delivering chronic care. Implementation will require strengthening components of health systems, including human resources capacity, effective supply management systems, laboratory capacity, training, supervision, and monitoring capacity to maximize the quality and benefits of long-term HIV care. Opportunities are highlighted for more concerted efforts to improve coordination and cooperation with other international initiatives, such as the Roll Back Malaria, StopTB, the Expanded Programme on Immunization (EPI) and programmes addressing safe water and reproductive health.[17-19] As new evidence or interventions become available, WHO will provide further guidance.

1.1 Involving people living with HIV

"Positive prevention," as it is commonly known, includes three key components: healthy living, prevention of HIV transmission and the involvement of people living with HIV. Effective positive prevention is based on proven interventions and the participation of people with HIV in implementing these, according to their needs and rights. This document addresses the "what" of positive prevention, presenting the evidence base that supports specific interventions recommended to help people with HIV live a healthy life and to engage in sexual activity without fear of transmitting the virus to their sex partners. It does not address the equally important "how" of positive prevention: how these recommended interventions should be implemented. Most successful implementation strategies do the following: 1) combine strategies to create enabling environments for the empowerment of people with HIV; 2) protect and promote human rights and ethical principles, including the right to privacy, confidentiality, informed consent and the duty to do no harm; 3) include measures to prevent the stigmatization of, and discrimination against, people with HIV, while still focusing on the particular needs and rights of people with HIV; and 4) balance the public need for HIV/STI prevention with the private need of people living with HIV for sexual well-being and their human rights. The meaningful involvement of people living with HIV is instrumental in facilitating understanding and an effective response. For a more complete discussion of the involvement of people living with HIV in positive prevention, see Positive Prevention: HIV prevention with People living with HIV (2007), published by the International HIV/AIDS Alliance.[20]

2. OBJECTIVES

The objective of these recommendations is to provide global, technical, evidence-based recommendations for prevention and care interventions, other than ART, that people living with HIV in resource-limited settings should expect as part of their health-care services. The recommendations also aim to promote the expansion of provider-initiated interventions for HIV prevention and non-ART care and treatment for adults and adolescents living with HIV. The recommendations focus on prevention of initial illness or opportunistic infections, rather than the on-going treatment of these. As well, they integrate prevention of HIV transmission as part of care and treatment services that are adaptable to the needs of countries with different epidemiology and capacities to deliver those services. It is anticipated that these recommendations will be valid for at least three years from the date of their publication. After that time, the need for revision based on the addition of new evidence will be assessed.

2.1 Target audience

The recommendations are primarily intended for use by managers of national and sub-national AIDS programmes and nongovernmental organizations that deliver HIV care services and for policy-makers involved in scaling up HIV prevention, care and treatment in settings with limited resources. This guidance and these recommendations should also be useful for clinicians and other providers of prevention and care services for people with HIV in such settings.

3. METHODS

WHO developed these recommendations in three phases. First, an organizing committee of WHO technical staff and key stakeholders was convened to identify interventions for consideration and the method for developing the guidance. Second, systematic reviews of the evidence were conducted (see Appendix A for details). Third, WHO organized a consultative meeting in June 2006 (Appendix B for participants), at which experts reviewed the evidence, supplemented by expert opinion, using the agreed, structured guidance development method.[21] Participants were invited based on their technical expertise in different topic areas, their contributions to the peer-reviewed literature, particularly related to resource-limited settings, or their responsibility to adapt and use the recommendations in countries. As such, a wide range of participants were included: academic researchers; representatives of ministries of health, bilateral donors, non-governmental organizations focusing on treatment and prevention; and UN organizations and WHO regional and headquarters staff. Efforts were made to ensure that these participants represented a wide range of different disciplines, organizations, and geographic regions. No conflicts of interest were identified. Established group judgement models,[22] such as the Delphi Process, the Nominal Group Technique, and the Appropriateness Method, were used to put in place a fair, transparent and structured process for the production of the guidance. As the review process covered so many specific areas, initial review and discussion of the evidence was conducted in small groups focusing on each. (Membership of those groups is identified in Appendix B.) Each small group then drafted specific recommendation statements which were voted on anonymously in the small group. Once consensus was reached on the need and the best phrasing of the each recommendation, they were presented to the entire group. All participants then voted on all statements anonymously. The results of the voting were then announced, followed by further open discussion, and when required, recommendation statements were modified and again voted on. These structured methods allowed a process for improving and refining draft recommendation statements and the opportunity for participants to modify their opinions, based on feedback from their peers. Following the meeting, principles for inclusion of recommendations in the guidance were finalized. A committee then wrote up the guidance for review by the meeting participants as well as institutional and organizational partners. The guidance was then prepared and posted on the website of WHO for a six-week period of public comment. Comments received were considered and the document was modified as needed.

3.1 Strength and quality of evidence

The strength of each recommendation in this guidance is graded: from strongly recommended (A) to optional (C). These grades are intended to guide the degree to which the recommendations should be considered by managers of regional and country-level programmes (see box below, "Grading of recommendations and level of evidence"). The guidance also indicate the quality of evidence in support of each recommendation. Evidence from randomized controlled trials and high-quality scientific studies, for example, are considered level I; those based on observational cohort or case-control data are considered level III, and those based on expert opinion, for example, level IV.

Grading of recommendations and level of evidence

Strength of recommendation	Level of evidence for recommendation
A. Recommended – should be followed B. Consider – applicable in most situations C. Optional	I. At least one randomized controlled trial with clinical or biological endpoints, or several relevant high-quality scientific studies II. At least one randomized controlled trial with surrogate markers, at least one high-quality study or several adequate studies III. Observational cohort data, or at least one case-controlled or analytic study adequately conducted IV. Expert opinion based on evaluation of other evidence

The above strength and quality ratings were adapted from three sources:

> Developing an evidence-based guide to community preventive service-methods. The Task Force on Community Preventive Services. *American Journal of Preventive Medicine,* 2000. 18 (1S):35-43.
>
> *EBM guidelines: evidence-based medicine* (online database). New York, Wiley (http://ebmg.wiley.com/ebmg/ltk.koti, accessed June 2006).
>
> *Guidelines on co-trimoxazole prophylaxis for HIV-related infections among children, adolescents and adults in resource-limited settings: Recommendations for a public health approach.* Geneva, WHO, 2006. (http://www.who.int/hiv/pub/guidelines/ctx/en/index.html)

While scales like these have been criticized for a lack of uniformity and being overly complex and non-explicit, they were the best available option in the absence of any other consistent methods in use by WHO. One uniform grading approach recommended in the WHO guideline for developing guidelines is the GRADE approach.[23,24] At the time of this conference, it was not yet widely adopted, was rarely used by WHO and was unfamiliar to the organizers of this consultation. The method used was the best available to assure transparency and objectivity in formulating recommendations and assigning "strength of evidence" scores.

This scheme for grading the level and strength of evidence gives priority to randomized controlled trials (RCTs). The main outcome of interest in studies of prevention of sexual transmission of HIV is often difficult if not impossible to measure in RCTs without serious ethical concerns. As a result, RCTs were rarely encountered in the literature on the prevention of transmission. This grading system, then, yielded higher gradings for strength of evidence for interventions addressing the prevention of disease than for interventions addressing the prevention of sexual transmission.

Simple, affordable, and easily implemented interventions were given high priority. The experts formulating this guidance did not formally consider cost of the interventions, though discussion included what was regarded as feasible in terms of costs for resource-constrained settings. The literature searches did not specifically address cost or cost effectiveness either. The state of human resources, health system infrastructure and socioeconomic issues should, however, be taken into account when adapting these recommendations to regional and country programmes.

4.1 Psychosocial counselling and support

Psychosocial counselling, including support of behaviour change and treatment adherence, is an essential component of HIV prevention, care and treatment. Unfortunately, psychosocial counselling has not always been consistently implemented as a prevention measure, particularly as countries have focused on scaling up access to life-saving antiretroviral treatment. Because HIV is a highly stigmatized and life-long, chronic disease, those who are infected often have to deal with anger, fear and self-stigmatization. Their partners, children, and family frequently face grief, bewilderment and high levels of stress. These psychosocial issues must be addressed for prevention, care and support to succeed.

Relatives, friends, traditional healers and those of religious faith are sources of strength and social support to many people. But more formal psychological support may *also* be needed as psychological needs vary, depending on serostatus, stage of disease, prognosis and other factors. Individual and couples counselling can bring about behavioural changes in support of prevention among people living with HIV, their partners and family. Together, counselling and antiretroviral therapy (ART), are effective in treating some of the mental conditions that affect people living with HIV. Recent experience of scaling up ART in low income countries has also highlighted the value of family counselling in helping relatives to understand the implications of a family member needing life-long HIV treatment, and how to support this person.

HIV programmes must incorporate effective psychosocial interventions, including those that focus on behaviour change and reduction of stigma and discrimination. Many countries, including those with limited resources, have embraced this approach as a key part of efforts to scale up prevention and treatment of HIV. Increasingly, prevention and care services include counselling and skills-building for people living with HIV on how to live a healthy and productive life and how to reduce transmission of HIV to sexual partners.

Numerous psychosocial interventions have been implemented for people living with HIV in resource-limited settings, but more research on the impact of these interventions is needed.[25] Conducting these type of studies is complicated by the difficulty of measuring psychosocial outcomes. Nevertheless, accumulated evidence supports the benefits of delivering a comprehensive set of interventions to individuals living with HIV, their families and social networks. In particular, evidence exists to support psychosocial interventions for reducing the risk of HIV transmission among discordant couples[26,27] identification and treatment of depression,[28] and drug adherence.[29]

Experience also suggests that psychosocial support should be sensitive to differences related to culture, gender, age, and the vulnerabilities of people with HIV—particularly among women, who are especially vulnerable to discrimination and domestic violence.

4.1.1 Comprehensive interventions

Counselling needs to be tailored to individual needs, as the needs of an adolescent girl, for example, will likely be different from those of an adult injecting drug user or a sero-discordant couple. A comprehensive set of psychosocial interventions should include individual and group

counselling, peer support groups, family counselling and support (including home visits), and couples counselling to reduce the risk of HIV transmission, promote adherence to prophylactic and therapeutic regimens, and minimize the socioeconomic impact of HIV on households. These interventions should be integrated into all care and treatment services.

All people with HIV should be offered or provided referral to a comprehensive set of psychosocial interventions (e.g., individual and group counselling, peer support groups, family and couples counselling and adherence support). **(A-IV)**

4.1.2 Counselling and condoms

Knowledge about one's HIV infection may not prompt an individual to change his or her behaviour in support of HIV prevention; therefore, additional support may be needed. Most people living with HIV will remain sexually active and health-care providers should respect their right to do so, and support them and their partners in preventing further HIV transmission, including through the provision of condoms. Correct and consistent use of condoms have been shown to reduce the risk of HIV transmission. A meta-analysis of 12 longitudinal studies reported that consistent condom use resulted in an estimated 87% reduction in the risk of HIV transmission among discordant heterosexual couples.[30-32]

People with HIV who choose to be sexually active should be counselled about safer sex interventions to prevent HIV transmission to others and how to avoid acquisition of sexually transmitted infections (STIs), and should be provided with condoms. **(A-III)**

4.1.3 Sero-discordant couples

In mature generalized HIV epidemics, a large proportion of HIV infections occur within HIV-discordant, stable partnerships.[33,34] Prevalence of HIV discordance among couples in sub-Saharan Africa is high.[35] In Kenya, 7% of couples were discordant, which translates to approximately 400,000 to 500,000 couples.[36] HIV-negative partners in discordant couples are at high risk of HIV infection and represent an important group for prevention efforts. Evidence from studies of individuals and sero-discordant couples show that counselling together with the provision of condoms is effective in preventing HIV transmission [26,27,37] and should be provided to HIV discordant couples. Couples counselling is particularly effective in limiting the chances of HIV transmission within the couple.[38-40]

Ongoing behavioural counselling and psychosocial support should be provided to HIV-discordant couples through couples counselling and support groups that cover topics such as HIV-transmission-risk reduction, reproductive health issues, couples communication and condom use. **(A-I)**

4.1.4 Sero-concordant couples

The potential risk of HIV superinfection has been used to support recommendations for the correct and consistent use of condoms even when both partners are infected with HIV. Though a complicated issue, it is difficult to find strong evidence to support condom use for monogamous, sero-concordant, HIV-infected couples to reduce the risk of superinfection. If either partner has sex with others, then the correct and consistent use of condoms are strongly advised for the couple to avoid STIs.

Concordant HIV-infected couples should use condoms consistently, if needed to avoid STIs and unintended pregnancy. **(A-IV)** Knowledge regarding HIV superinfection is not yet sufficient, however, to support a recommendation for consistent condom use specifically to prevent superinfection.

4.1.5 Adherence interventions

Treatment with ART is the most powerful tool for improving the health of people with HIV and, when combined with counselling, leads to reduction in transmission of HIV. [16,41] Client-centred behavioural counselling, psychosocial support and other interventions such as pill boxes and reminder systems, have been shown to help people adhere to ART, as well as to prophylactic and treatment regimens.[42] This leads to better outcomes [29] and should therefore be provided to people living with HIV. Although evidence is scant in low and middle income countries, experience in industrialized countries suggests that self-help groups provide valuable psychosocial support and increase adherence to antiretroviral therapy.[43,44]

People with HIV should be provided with interventions to support adherence to prophylactic and therapeutic regimens such as client-centred counselling, pillboxes, and treatment supporters. **(A-II)**

4.1.6 Mental health

Most countries allocate less than 1% of national health budgets to mental health, and there are proportionally very few mental health professionals in low- and middle- income countries, compared with high income countries.[45] Cognitive and neurological disorders, however, are common among people with HIV, especially those with opioid dependence or advanced HIV disease. Untreated mental conditions not only reduce the quality of life for HIV-affected individuals and households; they are also strongly associated with non-adherence to treatment regimens.[46] Initiatives to expand ART access in these countries should, therefore, be accompanied by efforts

to ensure that health-care providers are able to recognize mental illness, integrate psychosocial services in treatment programmes and ensure the proper and timely use of psychotropic medications.[47]

People living with HIV who have mental health conditions, such as depression and substance and alcohol dependence, should be provided with specific psychosocial assistance, including group counselling, disclosure support, caregiver support and, when indicated, medication for these conditions. **(A-II)**

4.2 Disclosure, partner notification and testing and counselling

Lack of knowledge of one's HIV serostatus is a significant barrier to global efforts to scale up towards universal access to HIV prevention, care and treatment.[48] Based on surveys conducted in 2003-2005 among the general population in high-burden countries of Sub-Saharan Africa, the median percentage of men and women who had been tested for HIV and received the results was estimated to be 12% and 10%, respectively.[2,45] Among people living with HIV in those countries, only an estimated 12 to 25% know their HIV-positive status.[2,45]

Among other priorities, testing and counselling programmes emphasize the importance of people with HIV disclosing their HIV status, particularly to sexual partners. Informing the sexual and drug-injecting partners of an individual's HIV infection is not only an effective means of halting the transmission of HIV, but informing partners allows access to care and support as well as further prevention efforts among the client's partners and family.

4.2.1 Partner notification and disclosure

Two main processes for informing partners of an individual's HIV infection are disclosure and partner notification.[49] Disclosure, or beneficial disclosure as it is often known, refers to actions by individuals themselves to notify their partners of their HIV serostatus. UNAIDS and WHO strongly recommend beneficial disclosure, when appropriate, as this process is voluntary, respectful of the autonomy and dignity of the affected individuals and mindful of maintaining confidentiality. Providers of testing and counselling prefer that individuals use beneficial disclosure to inform those who need to know that they are infected. For the individual, his or her sexual and drug-injecting partners, and family, beneficial disclosure allows for greater openness about HIV in communities and meets ethical imperatives.

To encourage beneficial disclosure, countries need to establish safe social and legal environments in which more people are willing and able to get tested for HIV and are empowered and encouraged to change their behaviour according to the results. This can be done by expanding access to counselling and testing services; providing incentives to get tested in the form of greater access to community care, treatment and support; and removing disincentives to testing and disclosure by protecting people from stigma and discrimination and removing legal barriers.

Disclosure can be difficult as people may be afraid of the consequences: for example, the threat of rejection and violence by partners and family or discrimination in the community and workplace. In some cases, people may have limited knowledge of their partners and how to locate them, or may not know the identity of their partners or where they can be located.

When a person with HIV, who has received counselling, is unable to notify partners—and after ethical weighing of the potential harms involved—it may be necessary for health-care providers to notify sexual and needle-sharing partners that an individual is infected with HIV. Although evidence of effectiveness of partner notification is limited in resource-limited settings, UNAIDS advises that partner notification—or ethical partner counselling—be based on the informed consent of the source client, and maintain the confidentiality of the source client, and where possible, protect individuals from physical abuse, discrimination and stigma that may result from partner notification.[49]

Ideally, partners of infected individuals should be encouraged to seek HIV testing and counselling, as this is a critical prevention and treatment tool in the control of HIV. In May 2007, WHO and UNAIDS released guidance on provider-initiated HIV testing and counselling in health facilities.[3] This guidance encourages health care providers to recommend HIV testing and counselling to all patients attending health care facilities in settings with generalized epidemics. The guidance also advises health care providers to recommend HIV testing and counselling in specific situations, such as harm reduction and drug dependence treatment facilities or STI clinics, in settings with concentrated or low level epidemics. In all cases, informed consent is required and people retain the right to refuse the test. Whenever testing is done, counselling must be provided and confidentiality must be ensured. (For details, see WHO/UNAIDS. *Guidance on provider-initiated HIV testing and counselling in health facilities*. May 30, 2007.)

Health-care providers should encourage and offer support to people with HIV to disclose their HIV status to those who need to know (e.g., sexual and drug-injecting partners). When self-disclosure is not possible, providers should assess the safety of disclosure and seek the consent of the individual with HIV before notifying his or her partners. **(A-IV)**

4.2.2 Testing and counselling of partners and family members

People who know they are infected can and should take steps both to protect their own health and the health and well-being of their partners. Evidence from many countries, including low and middle income countries, suggests that injecting drug users, for example, given the opportunity, change their behaviour after learning their serostatus.[50] As partners, drug-injecting partners and household members of people with HIV could also have been infected, health-care providers should ensure that they are offered testing and counselling, whenever possible. Ideally, the offer of HIV testing and counselling should follow appropriate disclosure of the source individual's HIV status, or partner notification by the health-care provider.

Sex partners **(A-II),** drug-injecting partners **(A-III)**, and children and household members **(A-IV)** of all people living with HIV should be offered HIV testing and counselling.

4.3 Co-trimoxazole prophylaxis

In 2006, WHO published *Guidelines on co-trimoxazole prophylaxis for HIV-related infection among children, adolescents and adults in resource-limited settings*.[9] These were developed by a panel of experts during consensus meetings at WHO in March 2005 and March 2006 and included ratings on the strength of recommendations and the quality of the supporting evidence. Due to the thoroughness and rigour of the review that resulted in these recent guidelines, co-trimoxazole was not re-examined in this current process. The rating system used was nearly identical to the one used for this document. Key elements of the co-trimoxazole (CTX) prophylaxis guidelines are included below. (Detailed recommendations regarding co-trimoxazole discontinuation and alternate regimens for persons who do not tolerate co-trimoxazole are available at http://www.who.int/hiv/pub/guidelines/WHO%20CTX.pdf).

Co-trimoxazole, a fixed-dose combination of sulfamethoxazole and trimethoprim, is a broad-spectrum antimicrobial agent. It has activity against *Plasmodium falciparum, Toxoplasma gondii, Pneumocystis jiroveci,* and many bacterial pathogens. The drug is widely available in both syrup and solid formulations at low cost, including in resource-limited settings. Since the early 1990s, providing co-trimoxazole has been part of the standard of care in high-income countries for preventing *Pneumocystis jiroveci* pneumonia (PCP, formerly *Pneumocystis carinii* pneumonia) and toxoplasmosis in individuals with HIV.

Randomized clinical trials [10,11,51-53], studies using historical controls and observational cohort studies [54-59] in settings with few resources have demonstrated the effectiveness of co-trimoxazole in reducing mortality and morbidity across varying levels of background resistance to co-trimoxazole and prevalence of malaria.

Evidence strongly supports the effectiveness of co-trimoxazole prophylaxis in reducing morbidity and mortality among people with CD4 counts less than 200 cells/uL and advanced HIV disease (WHO clinical stage 3 or 4, including tuberculosis).[10,11,57,59-61] In some studies, co-trimoxazole prophylaxis also reduced morbidity and mortality in people with higher CD4 counts and less advanced HIV disease. In one randomized controlled trial of co-trimoxazole prophylaxis for patients being treated for pulmonary TB in Cote d'Ivoire, mortality rates were lower among co-trimoxazole recipients with CD4 cell counts <350 cells/uL. [10,11] A second randomized controlled trial in Abidjan showed a significant reduction in severe adverse events (death or hospital admission) among people with symptomatic HIV disease, irrespective of CD4 count. [10] A cohort study in Uganda also demonstrated reductions in mortality associated with co-trimoxazole prophylaxis for patients with CD4 cell counts <200 cells/uL. [57] Mortality reductions have not reached statistical significance for those with CD4 cell counts >350 cells/uL. [55,57]

Recommendations for 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/uL [b] **(A-III)** OR WHO clinical stage 3 or 4 irrespective of CD4 level **(A-I)**
Universal option: Countries may choose to provide co-trimoxazole to everyone living with HIV with any CD4 count, regardless of clinical stage. This strategy may be considered in settings with high prevalence of HIV and limited health-care 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/uL. **(A-I)**

As described in the following paragraphs, 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. Criteria to be considered may include the burden of HIV and disease spectrum, as well as the capacity and infrastructure of health systems.

In settings where 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). Where CD4 testing is available, co-trimoxazole prophylaxis is recommended for everyone with a CD4-cell count < 350 cells/uL, particularly in resource-limited settings where bacterial infection and malaria are prevalent among people living with HIV. However, if the patient has advanced or severe HIV disease (WHO clinical stage 3 or 4), co-trimoxazole prophylaxis should be started irrespective of CD4 level.

Some countries may choose to adopt a CD4 threshold of 200 cells/uL below which co-trimoxazole prophylaxis is recommended. This option is especially recommended if the main targets for co-trimoxazole prophylaxis are *Pneumocystis jiroveci* and toxoplasmosis. People with HIV disease at WHO clinical stage 2, 3 or 4, (including those with pulmonary as well as extra-pulmonary TB), however, should still initiate co-trimoxazole prophylaxis irrespective of their CD4-cell counts.

Countries with high prevalence of HIV and very limited health infrastructure [57,62] may also choose the universal option: treating everyone living with HIV with co-trimoxazole. This has been shown to simplify operations and reduce severe events irrespective of CD4 count or clinical stage.

The recommended 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)[i]. (Table 3)

The general recommendation has been to continue co-trimoxazole prophylaxis among adults living with HIV indefinitely. Discontinuation of co-trimoxazole, however, can be considered taking drug toxicity and immune recovery promoted by ART into account. Controlled studies conducted in industrialized countries and emerging data from other countries have demonstrated the safety of discontinuing co-trimoxazole as prophylaxis against *Pneumocystis.jiroveci* and toxoplasmosis after six months of stable ART adherence. However, the evidence on safety and timing of the discontinuation following immune recovery in response to ART in other clinical situations and other CD4 thresholds, particularly in resource-limited settings, is still limited. Controlled trials are urgently needed to better support this.

4.3.1 Pregnant women and co-trimoxazole

A study of the prevention of mother-to-child transmission of HIV in Zambia analysed the birth outcomes from 1075 pregnant women living with HIV before and after co-trimoxazole was introduced as the standard of care for pregnant women with HIV. Significant improvements were found in outcomes, with reductions in chorioamnionitis, prematurity and neonatal mortality following the introduction of routine co-trimoxazole for women who had CD4 cell counts < 200 cells/uL. These data suggest that this intervention may have indirect benefits for neonatal and infant health in addition to its direct benefits for maternal health.[63]

Since the risk of life-threatening infections among pregnant women with low CD4 counts or clinical features of immunosuppression outweighs the risk of co-trimoxazole induced congenital abnormalities, women who fulfil the criteria for co-trimoxazole prophylaxis should stay on co-trimoxazole throughout their pregnancies.[64] If a woman requires co-trimoxazole prophylaxis during pregnancy, it should be started regardless of the stage of pregnancy. For pregnant woman with HIV who are receiving co-trimoxazole prophylaxis and who reside in a malarial zone, additional sulfadoxine-pyrimethamine-based intermittent preventive therapy for malaria is not recommended. HIV-infected breastfeeding women should continue to receive co-trimoxazole prophylaxis.

Co-trimoxazole is among the most cost-effective interventions available for people with HIV [65,66] and should be a top priority among efforts to reduce the risk of opportunistic infections in people with HIV. Additional information is urgently needed, however, regarding the effectiveness of co-trimoxazole for prevention of placental malaria and its consequences. This treatment can potentially change the spectrum of opportunistic illnesses affecting people with HIV, and further studies are needed regarding optimal approaches to diagnosis and treatment when people on co-trimoxazole develop fever or other symptoms, particularly in low and middle income countries.

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i An option is to prescribe one single-strength tablet (480 mg per dose or 400 mg sulfamethoxazole + 80 mg trimethoprim) twice daily, as this may help individuals prepare for initiating the twice-daily antiretroviral therapy regimens commonly available in settings with limited resources.

4.4 Tuberculosis (TB)

Tuberculosis and HIV are intimately related.[67,68] In sub-Saharan Africa, Asia and many other parts of the world, tuberculosis is the most common serious opportunistic infection in people with HIV and the most common cause of death. HIV increases the risk of TB-disease ten-fold, and although cure rates in those with and without HIV are similar, the risk of death, recurrence and specifically the risk of re-infection [69] is increased in people living with HIV (PLHIVs). The risk of TB is reduced among individuals receiving effective antiretroviral therapy,[70,71] but does not fall to the level seen in HIV-negative persons. Where HIV prevalence is high, the number of people diagnosed with TB has climbed dramatically, even when recommended approaches to tuberculosis control are being implemented. Given the substantial public health implications of coincident TB and HIV, targeted interventions aimed at recognition, treatment and prevention of tuberculosis among those with HIV are clearly warranted.

4.4.1 Counselling

Communities affected by HIV, particularly people with HIV, should be educated about the risks, symptoms, and management of tuberculosis.

> Information about tuberculosis should be provided to all people with HIV. **(A-IV)** Counselling should include information about the risk of acquiring TB, strategies for reducing exposure, clinical manifestations of TB disease, risk of transmitting TB to others, and, where appropriate, information about TB preventive therapy. **(A-III)**

4.4.2 Screening for TB disease

Efforts to recognize and treat TB disease are the primary means of controlling TB and should dominate TB management efforts, including efforts directed at people with HIV. Prevalence of unrecognized TB is high in many health care settings where people with HIV congregate [72]: antenatal clinics, voluntary testing-and-counselling centres, and, most notably, hospitals [73,74] and HIV-treatment clinics. Efforts to identify people with TB-disease are, therefore, needed in settings where people with HIV are identified and receive care. WHO guidelines outline evidence-based algorithms that should be used for screening and diagnosis of TB in people with HIV.[75-77]

Rates of smear-negative pulmonary and extrapulmonary TB have been rising in countries with HIV epidemics. Particularly for those with smear-negative pulmonary and extrapulmonary TB, the mortality rate among TB patients with HIV is high compared to people with TB who are HIV-negative. Delayed diagnosis may contribute to higher death rates in people living with HIV who have smear-negative pulmonary and extrapulmonary TB. As rapid, simple, and accurate diagnostic tools for smear-negative pulmonary and extrapulmonary TB are not available, health-care providers should use recently published WHO algorithms for diagnosing smear-negative TB in high HIV prevalence settings.[76] Screening for TB disease and all other TB-related care in HIV-treatment settings should be coordinated with national TB programmes.

All people with HIV should be screened for TB disease at each encounter; persons with symptoms or signs suggestive of TB disease should undergo further clinical investigation. **(A-II)**

Programmes to diagnose and treat TB disease should be complemented by other measures to reduce the risk of TB infection and TB disease in people with HIV. In health-care settings, administrative or engineering controls, as well as the use of personal respiratory protection, can reduce the risk of TB. Health-care providers and managers in resource-limited settings should adhere to the 2006 WHO recommendations for TB infection control, which includes specific work practice, administrative, and environmental control interventions, such as natural and mechanical ventilation, that have the greatest impact on preventing TB transmission within facilities providing HIV care. [78-80]

Providers who care for people living with HIV should adhere to the most recent WHO guidelines for TB-infection control in HIV care facilities. **(A-III)**

4.4.3 TB-preventive therapy

Approaches to reducing the risk that latent tuberculosis infection will progress to TB-disease include treatment of latent TB and improvement in immune function through antiretroviral therapy for HIV. Strong evidence was found in several randomized trials [81-86] and three meta-analyses [87-89] that TB-preventive therapy—for example, with isoniazid for six months—reduces the risk that persons with HIV who have latent tuberculosis infection (LTBI) will develop TB disease. TB-preventive therapy has been recommended by WHO where there is adequate HIV counselling, sufficient trained health-care providers, linkage of HIV-care and TB-control services, and TB-treatment services that have a high probability of curing cases of TB.[90] Some evidence suggests that the duration of protective benefits of isoniazid therapy may be limited to 24 months in settings of high transmission [83,85], however ongoing studies are evaluating the optimal duration of isoniazid therapy. Recent data suggest that preventive therapy may reduce TB incidence further among people with HIV on antiretroviral therapy.[91] The recommended regimen of TB preventive therapy is isoniazid (5 mg/kg (max 300 mg)) daily for six months, self-administered. (Table 3)

Treatment of TB disease with a single anti-tuberculosis drug can lead to the development of drug resistance. It is critical, therefore, to rule out TB disease before attempting to treat latent infection. As mentioned previously, evidence-based algorithms developed by WHO should be used for the diagnosis of TB in people with HIV, including smear negative TB,[75-77] HIV-treatment programmes should provide TB preventive therapy to people with HIV in whom there is no evidence of TB disease. It may be appropriate to target people with HIV whose immune systems are not yet suppressed significantly, as it may be relatively easier at this stage to distinguish TB disease. Health-care providers should also consider preventive therapy for people with HIV who have been in close contact with known cases of TB. [75-77]

Tuberculin skin testing, or another validated test for latent TB infection (QuantiFERON. ®. -TB **Gold** test (QFT-G) ,[92]) may be appropriate to identify individuals with latent TB infection who are likely to benefit most from TB-preventive therapy. In people with HIV, a tuberculin skin test $\geq$ 5mm is regarded as positive. In settings of high TB transmission, where it is not possible to perform tuberculin skin testing, preventive therapy should be provided to all eligible people with HIV.

In determining whether to offer this intervention, health care providers should consider a number of criteria: whether TB disease can be excluded; the likelihood that persons will complete screening procedures and adhere to treatment; and the adverse effects of anti-tuberculosis drugs, particularly during or immediately following pregnancy and in people at increased risk for hepatotoxicity.[93] With the emergence of multidrug-resistant tuberculosis (MDR TB) and, more recently, extensively drug-resistant TB (XDR TB),[94] isoniazid may not be appropriate for preventive therapy when exposure to MDR TB or XDR TB is a concern. If this is the case, health-care providers should seek expert advice, where exposure to resistant tuberculosis is a concern. Efforts to provide TB-preventive therapy should not divert resources from treating TB disease.

TB preventive therapy should be provided to people with HIV in HIV care settings where it is possible to exclude TB disease. **(A-I)** TB-preventive therapy should not be given to people with HIV who have symptoms suggestive of TB. In particular, people with advanced HIV disease who have any symptoms of TB disease should not be offered TB-preventive therapy. **(A-III)**

Tuberculin skin testing (or other proven tests for latent TB infection) may be appropriate to identify individuals with latent TB infection who are likely to benefit most from TB preventive therapy. **(A-I)** In people with HIV, a tuberculin skin test $\geq$ 5mm is regarded as positive. In settings of high TB transmission where it is not possible to perform tuberculin skin testing (or other validated tests for LTBI), TB-preventive therapy should be provided to all people with HIV, unless contraindicated. **(A-I)**

The recommended regimen of TB-preventive therapy is isoniazid daily for six months, self-administered. **(A-I)** This regimen applies to all settings regardless of the prevalence of isoniazid resistance. **(A-IV)** Specialist advice should be sought for preventive therapy for contacts of multidrug-resistant or extensively drug-resistant TB.

The risk of isoniazid hepatotoxicity increases among older people, pregnant women and those with pre-existing liver disease; these risks need to be weighed against the benefits of TB-preventive therapy. **(A-II)** Previous TB is not a contraindication to TB-preventive therapy.

Three small, randomized controlled trials [95] of secondary isoniazid preventive therapy have demonstrated reductions in TB incidence in people with HIV who have completed TB treatment. TB preventive therapy can, therefore, be considered for people with HIV after they have successfully completed TB treatment.

There is clear evidence of an increased risk of toxicity from isoniazid therapy during pregnancy or the first three months post-partum; however, not enough is known about the risks and benefits of TB preventive therapy in pregnancy to allow specific recommendations at this time.

To further refine use of TB preventive therapy, additional data are needed on the optimal duration of isoniazid prophylaxis in people with HIV, whether isoniazid prophylaxis prevents incident TB infection (as well as preventing progression from latent infection to TB disease), the added benefit of TB-preventive therapy in people on antiretroviral drugs, the consequences of TB-preventive therapy when given inadvertently to people with unrecognized TB disease, and the risks and benefits of TB preventive therapy during pregnancy. Many of the interventions to reduce tuberculosis disease in people with HIV are, however, cost-effective for people with HIV. [96-99] Programmes should be continuously evaluated to assure quality and effectiveness, and consistency of activities with recognized priorities and national TB guidelines.[75,77,92]

4.5 Preventing fungal infections

The yeast-like fungus *Cryptococcus neoformans* is a significant cause of illness and death in people with HIV. Cryptococcal disease, especially meningitis, is common and, though treatable, is a frequent cause of death in resource-limited countries [100,101], often due to the limited availability of appropriate diagnostic tests and treatment. Furthermore, in the absence of antiretroviral therapy, treatment must be followed by lifelong receipt of suppressive therapy to prevent recurrences. Several randomized clinical trials have demonstrated that primary prophylaxis with fluconazole (200 mg per day to 400 mg per week), or itraconazole (200 mg daily) reduces the incidence of cryptococcal disease in adults with advanced or severe HIV disease, particularly those with CD4 counts < 50-100 cells/uL.[102-108] All of these studies were conducted in the United States and Thailand. Evidence is not available from countries in sub-Saharan Africa. One controlled trial in Thailand also demonstrated a survival benefit.[104] Although primary prophylaxis with fluconazole to prevent cryptococcal disease is not generally recommended in high-income countries, it may be more beneficial in countries with limited resources because of the higher incidence of disease and more limited availability of diagnosis and antifungal treatment.

Where cryptococcal disease is common, antifungal prophylaxis with azoles should be considered for people with HIV who are severely immunocompromised, whether or not they are on ART. Frequency of cryptococcal disease may be assessed by looking at the incidence of disease, if data are available; prevalence of cryptococcal disease among OI diagnoses; and frequency of cryptococcosis as a cause of death. Health care providers should not only assess the incidence of cryptococcal disease when deciding on prophylaxis, they should also consider the ability to diagnose and treat cryptococcal infections; the limited evidence of survival benefit from prophylaxis; drug toxicity and drug interactions; potential for teratogenicity; potential for development of fluconazole-resistant *Candida* (yeast) infections; the uncertain benefit of prophylaxis in persons receiving antiretroviral therapy; and cost. The recommended dosages for fluconazole are 400mg weekly, 200 mg three times a week, or 200mg daily. (Table 3) Available data do not indicate that any of these regimens is superior to the others.

> In areas where cryptococcal disease is common, antifungal prophylaxis with azoles should be considered for severely immunocompromised people with HIV (WHO clinical stage 4 or CD4 < 100 cells/uL), whether they are on antiretroviral therapy **(C-IV)** or not. **(C-I)**

For example, in Thailand, due to the high prevalence of cryptococcal disease and evidence of survival benefit, national guidelines recommend fluconazole (400 mg weekly) for patients with CD4-cell counts of less than 100 cells/uL.[109] Fluconazole prophylaxis was found to be cost saving in a study conducted in Thailand.[110]

To further guide prevention and management strategies in settings with few resources, more data are needed on the incidence and prevalence of cryptococcal disease,[100] the relative cost-effectiveness of prophylactic and treatment strategies,[110] and the role of cryptococcal prophylaxis for persons receiving antiretroviral therapy.

Prior to beginning primary prophylaxis with azoles, people with HIV should be examined to exclude cryptococcal or other invasive fungal disease, because the dosages of azoles need to be adjusted to treat active disease. Cryptococcosis commonly presents as subacute meningitis or meningoencephalitis. Disseminated disease is also a common clinical manifestation, often preceded by pulmonary infection without meningeal involvement. [111,112] Health-care staff may not recognize the full extent of clinical disease if they test only patients with meningitis. Strategies to improve the recognition of clinical disease are needed, including consideration of screening for the presence of disease with cryptococcal antigen testing.[113-115] Whenever possible, candidates for primary prophylaxis of fungal infections should be screened with an antigen test.

> Active cryptococcal and other invasive fungal infection should be excluded before providing prophylaxis for people living with HIV, since the dosages of azoles used for prophylaxis might be insufficient for treating active disease. **(A-IV)**

Disseminated *Penicillium marneffei* infection is common in several areas of South-East Asia. In northern Thailand, penicilliosis is one of the most common serious opportunistic infections among people with HIV.[103] Itraconazole, but not fluconazole, is effective against penicilliosis and histoplasmosis. Itraconazole is also effective against cryptococcosis. Primary prophylaxis with itraconazole has been shown in a clinical trial to protect against penicilliosis among patients with advanced HIV disease, particularly those with CD4-cell counts of less than 100 cells/ul.[103] No survival benefit has been demonstrated. In settings with endemic penicilliosis and histoplasmosis, itraconazole may be considered as an alternative agent to fluconazole for primary antifungal prophylaxis. Monitoring for potential toxicities is recommended, as adverse events may occur more frequently with itraconazole. The recommended dose is one 200mg capsule daily. (Table 3)

Disseminated histoplasmosis, caused by *Histoplasma capsulatum*, is a common opportunistic infection in some areas of North, Central, and South America, but appears to be less frequent in Asia and in Africa. In a randomized trial in endemic areas of the United States, primary prophylaxis with itraconazole was effective at reducing incidence of histoplasmosis among people with advanced HIV disease.[105]

> In endemic areas of penicilliosis and histoplasmosis, itraconazole may be considered as an alternative agent to fluconazole for primary prophylaxis of cryptococcosis and penicilliosis or histoplasmosis among people living with HIV. **(C-I)**

Mucosal (oropharyngeal, oesophageal and vaginal) candidiasis caused by *Candida albicans* and other *Candida* species is likely the most common opportunistic infection experienced by people with HIV. Fortunately, mucosal candidiasis is treatable with a variety of topical and systemic agents. Primary azole prophylaxis should not be given for the sole purpose of preventing mucosal candidiasis. The toxicities, cost, drug interactions, and potential to create azole-resistant fungi outweigh any potential benefits in terms of reducing the incidence of mucosal disease. However, azole prophylaxis can be considered to prevent severe, recurrent mucosal disease.

Primary azole prophylaxis should not be administered to persons living with HIV solely to prevent mucosal candidiasis. **(A-IV)**

Due to risk of potential teratogenicity, azole anti-fungal prophylaxis should not be given to pregnant women with HIV.[116,117] For women with HIV who conceive while on primary prophylaxis and who elect to continue their pregnancies, prophylaxis should be discontinued. Effective birth-control measures should be recommended to all women with HIV on azole therapy for cryptococcosis. Azoles may be hepatotoxic, especially when given concomitantly with other hepatotoxic drugs (e.g., nevirapine). Azoles can also produce clinically important drug-drug interactions with other drugs metabolized by the cytochrome p-450 system. In settings with few resources, monitoring for hepatotoxicity might consist of clinical assessment of jaundice or, where available and feasible, laboratory monitoring of liver function.[16]

Primary azole prophylaxis should not be given to pregnant women with HIV. **(A-III)**

People with HIV who are taking azoles, especially those who are taking other hepatotoxic drugs, should be monitored for adverse events **(A-IV)**, and health care providers should be aware that the toxicities and drug-drug interactions with itraconazole may be more prominent than with fluconazole. **(A-IV)**

Evidence evaluating the discontinuation of cryptococcal primary prophylaxis with improved immune function is limited in settings with few resources However, data on the safe discontinuation of primary prophylaxis for other opportunistic diseases provide the basis for clinical consideration.[9,118]

Primary azole prophylaxis should be discontinued in people with HIV on antiretroviral therapy and with CD4-cell counts > 200 cells/uL. **(B-IV)** In settings where CD4-testing is not available, discontinuation may be considered for people with HIV who have completed one year of ART, who are asymptomatic and have good adherence to treatment. **(C-IV)**

4.6 Sexually transmitted and other reproductive tract infections

HIV, other sexually transmitted infections (STIs) and non-sexually transmitted infections of the reproductive tract (RTIs) frequently co-exist. Ulcerative and inflammatory STIs can increase HIV shedding and infectiousness, and treatment of STIs can lead to decreased HIV shedding.[119] Some RTIs (such as bacterial vaginosis) can increase susceptibility to HIV acquisition. Most STIs and RTIs are asymptomatic, especially in women; however, even asymptomatic STIs can cause complications for people with HIV, be transmitted to sexual partners, and enhance HIV transmission. This is especially true for the chronic, asymptomatic STIs, such as *Herpes simplex virus 2* (HSV-2), *Chlamydia*, and for bacterial vaginosis.

The objectives of STI/RTI diagnosis and management include the identification and care of the infected individual and, in the case of STIs, prevention of transmission. In addition, treatment of STIs/RTIs in people with HIV may help prevent HIV transmission to sexual partners.

Diagnosis can be etiological, clinical or syndromic.[120,121] Etiologic diagnosis relies upon laboratory test results, while clinical diagnosis is based on examination and judgment by the health-care provider without the use of specific laboratory tests. Syndromic diagnosis is based on the identification of consistent groups of symptoms and easily recognized signs (which, together, are grouped into "syndromes"), and the provision of treatment (syndromic management) for the most prevalent or the most serious organisms responsible for a particular syndrome. In developing countries, WHO recommends syndromic management of STIs and RTIs because of the lack of equipment and trained personnel for etiologic diagnosis at the primary health-care level. A systematic review of effectiveness of syndromic management in resource-limited settings found that in general, syndromic management performs well in men with urethral discharge, men and women with genital ulcers, and in women with vaginal infections. [122] Syndromic management is less effective, however, in women with cervical infections, such as gonorrhoea and *Chlamydia*, especially where the prevalence of these infections is low. Randomized controlled trials comparing the effectiveness of syndromic management in men and women with and without HIV have not been done.

4.6.1 Screening, diagnosis and management of STIs and RTIs

Screening for STIs and RTIs in people who initially present with HIV infection and in those in on-going medical care, allows health-care providers to diagnose and treat these illnesses effectively, identify those at highest risk for transmitting HIV sexually, and to provide care and treatment for partners exposed to HIV and STIs. WHO recommends that providers should obtain a thorough history from all newly diagnosed persons with HIV. This should include information about past STIs, contraceptive use, current STI/RTI symptoms and risk behaviours. Providers should also conduct a physical exam and a limited laboratory evaluation to detect and treat any STIs and RTIs. Several STIs may progress more rapidly in the presence of HIV coinfection, such as neurosyphilis and oncogenic HPV infections.[123] WHO recommends that screening should include a serologic test for syphilis. For women with HIV, screening should include a test for gonorrhoea and *Chlamydia* when possible. The type of test and specimen should be chosen in accordance with local guidance. As HSV-2 is common in people with HIV, HSV-2 serologic

testing should be considered, if available, and where HSV-2 treatment is available. When an STI is diagnosed, providers should manage people with HIV and their sex partners in accordance with the latest WHO STI treatment and RTI practice guidelines, including syndromic management of STIs and RTIs.[120,121] Providers should consider etiologic diagnosis and therapy for people with HIV who exhibit persistent or recurrent symptoms.

Expanded HIV services must include timely access to reliable STI diagnostic and treatment services for people with HIV who are symptomatic. Routine screening for STIs and risk behaviours among people with HIV should also be established or expanded. People at greater risk for STIs, including sex workers, should be presumptively treated for certain STIs, such as *Chlamydia* and gonorrhoea, at initial diagnosis and screened more frequently thereafter (see section 4.6.3, Screening for Ongoing Risk Behaviours and STIs).[124]

Women with HIV and vulvovaginal candidiasis (VVC) may benefit from a longer treatment regimen of antifungal therapy than single-dose or one-day regimens. As well, women with recurrent VVC may benefit from prophylaxis with fluconazole (see section 4.5).[61]

At initial diagnosis of HIV, health-care providers should obtain a thorough history of all persons, including information about previous STIs and RTIs, contraceptive use, current STI/RTI symptoms and risk behaviour,[1] and should conduct a physical examination along with limited laboratory screening for the presence of STIs and RTIs. **(A-III)**. Laboratory screening should include a serological test for syphilis **(A-III)** for all persons newly diagnosed with HIV. Where available and feasible, at initial diagnosis, women with HIV should be tested for gonorrhoea **(B-III)** and *Chlamydia*. **(B-II)**

People with HIV who are diagnosed with an STI and their sex partners should be managed in accordance with the most recent WHO STI treatment and RTI practice guidelines, **(A-III)** which include syndromic management of STIs and RTIs. **(A-II)** People with HIV who present with persistent or recurrent symptoms should be considered for definitive diagnoses and etiologic therapy. **(A-III)**

Sex workers, at initial diagnosis of HIV, should be presumptively treated for gonorrhoea and *Chlamydia* in accordance with WHO guidelines for periodic presumptive treatment for STIs. **(B-III)**

4.6.2 Genital herpes

Some STIs are more severe in people with HIV—genital herpes in particular, which may be prolonged or atypical in presentation, particularly in those with low CD4 counts.[125] Asymptomatic and symptomatic HSV-2 reactivation is also more frequent in people with HIV. Genital herpes has been associated with a two-to-three-fold increased risk of HIV acquisition, up to a five-fold

increased risk of HIV transmission per-sexual act, and may account for 40-60% of new HIV infections in populations with a high prevalence of HSV-2.[125-130]

Genital herpes is caused by infection with either HSV-2 or HSV-1, although globally the great majority of genital herpes is caused by HSV-2. HSV-2 is a major cause of genital ulcers worldwide.[126,131-134] While HSV-2 infection is highly prevalent (up to 80%) in people with HIV, the majority of coinfected persons do not recognize symptoms of genital herpes. Many health-care providers and patients do not recognize the broad clinical spectrum of genital herpes, ranging from trivial breaks in the skin to deeply eroded ulcers, and the frequent asymptomatic nature of genital herpes. In addition, providers as well as patients do not recognize the importance of HSV-2 in facilitating HIV transmission. People with HIV and genital ulcers should be provided with information regarding their increased risk of HIV transmission.

People with HIV who have genital ulcers should be counselled about genital herpes, their likelihood of having genital herpes, and the increased risk of HIV transmission from individuals with genital ulcers. **(A-I)**

Where there is a high prevalence of HSV-2, WHO syndromic management guidelines recommend acyclovir for persons presenting with vesicular lesions or genital ulcers. In people with HIV, acyclovir shortens the duration of genital herpes, and suppresses HSV-2 clinical and sub-clinical reactivation. Acyclovir is safe, efficacious, and well-tolerated, and is available in generic formulations. In addition, placebo-controlled trials of herpes suppression have indicated significant reductions (~0.5 log10 reduction) in plasma and genital HIV-1 RNA levels in HIV/HSV-2 co-infected persons.[135] Herpes antiviral suppressive therapy should be considered to treat sexually active persons with a history of frequent, severe or long-lasting genital herpes. See Table 3 for dosing information for episodic and suppressive herpes antiviral therapy.

Clinical trials nearing completion will determine the efficacy of suppressive acyclovir on HIV transmission from people coinfected with HIV and HSV-2, and of acyclovir episodic treatment on genital HIV-1 shedding. The results of these ongoing trials may, therefore, strengthen the rationale for diagnosing, counselling, and treating genital herpes in people with HIV.

In areas with high prevalence of HSV-2, episodic acyclovir should be routinely provided as part of syndromic management of genital ulcer disease in persons with HIV to shorten the clinical course of illness, except where HSV-2 can be ruled out. **(A-I)**

4.6.3 Screening for ongoing risk behaviours and STIs

Health care providers should routinely and at regular intervals, screen patients with HIV for ongoing risk behaviour and symptoms and use these opportunities to provide information and counselling for those who present with or acquire an STI. In an era of broadening availability of antiretroviral therapy and possible increased sexual activity among persons who are being treated for HIV infection, some STIs are markers of the continuance or reinitiation of unsafe

sexual behaviour and the failure of behavioural counselling. Evidence of ongoing risk, or diagnosis of STIs, should trigger discussions between providers and patients and encourage preventive behaviours that reduce the likelihood of reinfection with STIs or transmission of STIs and HIV to others. In antiretroviral-treated patients especially, transmission of HIV may involve antiretroviral-resistant strains. In particular, providers who care for persons at increased risk for STIs (sex workers, for example) should undertake screening at more frequent intervals, while providing condoms and promoting their consistent use. Additional recommendations regarding risk reduction among people with HIV are included in section 4 .1, Psychosocial Support.

All people with HIV should be evaluated to identify continuing risk behaviour and symptoms of STIs in themselves and their partners by obtaining a history at regular intervals (for example, annually).**(A-III)** Those at ongoing risk should receive counselling to reduce risky behaviour.

People at ongoing risk, or with intercurrent STIs, should be re-evaluated for STIs by conducting a history, physical examination and laboratory evaluation annually, as recommended for people at initial diagnosis of HIV. **(B-IV)** For male and female sex workers, screening for STIs should be done at more frequent intervals (quarterly, semi-annually or annually) depending on prevalence rates of syphilis, gonorrhoea and *Chlamydia* among screened sex workers **(A-IV)**.

Sex workers with HIV and other people with HIV at ongoing risk should receive intensive counselling on consistent condom use and be provided with easy access to condoms. **(A-II)**

4.6.4 Screening for cervical cancer

Globally, it is estimated that, each year, approximately 490,000 cases of cervical cancer are diagnosed and 270,000 women die from this disease—over 80% of them in low and middle income countries.[136-139] Women with HIV are at increased risk for invasive cervical cancer and cervical squamous intraepithelial lesions which are precursors to invasive cervical cancer.[140] Data also show that women with HIV have high rates of persistent infections with oncogenic types of HPV.[123] Furthermore, emerging data from some resource-limited settings suggest high prevalence of high-grade abnormal cytology among women with HIV.[141,142] These data highlight the urgent need to integrate effective cervical cancer screening with HIV care. New non-cytology-based, screen-and-treat approaches have been evaluated in settings with few resources and were found to be safe and effective;[143,144] however, infrastructure may not exist in all settings to support these programmes.[145] Where infrastructure does exist, women with HIV should be screened for cervical cancer at regular intervals. If cervical screening tests are not available, patients should be referred to specialized facilities where these tests are conducted.

In 2006, a quadrivalent HPV vaccine (HPV types 6, 11, 16, and 18) was licensed for use among females 9-26 years for the prevention of HPV-type-related cervical cancer, cervical cancer precursors, and vaginal and vulvar cancer precursors, and anogenital warts.[146] HPV 16 and 18 cause approximately 70% of cervical cancer worldwide. As data become available on the efficacy of the HPV vaccine among children, women and men with HIV in settings with few resources, WHO will update its guidelines on this topic.[147]

Where available, women with HIV should be screened for cervical cancer initially **(A-II)** and at regular (e.g., annual) intervals. **(A-IV)** If cervical screening tests are not available, persons should be referred to a higher-level of health care.

4.7 Preventing malaria

The global burden of both *Plasmodium falciparum* malaria and HIV is heaviest in sub-Saharan Africa, and coinfection is common in many areas. Evidence of interactions between malaria and HIV infection is accumulating. Specifically, adults and children with HIV suffer higher rates of parasitemia and clinical malaria,[148-150] with increased malaria morbidity among those with more advanced immunosuppression and those living in areas where malaria transmission is unstable[i].[151,152] People with advanced HIV disease may be at increased risk for failure of antimalarial treatment.[153,154] Pregnant women with HIV are at increased risk for placental malaria, severe anaemia, febrile illness, and adverse birth outcomes.[155] In addition, malaria can transiently increase viral load among people with HIV.[156] Given the substantial geographic overlap between the two infections, and the large numbers of people infected each year, these interactions have enormous public health implications.

Where there is a risk of malaria infection, services for people with HIV should aim to prevent and properly manage malaria. The recommendations below are drawn in part from existing WHO guidelines and reports, including those addressing co-trimoxazole prophylaxis for people with HIV,[9] malaria and HIV interactions and their implications, and prevention and control of malaria during pregnancy in the African region.[157] As previously recommended by WHO, interactions between malaria and HIV necessitate the integration of services for malaria and HIV.[158,159] Malaria and HIV programmes should jointly contribute to strengthening health systems and capacity for service delivery.[9,159]

Recommendations concerning malaria and HIV management are not universally applicable. Some recommendations apply to all areas where there is a risk of infection with *P. falciparum*. Others apply to areas of stable[ii] transmission, where most adult women have developed sufficient immunity that, even during pregnancy, *P. falciparum* infection does not usually result in fever or other clinical symptoms. In these areas, the principal impact of malaria infection in the mother is malaria-related

i Areas of unstable malaria are those where the intensity of malaria transmission is too low for the development of sufficient anti-malarial immunity to allow asymptomatic infection.

ii Areas of stable malaria are those in which malaria transmission occurs with sufficient intensity to establish immunity in adults, so that infected adults are generally asymptomatic.

anaemia. The presence of parasites in the placenta impairs fetal nutrition, contributes to low birth weight and is a leading cause of poor infant survival and development.[159]

4.7.1 Co-trimoxazole for malaria

In sub-Saharan Africa, clinical trials and observational studies have demonstrated the effectiveness of co-trimoxazole prophylaxis to reduce malaria morbidity in adults and children with HIV across a broad range of CD4 cell counts.[10,11,57,149] WHO recently published evidence-based guidelines on the use of co-trimoxazole prophylaxis for HIV-related infections among adults and adolescents in resource-limited settings, and these recommendations are summarized in section 4.3, Co-trimoxazole chemoprophylaxis.[9]

> People with HIV should take daily co-trimoxazole prophylaxis in accordance with co-trimoxazole guidelines. **(A-I)**

4.7.2 Insecticide-treated mosquito nets and indoor residual spraying

Randomized controlled studies have demonstrated that insecticide-treated mosquito nets (ITNs) reduce the risk of malaria when high coverage rates are achieved in general populations, including some populations with high HIV prevalence rates.[160] These studies were not stratified by HIV infection. Where general population coverage has not been achieved, nets may provide individual protective benefit. [160] The provision of two ITNs to households of index persons with HIV in Uganda has been shown to reduce the risk of malaria for the index person.[149] Consistent with other WHO guidelines, people with HIV living in areas of stable malaria transmission should routinely use insecticide-treated mosquito nets or have access to indoor residual spraying (IRS) to reduce their exposure to malaria infection. Though the entire population in endemic areas may benefit from malaria prevention, programmes can be designed to facilitate access to treated nets for groups at particular risk, including people with HIV.[159]

Insecticide may be applied to the net by periodically soaking it in insecticide solution; however, re-treatment rates are generally low and consistent presence of insecticide is probably best achieved by ensuring that nets are treated with a long-lasting insecticide or by using nets manufactured to retain insecticide.

The use of indoor residual spraying in the general population is as effective as ITNs.[160] Choices about the best malarial control method should be made based on operational feasibility and other local factors, such as housing density and the time of year when transmission rates are highest.

There are limited data concerning the effect of ITNs when provided in combination with other interventions. In Kenya, ITNs were shown to further reduce rates of anaemia among pregnant women who also received intermittent preventive treatment [161]. Limited data are available concerning sequential or concurrent implementation of these interventions. In Uganda, sequential administration of co-trimoxazole, antiretroviral treatment, and ITNs led to a 76%, 92% and 95% reduction in malaria rates, respectively (9.0 episodes, 3.5 episodes, and 2.1 episodes per 100 person years, respectively). By comparison, the baseline malaria incidence for this cohort was 50.8 episodes per 100 person years.[149]

Many malaria-related interventions are practical and affordable. The cost-effectiveness of insecticide-treated nets, indoor residual spraying, and sulfadoxine-pyrimethamine (SP)-based intermittent preventive treatment has been demonstrated in general populations [162-164].

In areas of stable malaria transmission, people with HIV should routinely use insecticide-treated mosquito nets (ITNs) or have access to indoor residual spraying (IRS) to reduce their exposure to malaria infection. **(A-I)**

Travelling to an area where malaria is endemic, including within a country, puts individuals at risk of acquiring malaria and the risk of severe disease is known to be greater among individuals without immunity to the disease.[118] Therefore, people with HIV who are travelling to a malarious zone from an area where malaria is not common should use insecticide-treated nets and drugs for malaria prevention.

People with HIV living in non-malarious areas, but travelling to areas with malaria transmission, including within a country, should sleep under an ITN and take an effective drug for prevention of malaria in accordance with the most recent recommendations for malaria prophylaxis for travellers. **(A-IV)**

4.7.3 Prevention of malaria infection in pregnant women with HIV

Women with HIV are at high risk for complications of malaria in pregnancy, and prevention and treatment services should give priority to this group. Pregnant women with HIV who live in malarious areas should sleep under ITNs.

Intermittent preventive treatment involves the periodic administration of full treatment doses of anti-malarial drugs. This approach has been shown in clinical trials to reduce the risk of placental malaria and its consequences in pregnant women, including those with HIV infection.[165-169] Monthly intermittent preventive treatment (median three doses) is superior to a two-dose schedule of IPT in women with HIV.[167,170] Pregnant women with HIV living in areas of stable malaria transmission who are not taking co-trimoxazole should be given at least three doses of intermittent preventive treatment for malaria as part of routine antenatal care; those who are taking co-trimoxazole prophylaxis should not be given sulfadoxine-pyrimethamine (SP) for intermittent preventive treatment (see Table 3). These recommendations regarding intermittent preventive treatment are consistent with other guidelines and reports[9,159]. The recommendation to avoid sulfa-based intermittent preventive treatment in pregnant women with HIV who are already taking co-trimoxazole prophylaxis is based primarily on concerns about potential toxicity of sulfa drugs when co-administered to people with, or without, HIV.[171] There are no data available regarding the efficacy of daily co-trimoxazole to reduce the risk of placental malaria or its consequences. As co-trimoxazole prophylaxis and intermittent preventive treatment for malaria may be delivered by different health-care providers, or supported by different partners, programme managers must coordinate their interventions for pregnant women.

Pregnant women with HIV who are living in areas of stable malaria transmission and are not taking co-trimoxazole should be given at least three doses of intermittent preventive treatment (IPT) for malaria as part of routine antenatal care. **(A-I)**

Pregnant women with HIV who are living in areas of stable malaria transmission and are taking co-trimoxazole prophylaxis should not be given intermittent preventive treatment with sulfadoxine-pyrimethamine (SP). **(A-III)**

Presumptive treatment of fever as malaria is a common practice in malarious areas. There are many possible causes for fever in adults with HIV living in malarious areas,[172] and the risk of malaria is greatly reduced among people with HIV who are taking co-trimoxazole prophylaxis;[10,149] therefore, the likelihood that a fever is due to malaria in a person with HIV taking co-trimoxazole is low compared to the risk in a person without HIV. People with HIV and fever should be evaluated for the cause of the fever and, where possible, laboratory confirmation of malaria infection should be obtained prior to initiation of malaria treatment.[173] Available tests include microscopy or rapid diagnostic tests (RDTs).

Prompt, effective treatment of malaria infection is a key part of malaria services. People with HIV who develop malaria should receive recommended antimalarial treatment [173]; however, patients with HIV who are on co-trimoxazole prophylaxis should not be given sulfadoxine-pyrimethamine. Drugs used to treat malaria and drugs used to treat HIV may share toxicities (particularly sulfa-based drugs) and may have clinically important pharmacokinetic interactions, (particularly artemesinins, lumefantrine, and non-nucleoside reverse transcriptase inhibitors and protease inhibitors).[174] For this reason, persons receiving treatment for both HIV and malaria should be monitored closely for adverse drug reactions.

Well-designed studies are needed concerning the effectiveness of certain malaria interventions among people with HIV, particularly the efficacy of daily co-trimoxazole on risk of placental malaria, and of the interactions between *P. vivax* infection and HIV.[9,159]

4.8 Selected vaccine-preventable diseases

This guidance addresses the use of vaccines for the prevention of pneumococcal disease, influenza, hepatitis B and yellow fever. These vaccines were selected for several reasons. Pneumococcus and hepatitis B are major causes of illness among adults with HIV. Although influenza is less well understood as a cause of morbidity, global concerns about influenza epidemics and pandemic preparedness require guidance on the use of influenza vaccine. Guidelines for the use of yellow fever vaccine exist, but have focused on travel-related issues. Vaccination for hepatitis A in adults is not addressed in this guidance as prior exposure to hepatitis A in childhood and early adulthood is common in many resource-limited settings and insufficient data exist on effectiveness of hepatitis-A vaccination in adults with HIV.

In most cases, recommendations for the use of vaccines in HIV-infected populations are based on evidence derived from surrogate end-points or extrapolations from populations without HIV rather than randomized controlled trials among people with HIV. For some vaccines, where data are available from randomized clinical trials, they have been inconsistent with results derived from observational cohort data in other locations. Furthermore, there is conflicting evidence as to whether vaccination is associated with increases in HIV viral load and decreases in CD4-cell counts. When observed these events have been transient and not clearly clinically relevant. Level of immunosuppression and increasingly widespread availability of antiretroviral therapy are additional considerations when providers are making decisions about vaccination.

4.8.1 Hepatitis-B vaccine

Hepatitis B rates are high in HIV-infected populations and in resource-limited settings. People with HIV are more likely to become chronic carriers of the hepatitis-B virus (HBV) and develop end-stage liver disease such as cirrhosis and hepatocellular carcinoma.[175] Vaccine efficacy is suboptimal in adults with HIV, measured by lower mean antibody titres and shorter duration of protective antibody levels. The efficacy of hepatitis-B vaccine is related to the degree of immunosuppression induced by HIV infection, but there are few data on how antiretroviral therapy influences responsiveness to the vaccine.[175,176] The results of two randomized controlled studies conducted in Mexico and Brazil suggest that increased antigen exposure through additional doses, increased doses, [177,178] or adjuvants [179] may improve the immunogenicity of hepatitis-B vaccine in HIV-infected populations.

Where serological testing for the hepatitis-B virus is available, WHO recommends three doses of standard- or double-strength hepatitis-B vaccine for adults with HIV who are susceptible (i.e., antibody to hepatitis B core antigen negative (anti-HBc)) and have not been vaccinated previously. Vaccine response (titre of hepatitis B surface antibody) should be measured and if suboptimal, revaccination may be considered. However, if antiretroviral therapy has been initiated, revaccination may be delayed until an adequate immune response occurs (e.g., CD4 count >200 cells/uL).

In settings where serologic testing is not available, and hepatitis-B prevalence is substantial, programme managers may choose to offer three doses of hepatitis-B vaccine to all adults with HIV. Health-care providers will need to take into account the extent of perinatal and childhood transmission of hepatitis-B virus, and, if available, measurement of the prevalence of hepatitis-B exposure in young adults, derived from a sentinel surveillance group (blood donors, for example).

In settings where serological testing for hepatitis-B infection and HBV vaccination are feasible, three doses of standard- or double-strength HBV vaccine should be offered to hepatitis-B-core-antibody-negative adults with HIV who have not been previously vaccinated. **(A-II)**

The response to the vaccine should be assessed with hepatitis B surface antibody (anti-HBs) testing after three doses of HBV vaccine. If the vaccine response is suboptimal, revaccination with three doses of standard- or double-strength HBV vaccine should be considered **(C-III)**; if antiretroviral therapy is to be initiated, re-immunization should be delayed until the person shows an adequate immune response (e.g., CD4 count >200 cells/uL). **(B-III)**

In settings where serologic testing is not available or feasible, and there is a high prevalence of hepatitis B, three doses of standard- or double-strength HBV vaccine should be considered routinely for adults with HIV. **(B-II)**

4.8.2 Pneumococcal vaccine

Streptococcus pneumoniae is another major cause of illness and death among people with HIV, worldwide. In both high income and low income countries, HIV infection is associated with a greater than ten-fold increased incidence of bacterial pneumonia.[180-183] Case-fatality rates are 8-10%. *S. pneumoniae* is the most common cause of community-acquired bacterial pneumonia in adults with HIV. Among persons on ART, pneumococcal disease remains among the leading causes of infectious morbidity.[181] Two pneumococcal vaccines are available: 1) the 23-valent pneumococcal polysaccharide vaccine (PPV), which confers protective immunity against *S. pneumoniae* via antibodies to 23 capsular polysaccharides; and 2) a newer polysaccharide-protein pneumococcal conjugate vaccine that conjugates seven polysaccharides to protein carriers to alter the immunological handling of the polysaccharide particularly in children's immune systems. It is unclear whether this different immunological processing could be of benefit to adults.

Conflicting data make it difficult to establish universal guidelines for the use of PPV in populations of people with HIV in settings with few resources. Data are available from one randomized controlled clinical trial conducted in HIV-infected persons in Uganda who were not receiving antiretroviral therapy[184,185] and a large observational cohort in the United States [186,187] where there was varied receipt of antiretroviral treatment. In the clinical trial in Uganda, PPV was not associated with a lower incidence of pneumonia[184]; instead, there was a higher rate of pneumonia among recipients of the vaccine, particularly those with higher CD4 counts. The researchers also observed, however, a 16% lower death rate among the vaccine recipients after 6 years—a difference that was of borderline statistical significance.[185] It is unknown whether the modest decrease in mortality could be sustained outside of a controlled trial, where treatment for pneumonia may not be optimal. The United States cohort study, by contrast, demonstrated

vaccine efficacy in individuals with CD4 counts greater than 200 cells/uL with better protection in those with CD4 counts greater than 500 cells/uL.[186] Recent data from the US suggest that viral load at the time of vaccination may be an important determinant of vaccine response, and viral loads greater than 100,000 may be associated with lack of efficacy of PPV.[187]

The below recommendation attempts to reconcile the evidence cited above. Managers of HIV-care programmes in low and middle income countries should decide on their approach after considering the impact of other care packages (most notably, those providing co-trimoxazole prophylaxis).

Insufficient evidence exists to provide guidance on the use of PPV in relation to antiretroviral therapy at this time. It may be prudent to provide PPV to patients with suppressed viral loads and increasing CD4 counts. Given the importance of pneumococcal disease among patients on ART and the increasing numbers of long-term survivors as ART becomes more available, this is an area that needs further investigation.

Insufficient evidence exists for the use of pneumococcal conjugate vaccine in adults; therefore, no recommendations have been made for adults with HIV. Use of pneumococcal conjugate vaccine in children, however, may protect parents from pneumococcal disease through herd immunity, as contact with children is a risk factor for invasive disease [188] and its use in children with and without HIV has been associated with dramatic reductions in vaccine-serotype invasive disease.[189,190] For this reason, where pneumococcal conjugate vaccine is available and national guidelines allow, pneumococcal conjugate vaccine may be offered to children under 5 in households with people with HIV. However, limited data from the US suggest that non-vaccine serotype replacement among adults with HIV may lessen the benefit. Further assessment of this intervention is needed in resource-limited settings.

Pneumococcal polysaccharide vaccine may be considered for people with HIV in WHO clinical stage 1 or, if CD4 testing is available, with a CD4 count > 500 cells/uL. **(C-III)**

Where available and feasible, pneumococcal conjugate vaccine may be offered to children under 5 in households with adults with HIV to prevent these adults from acquiring conjugate-vaccine-serotype invasive pneumococcal disease. **(C-III)** Dosing should be in accordance with national guidelines with a three- or four-dose regimen.

4.8.3 Influenza vaccine

There is limited information about the frequency and severity of influenza in adults with HIV.[191] Individuals with HIV may, however, be more susceptible to complications of influenza, including superimposed bacterial infections. There is conflicting evidence regarding the immunogenicity of the subunit influenza vaccines in adults with HIV.[192-197] In general, immune responses appear to be attenuated or lacking in individuals with HIV and CD4 counts < 100cells/uL, particularly in the absence of pre-existing antibodies to vaccine antigens.[198] Antiretroviral therapy may be

associated with a better immune response to influenza subunit vaccines.[197]. Small efficacy trials of vaccines have demonstrated that vaccination with subunit influenza vaccine is associated with a lower incidence of respiratory illness and culture-confirmed influenza in vaccinated individuals, where 56-96% of individuals across the studies were receiving ART.[199]

Unpublished data from South Africa[i] indicate an ecological and temporal association between increased mortality and the influenza epidemic across three consecutive seasons in adults aged 18-45 years. Studies on the burden of influenza illness from developing countries will be critical to inform local decision-making. WHO recommends that inactivated subunit influenza vaccine may be offered annually to adults with HIV. Moreover, if influenza vaccine is indicated in the context of a large epidemic or pandemic, adults with HIV should receive inactivated influenza vaccine.

The intra-nasally administered, live-attenuated influenza vaccine has been found to be safe and immunogenic in immunocompetent adults and children.[200,201] Because of theoretical concerns, however, about the effect of live attenuated vaccines in immunocompromised individuals and limited safety information, these vaccines should not be given to individuals with HIV.

> Where available and feasible, annual influenza vaccination with the inactivated subunit influenza vaccine should be offered to adults with HIV. **(B-II)**

4.8.4 Yellow fever vaccine

Yellow fever is a potentially deadly, mosquito-borne, viral hemorrhagic fever that is endemic in parts of Africa and South America. [202] It is estimated that 200,000 cases and 30,000 deaths are attributable to yellow fever annually, the majority in Africa.[203] There are no data on the interaction between yellow fever and HIV. It is unclear whether HIV constitutes a risk for altered severity of yellow fever infection. Since 1988, the Joint WHO/UNICEF Technical Group on Immunization in Africa has recommended incorporation of yellow fever vaccine into routine child and immunization schedules in 34 at-risk countries.[203] Yellow fever vaccine is a live, attenuated virus prepared from the 17D yellow fever virus strain.[204] The safety and efficacy of yellow fever virus in people with HIV is limited to reports on 58 adults who received vaccine without adverse effects and a single case report of meningo-encephalitis in a man with advanced untreated HIV who received yellow fever vaccine.[205-208]

Yellow fever vaccine is best used in two ways: to protect travellers to an endemic area; and in individuals living in endemic areas where yellow fever outbreaks necessitate the vaccination of whole populations. Yellow fever vaccine is generally not recommended for adults with HIV and should not be offered to those with HIV who are symptomatic (WHO clinical stage 3 or 4) or who have CD4 counts of less than 200 cells/uL.

Adults with HIV should be discouraged from travelling to areas where yellow fever is endemic. If travel is unavoidable, however, vaccination can be considered for adults in WHO HIV clinical stage 1 or 2, or for those with CD4 counts greater than 200 cells/uL . These individuals should

i Provided by A. Karstaedt, during a personal communication **[EDITOR'S NOTE: 2006].**

also be encouraged to avoid mosquito bites by sleeping under insecticide-treated mosquito nets, wearing protective clothing, and using insect repellents.

Decision-makers should assess the potential risks and benefits before using vaccine to control yellow fever outbreaks in endemic regions with HIV-infected populations. Such assessments should consider the size and extent of the outbreak, the size of the HIV-infected population and the consequences of excluding people with HIV from vaccination. They should also consider the availability of other control measures.

In general, yellow fever vaccine is not recommended for adults with HIV and should not be given to adults with HIV who are symptomatic (WHO clinical stage 3 or 4) or who have CD4-cell counts < 200 cells/uL. **(B-IV)** Yellow fever vaccination can be considered for adults with HIV in WHO clinical stage 1 or 2, or who have CD4 counts > 200 cells/uL, if they are required to travel to an area where there is an epidemic of yellow fever or the disease is endemic. **(B-IV)**

4.9 Nutrition

The following section is derived from existing WHO guidelines and was not addressed in the systematic reviews and consultation that informed the greatest part of these guidelines.

One of the greatest needs of people living with HIV is adequate nutrition.[13,209,210] HIV infection is often associated with poor nutrition due to many factors, including increased energy needs, decreased appetite, symptoms of HIV or opportunistic infections that lead to swallowing difficulty and malabsorption, and environmental factors such as lack of resources and inaccessibility of foods. Research has established weight loss and wasting as independent risk factors for HIV progression and mortality. Low body mass index (BMI)[i] is an independent predictor of mortality in people living with HIV.[211,212] In Gambia, a BMI of 18-20 was associated with a two-fold increase in risk of mortality, while BMIs of 16-18, and below 16 were associated with five-fold and eight-fold increases, respectively. The presence of severe malnutrition, defined by a BMI below 16, has also been associated with a two-fold increased risk of death among people with HIV on antiretroviral therapy.[213] Beyond a need for basic nutrition, many drugs for treatment of HIV and related infections need to be taken with food, and for some drugs, interactions with food need to be considered.

Evidence regarding nutrition and HIV has been reviewed by several WHO technical panels.[13,14,210,214-217] WHO recommends that evidence-based nutrition interventions should be part of all national HIV care and treatment programmes.[13,209,210,214,216,217] Although a need exists for additional information about the effectiveness of supplementary feeding[ii], therapeutic

i Body mass index (BMI): The indicator of weight adequacy in relation to height of older children, adolescents and adults. It is calculated as weight (in kilograms) divided by the squared height (in meters), squared. The acceptable range for adults is 18.5 to 24.9, and for children it varies with age.

ii Supplementary feeding refers to the provision of additional food to individuals with BMI 16-18.5 to treat mild-to-moderate malnutrition.

feeding[i], and multi-micronutrient supplementation in the prevention, care and treatment of HIV infection, specific evidence-based recommendations have been developed. In the recommendations below, strength and quality ratings have been applied to these previously published recommendations.

4.9.1 Nutrition assessment

Food insecurity, inadequate energy intake, general malnutrition and specific micronutrient deficiencies are endemic in many areas with high HIV prevalence, therefore, the diet and nutritional status of people living with HIV should be routinely assessed. Health-care providers should measure the person's weight and weight change, height, BMI, and mid-upper arm circumference. They should look for symptoms related to appetite, difficulty swallowing, nausea, diarrhoea, and effects of drug-food interaction and assess the patient's diet to ensure that she or he has adequate protein and micronutrients for their energy needs and is avoiding potential drug-food (or botanical) interactions. Patients should also be evaluated for individual and household food security.

> Full nutritional assessment (anthropometry, symptoms, and diet) should be routinely included within HIV treatment and care. **(A-IV)**

4.9.2 Nutrition support and micronutrient supplements

There is general agreement that people with HIV should have access to adequate nutrition, but experts do not agree entirely on what constitutes optimal nutrition, or how it is best provided. Energy requirements for adults with HIV who are not pregnant are 10-30% higher than for people without HIV,[13,14,214,215] and can be even higher following acute illness due to opportunistic infection or if past intake has been inadequate. When feasible, appropriate, equitable and sustainable, people with HIV and their families without the means to meet their basic dietary needs should be given food and helped to achieve food security: for example, by being provided with income or other livelihood assistance.

Multiple studies have established that malnourished adults with HIV are at an elevated and progressive risk of HIV disease progression and mortality as BMI decreases, especially below 18.5. WHO recommends providing supplementary feeding for mild-to-moderately malnourished adults (BMI <18.5), regardless of HIV status.[218] The most common and cheapest supplementary foods are micronutrient-fortified, blended flour (e.g. corn-soy blend or CSB) that can be prepared as a porridge, but other forms (e.g. biscuits or pastes) may be used. Severely malnourished adult patients (BMI <16) should be provided with a therapeutic food that is formulated to be nutritionally equivalent to the therapeutic F100 milk[ii]. [218] Therapeutic or supplemental feeding should be continued until the patient's BMI is stabilized above 16 or 16-18.5, respectively, for two-to-three consecutive months.

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i Therapeutic feeding refers to the provision of specialized foods to persons with BMI<16 to treat severe malnutrition.

ii F-100 milk is a formula diet used for the treatment of severely malnourished children. It provides 100 kcalth or 420 kJ/100ml, F-100 milk can be easily prepared from basic ingredients: dried skimmed milk, sugar, cereal flour, oil, mineral mix and vitamin mix. It is also commercially available as a powder formulation that is mixed with water.

Clinically malnourished people with HIV should be provided with therapeutic feeding support (BMI <16) or supplementary feeding support (BMI 16-18.5) until the patient's BMI stabilizes above 18.5. **(A-III)**

People with HIV (and their families) should be referred to programmes that will help them achieve household food-security and benefit from livelihood assessment and support. **(A-IV)**

A number of studies have evaluated the impact of micronutrient supplementation for people with HIV, but interpretation of their results is complex because of the use of different outcome measures and supplements (e.g., individual or combinations of micronutrients in physiological or pharmacological doses). These studies have also looked at people with widely varying baseline micronutrient status and varying stages of disease and treatment.[210] As a result, there is not yet consistent, compelling evidence that provision of more than a single recommended daily allowance (RDA) of any individual vitamin or mineral is beneficial.

Daily multi-vitamin supplementation has been recommended and commonly practiced in the United States and Europe for people with HIV, despite limited specific evidence to support this practice, or as a prophylactic approach for any disease. A recent randomized trial in the United States [219], and randomized trials in Thailand [220] and Tanzania [221] have reported associations between multi-vitamin supplementation and improvements in immunologic and clinical status of people with HIV. The design and other obstacles to interpretation of the results of these studies, however, makes it impossible to derive recommendations for people living with HIV about micronutrient supplementation above the currently recommended daily allowances. WHO recommends that people with HIV take the required daily allowance (RDA) of micronutrients. This allowance is best provided by food, including fortified foods, but where the micronutrient content of the daily diet is inadequate, daily supplementation with a multi-micronutrient supplement is recommended.

Recommended daily allowances of micronutrients should be consumed by adults with HIV through diversified diets, fortified foods and micronutrient supplements, as needed. **(A-III)**

People with HIV whose diets are determined likely to be inadequate in micronutrients (vitamins and minerals) should be provided a daily multi-micronutrient supplement (one RDA). **(A-III)**

4.9.3 Nutrition support for pregnant and lactating women

The nutrition of women with HIV during pregnancy affects the health of the mother and the foetus. Recommended intake of energy, protein and micronutrients is the same for pregnant and lactating women, whether or not they are HIV-seropositive.[214,216] Adequate micronutrient intake

is best achieved through a healthy, balanced diet. Where this is difficult to provide or secure, however, pregnant and lactating women may need multi-micronutrient supplements. Vitamin A supplementation during pregnancy and lactation should not exceed the RDA,[214] as higher doses during lactation have been associated with increased rates in mother-to-child transmission of HIV.[222,223] Transmission of HIV through breastfeeding has been well documented. The risk of transmission can be reduced by various interventions related to infant feeding, which are fully described in separate guidelines.[216,224-226]

The standard recommendations for nutrient intake and nutritional support for pregnant and lactating women should be followed, regardless of the woman's HIV status. **(A-IV)**

Pending additional information, micronutrient intakes at the RDA level are recommended for women with HIV during pregnancy and lactation. **(A-II)**

4.10 Family planning

Family planning is important for people living with HIV and contributes substantially to the prevention of mother-to-child transmission of HIV.[227] Too often, however, family planning services sensitive to the needs of people with HIV are not available. Scale-up of HIV testing and counselling and antiretroviral therapy will increase the number of people who know they are infected with HIV and who, as their health improves on treatment, may become more sexually active and their fertility may increase. Health-care providers need to recognize and address family planning and reproductive health issues as part of comprehensive HIV care and prevention services. [228]

People with HIV have similar family-planning needs as the general population, but also have unique needs. To avoid unintended pregnancies and transmission of HIV to their child and uninfected partners, women with HIV, many of whom are young, need counselling about their sexual and reproductive health choices and need access to a broad range of contraceptives, including condoms. The vast majority of HIV infections in children are through mother-to-child transmission during pregnancy, labour or delivery or through breastfeeding.[45] Family planning is crucial to help limit mother-to-child transmission of HIV and has been shown to be cost-effective.[227,229]

In addition to reducing unintended pregnancy, men, women and young people with HIV also need to have information and support to prevent acquisition and transmission of sexually transmitted infections. Serodiscordant couples need information and support on family planning that considers not only prevention of pregnancy but also prevention of HIV transmission, requiring access to both condoms and a range of other contraceptives.

More generally, family planning provides benefits by saving lives and enhancing the health of women and their families. Enabling women to time and space births leads to improvements in their health, reduces maternal mortality and significantly increases child survival.

Many low and middle income countries have established family-planning programmes. Too often, however, these are not well integrated with more recently introduced HIV programmes,

despite the overlapping nature of their work and the potential synergy. In industrialized countries, the integration of these services has contributed to the virtual elimination of mother-to-child transmission. Similarly, integration of services in low income countries can expand access to HIV care and treatment and as a result may contribute to reductions of HIV transmission. Studies show that expansion of HIV voluntary testing and counselling contributes to the scaling up the prevention of mother-to-child transmission of HIV. In low and middle income countries, however, in 2005, fewer than one-in-ten pregnant women had access to the package of ante- and postnatal services that includes HIV counselling and testing and the consistent follow-up that is needed to reduce mother-to-child transmission of HIV.

In delivering these services, it is critical not to coerce individuals. Stigma and discrimination often undermine the human rights of people living with HIV. Therefore, family-planning counselling and services should never be imposed on people living with HIV. Rather, providers must safeguard the rights of people with HIV—women, in particular—to make informed choices about their sexual and reproductive lives. (These rights are formally recognized in paragraph 95 of the Beijing Declaration of United Nations Fourth World Conference on Women, 1995).[230]

4.10.1 Family planning counselling and services

With the exception of spermicides, WHO guidelines endorse the same contraceptive methods for women living with HIV as for women without HIV. A broad range of contraceptive choices (periodic abstinence, cervical cap, sponge, male and female condoms, hormonal contraceptives, intra-uterine devices (IUD), sterilization, etc.) should be offered to all people of reproductive age living with HIV, irrespective of marital status, to prevent unintended pregnancies. In doing so, health-care providers should take into account WHO medical eligibility criteria for contraceptive use and the 2006 WHO/UNFPA guidelines for care, treatment and support in *Sexual and reproductive health of women living with HIV/AIDS*.[227,229,231]

Women, men and young people on antiretroviral therapy often need assistance in making decisions on family planning and require information and counselling on such topics as:

- Effective contraceptive methods to prevent pregnancy, if so desired, including potential drug interactions with hormonal contraceptives;[16]
- The risk of HIV transmission for serodiscordant couples when trying to become pregnant and available interventions to reduce this risk, such as limiting unprotected sexual intercourse to only those days when chances of conception are maximized or, pending the results of further research, the use of pre-exposure prophylaxis with an ARV;
- The risk of birth defects associated with some antiretroviral therapy and other drugs used to treat HIV, particularly those received during the first trimester; [15,16,227]
- The risk of HIV transmission to the infant and the effectiveness and availability of antiretroviral therapy in reducing transmission.

Family planning counselling and services, based on a broad range of contraceptive choices, should be provided to couples, and individual men, women and young people with HIV, to prevent unintended pregnancies and mother-to-child transmission of HIV. Assessing and assisting individuals and couples living with HIV with desires for children should be part of family planning counselling and services. **(A-II)**

4.10.2 Condoms and counselling

Condom use is a vital family planning strategy.[231,232] In addition, the correct and consistent use of the male condom reduces the risk of sexual transmission of HIV by 80-90%.[30-32,233,234] Observational studies, laboratory experiments and mathematical modelling indicate that female condoms also offer strong protection against HIV infections.[235] UNFPA, the largest public-sector purchaser of male condoms, estimates the global supply of public-sector condoms is less than 50% of that needed to ensure adequate condom coverage. Among other major barriers, weak systems of health commodity procurement and management contribute to this shortage, so there is an urgent need to strengthen these.

WHO recommends that people living with HIV use dual protection—defined as the simultaneous use of condoms with other contraceptive methods, or the consistent and correct use of condoms alone— to prevent unintended pregnancy and sexually transmitted infections, including HIV.[227,229,231]

People living with HIV, who access family-planning services, should be given condoms and strongly encouraged to use them consistently and correctly, with or without another contraceptive method. **(A-II)**

4.10.3 Safe reproductive services

Countries with a high burden of HIV are often those with a large unmet need for contraception. Even where contraception is widely available, women, irrespective of their serostatus, may experience unintended pregnancies. Women living with HIV, therefore, need accurate information and support in making decisions about whether to continue a pregnancy, and access to safe methods of termination, where legal, should they choose not to carry a pregnancy to term. Where access to safe termination of pregnancy is restricted, the incidence of unsafe procedures may be high.[236] Women living with HIV are prone to septicaemia and may be particularly at risk of complications from unsafe procedures. Preventing unintended pregnancies and unsafe termination of pregnancy is, therefore, essential for improving the health of these women.

WHO guidelines advise that women with HIV who wish to terminate a pregnancy should be treated in the same manner as other women.[227,229] Safe termination of pregnancy should also be coupled with counselling. Women with HIV have reported that unfounded concerns about the negative effects of pregnancy on their own health and about HIV transmission to their infant influenced their decision to terminate a pregnancy.[237] To make an informed decision about whether to continue a pregnancy, women living with HIV need to know that the risks of pregnancy

to their own health are no different than for women without HIV, that risks associated with unsafe termination of pregnancy are very high, and that interventions to reduce the risk of HIV transmission to their infants should be available and effective. Women also need to know the side effects and risks of the available procedures for pregnancy termination, where legal.

In some cases, a woman with HIV, especially an adolescent with HIV, may be under pressure from her partner, other family members or health-care providers either to continue or not continue the pregnancy. If health workers suspect coercion from any of these persons, they should talk with the woman alone or refer her for additional counselling, to ensure that she is fully informed and able to make the decision freely.[238]

> Ensuring the availability of safe, non-coercive termination of pregnancy, where permitted by law, should be considered to protect the health of women living with HIV who do not wish to carry a pregnancy to term. **(B-II)**

4.11 Preventing mother-to-child transmission of HIV

A comprehensive approach to prevent HIV infection in infants and young children includes following interventions (i) to prevent HIV infection in women of childbearing age; (ii) to prevent unintended pregnancies among women living with HIV, (iii) to prevent HIV transmission from a woman living with HIV to her infant; and (iv) to provide care, support and treatment to women living with HIV and to their children and families. WHO has addressed (iii) and (iv) in guidelines released in August 2006 titled *Antiretroviral drugs for treating pregnant women and preventing HIV infection in infants: towards universal access*.[15] The document contains evidence-based recommendations, including strength and quality ratings, for the use of antiretroviral drugs, the selection of medicines and dosing in pregnant women for their own health and for preventing HIV infection in infants and young children, and a summary of the scientific rationale for the recommendations. Therefore the PMTCT recommendations were not re-examined in the current process and a summary of those recommendations is included below.

For the goal of reducing HIV infection in infants and young children, all pregnant women eligible for ART must start such treatment and pregnant women who do not yet require ART should be given ARV regimens for preventing MTCT.[15] Various ARV drugs, including nucleoside reverse transcriptase inhibitors (NRTIs) such as azidothymidine (AZT) and lamivudine (3TC), and the non-nucleoside reverse transcriptase inhibitors (NNRTIs) nevirapine (NVP), either alone or in combinations of two or three drugs, have been shown to reduce MTCT.

4.11.1 Pregnant women with indications for ART

ART for pregnant women not only addresses their own health and well-being but also reduces the risk of MTCT, particularly for women at an advanced stage of disease.[15] HIV-infected pregnant women should be offered a clinical and immunological assessment. Criteria for initiating ART for pregnant women are the same as for non-pregnant women, with the exception that initiation of ART is recommended for pregnant women who have clinical stage III disease and a CD4 cell count below 350cells/mm3. ART for pregnant women is therefore recommended for:

- All women in clinical stage 4 irrespective of CD4 cell count
- Women in stage 3,with CD4<350 cells/mm3 if available. If CD4 is not available, all women in stage 3 should be treated
- Women in stage 1 and 2 with CD4 < 200cells/mm3

From first-line regimens recommended for adults and adolescents, the recommended regimen for pregnant women is AZT + 3TC and NVP.[15] However, there are concerns about toxicity, including hepatitis, in women initiating NVP-containing ARV regimens with a CD4 cell count between 250 and 350cells/mm3 as outlined in the above guideline. There are a number of different approaches to treatment of pregnant women with a CD4 cell count in this range, including initiating an NVP-containing regimen with close monitoring in the first 12 weeks of therapy as the benefit may outweigh the risk in this situation; starting an EFV-containing regimen if the woman is in the second or third trimester of pregnancy, and effective contraception can be assured postpartum; or giving a triple NRTI or a protease inhibitor (PI)-based regimen. Each of these approaches has advantages and disadvantages and there are currently no data to favour one approach over the other.[15]

Recommendations for women who become pregnant while receiving ART are described elsewhere.[15]

- All pregnant women with indications for ART should receive ART **[A-II]**.
- The preferred first-line regimen for ART for pregnant women is AZT+3TC+NVP **[A-II]**.
- Pregnant women with a CD4 cell count between 250 and 350cells/mm3 who have indications for ART can either be started on an NVP-containing regimen with close monitoring in the first 12 weeks of therapy or an EFV-containing regimen if they are in the second or third trimester of pregnancy; or receive a triple NRTI or a PI-based regimen **[C-IV]**.
- EFV remains an option for the NNRTI component of a first-line regimen in pregnant women in the second or third trimester of pregnancy **[C-IV]**.
- The recommended regimen for infants is AZT for seven days from birth. For women who receive less than four weeks of ART before delivery, the infant AZT dose should be extended to four weeks **[A-II]**.
- Women with indications for ART who present very late in pregnancy should be started on ART, irrespective of gestational age of pregnancy **[A-IV]**.

4.11.2 ARV prophylaxis for preventing HIV infection in infants

Important recommendations for the prevention of mother to child transmission are also included under Section 4.10 Family Planning. Once a woman living with HIV becomes pregnant, ARV prophylaxis is needed to prevent MTCT.

- Pregnant women who do not have indications for ART should be given the following regimen to prevent MTCT: AZT starting from 28 weeks of pregnancy (or as soon as possible thereafter); AZT and 3TC plus single dose NVP intrapartum; and AZT and 3TC postpartum for seven days for women, and single dose NVP and AZT for one week for infants **[A-I]**. Omission of the NVP dose for the mother may be considered for women who receive at least four weeks of AZT before delivery **[C-I]**. The infant NVP dose should preferably be given as soon as possible after delivery and in any case no more than 72 hours afterwards **[A-II]**. If the mother receives less than four weeks of AZT before delivery, the infant AZT dose should be extended to four weeks **[A-I]**
- When single dose NVP is used for MTCT prophylaxis, either alone or in combination with AZT, women should be given AZT and 3TC intrapartum and for seven days postpartum to prevent NVP resistance **[A-I]**
- When delivery occurs within two hours of a woman taking NVP, the infant should receive single dose NVP as soon as possible after delivery and AZT for four weeks **[A-I]**

4.11.3 Recommended ARV regimen for preventing MTCT among women in labour who have not received antenatal antiretroviral prophylaxis

The recommended ARV regimen for preventing MTCT among women in labour who have not received antenatal antiretroviral prophylaxis consists of intrapartum single dose NVP plus AZT and 3TC, and a seven-day course of AZT plus 3TC for women and Sd-NVP immediately after delivery and four week AZT for infants.

- HIV-infected women in labour who have not yet received ARV drugs should be given intrapartum single dose NVP plus AZT and 3TC followed by postpartum AZT and 3TC given for seven days; plus infant single dose NVP immediately after delivery and AZT for four weeks. **[A-I]** If imminent delivery is expected, the maternal NVP dose should be omitted; the same recommendations and considerations apply as for infants born to HIV-infected women who did not receive antenatal or intrapartum ARV prophylaxis. **[A-II]**
- When delivery occurs within two hours of the woman taking NVP, the infant should receive single-dose NVP as soon as possible after delivery and AZT for four weeks. **[A-I]**

4.11.4 Infants born to HIV-infected women who did not receive antiretroviral drugs during pregnancy or labour

The recommended regimen for infant prophylaxis when the mother has not received any ARV prophylaxis is single dose NVP plus four weeks of AZT when possible. In programs without adequate capacity to delivery the recommended regimen, single dose NVP with one week of AZT or single dose NVP alone should be administered.

For infants born to HIV-infected women who did not receive any ARV prophylaxis, administering ARV drugs to infants immediately after delivery as post-exposure prophylaxis solely is likely to result in a larger reduction in transmission than later initiation. When feasible, infant ARV prophylaxis should be initiated as soon as the infant can tolerate oral feeding and within 12 hours following delivery. If ARV prophylaxis is delayed more than two days, it is unlikely to have any benefit.

- Single dose NVP immediately after delivery and AZT for four weeks are recommended for infants born to HIV-infected women who did not receive any ARV prophylaxis because this regimen results in a greater reduction in transmission than single-dose NVP for the infant alone. **[A-III]**
- ARV prophylaxis for infants born to HIV-infected women who had not received antenatal or intrapartum ARV prophylaxis should begin immediately after delivery within 12 hours after delivery if possible. **[A-III]**

Operational contexts vary considerably between countries and even within a country. In settings that do not currently have the capacity to deliver the recommended MTCT prophylaxis regimen, it may be necessary – as an absolute minimum – to implement the single-dose (maternal and infant) NVP regimen. However in these circumstances, the specific obstacles to delivering more effective regimens should be identified and concrete actions taken to overcome them. Expansion of PMTCT programmes using single dose NVP should be considered a short-term interim measure while steps are being taken to enable more effective regimens to be delivered.

The use of antiretroviral treatment regimens for PMTCT is rapidly evolving as a result of research for better interventions and experience from country scale-up activities. Therefore we recommend that the relevant web sites be regularly checked for updated versions of recommendations.

For a copy of the guidelines, go to http://www.who.int/hiv/pub/guidelines/pmtctguidelines2.pdf or contact WHO.

4.12 Needle-syringe programmes and opioid substitution therapy

Injecting drug use—to administer opioids such as heroin, as well as other drugs such as amphetamine-type stimulants and cocaine—is estimated to account for just under one-third of new HIV infections outside sub-Saharan Africa. Once HIV enters a community of injecting drug users, the virus can spread rapidly throughout the community and into the rest of the population, if appropriate measures are not taken early. Yet, in spite of the importance of injecting drug users in the response to HIV, coverage of HIV prevention for this population is low, an estimated coverage of approximately 8% in low and middle income countries in 2005.[1,2] There are approximately 13 million injecting drug users worldwide, of whom 8.8 million live in Eastern Europe and Central, South and South-East Asia. Injecting drug use is also widespread in Europe and the Americas, and new epidemics of injecting drug use are being witnessed in some countries of sub-Saharan Africa.

There is solid evidence on the effectiveness of a comprehensive set of interventions, including needle-syringe programmes and opioid substitution therapy for reducing the harms of injecting drug use, such as bloodborne infections with HIV, hepatitis C virus (HCV) and hepatitis B virus (HBV), skin abscesses and other infections and drug-related overdose.[7,239-242] Needle-syringe programmes (NSPs) allow for the exchange, distribution, or sale of sterile needles and syringes and other injecting equipment. Some also provide for the collection of used equipment and encourage more appropriate disposal of equipment. These programmes operate from primary health-care and social-service centres, pharmacies, outreach agencies and in diverse settings including prisons. Some make use of vending machines. Opioid substitution therapy (OST) refers to the use of methadone, buprenorphine and less commonly other opioid drugs including sustained-release oral morphine, tincture of opium or medically prescribed heroin, in combination with psychosocial support.

4.12.1 Needle-syringe programmes

The evidence base for needle-syringe programmes in HIV prevention, safety and cost-effectiveness has developed over more than two decades and includes studies from well-resourced and resource-limited settings and community and closed settings (such as prisons).[243-250] In addition, coinfection with HIV and hepatitis C is now common and has major implications for disease progression and for HIV treatment.[251] There is, however, no evidence of any serious negative consequences related to needle-syringe programmes, including increases in drug use or injecting. Authorities in all countries with drug-using populations should implement and rapidly expand needle-syringe programmes providing sufficient coverage to prevent, avert or reverse epidemics, taking into account, and addressing when needed, legal impediments to doing so.[i]

Evidence indicates that needle-syringe programmes are most effective when well-integrated with a comprehensive set of harm-reduction services, including information and education, condom promotion, referral to other specialized services such as HIV care and treatment, STI diagnosis and management, drug dependence treatment (particularly opioid substitution therapy) and HIV treatment and care. Harm reduction programmes should also be linked to primary health care and, where appropriate, delivered through peer outreach.[239-242] As well, NSPs should be easily accessible to HIV-negative injecting drug users.

In implementing and scaling up of needle-syringe programmes, decision makers should set targets for the level of coverage needed in different settings, according to WHO criteria, and methods of improving access to NSPs for those who may benefit but are less likely to use, such as women, migrant workers, ethnic minorities, young injectors and sex workers. The quality of NSPs needs to be maintained by ensuring adequate levels of staff training, regular review of guidelines and maintenance of non-judgemental staff attitudes. Authorities must ensure that NSPs continue to remain attractive to the target population and achieve high levels of client satisfaction.

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i Randomized controlled trials of NSPs are seldom feasible because of logistical and ethical problems; however, these programmes meet almost all of the criteria required for evaluation of public health interventions and have been supported by all major systematic and comprehensive reviews.

Evidence does not support the use of bleach as a means of disinfecting needles and syringes. Undiluted bleach has been shown to inactivate HIV on injecting equipment in laboratory studies. In field studies, however, IDUs do not use bleach correctly.[7] Nevertheless, where authorities refuse to accept or expand needle-syringe programmes—for example, in prisons—the provision of bleach is preferable to doing nothing and may be acceptable provided that authorities also give users information and training on the limited benefits of bleach and appropriate methods of using it.

HIV-seropositive injecting drug users, including those in closed settings such as detention centres and prisons, should have ready access to needle-syringe programmes (NSPs) to reduce transmission of HIV and the acquisition of other infections. **(A-II)**

4.12.2 Opioid substitution therapy

There is strong evidence that opioid substitution therapy is effective in three critical areas: [7,252-254] reducing HIV infections, improving ART adherence, and providing other health, social and economic benefits, including reduction of crime.

HIV epidemics in Eastern Europe and Central and South-East and East Asia, among other regions, are being fuelled by injecting drug use; so, growing numbers of people in need of HIV treatment are dependent on heroin and other opioids. Studies show that this population responds well to HIV treatment if it is properly tailored to their needs and complemented by opioid substitution therapy.

Both methadone and buprenorphine are included on the WHO list of essential medicines. Evidence indicates that these medicines address opioid dependence, reduce the health and social burden associated with opioid dependence, and reduce HIV and other disease transmission through shared needles, if provided in adequate doses and for sufficient duration. Methadone is given priority on the list and both are recommended for use only within established drug dependence treatment and support programmes.

Opioid substitution therapy should be adopted and rapidly expanded to a scale commensurate with achieving control in all countries experiencing or threatened by an HIV epidemic among opioid users.

People with HIV with opioid dependence should be encouraged to enter or continue long-term opioid substitution therapy, a key component of harm reduction programmes, to reduce HIV transmission **(A-I)**, support ART adherence, and improve other health, social, and economic outcomes.

Formal efforts to assess and maintain quality services should be integral parts of harm reduction programmes. Adequate funding should be ensured to sustain quality NSPs and opioid substitution programmes with properly trained staff. As the nature and extent of psychoactive drug use can change swiftly, authorities should monitor trends in drug use regularly and ensure

that the resulting data inform planning and conduct of NSPs, OST and other harm reduction services. Additional information about the relationship between stimulant use and HIV transmission is needed, including information about pharmacological treatment for stimulant users. Needle-syringe and opioid substitution therapy programmes are most effective when they draw on the collaboration of the police, private sector, and community organisations representing injecting drug users and other stakeholders.

The scaling up of needle-syringe programmes and OST is greatly facilitated by enabling policies and laws. A balance must be struck so that an undue emphasis on law enforcement does not inhibit the expansion of NSPs and OST, or worsen epidemics. In general, policies and laws are also needed to reduce stigma and discrimination that often undermine the implementation of needle-syringe programmes and other measures needed to prevent and treat HIV. Authorities should ensure that HIV-prevention, care and treatment services in prisons and other closed settings are easily accessible and of the same quality as those in the wider community.

Information about the risks of injecting with non-sterile equipment should not be provided exclusively to people living with HIV and other diseases—it should be easily available to all drug users and to health care providers.

4.13 Water, sanitation and hygiene

Diarrhoea is a major cause of morbidity and mortality in people with HIV.[57,255] In developing countries, lack of infrastructure to guarantee access to safe water and safe management of human waste expose people with HIV to increased risk of transmission of waterborne and other enteric pathogens. Simple, accessible and affordable interventions to guarantee the quality of household-based water, hygiene, and sanitation have been effective in reducing the risk of enteric diseases in controlled trials. These interventions have been generally acceptable to households, especially when supported by educational and promotion efforts for effective implementation and sustained use. Recent meta-analyses demonstrated a 44% reduction in diarrhoea with interventions focused on hand washing with soap, and reductions of 39% with point-of use household water treatment.[256-259] Current research data do not suggest a synergistic effect of water, hygiene, and sanitation interventions implemented simultaneously; however, consideration should be given to implementing multiple interventions, given the proven effectiveness of each type of intervention and the different modes of diarrhoeal pathogen transmission in different settings.

Current WHO guidelines for drinking-water quality support efforts to ensure safe collection, treatment and storage of drinking water.[255] These safe water interventions should be implemented not only where supplies are absent but also where community supplies are known to be contaminated or are causing waterborne diseases.[257,258] Point-of-use water, personal hygiene, and sanitation interventions have been found to be cost-beneficial.[260]

Evidence supporting the effectiveness of safe water and hygiene interventions is from randomized controlled trials directed at the household level, where the infrastructure to deliver safe water to households is not in place. Therefore, programmes implementing these technologies and

methods should be household-based. Each of these interventions requires continued efforts to motivate and reinforce change in individual and household behaviours; therefore, implementation programmes would be best carried out through a series of home visits or, where home visits are not feasible, through regular visits to health facilities. Evaluations of the impact of programmes implementing the WHO guidelines should be conducted to ensure that the desired impact is being achieved and maintained.

To implement treatment programmes for people with HIV—to provide ART, cotrimoxazole and medicines for TB, for example—access to safe water is essential, as this allows patients to take their drugs and avoid diarrhoeal diseases that reduce drug absorption.[261] When implementing programmes for replacement (i.e., formula) feeding of infants of mothers with HIV, or early weaning of breastfed infants of HIV-infected mothers, the provision of effective water treatment is essential to protect the health of the infants.[262]

In addition to water quality, hygiene and sanitation, basic access (within 1 km or a 30-minute round trip) to obtain enough water to provide a minimum of 20 litres per person per day has been shown to reduce the risk of enteric diseases.[259] Programmes serving people with HIV should advocate for adequate water supplies for their populations, particularly because people with HIV are at higher risk than those with intact immune systems of opportunistic infections transmitted through faecal-contamination.

4.13.1 Safe water

Data from randomized, controlled trials and high-quality observational studies in settings with few resources have demonstrated the effectiveness of four interventions to improve water quality and reduce the risk of diarrhoea: the Safe Water System, solar disinfection, flocculent-disinfectant and ceramic filters. Although more data are needed among people living with HIV, analyses of household treatment studies have found these interventions to be effective in reducing diarrhoeal illness in resource-limited settings.[263] Use of these household-based water treatment and storage methods are recommended for people with HIV and their households.

The Safe Water System (SWS) is a household-based intervention developed by the United States Centers for Disease Control and Prevention (CDC) and the Pan American Health Organization (PAHO, the WHO Regional Office for the Americas) to treat water at the point-of-use.[i] There are three components to this system: water treatment with locally produced sodium hypochlorite solution, safe water storage in a narrow-mouth container and spigot designed to prevent recontamination, and behaviour-change techniques. The SWS has reduced the risk of diarrhoea by 17-85% in developing countries.[264-269] In a randomized controlled trial in rural Uganda among people with HIV, SWS reduced the risk of diarrhoea by 25% and reduced the number of days ill with diarrhoea by 33%.[264] All people with HIV received daily co-trimoxazole as well. SWS and co-trimoxazole together reduced the risk of diarrhoea among people with HIV by 67%, and there was no interaction between co-trimoxazole and SWS-effect on diarrhoea. The cost for locally produced sodium hypochlorite was less than US$0.01/day and the cost of the water vessel was US$3.50 per family.[264,270]

i For details about this system, go to http://www.cdc.gov/safewater

Solar disinfection exposes water in one-to-two-litre, clear plastic bottles to sunlight for five hours, or for two days when skies are cloudy. In randomized trials in Kenya, solar treatment of drinking water reduced the risk of diarrhoea by 16-26% and of cholera by 86%, [271,272] although no data were available specifically among people with HIV in these settings.

Flocculent-disinfectant is a technology for treating water at home that incorporates techniques used in municipal water purification. This powder is available in single-use sachets and when added to the water it facilitates removal of suspended organic matter, bacteria, viruses, parasites, and heavy metals. After decanting, the treated water looks clearer, and is left with free residual chlorine that produces microbiologically and chemically cleaner water. This type of system has reduced the risk of diarrhoea by 20-40% in Guatemala and Kenya, although effectiveness in individuals with HIV has not been evaluated, and costs of this intervention may be higher than that of sodium hypochorite.[267,273,274]

Studies indicate that ceramic filters reduce the risk of diarrhoea by 68-90%.[275] Clinical trials of the health impact of the use of at least three other household water-purification systems are underway.

In the short term, household-based water treatment and safe-storage interventions can be implemented swiftly, particularly if programme staff visit people in their homes to teach them how to use these technologies properly. These methods provide only an interim solution to the health-threat posed by contaminated water, however. In the long-term, governments and development partners must address the larger problem of inadequate access to piped supplies of safe (effectively treated) water in the home.

> Household-based water treatment methods that are effective in reducing diarrhoea and the storage of water in containers that inhibit manual contact are recommended for people with HIV and their households. **(A-I)**

4.13.2 Sanitation

Sanitation interventions provide means to dispose of human waste, including latrines in households or communities. To reduce diarrhoeal disease among people living with HIV and their families or households, disposal of faeces in a toilet or, at a minimum, buried in the ground is recommended. In a randomized controlled trial of a safe-water intervention for people living with HIV in Uganda, access to latrines was independently associated with a reduced risk of diarrhoea of 31% and the number of days ill with diarrhoea by 37%. [264] The Uganda study results are consistent with those from studies that show that access to latrines reduces the risk of diarrhoea among people without HIV.[259]

Adoption and maintenance of effective sanitary practices requires changes in individual and household behaviours. Health and development programmes should, therefore, support these changes with education provided during home visits or regular client visits to a care facility. Programmes should also bring together other stakeholders to contribute to the cost of building latrines and providing other sanitation infrastructure.

Proper disposal of faeces in a toilet, latrine, or at a minimum, buried in the ground is recommended for people with HIV and their households. **(A-II)**

4.13.3 Hygiene

Hygiene interventions include health and hygiene education and the promotion of hand washing.[263,276,277] Several studies have documented that hand washing with soap reduces the risk of diarrhoeal disease.[278] Although studies have not specifically addressed the efficacy of hand washing in diarrhoea prevention in people with HIV, those belonging to this group have a two-fold higher risk of diarrhoeal diseases than people without HIV. In the randomized trial in Uganda, the presence of soap in the home was associated with 42% fewer days ill with diarrhoea.[264] Promoting hand washing with soap in the household, at critical times—after defecation and handling human or animal faeces, and before preparing food and eating, for example—along with the provision of soap are recommended for people with HIV and their households.

Education alone does not motivate people to wash their hands regularly. Regular follow-up is required to promote and reinforce this behaviour. This can be done through both home-based and clinic-based HIV-care programmes. Soap is a critical component of effective hand washing and consideration should be given to provide soap to clients of HIV care programmes, particularly those who lack income. Follow-up evaluations are important to assess the degree to which hygienic behaviours are adopted and continued and to improve programmes, if required.

Promotion of hand washing with soap after defecation and handling of human or animal faeces and before food preparation and eating, along with the provision of soap, are recommended for people with HIV and their households. **(A-II)**

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Table 1. Interventions to prevent illness*

A. Recommended – should be followed

Co-trimoxazole+

Adults and adolescents with HIV should take daily co-trimoxazole prophylaxis in accordance with co-trimoxazole guidelines:

In settings where co-trimoxazole is initiated based on WHO clinical staging criteria, co-trimoxazole prophylaxis is recommended for all symptomatic persons with mild, advanced or severe HIV disease (WHO clinical stages 2, 3, or 4). (A-I)

Where CD4 testing is available, co-trimoxazole prophylaxis is recommended for everyone with a CD4-cell count < 350 cells/uL, particularly in resource-limited settings where bacterial infection and malaria are prevalent among people living with HIV (A-III). If the main targets for co-trimoxazole prophylaxis are PCP and toxoplasmosis, some countries may choose to adopt a CD4 threshold of 200 cells per $mm^{3,}$ below which prophylaxis is recommended. (A-I)

Safe Water

Environmental interventions

Use of household-based water treatment methods that are effective in reducing diarrhoea, and water storage in containers that inhibit manual contact are recommended for people living with HIV and their households. (A-I)

Proper disposal of feces in a toilet, latrine, or, at minimum, buried in the ground is recommended for people living with HIV and their households. (A-II)

Promotion of hand washing with soap after defecation, after handling human or animal feces, before food preparation and before eating, along with the provision of soap, are recommended for people living with HIV and their households. (A-II)

Hepatitis B

Vaccination

In settings where serological testing for hepatitis B infection is available and feasible, three doses of standard- or double-strength hepatitis-B-virus (HBV) vaccine should be offered to hepatitis-B-core-antibody-negative adults with HIV who have not been previously vaccinated. (A-II)

Response to vaccine should be assessed with anti-HBs (hepatitis-B-surface-antibody) testing after three doses of HBV vaccine. If vaccine response is suboptimal, revaccination with three doses of standard- or double-strength HBV vaccine may be considered (C-III); if ART is to be initiated, re-immunization should be delayed until immune response is demonstrated (e.g. CD4 count >200 cells/uL). (B-III)

In settings where serologic testing is not available or feasible, three doses of standard- or double-strength HBV vaccine should be considered routinely for all adults with HIV, depending on local hepatitis-B epidemiology. (B-II)

Malaria

Intermittent Preventive Treatment

Pregnant women with HIV who are living in areas of stable malaria transmission, and who are not taking co-trimoxazole, should be given at least three doses of intermittent preventive treatment for malaria as part of routine antenatal care. (A-I)

Pregnant women with HIV who are living in areas of stable malaria transmission, and who are taking co-trimoxazole, should not be given intermittent preventive treatment with sulfadoxine-pyrimethamine (SP). (A-III)

Chemoprophylaxis

People living with HIV who are living in non-malarious areas, but traveling to areas with malaria transmission, including within country, should sleep under an insecticide-treated net (ITN) and take an effective drug for prevention of malaria in accordance with the most recent recommendations for malaria prophylaxis for travelers. (A-IV)

Environmental interventions

In areas of stable malaria transmission, people living with HIV should routinely use ITNs or have access to indoor residual spraying (IRS) to reduce their exposure to malaria infection. (A-I)

Tuberculosis

Counselling

Information about tuberculosis should be provided to all people with HIV. (A-IV) Counselling should include information about the risk of acquiring TB, strategies for reducing exposure, clinical manifestations of TB disease, risk of transmitting TB to others, and, where appropriate, information about TB preventive therapy. (A-III)

Screening

All people with HIV should be screened for TB disease at each encounter; persons with symptoms or signs suggestive of TB disease should undergo further clinical investigation. (A-II)

Chemoprophylaxis

TB preventive therapy should be provided to people with HIV in HIV care settings where it is possible to exclude TB disease. (A-I) TB-preventive therapy should not be given to people with HIV who have symptoms suggestive of TB. In particular,

people with advanced HIV disease who have any symptoms of TB disease should not be offered TB-preventive therapy. (A-III)

Tuberculin skin testing (or other proven tests for latent TB infection) may be appropriate to identify individuals with latent TB infection who are likely to benefit most from TB preventive therapy. **(A-I)** In people with HIV, a tuberculin skin test $\geq$ 5mm is regarded as positive. In settings of high TB transmission where it is not possible to perform tuberculin skin testing (or other validated tests for LTBI), TB-preventive therapy should be provided to all people with HIV, unless contraindicated. (A-I)

The recommended regimen of TB-preventive therapy is isoniazid daily for six months, self-administered. (A-I) This regimen applies to all settings regardless of the prevalence of isoniazid resistance. (A-IV) Specialist advice should be sought for preventive therapy for contacts of multidrug-resistant or extensively drug-resistant TB.

The risk of isoniazid hepatotoxicity increases among older people, pregnant women and those with pre-existing liver disease; these risks need to be weighed against the benefits of TB-preventive therapy. **(A-II)** Previous TB is not a contraindication to TB-preventive therapy.

Environmental interventions

Providers who care for people living with HIV should adhere to the most recent WHO guidelines for TB-infection control in HIV care facilities. (A-III)

B. Consider – applicable in most situations

Influenza

Vaccination

Where available and feasible, annual influenza vaccination with the inactivated subunit influenza vaccine should be offered to adults with HIV. (B-II)

Yellow fever

Vaccination

In general, yellow fever vaccine is not recommended for adults with HIV and should not be given to adults with HIV who are symptomatic in WHO clinical stage 3 or 4, or (where CD4 testing is available) who have a CD4 count $<$200 cells/uL. (B-IV) Yellow fever vaccination can be considered for adults in WHO clinical stage 1 or 2 and, if CD4 testing is available, CD4 $>$ 200 cells/uL, if they must travel to an area with endemic, or epidemic-levels of, yellow fever. (B-IV)

C. Optional

Cryptococcus and other fungal infections

Chemoprophylaxis

In areas where cryptococcal disease is common, antifungal prophylaxis with azoles should be considered for severely immunocompromised people with HIV (WHO clinical stage 4 or CD4 < 100 cells/uL), whether they are on antiretroviral therapy (C-IV) or not (C-I).

In endemic areas of penicilliosis and histoplasmosis, itraconazole may be considered as an alternative agent to fluconazole for primary prophylaxis of cryptococcosis and penicilliosis or histoplasmosis among people living with HIV. (C-1)

Active cryptococcal and other invasive fungal infection should be excluded before providing prophylaxis for people living with HIV, since the doses of azoles used for prophylaxis might be insufficient for treating active disease. (A-IV)

Primary azole prophylaxis should not be given to pregnant women with HIV. (A-III)

People with HIV who are taking azoles, especially those who are taking other hepatotoxic drugs, should be monitored for adverse events (A-IV); health care providers should be aware that the toxicities and drug-drug interactions with itraconazole may be more prominent than with fluconazole. (A-IV)

Primary azole prophylaxis should not be administered to persons living with HIV solely to prevent mucosal candidiasis. (A-IV)

Primary azole prophylaxis should be discontinued in people with HIV on antiretroviral therapy and with CD4-cell counts > 200 cells/uL. (B-IV)

In settings where CD4-testing is not available, discontinuation may be considered for people with HIV who have completed one year of ART, who are asymptomatic, and who have good adherence to treatment. (C-IV)

Pneumococcus

Vaccination

Pneumococcal polysaccharide vaccine may be considered for people living with HIV in WHO clinical stage 1, or if CD4 count is available, CD4 > 500 cells/uL. (C-III)

Where available and feasible, pneumococcal conjugate vaccine may be offered to children under 5 who are living in households with adults with HIV to prevent adults with HIV from acquiring conjugate-vaccine-serotype-invasive pneumococcal disease. (C-III) Dosing should be in accordance with national guidelines with a three- or four-dose regime.

* Nutrition recommendations are presented from previously published, evidence-based WHO guidelines and ratings on strength and grade of the evidence were applied:

1) Full nutritional assessment (anthropometry, symptoms and diet) should be routinely included as part of HIV treatment and care. (A-IV)
2) Clinically malnourished people with HIV should be given therapeutic feeding support (body-mass index (BMI<16) and/or supplementary feeding support (BMI 16-18.5) until the patient's BMI stabilizes above 18.5. (A-III)
3) People with HIV (and their families) should be linked with household food security and livelihood assessment and support.(A-IV)
4) Micronutrient intakes at RDA are recommended in adults with HIV through consumption of diversified diets, fortified foods, and micronutrient supplements as needed. (A-III)
5) People living with HIV whose diets are likely to be inadequate in micronutrients (vitamins and minerals) should be provided a daily multi-micronutrient supplement (1 RDA). (A-III)
6) The standard recommendations for nutrient intake and nutritional support for pregnant and lactating women should be followed, irrespective of HIV status. (A-IV)
7) Pending additional information, micronutrient intakes at the RDA level are recommended for women with HIV during pregnancy and lactation. (A-II)

\+ 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)

Table 2. Interventions to prevent HIV transmission

A. Recommended – should be followed

HIV counselling and testing

Counselling

Sex partners (A-II), drug injecting partners (A-IV), and children and household members (A-IV) of all people living with HIV should be offered HIV testing and counselling.

Health-care providers should encourage and offer support to people with HIV to disclose their HIV status to those who need to know (e.g., sexual and needle-sharing partners). When self-disclosure is not possible, providers should assess the safety of disclosure and seek the consent of the individual with HIV before notifying his or her partners. The client should choose to whom the information is disclosed. (A-IV)

Psychosocial and Behavioural Interventions

Counselling

All people with HIV should be offered or provided a referral to a comprehensive set of psychosocial interventions (e.g., individual and group counselling, peer support groups, family and couples counselling and adherence support). (A-IV)

Ongoing behavioural counselling and psychosocial support should be provided to HIV-discordant couples through couples counselling and support groups that cover topics such as HIV-transmission-risk reduction, reproductive health issues, couples communication and condom provision. (A-I)

People living with HIV who have mental health conditions such as depression and substance and alcohol dependence should be provided with specific psychosocial assistance, including group counselling , disclosure support, caregiver support, and, when indicated, medication for these conditions. (A-II)

Environmental

People with HIV should be provided with adherence interventions to support prophylactic and therapeutic regimens such as client-centred counselling, pillboxes, and treatment supporters. (A-II)

People with HIV who choose to be sexually active should be counselled about safer sex interventions to prevent HIV transmission to others and to avoid acquisition of sexually transmitted infections (STIs) and be provided with condoms. (A-III)

Concordant HIV-infected couples should use condoms consistently, if needed to avoid STIs and unintended pregnancy. (A-IV) Knowledge regarding the significance of superinfection is not yet sufficient, however, to support a recommendation for consistent condom use specifically to prevent superinfection.

HIV-seropositive injecting drug users, including those in closed settings such as detention centres and prisons, should have ready access to needle-syringe programmes (NSP) to reduce transmission of HIV and acquisition of other infections. (A-II)

People living with HIV with opioid dependence should be encouraged to enter or continue long-term opioid substitution therapy, a key component of harm reduction programmes, to reduce HIV transmission (A-I), support ART adherence and improve other health, social, and economic outcomes.

Family planning

Counselling

Family-planning counselling and services, based on a broad range of contraceptive choices, should be provided to couples, individual men, women and young people living with HIV, to prevent unintended pregnancies and to prevent mother-to-child transmission of HIV. Assessing and assisting individuals and couples living with HIV with desires for children should be part of family-planning counselling and services. (A-II)

Environmental

People living with HIV who seek family planning services should be provided with condoms and strongly encouraged to use them consistently and correctly, with or without another contraceptive method. (A-II)

STI screening and management

Screening

At initial diagnosis of HIV, health-care providers should obtain a thorough history for all persons, including information about previous STIs and RTIs, contraceptive use, current STI/RTI symptoms and risk behaviour[i] and should conduct a physical examination along with limited laboratory screening for the presence of STIs and RTIs. (A-III). Laboratory screening should include a serological test for syphilis (A-III) for all persons newly diagnosed with HIV

For male and female sex workers, screening for STIs should be done at more frequent intervals (quarterly, semi-annually or annually) depending on prevalence rates of syphilis, gonorrhoea and *Chlamydia* among screened sex workers. (A-IV)

Where available, women with HIV should be screened for cervical cancer initially (A-II) and at regular (e.g., annual) intervals. (A-IV) If cervical cytology tests, such as the Papanicolau test, are not available, persons should be referred to a higher-level of health care.

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i Sexual risk behaviours include numbers and types of sexual partners, frequency of intercourse, condom use with regular and casual partners and drug- and alcohol-use during sex. No precise combination of these factors can separate "high risk" from "low risk"; judgment is required.

All people with HIV should be evaluated to identify continuing risk behaviour and symptoms of STIs in themselves and in their partners by obtaining a history at regular intervals (for example, annually). (A-III) Those at ongoing risk should receive counselling to reduce risky behaviour.

Counselling

Sex workers with HIV and other people with HIV at ongoing risk should receive intensive counselling on consistent condom use and be provided with easy access to condoms. (A-II)

People with HIV who have genital ulcers should be counselled about genital herpes, their likelihood of having genital herpes, and the increased risk of HIV transmission from individuals with genital ulcers. (A-I)

Chemoprophylaxis/treatment

People with HIV who are diagnosed with an STI and their sex partners should be managed in accordance with the most recent WHO STI treatment and RTI practice guidelines, (A-III) which include syndromic management of STIs and RTIs. (A-II) People with HIV who present with persistent or recurrent symptoms should be considered for definitive diagnoses and etiologic therapy. (A-III)

In areas with high prevalence of HSV-2 episodic acyclovir should be routinely provided as part of syndromic management of genital ulcer disease in persons with HIV to shorten the clinical course of illness, except where HSV-2 can be ruled out. (A-I)

Preventing HIV infection in infants and young children

Counselling

Counselling and services, based on a range of antiretroviral and infant feeding options, should be provided to individual pregnant women and couples, to prevent transmission of HIV to their infant.

Clinical and immunological assessment

HIV-infected pregnant women should be offered a clinical and immunological assessment.

Antiretroviral treatment

All pregnant women with indications for ART should receive ART **[A-II]**.

The preferred first-line regimen for ART for pregnant women is AZT+3TC+NVP **[A-II]**.

Pregnant women with a CD4 cell count between 250 and 350cells/mm3 who have indications for ART can either be started on an NVP-containing regimen with close monitoring in the first 12 weeks of therapy or an EFV-containing regimen if they are in the second or third trimester of pregnancy; or receive a triple NRTI or a PI-based regimen **[C-IV]**.

EFV remains an option for the NNRTI component of a first-line regimen in pregnant women in the second or third trimester of pregnancy **[C-IV]**.

The recommended regimen for infants is AZT for seven days from birth. For women who receive less than four weeks of ART before delivery, the infant AZT dose should be extended to four weeks **[A-II]**.

Women with indications for ART who present very late in pregnancy should be started on ART, irrespective of gestational age of pregnancy **[A-IV]**.

ARV prophylaxis for preventing HIV infection in infants

Recommended ARV regimens for preventing transmission HIV infection in infants among pregnant women who do not have indications for ART are consisting of AZT starting from 28 weeks of pregnancy (or as soon as possible thereafter); intrapartum AZT and 3TC plus single dose NVP intrapartum; and AZT and 3TC postpartum for seven days for women, and for infants single dose NVP and AZT for one week **[A-I]**.

Omission of the NVP dose for the mother may be considered for women who receive at least four weeks of AZT before delivery [C-I].

The infant NVP dose can be given up to 72 hours after childbirth but preferably should be given as soon as possible after delivery [A-II]

If the mother receives less than four weeks of AZT before delivery, the infant AZT dose should be extended to four weeks [A-I]

When single dose NVP is used for MTCT prophylaxis, either alone or in combination with AZT, women should be given AZT and 3TC intrapartum and for seven days postpartum to prevent NVP resistance [A-I]

When delivery occurs within two hours of a woman taking NVP, the infant should receive single dose NVP as soon as possible after delivery and AZT for four weeks [A-I]

Recommended ARV regimen for preventing MTCT among women in labour who have not received antenatal antiretroviral prophylaxis

The recommended regimen for HIV-infected women in labour who have not yet received ARV drugs is intrapartum single dose NVP plus AZT and 3TC and postpartum AZT and 3TC given to the woman for seven days; plus infant single dose NVP and AZT for four weeks. [A-I]

If imminent delivery is expected, the maternal NVP dose should be omitted, and the same recommendations and considerations apply as for infants born to HIV-infected women who did not receive antenatal or intrapartum ARV prophylaxis. [A-II]

When delivery occurs within two hours of the woman taking NVP, the infant should receive single-dose NVP as soon as possible after delivery and AZT for four weeks. [A-I]

Infants born to HIV-infected women who did not receive antiretroviral drugs during pregnancy or labour

Single dose NVP and AZT for four weeks are recommended for infants born to HIV-infected women who did not receive any ARV prophylaxis because this regimen results in a greater reduction in transmission than single-dose NVP for the infant alone. [A-III]

ARV prophylaxis for infants born to HIV-infected women who had not received antenatal or intrapartum ARV prophylaxis should begin immediately after delivery within 12 hours after delivery if possible. [A-III]

B. Consider – applicable in most situations

Family planning

Counselling

To reduce morbidity among women with HIV who do not wish to carry a pregnancy to term, health authorities should ensure the availability of safe, non-coercive procedures to terminate pregnancies, where permitted by law. (B-II)

STI screening and management

Screening

Where available and feasible, at initial diagnosis, women with HIV should be tested for gonorrhoea (B-III) and *Chlamydia.* (B-II)

People at ongoing risk, or with intercurrent STIs, should be re-evaluated for STIs by conducting a history, physical examination and laboratory evaluation annually, as recommended for people at initial diagnosis of HIV. (B-IV)

Chemoprophylaxis/treatment

Sex workers, at initial diagnosis of HIV, should be presumptively treated for gonorrhea and Chlamydia in accordance with WHO guidelines for periodic presumptive treatment for STIs. (B-III)

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* Sexual risk behaviours include numbers and types of sexual partners, frequency of intercourse, condom use with regular and casual partners and drug and alcohol use during sex.

Table 3. Medication indications, dosages and contraindications

Medication	Indication	Dosages	Monitoring**	Contraindications
Co-trimoxazole	Prevention of bacterial infections including malaria and *Pneumocystis jiroveci* pneumonia	Trimethoprim160 mg + sulfamethoxazole 800mg daily **(A-I)**		
Sulfadoxine-pyrimethamine	Intermittent preventive therapy for pregnant women with HIV in malaria-endemic areas	1500mg sulfadoxine + 75 mg pyrimethamine – at least three doses during pregnancy **(A-I)**		Do not give to pregnant women taking co-trimoxazole
Isoniazid	Tuberculin skin test >5mm or any HIV-infected patient without active TB	5mg/kg – max 300mg daily for 6 months **(A-I)**	Monitor for liver toxicity. Risk increases with liver disease, older age and pregnancy	Any symptoms suggestive of active TB disease
Fluconazole	Severely immuno-compromised people with HIV (WHO clinical stage 4 or CD4< 100) in areas where cryptococcal disease is common	400mg weekly **(A-I)** or 200mg 3 times a week **(A-I)** or 200 mg daily **(A-I)**	Monitor for adverse hepatic events, especially if taking other hepatotoxic medications	Pregnancy or active invasive fungal infection, including cryptococcosis
Itraconazole	In endemic areas of penicilliosis and histoplasmosis, itraconazole should be considered for primary prophylaxis	200mg capsule daily **(A-I)**		
Acyclovir	Genital ulcer disease with symptoms consistent with herpes simplex virus	Episodic*: 400mg TID to 800mg 5 times a day for 5 – 10 days Suppressive**: 400mg -800mg BID		

Medication	Indication	Dosages	Monitoring**	Contraindications
Famciclovir	Herpes simplex virus	Episodic*: 500mg BID to 750mg TID		
		Suppressive**: 500mg BID		
Valacyclovir	Herpes simplex virus	Episodic*: 500-1000mg BID to 1000mg TID		
		Suppressive***: 500mg BID		

* Begin with lower dose and escalate if genital lesions do not show a clinical response. Acyclovir-resistance testing, where available, is not routinely indicated, given the low frequency of acyclovir resistance, and even lower prevalence of clinically refractory genital herpes due to acyclovir resistance.

** Consider suppressive therapy for persons with a history of frequent, severe or long-lasting genital herpes. Higher efficacy with valacyclovir 500 mg BID than 1 gm QD in people living with HIV, although in some patients adherence might be greater with 1 gm QD dosing.

Table 4. Interventions for integrated HIV prevention, care, and treatment, by type and strength of recommendation

Intervention type	Strongly recommended	Strongly recommended where available and feasible	Consider	Optional
Screening	Screening for mental health problems, risk behaviours, contraceptive use Screening for active TB Family and partner testing and counselling STI screening and management Special interventions for sex workers: STI screening and treatment Serological test for syphilis Nutritional assessment	Screening to assess hepatitis B susceptibility and vaccine response (Anti-HBc[i], Anti-HBs[ii]) Screening for cervical cancer	Screening of women for gonorrhea and *Chlamydia* at initial HIV diagnosis	
Chemopro-phylaxis/ treatment	Co-trimoxazole prophylaxis Intermittent preventive treatment (IPT) for malaria for pregnant women, if not taking co-trimoxazole* TB-preventive therapy	Opioid substitution therapy* Presumptive treatment of gonorrhea and *Chlamydia* for sex workers*	Episodic acyclovir for symptomatic herpes simplex	Primary fluconazole prophylaxis* Primary itraconazole prophylaxis*
Vaccination		Hepatitis B vaccination, where serologic screening is available	Hepatitis B vaccination, where serologic screening is not available Influenza vaccination	Pneumococcal polysaccharide vaccine* Pneumococcal conjugate vaccine for children under 5, who are household members

i Antibody to hepatitis B core antigen
ii Antibody to hepatitis B surface antigen

Intervention type	Strongly recommended	Strongly recommended where available and feasible	Consider	Optional
Environmental interventions	Insecticide-treated nets* Water treatment * Soap Sterile needle-syringe programmes (provision and exchange)* Condom provision Special interventions for sex workers: condom provision	Nutrition support Insecticide treated nets* Indoor residual spraying* Pill boxes		
Counselling and education	Safer sex and risk-reduction counselling Condom promotion TB risk Psychosocial support Increased risk of HIV transmission among persons with genital ulcer disease Special interventions for sex workers: condom use, risk reduction Family planning Use of insecticide-treated nets Malaria prophylaxis for travelers Compliance with IPT for pregnant women Hygiene, disposal of feces, hand washing	Nutrition counselling and education		

*Where indicated by local epidemiology

Appendix A: Systematic review of evidence

A.1 Interventions to prevent disease: evidence searching

Search strategy

The authors of these guidelines searched the databases of MEDLINE, EMBASE and the Cochrane Library to gather evidence for the essential prevention and care interventions related to safe water systems, insecticide-treated nets (ITNs), intermittent preventive treatment in pregnancy (IPTp), vaccines, acyclovir, sexually transmitted infections, azole prophylaxis, and isoniazid preventive therapy. They conducted their searches from July 2005 to May 2006 and retrieved only articles published from 1980 on. All reference lists for major trials, topic reviews, and other guidelines found were reviewed for relevant trials. Experts in each field were contacted for any additional trials and data. All topics were initially searched for randomized controlled trials (RCTs) using the Cochrane RCT search strategy with the appropriate search terms. If no RCTs were identified, the search was broadened to include any evidence from other sources. As well, the authors searched specifically for evidence from studies done in settings with limited resources. Evidence from articles about studies conducted in high income countries was included when data from resource-limited settings were not available.

Search terms

For each intervention, the search terms are included below.

Intervention topic	Search terms* (all include "and HIV or AIDS" or equivalent)
Isoniazid	Isoniazid, tuberculosis, prophylaxis, chemoprevention, treatment
Fluconazole	Fluconazole, antifungal agents, meningitis, cryptococcal, Cryptococcus, cryptococcosis, Candidiasis, candida
Itraconazole	Itraconazole, antifungal agents, meningitis, cryptococcal, Cryptococcus, cryptococcosis, Candidiasis, candida
Insecticide-treated mosquito nets	bedding and linens, malaria, insecticides, anopheles, mosquito control, antimalarials, pyramethamine, sulfadoxine, bednets, curtains, malaria prevention, long-lasting insecticide treated bed nets, mosquito net
Water, sanitation and hygiene	cholera, diarrhea, health status, water microbiology, water pollution, water supply, hygiene, water vessel, chlorination, chlorine, hand washing, safe water system, water purification, storage, drinking water, point of use, sanitation, sodium hypochlorite, flocculant
Syndromic treatment of STIs and screening	Syndromic treatment, syndromic management, sexually transmitted diseases treatment, sexually transmitted infections treatment, screening

Intervention topic	Search terms* (all include “and HIV or AIDS” or equivalent)
Acyclovir	Acyclovir, antiviral agents, prophylaxis, chemoprevention, treatment, therapy, herpes simplex virus 1, herpes simplex virus 2, genital herpes, hiv shedding, disease transmission, herpes genitalis, herpesvirus 2, herpesvirus 1
Pneumococcal vaccine	Pneumococcal vaccination, pneumococcal polysaccharide vaccine, pneumococcal conjugate vaccine, streptococcus pneumoniae, pneumococcal disease, pneumococci, pneumonia
Influenza vaccine	Influenza vaccination, influenza immunization, influenza vaccine, inactivated influenza vaccine, live attenuated influenza vaccine, influenza virus
Hepatitis B vaccine	Hepatitis B vaccination, hepatitis B immunization, hepatitis B vaccine, HBV, HIV-HBV, HIV coinfection
Yellow fever vaccine	Yellow fever vaccination, yellow fever immunization, yellow fever vaccine, yellow fever virus

A.2 Interventions to prevent HIV transmission: evidence searching

Search strategy

Essential prevention interventions included partner notification, family planning for women with HIV, needle-syringe programmes, psychosocial support, abstinence and abstinence-only and treatment. For testing and counselling interventions, the review was broken into free-standing and provider-initiated testing and counselling. To obtain evidence on disclosure and partner notification, elements of other systematic reviews were used. The systematic review found no evidence, however, on interventions for partner notification in resource-limited settings. Randomized controlled trials and other studies were included if they met the following criteria**:** 1) study was conducted in a developing country or emerging economy as defined by the World Bank (no US data included); 2) study evaluated the specific intervention being examined; 3) results presented were from pre- and post-assessments, or comparing persons who received the intervention to those who did not; 4) study measured HIV-related intermediate outcomes, or health outcomes such as knowledge, perceptions, attitudes, beliefs, and HIV-risk behaviours; and 5) study was published between January 1990 and December 31, 2004 (reviews of VCT ended April 15, 2005 and treatment ended January 31, 2006).

The databases searched were the U.S. National Library of Medicine's (NLM) Gateway (including PubMed, MEDLINE and AIDSLINE), EMBASE, PsycINFO, Sociological Abstracts, and the Cumulative Index to Nursing and Allied Health Literature (CINAHL). Hand-searches were conducted of four HIV-related journals: *AIDS Care, AIDS, AIDS and Behavior*, and *AIDS Education and Prevention*. Additional hand-searching was done of *International Journal of Drug Policy* for the needle-exchange review and the *Journal of AIDS* for the VCT review. References of papers included were also searched. Unpublished data and conference abstracts were excluded.

Search terms

For each intervention, the search terms are included below.

Intervention Topic	Search terms
Partner notification	partner notification, contact tracing, HIV and self-disclosure, interpersonal communication and HIV, HIV partner notification, HIV and partner referral, HIV and partner disclosure
Family planning for women with HIV	family planning and HIV, fertility and HIV, family planning and counselling and HIV, family planning and developing country
Needle-syringe programmes	needle exchange and HIV, NEP and HIV, needle distribution and HIV, NESP and HIV, needle sales, syringe sales, syringe distribution and HIV, syringe exchange, SEP and HIV, shooting galleries and HIV, injecting drug users and HIV

Intervention Topic	Search terms
Psychosocial support	support groups and HIV, support groups and AIDS, palliative care and AIDS, palliative care and HIV, ongoing counselling and HIV, ongoing counselling and AIDS, psychotherapy and AIDS, psychotherapy and HIV, HIV counselling and developing country, AIDS counselling and developing country
Abstinence and abstinence-only	abstinence and HIV, abstinence only and HIV, no sex partners and HIV, no sex partners and intervention and HIV, until marriage and HIV, abstinence only until marriage and HIV, chastity and HIV, virginity and HIV, wait until marriage and HIV, abstinence plus and HIV, born again virgin and HIV, no sex partners and education and HIV, abstinence based interventions and HIV, virginity pledge and HIV, celibacy and HIV, sex can wait and HIV, true love waits and HIV, true sexual freedom and HIV, not me not now and HIV, ABC and HIV, abstain from sex and HIV
Treatment	ARV treatment and risk behavior, opportunistic infection treatment and risk behavior, ARV, medical treatment and risk behavior, HAART, risk behaviors, and HIV, medical care, risk behaviors and HIV, medical treatment, HIV, and risk behavior, treatment, HIV, and risk behavior, ARV, HIV, and risk behavior, opportunistic infection, risk behavior, and HIV, HAART and risk behaviors, medical care, HIV, and risk behavior, medical intervention, HIV, and risk behavior, clinical care, HIV, and risk behavior

A.3 Coding and rigour

Coding

Two coders extracted data from each eligible citation independently using a highly detailed coding form. Data were extracted in 15 content areas: (1) citation information; (2) study inclusion criteria; (3) study methods; (4) study population characteristics; (5) setting; (6) sampling; (7) study design; (8) unit of analysis; (9) loss to follow-up rates; (10) study group (arms or comparison groups) characteristics; (11) intervention characteristics; (12) intervention topic specific questions; (13) outcome measures; (14) eligible outcome results; and (15) additional information (costs; limitations, potential harms, community-acceptance, and other relevant information).

All outcome variables reported in a study were noted, but detailed results were only recorded for those outcomes with either a pre/post or between study group arm comparisons. Such eligible outcome results were coded in a structured format. This included: (1) the type of statistical analysis used; (2) the effect size and base rate; (3) the independent variable; (4) catchments and/or follow-up times; (5) the confidence interval and/or p-value; (6) the page number and table where the results are located; and (7) any additional brief information thought to be important. All eligible outcome results were coded, including sub-group presentation of results (such as by gender) even when aggregated results were also presented. Once each of the two coders independently coded the citation, the data were transferred to a statistical database (using SPSS Data Entry software, SPSS™, Chicago, IL).

Inter-coder discrepancies were then resolved to correct for data entry errors, and to identify different interpretations in the presentation of results. A resolution report, containing a comparison of each coder's textual data fields and highlighting any differences between coders, was generated from the SPSS™ quantitative database. Senior staff resolved any discrepancies in consultation with the study's principal investigator and other senior collaborators. When needed, attempts were made to contact authors to resolve differences. After resolving the discrepancies, the principal investigator reviewed the final records of each coding form. Detailed records were kept on the reason for discrepancies across coders, and how they were resolved.

Assessing the rigour of studies

The authors analysed the rigour of each study using an eight-point scale developed for the project. This scale descriptively measures adherence to standards for unbiased research, allowing for a standard comparison of rigour across analyses. One point is given for each item. The default value for each criterion is nil, and analyses are only scored on each criterion when data are available to assess the criterion. The rigour scale contains the following items and definitions:

- **Prospective cohort analyses** presented data for a cohort of study participants followed over time, including pre-intervention to post-intervention analyses with or without a control or comparison group. Serial cross-sectional analyses, or post-only comparisons, were not scored on this criterion. Control or comparison groups were defined as analyses that compare those who received the intervention under study to those who did not, or who received a more-versus-less intensive intervention. These include analyses that compare intervention, control and/or comparison groups, and stratified cross-sectional analyses. This item does not include before-after analyses without stratification.

- **Pre/post intervention outcome data**: These were assessed as it is common for studies to only assess outcome measures in the post-intervention catchments, especially for post-hoc analyses and secondary study aims.
- **Random assignment to treatment groups**: This is defined as when study participants are randomly assigned to treatment groups in multi-arm studies, and includes group-randomized designs. This criterion is nested within a criterion for a control or comparison group to give added weight to designs that include randomization and controls.
- **Random selection of study participants**: The authors of the guidelines assessed whether the quality of data was undermined by selection bias in study enrollment.
- **Attrition**: This was assessed to determine if the follow-up rate was 80% or more at each analysis point.
- **Comparison-group matching** was assessed in multi-arm studies to determine if there were statistically significant differences in socio-demographic measures (such as age) across arms.
- **Comparison-group matching on outcome measures** was also assessed to establish whether studies had statistically significant baseline differences in study outcome measures.

Appendix B: List of participants at WHO expert consultation

The following experts attended the WHO consultative meetings on essential care and prevention interventions for people living with HIV: reviewing the evidence and developing guidelines, June 28-30, 2006, in Montreux, Switzerland (topic groups and roles are given in parentheses):

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Appendix C: WHO clinical staging of HIV/AIDS for adults and adolescents with confirmed HIV infection

Primary HIV infection
Asymptomatic Acute retroviral syndrome
Clinical stage 1
Asymptomatic Persistent generalized lymphadenopathy
Clinical stage 2
Unexplained moderate weight loss (<10% of presumed or measured body weight) Recurrent respiratory tract infections (sinusitis, tonsillitis, bronchitis, otitis media, pharyngitis) Herpes zoster Angular cheilitis Recurrent oral ulceration Papular pruritic eruptions Seborrhoeic dermatitis Fungal nail infections
Clinical stage 3
Unexplained severe weight loss (>10% of presumed or measured body weight) Unexplained chronic diarrhoea for longer than one month Unexplained persistent fever (above 37.5°C intermittent or constant, for longer than one month) Persistent oral candidiasis Oral hairy leukoplakia Pulmonary tuberculosis Severe presumed bacterial infections (e.g., pneumonia, empyema, pyomyositis, bone or joint infection, meningitis, bacteraemia) Acute necrotizing ulcerative stomatitis, gingivitis or periodontitis Unexplained anaemia (<8 g/dl), neutropenia (<0.5 x 10^9 per litre) and/or chronic thrombocytopenia (<50 x 10^9 per litre)

Clinical stage 4
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 tuberculosis
Kaposi's sarcoma
Cytomegalovirus infection (retinitis or infection of other organs)
Central nervous system toxoplasmosis
HIV encephalopathy
Extrapulmonary cryptococcosis, including meningitis
Disseminated non-tuberculous mycobacteria 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

Source: *WHO case definitions of HIV for surveillance and revised clinical staging and immunological classification of HIV-related disease in adults and children.* Geneva, WHO, 2006.

Appendix D: Presumptive and definitive criteria for recognizing HIV/AIDS-related clinical events in adults (15 or older) 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	Painless enlarged lymph nodes >1 cm in two or more non-contiguous sites (excluding inguinal nodes) in the absence of known cause, and persisting for three months or more	Histology
Clinical Stage 2		
Moderate unexplained weight loss (<10% of body weight)	Reported unexplained involuntary weight loss; in pregnancy failure to gain weight	Documented weight loss <10% of body weight
Recurrent 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 tonsillopharyngitis 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, usually respond to antifungal treatment	Clinical 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

Clinical event	Clinical diagnosis	Definitive diagnosis
Papular pruritic eruption	Papular pruritic lesions, often with marked post-inflammatory pigmentation	Clinical diagnosis
Seborrhoeic dermatitis	Itchy scaly skin condition, particularly affecting hairy area (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 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		
Unexplained severe weight loss (more than 10% of body weight)	Reported unexplained involuntary 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
Unexplained persistent fever (intermittent or constant and 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 fever >37.5ºC with negative blood culture, negative Ziehl-Nielsen stain, negative malaria slide, normal or unchanged chest X-ray and no other obvious focus of infection

Clinical event	Clinical diagnosis	Definitive diagnosis
Oral candidiasis	Persistent or recurring creamy white curd-like plaques that can be scraped off (pseudomembranous), or red patches on tongue, palate or lining of mouth, usually painful or tender (erythematous form)	Clinical diagnosis
Oral hairy leukoplakia	Fine white small linear patches or corrugated lesions on lateral borders of the tongue that do not scrape off	Clinical diagnosis
Pulmonary tuberculosis (current)	Chronic symptoms: (lasting more than two-to-three weeks) cough, haemoptysis, shortness of breath, chest pain, weight loss, fever, night sweats, and no clinical evidence of extrapulmonary disease Discrete peripheral lymph node *M. 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 tuberculosis and/or culture positive for *Mycobacterium*
Severe bacterial infection (e.g., pneumonia, meningitis, empyema, pyomyositis, bone or joint infection, bacteraemia and 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), neutropenia (<0.5 x 10^9 per litre) or chronic (more than one month) thrombocytopenia (<50 x 10^9 per litre)	No 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 other anthelmintic agents as outlined in relevant national treatment guidelines, WHO Integrated Management of Adult Illness guidelines or other relevant guidelines
Clinical Stage 4		
HIV wasting syndrome	Unexplained involuntary weight loss (>10% baseline 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 > 37.5ºC 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 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 severe presumed bacterial pneumonia	Current episode plus one or more previous episodes in the past six months; acute onset (two weeks) of severe 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 recurrence of herpes simplex virus infection and reported for more than one month. History of previous episodes. Visceral herpes simplex visura 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 (foods and fluids) together with oral *Candida*	Macroscopic appearance at endoscopy or bronchoscopy, or by microscopy or histology

Clinical event	Clinical diagnosis	Definitive diagnosis
Extrapulmonary tuberculosis	Systemic illness (such as fever, night sweats, weakness and weight loss). Other evidence for extrapulmonary or disseminated tuberculosis varies by site, such as pleura, pericardia, meninges, mediastinum or abdominal Discrete peripheral lymph node *Mycobacterium tuberculosis* infection (especially cervical) is considered a less severe form of extrapulmonary tuberculosis	*M. tuberculosis* isolation or compatible histology from appropriate site or radiological evidence of military TB (diffuse uniformly distributed small military shadows or microdules on chest X-ray)
Kaposi sarcoma	Typical gross appearance in skin or oropharynx of persistent, initially flat, patches with a pink or violaceous colour, skin lesions that usually develop into 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)
Central nervous system toxoplasmosis	Recent onset of a focal nervous system abnormality consistent with intracranial disease 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)

Clinical event	Clinical diagnosis	Definitive diagnosis
HIV encephalopathy	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 respond 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 lungs
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 polymerase chain reaction on cerebrospinal fluid
Chronic 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 (such as coccidiomycosis, histoplasmosis, or penicilliosis)	No presumptive clinical diagnosis	Histology, antigen detection or culture from clinical specimen or blood culture

Clinical event	Clinical diagnosis	Definitive diagnosis
Recurrent non-typhoid *Salmonella* bacteraemia	No presumptive clinical diagnosis.	Blood culture
Lymphoma (cerebral or B-cell non-Hodgkin)	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
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: *WHO case definitions of HIV for surveillance and revised clinical staging and immunological classification of HIV-related disease in adults and children.* Geneva, WHO, 2006.

Appendix E: WHO guidelines and links

Antiretroviral Therapy

- *Antiretroviral therapy for HIV infection in adults and adolescents: towards universal access: recommendations for a public health approach*. Geneva, WHO, 2006. http://www.who.int/hiv/pub/guidelines/adult/en/index.html
- *Antiretroviral therapy of HIV infection in infants and children: towards universal access: recommendations for a public health approach*. Geneva, WHO, 2006. http://www.who.int/hiv/pub/guidelines/art/en/index.html
- *Antiretroviral drugs for treating pregnant women and preventing HIV infection in infants: towards universal access: recommendations for a public health approach*. Geneva, WHO, 2006. http://www.who.int/hiv/pub/guidelines/pmtct/en/index.html

Co-trimoxazole

- *Guidelines on co-trimoxazole prophylaxis for HIV-related infections among children, adolescents and adults: recommendations for a public health approach.* Geneva, WHO, 2006. http://www.who.int/hiv/pub/guidelines/ctx/en/index.html

Clinical staging

- *WHO case definitions of HIV for surveillance and revised clinical staging and immunological classification of HIV-related disease in adults and children.* Geneva, WHO, 2006. http://www.who.int/hiv/pub/guidelines/hivstaging/en/index.html

Nutrition

- *Nutrient requirements for people living with HIV/AIDS: report of a technical consultation, 13-15 May 2003.* Geneva, WHO, 2003. http://www.who.int/nutrition/publications/Content_nutrient_requirements.pdf
- Nutrition counselling, care and support for HIV-infected women: guidelines on HIV-related care, treatment and support for HIV-infected women and their children in resource-constrained settings. Geneva, WHO, 2004. http://www.who.int/hiv/pub/prev_care/en/nutri_eng.pdf
- WHO technical papers prepared for the April 2005 WHO Consultation on HIV/AIDS and Nutrition in Durban, South Africa, as well as the *Participants' Statement* from the consultation, and the December 2005 *Report on HIV/AIDS and Nutrition* to the WHO Executive Board.

  Participants' Statement [pdf 137kb]
  Macronutrients and HIV/AIDS [pdf 579kb]
  Micronutrients and HIV infection [pdf 707kb]
  HIV and nutrition: pregnant and lactating women [pdf 594kb]
  Growth failure in HIV-infected women [pdf 505kb]
  Infant feeding and HIV transmission [pdf 311kb]
  Nutritional considerations in the use of ART in resource-limited settings [pdf 742kb]

Sexually transmitted infections

- *Guidelines for the management of sexually transmitted infections.* Geneva, WHO, 2003. http://www.who.int/reproductive-health/publications/rhr_01_10_mngt_stis/guidelines_mngt_stis.pdf
- *Sexually transmitted and other reproductive tract infections*. Geneva, WHO, 2005. http://www.who.int/reproductive-health/publications/rtis_gep/rtis_gep.pdf

Tuberculosis

- *Treatment of Tuberculosis: Guidelines for National Programmes*. 3rd ed. Geneva, WHO, 2003. http://whqlibdoc.who.int/hq/2003/WHO_CDS_TB_2003.313_eng.pdf
- *Guidelines for the prevention of tuberculosis in health care facilities in resource-limited settings*. Geneva, WHO, 1999. http://www.who.int/tb/publications/who_tb_99_269.pdf
- Tuberculosis infection control in the era of expanding HIV care and treatment: Addendum to "WHO guidelines for the prevention of tuberculosis in health care facilities in resource-limited settings, 1999". Geneva, WHO, 2006. http://www.who.int/tb/publications/who_tb_99_269/en/index.html
- *TB/HIV: A clinical manual*. 2nd ed. Geneva, WHO, 2004. http://whqlibdoc.who.int/publications/2004/9241546344.pdf
- *International Standards for Tuberculosis Care*. The Hague, Tuberculosis Coalition for Technical Assistance/WHO, 2006. http://www.who.int/tb/publications/2006/istc_report.pdf

Malaria

- Malaria and HIV interactions and their implications for public health policy. Report of a technical consultation: Geneva, Switzerland, 23-25 June 2004. Geneva, WHO, 2005. http://www.who.int/hiv/pub/prev_care/malariahiv.pdf
- Roll Back Malaria Partnership Working Group for Scaling up Insecticide-treated Nets. *Statement Regarding Use of ITNs in Pregnancy, April 2004.* http://www.rbm.who.int/partnership/wg/wg_itn/docs/RBMWINStatementMPWG.pdf
- *Guidelines for the treatment of malaria.* Geneva, WHO, 2006. http://www.who.int/malaria/docs/TreatmentGuidelines2006.pdf
- *Recommendations on the use of sulfadoxine-pyrimethamine (SP) for intermittent preventive treatment during pregnancy (IPT) in areas of moderate to high resistance to SP in the African Region.* Brazzaville, WHO Regional Office for Africa, 2005. http://www.afro.who.int/malaria/publications/malaria_in_pregnancy_sulfadoxine.pdf

Family planning

- *Sexual and reproductive health of women living with HIV/AIDS. Guidelines on care, treatment and support for women living with HIV/AIDS and their children in resource-constrained settings*. Geneva, WHO/UNFPA, 2006. http://www.who.int/reproductive-health/docs/srhwomen_hivaids/index.html

Interventions for injecting drug users

- *Evidence for Action: Effectiveness of drug dependence treatment in preventing HIV among injecting drug users.* Geneva, WHO, 2004. http://www.emro.who.int/aiecf/web203.pdf
- *Evidence for Action: Effectiveness of sterile needle and syringe programming in reducing HIV/AIDS among injecting drug users.* Geneva, WHO, 2004.
- *Evidence for Action : Effectiveness of community-based outreach in preventing HIV/AIDS among injecting drug users.* Geneva, WHO, 2004. http://www.who.int/hiv/pub/prev_care/evidenceforactionreprint2004.pdf
- *Evidence for action: comprehensive review of effectiveness of interventions addressing HIV in Prisons*. Geneva, WHO/UNODC/UNAIDS, 2007.
- *Position paper. Substitution maintenance therapy in the management of opioid dependence and HIV/AIDS prevention.* Geneva, WHO/UNODC/UNAIDS , 2004.
- *Clinical Protocol on HIV/AIDS Treatment and Care for Injecting Drug Users.* Copenhagen, WHO Europe, 2006.

Safe water

- Howard G et al. *Healthy villages: a guide for communities and community health workers*. Geneva, WHO, 2002. http://www.who.int/water_sanitation_health/hygiene/settings/healthvillages/en
- Sobsey M ed. *Managing water in the home: accelerated health gains from improved water supply.* Geneva, WHO, 2002. http://www.who.int/water_sanitation_health/dwq/wsh0207/en/index2.html
- *Guidelines for drinking water quality* [electronic resource]*: incorporating 1st addendum. Vol 1, Recommendations* - 3rd ed. Geneva, WHO, 2006. http://www.who.int/water_sanitation_health/dwq/gdwq0506.pdf
- *Guidelines for drinking-water quality, 3rd ed. Vol 1 – Recommendations.* Geneva, WHO, 2004. http://www.who.int/water_sanitation_health/dwq/gdwq3/en/index.html
- Other WHO Guidelines for drinking, waste-, bathing water, etc.: http://www.who.int/water_sanitation_health/dwq/guidelines/en/
- *Howard G, Bartram J. Domestic Water Quantity, Service Level and Health.* Geneva, WHO, 2003. http://www.who.int/water_sanitation_health/diseases/wsh0302/en/index.html

Testing and counselling

- *Guidance on provider-initiated HIV testing and counselling in health facilities,* WHO, 2007. http://whqlibdoc.who.int/publications/2007/9789241595568_eng.pdf

Vaccines

- WHO Vaccine Position Papers*: http://www.who.int/immunization/documents/positionpapers/en/index.html*
- Yellow fever vaccine: WHO position paper. *Weekly Epidemiological Record,* 2003, 78(40):349-59. http://www.who.int/wer/2003/en/wer7840.pdf
- Hepatitis B vaccine: WHO position paper. *Weekly Epidemiological Record*, 2004, 79(28):253-264. http://www.who.int/immunization/wer7928HepB_July04_position_paper.pdf
- Pneumococcal vaccine: WHO position paper. *Weekly Epidemiological Record*, 2003. 78(14)97-120. http://www.who.int/immunization/documents/positionpapers/en/index.html
- Influenza vaccines: WHO position paper. *Weekly Epidemiological Record*, 2005. 80(33):277-288. http://www.who.int/immunization/wer8033influenza_August2005_position_paper.pdf

Other WHO references

- WHO Integrated Management of Adolescent and Adult Illness http://www.who.int/hiv/pub/imai/en/
- WHO List of Essential Medicines http://www.who.int/topics/essential_medicines/en/
- *Towards Universal Access by 2010: How WHO is working with countries to scale-up HIV prevention, treatment, care and support*. Geneva, WHO, 2006. http://www.who.int/hiv/toronto2006/towardsuniversalaccess.pdf

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Photograph: Gideon Mendel/The International HIV/AIDS Alliance/Corbis

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ISBN 978 92 4 159670 1