Guidance for United States Government In-Country Staff and Implementing Partners for a Preventive Care Package for Adults* - #1

The President's Emergency Plan for AIDS Relief
Office of the U.S. Global AIDS Coordinator

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*Please refer to companion Emergency Plan guidance for children aged 0-14 years of age

I. Introduction

A key objective of the Emergency Plan is to reduce HIV-related morbidity and mortality rates and slow the progression of HIV disease in affected communities. A specific Emergency Plan goal is to support the provision of care for 10 million people infected and affected by HIV/AIDS. To address these priorities, it is necessary to identify and implement interventions targeted at the primary causes of HIV-related illness and death.

The use of antiretroviral treatment (ART) is one approach to slowing the progression of disease. However, is also important to provide adults and children with interventions that prevent the onset of conditions such as *Pneumocystis carinii* pneumonia (PCP), tuberculosis (TB), malaria, malnutrition, and others, regardless of stage of HIV disease or eligibility for antiretroviral treatment. Each of these conditions can be complicated, severe, and even fatal to persons with HIV disease. Provision of preventive care interventions may also augment counseling and testing and HIV prevention programs by attracting more clients who will perhaps be more receptive to behavioral change messages. Counseling HIV-infected persons to refrain from high-risk behaviors offers an opportunity to prevent exposure to additional sexually-transmitted infections and to reduce transmission of HIV to others. Similarly, counseling and testing of family members and other contacts of HIV-infected persons offer an opportunity to identify additional HIV-infected persons and to refer them to appropriate care and prevention.

Emergency Plan countries should consider implementation of a standard "preventive care package" as part of their palliative care programs. Funding for the Preventive Care Package should be requested in Country Operational Plans, in appropriate program areas such as: Laboratory; Orphans and Vulnerable Children (OVCs); Palliative Care; TB/HIV; Treatment; and Strategic Information. United States Government (USG) teams in countries that are also part of the President's Malaria Initiative (PMI) and/or are recipients of grants for the Global Fund to Fight AIDS, Tuberculosis and Malaria (GFATM), should work closely to integrate Emergency Plan work with activities funded by these two programs.

There is ongoing discussion regarding which interventions should be included in a preventive care package. Recognizing that a package cannot be standardized for all situations and countries, components of a care package are likely to vary within regions, and even within countries, depending on the setting and the capacity of the partners who are implementing such programs. However, it is valuable to offer a "menu" of interventions that should be considered. Emergency Plan programs should link the preventive components within this document to other key health care, such as routine medical care and voluntary family planning, which play a key role in reducing morbidity and mortality. Those interventions for people living with HIV/AIDS (PLWHA) and their families that cannot be funded directly should be considered for "wrap-around" funding from other sources including the PMI, the GFATM, and family planning programs. "Wrap-around" services may benefit non-HIV-infected, as well as HIV-infected, persons in the household or elsewhere in the community. An example of such an activity is the construction of latrines, which have been shown to prevent diarrheal disease in resource-

constrained settings. This intervention is mentioned under "Safe water and personal hygiene," but is not included in the recommendations, since latrine construction is not currently supported by PEPFAR. Prioritization and selection of the components of a preventive care package must be performed locally, and should be consistent with national guidelines and those sponsored by the World Health Organization (WHO) operative within the country.

The following sections provide the scientific basis for the interventions that could be included in a "preventive care package." Although most interventions included here are pertinent to both adults and children, HIV-infected/exposed children require additional consideration. Therefore, a separate document focusing on a preventive care package for such children has been developed. It should also be emphasized that the preventive care package described here constitutes only a fraction of palliative care to be considered by USG programs. Treatment of symptomatic conditions, alleviation of pain, and psychological, spiritual and social support are important components of palliative care but are beyond the scope of this document (see "HIV/AIDS Palliative Care Guidance #1: An Overview of Comprehensive HIV/AIDS Care Services in the President's Emergency Plan for AIDS Relief (section 1.5)).

II. Activities Supported by the Emergency Plan

1. Cotrimoxazole prophylaxis

In industrialized countries, the combination antibiotic trimethoprim-sulfamethoxazole (or cotrimoxazole) has been recommended to prevent *Pneumocystis jiroveci* (formerly *P. carinii*) pneumonia (PCP) in HIV-infected adults with CD4 counts of less than 200 cells/µl since 1989[1] and in children born to HIV-infected mothers since 1991.[2] Cotrimoxazole prophylaxis is standard practice in areas of the world where PCP is common in HIV-infected persons. PCP appears to be less common in sub-Saharan Africa than in other regions,[3] but cotrimoxazole is also effective in African countries in preventing diarrhea and malaria and in prolonging life.

Several studies have addressed the efficacy of cotrimoxazole in HIV-infected persons in sub-Saharan Africa. A randomized placebo-controlled trial of cotrimoxazole prophylaxis for HIV-infected adults (WHO clinical stage 2 or 3) in Cote d'Ivoire demonstrated a reduction of the rate of severe events (death or hospitalization) by 43 percent in the intervention group, but did not show a decline in mortality.[4] Another randomized trial in Cote d'Ivoire of cotrimoxazole prophylaxis for HIV-infected adults with active pulmonary TB showed a 46 percent reduction in mortality and a 43 percent reduction in hospitalization.[5] A study in South Africa found that cotrimoxazole reduced mortality by 44 percent and severe HIV-related illnesses by 48 percent in patients with WHO stage 3 or 4 disease or with CD4 counts less than 200 cells/µl.[6] These findings were further supported by a meta-analysis of randomized trials in adult African HIV-infected patients, which showed that cotrimoxazole reduced death by 31 percent, morbidity by 24 percent and hospitalization by 34 percent.[7] In a recent study in Uganda, cotrimoxazole, when taken daily by persons with HIV, reduced death by 46 percent, malaria by 72 percent, diarrhea by 35 percent, and hospitalizations by 31 percent. It also slowed the rate of CD4 decline and the rate of viral load increase.[8] PCP appears to be more common in HIV-

infected African children than in adults, and one study that evaluated the efficacy of cotrimoxazole prophylaxis in South African children documented an 89 percent reduction in PCP incidence.[9]

Several criteria for cotrimoxazole prophylaxis eligibility in African patients have been proposed: Wiktor et al. found the benefit of cotrimoxazole was most significant in patients with CD4 counts less than 350 cells/µl,[5] and Badri et al. suggested prophylaxis for patients at WHO clinical stage 3 or 4.[6] However, Anglaret et al. found benefit at all CD4 levels,[4] as did Mermin et al..[8] A cost-effectiveness study by Yazdanpanah also recommended prophylaxis for adults with WHO stage 2, 3 or 4;[10] another by Pitter et al. reports cost-savings when cotrimoxazole is given to all HIV-infected adults in Uganda (Dr. Christian Pitter, personal communication). National recommendations in Uganda suggest cotrimoxazole for all HIV-infected persons.

Cotrimoxazole is relatively safe and available, does not require laboratory monitoring, and in the Ugandan study, its effect did not decrease over the 1.5-2 year follow-up period.[8] The most common toxicity - skin rash - appears to be uncommon in African patients, and its severe manifestation - Stevens-Johnson syndrome - is rare.[4,5] Cotrimoxazole is widely available in sub-Saharan Africa and when purchased in bulk costs only $6 per person per year. Concerns remain about the generation of widespread antimicrobial resistance to cotrimoxazole, including resistance of Plasmodium species to the closely related antimalarial Fansidar. However, current data actually support a benefit to household contacts of persons receiving cotrimoxazole. Therefore, these concerns remain largely theoretical.

WHO/UNAIDS provisionally recommends cotrimoxazole for all HIV-infected adults with WHO clinical stage 2, 3 or 4 disease or with CD4 counts less than 500 cells/µl.[11] For children, WHO/UNAIDS currently recommends cotrimoxazole for all HIV-exposed/infected infants and older children with HIV-related symptoms or with severe immunosuppression (see companion guidance - *Emergency Plan guidance for children aged 0-14 years of age*). Updated WHO recommendations on cotrimoxazole prophylaxis were discussed at an international consultation in Geneva in May 2005 and are expected to be released soon. When available, this document will be posted on the OGAC website.

<u>Emergency Plan funds may support</u>:

1. Technical assistance to develop national policy, guidelines and training for the utilization of cotrimoxazole in adults and children.
2. Cotrimoxazole prophylaxis for HIV-infected adults and children who are eligible based on national guidelines.

2. Effective tuberculosis (TB) interventions for HIV-infected persons

TB is a leading cause of severe morbidity and mortality among persons with HIV/AIDS, especially in sub-Saharan Africa where 32 percent of TB patients are HIV-infected;[12] and in some areas, the prevalence of HIV infection among TB patients can be as high as 70 percent.[13] In sub-Saharan Africa, approximately 39 percent of TB deaths are attributable to HIV.[14]

HIV-induced immunosupression promotes the development of active TB in persons co-infected with HIV and *Mycobacterium tuberculosis*,[15] and active TB accelerates the progression of HIV disease.[16] Therefore, in high HIV prevalence populations, the identification and treatment of active TB are high priorities not only for care of HIV-infected persons but also for control of TB.[17] Furthermore, operational research in Africa[18] and elsewhere[19] has shown that up to 11 percent of HIV-infected persons identified in HIV counseling and testing have undiagnosed TB. Thus, HIV care programs are very likely to include patients with undiagnosed, active TB.

After active TB has been excluded, daily isoniazid (INH) prophylaxis for 6-9 months has been associated with a reduction in the incidence of TB among HIV-infected persons. This effect is most pronounced in persons with a positive tuberculin skin test (TST), in whom a 60 percent reduction in incidence of TB has been observed.[20] However, this meta-analysis of seven randomized controlled trials showed that INH preventive therapy (IPT) for 6-12 months given to HIV-infected persons was associated with a 42 percent reduction in TB incidence regardless of TST result. The effect of IPT on mortality is not as clear.

<u>Emergency Plan funds may support</u>:

1. Technical assistance to develop national policy, guidelines and training for the implementation of TB/HIV related prevention and treatment.

2. Screening of HIV-infected persons for active TB according to national guidelines (at a minimum using a simple set of questions to identify suspected TB cases [e.g., prolonged cough, weight loss, night sweats]).

3. With a goal of performing an HIV test in all persons who access TB clinics, a referral system that links HIV counseling, testing, and care with TB diagnostic and treatment centers, consistent with national guidelines for referral, treatment, and reporting of TB.

4. Tuberculin skin testing to identify HIV-infected persons at highest risk.

5. INH preventive therapy for persons living with HIV/AIDS once active TB has been excluded.

6. INH for HIV-exposed and HIV-infected children who have been exposed to a case of smear-positive TB in their households, once active TB has been excluded.

3. Safe drinking water and personal hygiene

People living in resource-poor settings often have limited access to safe water and basic methods of hygiene and sanitation (*e.g.* hand washing with soap). Most research on the impact of safe water, sanitation, and hygiene interventions on diarrheal disease has focused on children under 5 years of age because most diarrhea-associated mortality has been associated with this group. Use of a safe water supply was shown to reduce diarrhea by 20 percent in children in a study in Malawi.[21] In a review of 144 studies, water treatment and safe storage at the point-of-use (typically the household) were effective in reducing diarrheal prevalence by 26 percent;[22] in another review, Gundry et al. estimated a 65 percent reduction in diarrhea from such household-level interventions.[23] A study of HIV-infected persons and their families in Uganda showed that use of a simple, home-based safe water system reduced the incidence of diarrheal episodes by 25 percent, the number of days with diarrhea by 33 percent, and the frequency of visible blood or pus in stool.[24] The cost of the intervention was less than $5 per family per year. Provision of safe water at the household level in resource-constrained settings is consistent with WHO policies.

A recent review by Curtis showed that hand washing with soap was associated with a 43 percent reduction in diarrheal disease.[25] The benefit of hand washing was further supported by a reduction in diarrhea by 62 percent in people in rural Bangladesh,[26] and by 53 percent in a randomized controlled trial of children in Pakistan.[27] Reviews by Esrey *et al.* and Huttly *et al*. of the effect of hygiene promotion interventions on diarrhea morbidity found a median reduction of roughly one-third.[22,28] However, the HIV status of the subjects of all of these studies was unknown.

Protecting the water supply by use of latrines has also been associated with a reduction in incidence of diarrheal disease. Latrine construction is currently beyond the scope of PEPFAR funding but should be considered for "wrap-around" support by other funding sources.

Diarrhea incidence, duration, severity, and mortality are all higher in children with HIV/AIDS than in HIV-uninfected children, and chronic diarrhea is also a major cause of morbidity and mortality in HIV-infected adults. Therefore, interventions that reduce diarrheal episodes should be considered for use in all HIV-infected persons.

<u>Emergency Plan funds may support</u>:

1. Home-based, safe drinking water interventions, (*e.g.,* dilute sodium hypochlorite (bleach) water treatment, water vessels, etc.) for HIV-infected persons in communities where there is not a reliable source of safe water.

2. Soap and hand washing instructions for HIV-infected persons.

4. Insecticide-treated nets

Malaria is a life-threatening parasitic disease transmitted from person-to-person through the bite of a mosquito. The disease exerts its heaviest toll in Africa, where about 90 percent of the more than one million deaths from malaria worldwide occur each year. Prevalence of parasitemia ranges from 22-61 percent in the general population and can be as high as 82 percent in children 5-10 years of age.[29] In a study in Uganda, the prevalence of parasitemia and clinical malaria in HIV-infected persons was found to be almost twice that in HIV-uninfected persons.[30] In another study, malaria was found to be 1.7-fold more common in HIV-infected children compared to HIV-uninfected children.[8] HIV was also associated with more severe manifestations of malaria.[31,32]

Insecticide-treated nets (ITN) have proven to be effective in reducing the risk of malaria in children living in areas with high transmission: 27.8 percent reduction in malaria parasitemia,[33] 17 percent reduction in mortality in children under 5 years of age,[34] and 25 percent reduction in all-cause mortality in children 1-9 years old.[35] In randomized controlled trials in Kenya, bednets reduced symptomatic malaria in children by 52 percent, placental malaria by 35 percent and the prevalence of low birth weight by 28 percent.[36,37] ITNs also had a protective effect on persons in nearby homes.[38] Mermin et al. recently addressed the effects of ITNs on malaria in HIV-positive persons.[39] They found that the combination of co-trimoxazole, antiretroviral therapy, and ITNs substantially reduced the frequency of malaria in adults with HIV. Compared with a baseline malaria incidence of 50.8 episodes per 100 person-years, co-trimoxazole prophylaxis was associated with 9.0 episodes per 100 person-years (adjusted incidence rate ratio [IRR] 0.24, 95% CI 0.15-0.38); ART and co-trimoxazole with 3.5 episodes per 100 person-years (0.08, 0.04-0.17); and co-trimoxazole, ART, and ITNs with 2.1 episodes per 100 person-years (0.05, 0.03-0.08).

The currently recommended bednet is the long-lasting, insecticide-treated net. The insecticide in these nets lasts for 3-5 years - the life of the net. The average cost of an ITN is about $5, making it a low-cost public health intervention.

<u>Emergency Plan funds may support</u>:

USG teams in Emergency Plan countries that are also part of the President's Malaria Initiative should coordinate closely and use both funding streams creatively to serve HIV-affected individuals in the distribution of (long-lasting) insecticide-impregnated nets. Emergency Plan support can be used for insecticide-treated nets to cover the sleeping areas of households of HIV-infected persons in areas in which malaria is endemic.

5. Nutrition and micronutrient supplementation

Micronutrients, including vitamins, have gained increasing interest as a preventive measure for HIV-infected persons. Several studies have shown positive benefits of daily high-dose multiple micronutrient supplements for HIV-positive adults. In one trial of HIV-infected men and women in Thailand, a daily supplement containing 21 vitamins

and minerals was associated with a 47 percent reduction in mortality, primarily among those with CD4 counts <200 who would normally be eligible for HAART, but were not on antiretroviral drugs during this study.[40] Multi-vitamins (doses of vitamins B, C, E from 6-23 times the recommended daily allowance) administered to HIV-infected pregnant women reduced fetal death by 39 percent, and decreased the risk of low birth weight (<2500 g) by 44 percent and pre-term birth (<34 weeks gestation) by 39 percent. Multi-vitamins also significantly increased maternal CD4, CD8, and CD3 counts.[41] Daily multi-vitamin supplementation improved weight gain among HIV-infected Tanzanian pregnant women.[42] In this same trial, daily vitamin A plus beta-carotene was associated with an increased risk of HIV transmission during breastfeeding.[43] Extended follow-up of these women revealed that daily multi-vitamin supplementation of high doses of vitamins B, C, E taken during pregnancy and throughout the breastfeeding period reduced progression to WHO clinical stage 4 or death by 29 percent, and resulted in higher CD4 and lower viral load; inclusion of vitamin A plus beta-carotene in the supplement attenuated its benefits.[44] WHO has concluded that while these studies are promising, they do not warrant recommending higher daily micronutrient intakes for PLWHAs than those recommended for the general population.

Emergency Plan funds may support:

1. Daily multiple micronutrient supplements (1RDA) for PLWHA, especially pregnant and lactating women and children, according to national guidelines, where dietary assessment indicates inadequate intake of micronutrients from food.

2. Nutrition counseling linked to clinical- and home-based care for all HIV-infected persons, especially in areas in which malnutrition is endemic.

6. Services and counseling to prevent the transmission of HIV to others

HIV post-test counseling is the first step to introducing HIV-infected persons to appropriate prevention messages, medical care and treatment. Providing test results and appropriate counseling to HIV-infected persons has been shown to decrease high-risk sexual behavior and HIV transmission.[45,46] In the Democratic Republic of Congo, condom use among HIV discordant couples increased from 5 percent before counseling to 71 percent after counseling, and a low rate of HIV seroconversion was noted among this group.[47] The provision of low-cost condoms has also been associated with an 80 percent reduction in HIV transmission among discordant couples.[48] Therefore, counseling HIV-infected persons to refrain from high-risk behaviors offers an opportunity to reduce transmission of HIV to others. It will also reduce the risk to the patient of acquiring additional sexually transmitted infections.

It is important to provide ongoing prevention messages for people with HIV infection to support their maintenance of safe sexual practices using abstinence, being faithful and the correct and consistent use of condoms (ABC). Integrating prevention into care and treatment settings, including provider-delivered risk reduction information, will allow

patients to receive routine access to important messages about eliminating, or decreasing frequency of, high-risk behavior.

Emergency Plan funds may support:

1. Technical assistance to develop national policy, guidelines and training for the implementation of prevention programs for PLWHA.

2. HIV counseling about high risk behavior for all HIV-infected persons based on ABC, on an ongoing basis.

3. Condoms and referral for HIV-infected persons to other preventive services, especially family planning and STD clinics.

7. HIV counseling and testing of family members and other contacts

HIV counseling and testing may also benefit family members and other contacts of HIV-infected persons by facilitating early referral of HIV-infected persons to care and prevention. As indicated above, couples counseling and testing has been demonstrated to be effective in reducing HIV transmission risk among HIV-discordant couples. Counseling and testing models within care programs may include: 1) family-based (including home-based) counseling and testing that encourages HIV counseling and testing of family members, including children; 2) couples counseling and testing in which the partner of the HIV-infected person is counseled and tested; and 3) work site-based counseling and testing.

Emergency Plan funds may support:

1. HIV counseling and testing for family members of HIV-infected persons at a single, low-cost visit using rapid testing methods and abbreviated pre-test counseling to the family unit.

2. Counseling for discordant couples to promote risk reduction behaviors (*e.g.*, discussion of ABC and, when applicable, provision of condoms).

3. HIV counseling and testing for sex partners of HIV-infected persons.

4. Referral to care and prevention for persons identified as HIV-infected.

III. References

[1] CDC. Guidelines for prophylaxis against Pneumocystis carinii pneumonia for persons infected with human immunodeficiency virus. MMWR Morb Mortal Wkly Rep. 1989 Jun 16;38 Suppl 5:1-9.

[2] CDC. Guidelines for Prophylaxis Against Pneumocystis carinii Pneumonia for Children Infected with Human Immunodeficiency Virus. MMWR Morb Mortal Wkly Rep. Vol 40, No RR02;001 03/15/1991.

[3] Malin AS, Gwanzura LK, Klein S, Robertson VJ, Musvaire P, Mason PR. Pneumocystis carinii pneumonia in Zimbabwe. Lancet. 1995 Nov 11;346(8985):1258-61.

[4] Anglaret X, Chene G, Attia A, Toure S, Lafont S, Combe P, Manlan K, N'Dri-Yoman T, Salamon R. Early chemoprophylaxis with trimethoprim-sulphamethoxazole for HIV-1-infected adults in Abidjan, Cote d'Ivoire: a randomised trial. Cotrimo-CI Study Group. Lancet. 1999 May 1; 353(9163):1463-8.

[5] Wiktor SZ, Sassan-Morokro M, Grant AD, Abouya L, Karon JM, Maurice C, Djomand G, Ackah A, Domoua K, Kadio A, Yapi A, Combe P, Tossou O, Roels TH, Lackritz EM, Coulibaly D, De Cock KM, Coulibaly IM, Greenberg AE. Efficacy of trimethoprim-sulphamethoxazole prophylaxis to decrease morbidity and mortality in HIV-1-infected patients with tuberculosis in Abidjan, Cote d'Ivoire: a randomised controlled trial. Lancet. 1999 May 1; 353(9163):1469-75.

[6] Badri M, Ehrlich R, Wood R, Maartens G. Initiating co-trimoxazole prophylaxis in HIV-infected patients in Africa: an evaluation of the provisional WHO/UNAIDS recommendations. AIDS. 2001 Jun 15; 15(9):1143-8.

[7] Grimwade K, Swingler, G. Cotrimoxazole prophylaxis for opportunistic infections in adults with HIV. Cochrane Database Syst Rev. 2003; (3):CD003108.

[8] Mermin, J., Lule, J., Ekwaru, J.P., Malamba, S., Downing, R., Ransom, R., Kahazura, F., Culver, D.H., Kizito, F., Bunnell, R., Kigozi, A., Nakanjako, D., Wafula, W., and Quick, R. Effect of cotrimoxazole prophylaxis on morbidity, mortality, CD4 cell count, and HIV viral load among presons with HIV in rural Uganda. Lancet. 2004 Oct 16;364(9443):1428-34.

[9] Zar HJ, Dechaboon A, Hanslo D, Apolles P, Magnus KG, Hussey G. Pneumocystis carinii pneumonia in South African children infected with human immunodeficiency virus. Pediatr Infect Dis J. 2000 Jul; 19(7):603-7.

[10] Y.Yazdanpanah, E.Losina, X.Anglaret, S.J. Goldie, R.P.Walensky, M.C.Weinstein, S.Toure, H.E. Smith, A.D. Kimmel, H.Zhang, T.N'Dri-Yoman, R.Salamon, J.Kaplan, K.A.Freedberg. Clinical impact and cost-effectiveness of co-trimoxazole prophylaxis in patients living with HIV/AIDS in Côte d'Ivoire: a trial-based analysis. World AIDS Conference, Bangkok, July 11-14, 2004.

[11] Provisional WHO/UNAIDS secretariat recommendations on the use of cotrimoxazole prophylaxis in adults and children living with HIV/AIDS in Africa. 2000.

[12] Dye C, Scheele S, Dolin P, Pathania V, Raviglione MC. Consensus statement. Global burden of tuberculosis: estimated incidence, prevalence, and mortality by country. WHO Global Surveillance and Monitoring Project. JAMA. 1999 Aug 18;282(7):677-86.

[13] WHO Guidelines for implementing collaborative TB and HIV program activities. WHO 2003.

[14] Corbett EL, Watt CJ, Walker N, Maher D, Williams BG, Raviglione MC, Dye C. The growing burden of tuberculosis: global trends and interactions with the HIV epidemic. Arch Intern Med. 2003 May 12;163(9):1009-21.

[15] Daley CL, Small PM, Schecter GF, et. al. An outbreak of tuberculosis with accelerated progression among persons infected with the human immunodeficiency virus: an analysis using restriction-fragment_length polymorphisms. N Engl J Med 1992;326:231-235.

[16] Whalen C, Horsburgn R, Hom D, Lahart C, Simberkoff M, Ellner J. Accelerated course of human immunodeficiency virus infection after tuberculosis. Am J Crit Care Med 1995; 151:129-135.

[17] World Health Organization. Strategic framework to decrease the burden of TB/HIV. WHO/CDS/TB/2002.296, WHO/HIV_AIDS/2002.2.

[18] Zar HJ, Cotton MF, Lombard C et al. The impact of isoniazid prophylaxis on mortality in HIV-infected children from a high tuberculosis prevalence are. Abstract in XV AIDS Conference, Bangkok July 11-15.

[19] Grant AD, Kaplan JE, de Cock KM. Preventing opportunistic infections among human immunodeficiency virus-infected adults in African countries. Am J Trop Med Hyg., 65(6), 2001, pp 810-21.

[20] Bucher HC, Griffith LE, Guyatt GH, Surde P, Naef M, Sendi P, Battega M. Isoniazid prophylaxis for tuberculosis in HIV infection: a meta-analysis of randomized trials. AIDS 1999 Mar 11; 13(4): 501-7.

[21] Young B, Brisco J. A case control study of the effect of environmental sanitation on diarrhea morbidity in Malawi. J Epidemiol Community Health. 1988 Mar; 42(1): 83-8.

[22] Esrey SA, Potash JB, Roberts L, Shiff C. 1991. Effects of improved water supply andsanitation on ascariasis, diarrhea, dracunculiasis, hookworm infection, schistosomiasis, and trachoma. Bulletin of the World Health Organization 69(5):609-621.

[23] Gundry S, Wright S, Conroy R 2004. A systematic review of the health outcomes related to household water quality in developing countries. Journal of Water and Health 2(1): 1-13.

[24] Lule JR, Mermin J, Ekwaru JP, Malamba S, Downing R, Ransom R, Nakanjako D, Wafula W, Hughes P, Bunnell R, Kaharuza F, Coutinho A, Kigozi A, Quick R. Effect of home-based water chlorination and safe storage on diarrhea among persons with human immunodeficiency virus in Uganda. Am J Trop Med Hyg. 2005 Nov;73(5):926-33.

[25] Curtis V, Cairncross S. 2003. Effect of washing hands with soap on diarrhea risk in the community: a systematic review. Lancet Infectious Diseases 3 (5) :275-81.

[26] Shahid NS, Greenough WB 3rd, Samadi AR, Huq MI, Rahman N. Hand washing with soap reduces diarrhoea and spread of bacterial pathogens in a Bangladesh village. J Diarrhoeal Dis Res. 1996 Jun; 14(2):85-9.

[27] Luby SP, Agboatwalla M, Painter J, Altaf A, Billhimer WL, Hoekstra RM. Effect of intensive handwashing promotion on childhood diarrhea in high-risk communities in Pakistan: a randomized controlled trial. JAMA. 2004 Jun 2; 291(21):2547-54.

[28] Huttly SRA, Moriss SS, Pisni V 1997. Prevention of diarrhea in young children in developing countries. Bulletin of the World Health Organization 75 (2): 165-174.

[29] Koram KA, Owusu-Agyei S, Fryauff DJ, Anto F, Atuguba F, Hodgson A, Hoffman L, Nkrumah FK. Seasonal profiles of malaria infection, anaemia, and bed net use among age groups and communities in northern Ghana. Trop Med Int Health. 2003 Sep;8(9):793-802.

[30] Whitworth J, Morgan D, Quigley M, Smith A, Mayanja B, Eotu H, Omoding N, Okongo M, Malamba S, Ojwiya A. Effect of HIV-1 and increasing immunosuppression on malaria parasitaemia and clinical episodes in adults in rural Uganda: a cohort study. Lancet. 2000 Sep 23; 356 (9235):1051-6.

[31] Grimwade K, French N, Mbatha DD, Zungu DD, Dedicoat M, Gilks CF. Childhood malaria in a region of unstable transmission and high human immunodeficiency virus prevalence. Pediatr Infect Dis J. 2003 Dec;22(12):1057-63.

[32] Grimwade K, French N, Mbatha DD, Zungu DD, Dedicoat M, Gilks CF. HIV infection as a cofactor for severe falciparum malaria in adults living in a region of unstable malaria transmission in South Africa. AIDS. 2004 Feb 20;18(3):547-54.

[33] Holtz TH, Marum LH, Mkandala C, Chizani N, Roberts JM, Macheso A, Parise ME, Kachur SP. Insecticide-treated bed net use, anaemia, and malaria parasitaemia in Blantyre District, Malawi. Trop Med Int Health. 2002 Mar;7(3):220-30.

[34] Lengeler C. Insecticide-treated bednets and curtains for preventing malaria. Cochrane Database Syst Rev. 2000; (2): CD000363.

[35] D'Alessandro U, Olaleye BO, McGuire W, Langerock P, Bennett S, Aikins MK, Thomson MC, Cham MK, Cham BA, Greenwood BM. Mortality and morbidity from malaria in Gambian children after introduction of an impregnated bed net programme. Lancet. 1995 Feb 25;345(8948):479-83.

[36] ter Kuile FO, Terlouw DJ, Kariuki SK, Phillips-Howard PA, Mirel LB, Hawley WA, Friedman JF, Shi YP, Kolczak MS, Lal AA, Vulule JM, Nahlen BL. Reduction of malaria during pregnancy by permethrin-treated bednets in an are of intense perennial malaria transmission in western Kenya. Am J Trop Med Hyg. 2003 Apr; 68 (4 Suppl): 50-60.

[37] ter Kuile FO, Terlouw DJ, Kariuki SK, Phillips-Howard PA, Mirel LB, Hawley WA, Friedman JF, Shi YP, Kolczak MS, Lal AA, Vulule JM, Nahlen BL. Impact of permethrin-treated bed nets on malaria, anemia, and growth in infants in an area of intense perennial malaria transmission in western Kenya. Am J Trop Med Hyg. 2003 Apr;68(4 Suppl):68-77.

[38] Hawley WA, Phillips-Howard PA, ter Kuile FO, Terlouw DJ, Vulule JM, Ombok M, Nahlen BL, Gimnig JE, Kariuki SK, Kolczak MS, Hightower AW. Community-wide effects of permethrin-treated bed nets on child mortality and malaria morbidity in western Kenya. Am J Trop Med Hyg. 2003 Apr;68(4 Suppl):121-7.

[39] Mermin J, Ekwaru JP, Liechty CA, Were W, Downing R, Ransom R, Weidle P, Lule J, Coutinho A, Solberg P. Effect of co-trimoxazole prophylaxis, antiretroviral therapy, and insecticide-treated bednets on the frequency of malaria in HIV-1-infected adults in Uganda: a prospective cohort study. Lancet. 2006 Apr 15;367(9518):1256-61.

[40] Jiamton S, Pepin J, Suttent R, Filteau S, Mahakkanukrauh B, Hanshaoworakul W, Chaisilwattana P, Suthipinittharm P, Shetty P, Jaffar S. A randomized trial of the impact of multiple micronutrient supplementation on mortality among HIV-infected individuals living in Bangkok. AIDS. 2003 Nov 21;17(17):2461-9.

[41] Fawzi WW, Msamanga GI, Spiegelman D, Urassa EJ, McGrath N, Mwakagile D, Antelman G, Mbise R, Herrera G, Kapiga S, Willett W, Hunter DJ. Randomised trial of effects of vitamin supplements on pregnancy outcomes and T cell counts in HIV-1-infected women in Tanzania. Lancet. 1998 May 16; 351(9114):1477-82.

[42] Villamor E, Msamanga G, Spiegelman D, Antelman G, Peterson KE, Hunter DJ, Fawzi WW. Effect of multi-vitamin and vitamin A supplements on weight gain during pregnancy among HIV-1-infected women. Am J Clin Nutr. 2002 Nov;76(5):1082-90.

[43] Fawzi WW, Msamanga GI, Hunter D, Renjifo B, Antelman G, Bang H, Manji K, Kapiga S, Mwakagile D, Essex M, Spiegelman D. Randomized trial of vitamin supplements in relation to transmission of HIV-1 through breastfeeding and early child mortality. AIDS. 2002 Sep 27;16(14):1935-44.

[44] Fawzi WW, Msamanga GI, Spielgeman D, Wei R, Kapiga S, Villamor E, Mwakagile D, Mugusi F, Hertzmark E, Essex M, Hunter DJ. A randomized trial of multi-vitamin supplements and HIV disease progression and mortality. N Engl J Med 2004 Jul 1; 351 (1): 23-32.

[45] Weinhardt LS, Carey MP, Johnson BT, Bickham NL. Effects of HIV counseling and testing on sexual risk behavior: a meta-analytic review of published research, 1985-1997. Am J Public Health. 1999 Sep; 89(9):1397-405.

[46] Painter TM. Voluntary counseling and testing for couples: a high-leverage intervention for HIV/AIDS prevention in sub-Saharan Africa. Soc Sci Med. 2001 Dec; 53(11):1397-411.

[47] Kamenga M, Ryder RW, Jingu M, Mbuyi N, Mbu L, Behets F, Brown C, Heyward WL. Evidence of marked sexual behavior change associated with low HIV-1 seroconversion in 149 married couples with discordant HIV-1 serostatus: experience at an HIV counselling center in Zaire. AIDS. 1991 Jan; 5(1):61-7.

[48] Weller S, Davis K. Condom effectiveness reducing heterosexual HIV transmission. Cochrane Database Syst Rev 2001: 93)CD003255.