

Developing an evidence-based, preventive care package for persons with HIV in Africa

Jonathan Mermin¹, Rebecca Bunnell¹, John Lule¹, Alex Opio², Amanda Gibbons³, Mark Dybul⁴ and Jonathan Kaplan¹

1 CDC-Uganda, Global AIDS Program, National Center for HIV, STD and TB Prevention Centers for Disease Control and Prevention, Entebbe, Uganda

2 Uganda Ministry of Health, Kampala, Uganda

3 United States Agency for International Development, Washington DC, USA

4 Office of the US Global AIDS Coordinator, United States Department of State, Washington DC, USA

Summary

Currently, 95% of the 40 million persons with HIV live in low and middle income countries; 27 million in sub-Saharan Africa. HIV/AIDS is a leading cause of death in the region, yet access to care and treatment considered standard-of-care in the industrialized world is extremely limited. There is a need for standardized, evidence-based recommendations on preventive measures. We developed a list of potential interventions based, when possible, on documented efficacy in reducing morbidity or mortality among persons with HIV in Africa. We considered the accessibility, affordability, and potential for implementation using existing health care infrastructure. Potential components included cotrimoxazole prophylaxis, safe drinking water, isoniazid prophylaxis, insecticide-treated bed nets, micronutrients, and provision of HIV counseling and testing and condoms to family members of persons with HIV. There are several additional interventions for which further evaluation would be useful before inclusion in a standard package of care, including acyclovir prophylaxis, food supplementation, hand washing, and fluconazole prophylaxis. The provision of a basic care package could be an important step toward reducing health care disparities and gaining more control of the global HIV/AIDS epidemic.

keywords HIV, opportunistic infections, Africa, care, prevention, voluntary counselling and testing

Introduction

Currently, 95% of the 40 million persons with HIV live in low and middle income countries (UNAIDS 2004b); 27 million in sub-Saharan Africa (UNAIDS 2004a). HIV/AIDS is a leading cause of death in the region, yet access to care and treatment considered standard-of-care in the industrialized world is extremely limited (Grubb *et al.* 2003). Whereas considerable attention has been given to increasing the availability of antiretroviral (ARV) therapy, few advocates have focused on more easily accessed interventions for preventing opportunistic infections (Grant *et al.* 2001).

A 'basic preventive care package' specifically designed for persons with HIV in Africa would be useful for several reasons: (1) some of the infections discussed in current US-based guidelines (Kaplan *et al.* 2002), such as *Mycobacterium avium* complex are rare in Africa and the beneficial effect of prophylaxis for persons with HIV in the region has never been evaluated (Holmes *et al.* 2003); (2) certain illnesses not discussed in current recommendations, such as

malaria, are common in sub-Saharan Africa; (3) interventions, such as provision of clean drinking water, are regularly provided by governmental services in the industrialized world, but less available in Africa; and (4) some medications for prophylaxis have limited availability in Africa. There is a need for standardized, evidence-based recommendations on preventive measures that can be used by health practitioners, Ministries of Health, and non-governmental organizations. Although data presented in this paper focus on Africa, many recommended interventions would also be useful in other areas of the world. If applied widely, a basic care package would allow for provision of effective care to millions of persons with HIV who currently have limited or no access to HIV-related services.

We developed a list of potential interventions based, when possible, on documented efficacy in reducing morbidity or mortality among persons with HIV in Africa. We considered the accessibility, affordability, and potential for implementation using existing health care infrastructure (Table 1). In addition, we assessed the evidence of

J. Mermin *et al.* Preventive care package for persons with HIV**Table 1** Potential components of a preventive care package for persons with HIV/AIDS in Africa

Intervention	Impact		
	Individual with HIV	Household	Comments
Cotrimoxazole prophylaxis	<ul style="list-style-type: none"> Reduction in mortality, malaria, diarrhoea, clinic visits, hospitalizations (Anglaret <i>et al.</i> 1999; Badri <i>et al.</i> 1999, 2001; Wiktor <i>et al.</i> 1999; Castetbon <i>et al.</i> 2001; Zachariah <i>et al.</i> 2002; Mermin <i>et al.</i> 2004) Possible beneficial effect on viral load and CD4 cell count (Mermin <i>et al.</i> 2004) 	<ul style="list-style-type: none"> Reduction in diarrhoea, malaria, and mortality in children (Mermin <i>et al.</i> 2005) 	<ul style="list-style-type: none"> Reduction in morbidity for wide range of CD4 cell counts (Anglaret <i>et al.</i> 1999; Wiktor <i>et al.</i> 1999; Mermin <i>et al.</i> 2005a) Low rate of adverse events in Africa (Wiktor <i>et al.</i> 1999; Badri <i>et al.</i> 2001; Castetbon <i>et al.</i> 2001; Zachariah <i>et al.</i> 2002; Mermin <i>et al.</i> 2004)
Safe drinking water	<ul style="list-style-type: none"> Reduction in diarrhoea (Lule <i>et al.</i> 2004) 	<ul style="list-style-type: none"> Reduction in diarrhoea among HIV-negative children (Lule <i>et al.</i> 2004) Theoretical benefit of reduced TB transmission 	<ul style="list-style-type: none"> Efficacy data based on home-based disinfection with chlorine and a plastic water vessel with spigot Questionnaire and physical exam may be adequate to screen out persons with active TB (Mosimaneorsile <i>et al.</i> 2003) Need to have referral system for persons with possible active TB Long-lasting insecticide-treated bed nets available that reduce the need for retreatment
Isoniazid prophylaxis	<ul style="list-style-type: none"> Reduction in incidence of TB (Grant <i>et al.</i> 2001) Possible reduction in mortality (Grant <i>et al.</i> 2001) 		
Insecticide-treated bed nets	<ul style="list-style-type: none"> Not assessed, but theoretically same efficacy as documented for persons without HIV 	<ul style="list-style-type: none"> Reductions in malaria and all cause mortality among children (Lengeler 2004) 	<ul style="list-style-type: none"> One study suggests that regimens containing high levels of vitamin A may not be as beneficial for pregnant women as vitamin B complex, vitamin C, and vitamin E alone (Fawzi <i>et al.</i> 2002; Villamor <i>et al.</i> 2002b; Fawzi <i>et al.</i> 2004)
Micronutrients and vitamin A	<ul style="list-style-type: none"> Reduction in morbidity, mortality, and disease progression in adults (Villamor <i>et al.</i> 2002b; Jiamton <i>et al.</i> 2003; Fawzi <i>et al.</i> 2004) Possible beneficial effect on CD4 cell count and HIV viral load (Villamor <i>et al.</i> 2002b; Fawzi <i>et al.</i> 2004) Vitamin A reduces morbidity and mortality, and improves growth among children with HIV/AIDS (Coutsoudis <i>et al.</i> 1995; Fawzi <i>et al.</i> 1999; Villamor <i>et al.</i> 2002a) Psychological benefits of HIV-status disclosure (Hays <i>et al.</i> 1993; Armistead <i>et al.</i> 1999; Maman <i>et al.</i> 2003) Reduction in HIV transmission (Kamenga <i>et al.</i> 1991; Allen <i>et al.</i> 1992, 2003; Allen <i>et al.</i> 1992a; The Voluntary HIV-1 Counseling and Testing Efficacy Study Group 2000) 	<ul style="list-style-type: none"> Micronutrient supplementation for pregnant or lactating women improves infant outcomes and may reduce rate of mother-to-child transmission of HIV (Coutsoudis <i>et al.</i> 1999; Fawzi <i>et al.</i> 2002; Kumwenda <i>et al.</i> 2002) 	<ul style="list-style-type: none"> High uptake with home-based VCT (Mermin <i>et al.</i> 2004)
Family HIV counselling and testing		<ul style="list-style-type: none"> High proportion of adults and children in family have undiagnosed HIV and benefit from care and prevention efforts (Kabatesi <i>et al.</i> 2002; Lurie <i>et al.</i> 2003) 	

beneficial effects of using specific interventions, e.g. insecticide-treated bed nets or safe drinking water systems, on household members living with persons with HIV.

Potential interventions were separated into two categories: those for which randomized controlled trials in Africa have indicated effectiveness and cost and feasibility support relatively easy implementation, e.g. cotrimoxazole prophylaxis (Table 1), and interventions for which efficacy in Africa has not been assessed, e.g. food supplementation and fluconazole prophylaxis, or target groups for implementation have not been established and studies among persons with HIV have not been conducted, e.g. hand washing with soap. Most of the interventions are relatively inexpensive, but some require routine follow-up to ensure appropriate use and monitoring for adverse effects.

We did not consider the sometimes complex issues associated with implementing systems for providing these interventions in diverse situations. Nor did we address the question of why these interventions, some of which have had evidence of efficacy for several years, have not been widely implemented. Part of the reason may be that preventive interventions, such as daily prophylactic medication, often do not provide noticeable improvements in health or well-being for people taking them and therefore require education of patients and focused public health programs. Another may be the lack of formal policy for several of the interventions by international health organizations, such as the World Health Organization.

Potential components of a basic care package well-evaluated in Africa

Cotrimoxazole prophylaxis

Cotrimoxazole prophylaxis (160 mg trimethoprim/800 mg sulphamethoxazole for adults and equivalent dose per kg for children) is recommended for and widely used by persons with AIDS in Europe and the USA (Kaplan *et al.* 2002), but rarely used in Africa (Brou *et al.* 2003). A conference convened by the Joint United Nations Programme on HIV/AIDS (UNAIDS) and the World Health Organization (WHO) in 2000 provisionally recommended the use of cotrimoxazole prophylaxis for children and symptomatic adults with HIV in Africa (WHO, UNAIDS 2000), based primarily on two randomized controlled trials from Ivory Coast (Anglaret *et al.* 1999; Wiktor *et al.* 1999) and a cohort analysis from South Africa (Badri *et al.* 1999). There has been increasing evidence of effectiveness, even in areas with high bacterial resistance to cotrimoxazole (Badri *et al.* 2001; Castetbon *et al.* 2001; Zachariah *et al.* 2002; Mermin *et al.* 2004). Daily cotrimoxazole prophylaxis has been associated with 25–46% less

mortality (Wiktor *et al.* 1999; Badri *et al.* 2001; Zachariah *et al.* 2002; Mermin *et al.* 2004) and reductions in malaria, diarrhoea, and hospitalization (Wiktor *et al.* 1999; Zachariah *et al.* 2002; Mermin *et al.* 2004) among persons with HIV both with and without TB. Cotrimoxazole prophylaxis by persons with HIV may also have beneficial effects on the rates of malaria, diarrhoea, and mortality among HIV-negative household members <10 years old (Mermin *et al.* 2005b). There are indications that cotrimoxazole prophylaxis might benefit even those persons with HIV with high CD4 cell counts (Anglaret *et al.* 1999; Mermin *et al.* 2004, 2005a). Adverse reactions are rare in Africa (Wiktor *et al.* 1999; Zachariah *et al.* 2002). The cost of the medication is low; generally less than US\$15 per year, and the cost per life year saved is US\$160 (Yazdanpanah *et al.* 2004).

Safe drinking water

In Africa, diarrhoea is four times more common among children with HIV and seven times more common among adults with HIV than their HIV-negative household members (Mermin *et al.* 2004). Bacterial contamination of drinking water is common (Quick *et al.* 2002). A randomized controlled trial of the provision of a plastic water vessel with a spigot and a supply of dilute chlorine solution for water purification was associated with a reduction in microbial contamination of household water and less diarrhoea and dysentery among persons with HIV (Lule *et al.* 2004, 2005). There was a similar effect among HIV-negative children in the same household. This type of drinking water intervention has been effective in reducing sporadic (Quick *et al.* 2002) and epidemic (Reller *et al.* 2001) diarrhoea among persons without HIV, and, at less than US\$10 per year, is considered the least expensive method for providing safe drinking water (WHO 2004).

Isoniazid prophylaxis

Tuberculosis (TB) is the leading cause of severe morbidity and mortality among persons with HIV in Africa (Holmes *et al.* 2003) where a substantial proportion of persons have latent TB. It is estimated that 5–10% of persons with HIV and TB co-infection will develop active TB per year (Holmes *et al.* 2003). Although the priority for TB programs is to find and treat all cases of TB disease, daily isoniazid (INH) prophylaxis for 6–9 months or longer has been recommended for persons with HIV. In randomized clinical trials in Africa, INH prophylaxis has been associated with a substantial reduction in the incidence of TB, and possible reductions in mortality (Grant *et al.* 2001). The effect has almost

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exclusively been observed among persons with HIV who have a positive tuberculin skin test (Grant *et al.* 2001). To avoid treating persons who have active TB with monotherapy it is important to screen for symptoms of active disease for which a simple questionnaire and physical exam may be adequate (Mosimaneotsile *et al.* 2003), although some evidence supports increased sensitivity with the use of chest radiography (Hawken *et al.* 2001). Screening should be conducted before initiating INH prophylaxis. Persons with potential symptoms of active TB should be referred for further evaluation and treatment. Persons who report no symptoms and have a normal exam can be given a tuberculin skin test, and if positive, receive isoniazid (INH) prophylaxis. If skin testing is not available in areas where the prevalence of latent TB infection is >30%, all persons without active TB can be offered prophylaxis. It is still effective in this situation, although a greater number of persons need to be treated per case of TB prevented. The per person program cost of screening and providing a course of isoniazid prophylaxis is US\$145 (Lugada *et al.* 2002). Incorporating medical costs saved from preventing TB, the per person cost of treatment decreases to US\$13, and the cost per quality-adjusted life-year gained is US\$114 (Bell *et al.* 1999). Including social costs, INH prophylaxis saves US\$13 per person treated (Bell *et al.* 1999).

Insecticide-treated bed nets

Malaria is twice as common, and parasitemia higher for adults and children with HIV than persons without HIV (Whitworth *et al.* 2000; Mermin *et al.* 2004). Severe complications from malaria, including death, are probably more common among persons with HIV, at least in areas with episodic transmission (Grimwade *et al.* 2004). There have been no studies of the effect of insecticide-treated bed nets on the incidence of malaria among persons with HIV; however, randomized trials of bed nets have shown a 50% reduction in malaria and a 17% reduction in all cause mortality among children (Lengeler 2004). Theoretically, bed nets should be as effective among persons with HIV as they are for those without, and ethical considerations may preclude the implementation of randomized controlled trials. Bed nets cost about US\$5 each, and generally two are provided per household. Among children, the cost per life-year gained is US\$25 (Wiseman *et al.* 2003).

Micronutrients and vitamin A

Several studies have shown that persons with HIV have micronutrient deficiencies, and a few have evaluated the effect of micronutrient supplementation among persons

with HIV. In a randomized trial of pregnant women, multivitamins containing vitamins B, C, and E, but not vitamin A, were associated with reduced maternal and infant mortality, lower rates of mother-to-child transmission of HIV, greater birth weight, and short- and long-term beneficial effects on CD4 cell count and viral load (Fawzi *et al.* 2002; Villamor *et al.* 2002b; Fawzi *et al.* 2004). Vitamin A supplementation alone of pregnant women appears to reduce pre-term deliveries and increase birth weight and haemoglobin among infants, but has had mixed effects on rates of mother-to-child transmission (Coutsoudis *et al.* 1999; Fawzi *et al.* 2002; Kumwenda *et al.* 2002). A small study of vitamin A supplementation among men and women showed no effect on viral load or CD4 cell count (Semba *et al.* 1998). One randomized trial among men and women with HIV in Thailand found a multivitamin and mineral supplement containing vitamin A was associated with reduced mortality (Jiamton *et al.* 2003).

Children with HIV receive substantial morbidity, mortality, and growth benefits from vitamin A supplementation (Coutsoudis *et al.* 1995; Fawzi *et al.* 1999; Villamor *et al.* 2002a). Costs for a year supply of multivitamins is generally <US\$5. Given available information, it is reasonable to consider daily micronutrient supplementation among adults and children with HIV, but close monitoring, particularly among pregnant women would be beneficial. Vitamin A should be given to all children with HIV.

Provision of HIV counselling and testing to family members

Providing HIV counselling and testing to family members of HIV-positive clients can be an effective method for facilitating HIV disclosure among couples and family members, for identifying and preventing new HIV infections within the family, and linking previously undiagnosed family members with care and treatment. HIV-disclosure has been shown to increase support to infected persons and to reduce negative psychological outcomes (Maman *et al.* 2003), including depression (Hays *et al.* 1993; Armistead *et al.* 1999). Although limited data are available, disclosing status and providing testing to family members may also improve adherence to medication and enhance support systems. While providing family counselling and testing may have positive effects for the initial person with HIV, substantial benefit primarily accrues to family members. For example, a substantial proportion of family members, especially spouses and children under 5 years old, of persons with HIV are infected (Kabatesi *et al.* 2002; Lurie *et al.* 2003). About 2.5 million children in Africa have HIV

(UNAIDS 2004b) and without effective care almost half will die before their third birthday (Spira *et al.* 1999). Yet, testing of children is rarely conducted.

Providing couples with HIV testing and counselling decreases high risk sexual behaviour and HIV transmission (Allen *et al.* 1992a; The Voluntary HIV-1 Counselling and Testing Efficacy Study Group 2000), particularly among HIV-discordant couples (Kamenga *et al.* 1991; Allen *et al.* 1992, 2003). Many persons with HIV believe that their partners are already infected and therefore do not avoid high-risk practices; however, more than 30% of HIV positive patients in Africa have HIV-negative spouses (Allen *et al.* 1992b; Kilewo *et al.* 2001; Trask *et al.* 2002; Lurie *et al.* 2003). Counselling for HIV-infected persons and their partners can include information regarding HIV-discordance, abstinence, safer sex, and the consistent use of condoms. The basic care package should include the provision of condoms, as their use has been associated with an 80% reduction in HIV transmission (Weller & Davis 2001). Reduction of HIV transmission within HIV-discordant couples should also help control the spread of ARV-resistant virus from persons taking ARVs.

Although facility-based prevention of mother-to-child-transmission programmes have had limited success with partner testing – generally less than 10% (Kilewo *et al.* 2001) – over 95% of family members of men and women with HIV accepted testing when it was offered in their homes (Mermin *et al.* 2004). Household members who are HIV-positive should also be offered basic care and ARV therapy if clinically eligible.

Discussion

In the USA, morbidity and mortality from HIV/AIDS was first reduced with the introduction of prophylaxis against opportunistic infections, and the development of widely used guidelines (Kaplan *et al.* 2002). Prophylaxis is beneficial even among persons receiving ARV therapy; in a cohort of 20 000 persons with HIV, a 21% reduction in mortality was noted with the use of prophylaxis against *Pneumocystis jiroveci* (formerly *Pneumocystis carinii*) pneumonia, and a 24% reduction in mortality with the use of prophylaxis against *Mycobacterium avium* complex, among a sub-group of patients receiving ARVs (McNaghten *et al.* 1999). To optimize care and treatment for persons with HIV in Africa a similar two-pronged approach of ARV therapy and prophylaxis against opportunistic illness is necessary.

There are advantages to providing interventions that are easily implemented and for which people with HIV can take responsibility, such as daily prophylaxis. The pro-

posed basic care package focuses on preventing illness rather than on diagnosis and treatment because curative services are difficult to access for persons living in many parts of Africa (Peterson *et al.* 2004) and other resource-limited settings. Individuals often live far from clinics and, in the case TB for example, distance from a health centre has been associated with increased risk of mortality (Barker *et al.* 2002), probably because of a lack of transportation to maintain necessary appointments. Due to the focus on preventing illness, several interventions with proven benefits for persons with HIV, such as treatment for active TB or sexually transmitted diseases were not included. These important services require more extensive health care infrastructure and are of a curative, rather than preventive nature.

National programs and international initiatives, such as the Global Fund for AIDS, TB, and Malaria, the World Bank, and the US President's Emergency Plan for AIDS Relief are providing increased HIV/AIDS funding for programs in many parts of the world. Hospitals, clinics, and HIV/AIDS programmes that previously focused on either curative services or prevention messages are now interested in expanding services to include comprehensive care and prevention. ARV therapy is the most effective approach to reducing morbidity and mortality among persons with HIV/AIDS living in Africa and elsewhere. However, the expense of ARVs, the current standard for monitoring of CD4 cell counts and viral loads, and limited infrastructure in many countries, makes ARV therapy challenging to implement. Developing a basic care package that could be easily and quickly introduced, especially in rural areas with limited infrastructure, could not only increase access to effective HIV/AIDS care, but also could lay the groundwork for ARV therapy. Taking daily prophylaxis and using other preventive interventions has the additional benefit of providing a foundation for ARV implementation, both on an individual basis with regard to adherence and HIV disclosure to family members, and on a health system level in relation to establishing reliable drug and commodity distribution mechanisms. A basic care package could benefit persons taking ARVs, persons not yet eligible for ARVs because of high CD4 cell counts and lack of clinical symptoms, and persons who cannot access ARVs.

Two of the interventions included in the Table, multi-vitamin supplementation and cotrimoxazole prophylaxis, may have beneficial effects on CD4 cell count and HIV viral load, potentially through lessening the production of cytokines and tumour necrosis factor (Kaplan *et al.* 1999; Mermin *et al.* 2004), and reduction in oxidative stress (Fawzi *et al.* 2004). These data suggest that components of a basic care package might prolong the time period

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between HIV infection and the development of AIDS, and consequently delay the need for ARV therapy.

Often, primary or secondary prophylaxis is not recommended for persons whose CD4 cell counts have risen above predetermined levels (Kaplan *et al.* 2002) because chemoprophylaxis may have adverse side effects and increase health care costs. However, some interventions, such as cotrimoxazole prophylaxis (Anglaret *et al.* 1999; Mermin *et al.* 2004) and multivitamins (Villamor *et al.* 2002b; Fawzi *et al.* 2004), may benefit persons with HIV in Africa even when they have high CD4 cell counts. The question of whether to continue preventive interventions among persons in Africa taking ARVs with CD4 cell counts above specified levels is not resolved, and would be a fruitful area for research.

There are several additional interventions for which further evaluation might be useful before inclusion in a standard package of care, including acyclovir prophylaxis, food supplementation, hand washing, and fluconazole prophylaxis. HSV-2 upregulates HIV replication *in vitro*, and clinical and subclinical outbreaks have been shown to increase HIV viral load in dually infected persons (Mole *et al.* 1997; Schacker *et al.* 2002). The use of acyclovir has been shown to prevent this increase in viral load. A meta-analysis of eight randomized controlled trials of the use of daily acyclovir prophylaxis among persons with HIV showed a 22% reduction in mortality as well as beneficial effects on outbreaks of varicella zoster and herpes simplex virus (Ioannidis *et al.* 1998). These studies were conducted before the development of effective combination ARVs. It would be useful to repeat similar studies among persons with HIV in Africa, where HSV-2 infection is more common, and also evaluate potential effects among persons on ARVs and persons who have CD4 cell counts above the initiation threshold for ARV therapy.

Persons with HIV have increased energy demands, intermittent malabsorption, and decreased caloric intake (Gibert *et al.* 1999). Loss of body cell mass among persons with HIV is associated with increased risk of morbidity and mortality (Gibert *et al.* 1999). The causal relationship between weight loss and disease progression is not well established. Several small studies in industrialized countries have examined the effect of food supplements on weight gain, HIV viral load, and CD4 cell count (Pichard *et al.* 1998; Gibert *et al.* 1999; de Luis Roman *et al.* 2001). The results have been mixed, with either no effect (Rabeneck *et al.* 1998; Gibert *et al.* 1999; Keithley *et al.* 2002) or small improvements in weight (Pichard *et al.* 1998) or immunologic markers (Pichard *et al.* 1998; de Luis Roman *et al.* 2001). Nutritional counselling alone had no impact (Chlebowski *et al.* 1995; Rabeneck *et al.* 1998). No studies have been conducted in Africa where chronic food short-

ages and malnutrition are more common. It is reasonable to conclude that lack of access to an adequate food supply would harm persons with HIV at least as much as persons without HIV. However, more research would be useful to determine the benefits of generalized food supplementation for all persons with HIV in Africa. The provision of limited food support may be of particular benefit for patients receiving certain ARVs because of dietary restrictions and gastrointestinal side effects.

Africans often have reduced access to basic methods for improving hygiene and sanitation. One study showed an association between the presence of soap in the home and reduced incidence of diarrhoea among persons with HIV; however, the study was not randomized on this intervention (Lule *et al.* 2004). A randomized controlled study in Pakistan showed that supplying households with soap and education on hand washing reduced diarrhoea among children by 50% (Luby *et al.* 2004), and a study of hand washing education alone in Zaire reduced diarrhoea among children by 11% (Haggerty *et al.* 1994), but the HIV status of participants was unknown and the effect on adults was not measured. There are no data on the efficacy of hand washing education with or without provision of soap in preventing illness among persons with HIV.

Cryptococcal meningitis and invasive candidal disease are common among persons with AIDS in Africa, and also are a leading cause of death (French *et al.* 2002; Holmes *et al.* 2003). A randomized controlled trial (Powderly *et al.* 1995) and several cohort studies (Nightingale *et al.* 1992; Newton *et al.* 1995) in the USA, and two small randomized controlled trials in Thailand (Chariyalertsak *et al.* 2002; Chetchotisakd *et al.* 2004), indicate potential efficacy for azoles in preventing cryptococcal meningitis. One study showed potential reductions in mortality (Chariyalertsak *et al.* 2002; Chetchotisakd *et al.* 2004). The lack of a strongly documented mortality effect, expense of the drugs, and potential toxicity led to a lack of recommendation for primary prophylaxis (Kaplan *et al.* 2002). However, the company that originally produced fluconazole currently provides the drug free-of-charge for treatment of severe disease in Africa, and the US patent expired in January 2004, making fluconazole available at considerably lower cost. In Thailand, primary prophylaxis with azoles is national policy (Chetchotisakd *et al.* 2004). Because the illness appears to be more common in Africa than the USA, it would be useful to conduct more studies of primary fluconazole prophylaxis among persons with HIV in Africa to assess its effectiveness, cost and potential utility in a basic care package. A randomized controlled trial of primary fluconazole prophylaxis is currently underway in Uganda.

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The components of a basic care package for persons with HIV/AIDS in Africa will vary by country and will be influenced by available resources. The contents could be modified to meet the unique conditions found in other regions of the world. Our hope is that a consensus meeting will be held to gather more information and develop guidelines using a standardized rating system regarding the quality of available evidence and the strength of recommendations (Kaplan *et al.* 2002).

Conclusion

Similar to people in the industrialized world, persons with HIV/AIDS in Africa should receive effective, evidence-based health care (Buekens *et al.* 2004). These interventions should be tailored to meet the specific needs of the region and include a broad package of care and prevention services in addition to ARV medications. The provision of a basic care package could be an important step toward reducing health care disparities and gaining more control of the global HIV/AIDS epidemic.

References

- Allen S, Tice J, de Perre P, Seruflira A, Hudes E, Nsengumurenyi F *et al.* (1992a) Effect of serotesting with counselling on condom use and seroconversion among HIV discordant couples in Africa. *British Medical Journal* **304**, 1605–1609.
- Allen S, Seruflira A, Bogaerts J, de Perre P, Nsengumurenyi F, Lindan C *et al.* (1992b) Confidential HIV testing and condom promotion in Africa. Impact on HIV and gonorrhoea rates. *JAMA* **268**(23), 3338–3343.
- Allen S, Meinzen-Derr J, Kautzman M, Zulu I, Trask S, Fideli U *et al.* (2003) Sexual behavior of HIV discordant couples after HIV counseling and testing. *AIDS* **17**(5), 733–740.
- Anglaret X, Chêne G, Attia A, Toure S, Lafont S, Combe P *et al.* (1999) Early chemoprophylaxis with trimethoprim-sulphamethoxazole for HIV-1-infected adults in Abidjan, Côte d'Ivoire: a randomised trial. *Lancet* **353**, 1463–1468.
- Armistead L, Morse E, Forehand R, Morse P & Clark L (1999) African-American women and self-disclosure of HIV infection: rates, predictors, and relationship to depressive symptomatology. *AIDS and Behavior* **3**(3), 195–204.
- Badri M, Maartens G, Wood R & Ehrlich R (1999) Co-trimoxazole in HIV-1 infection. *Lancet* **354**(9175), 334–335.
- Badri M, Ehrlich R, Wood R & Maartens G (2001) Initiating co-trimoxazole prophylaxis in HIV-infected patients in Africa: an evaluation of the provisional WHO/UNAIDS recommendations. *AIDS* **15**(9), 1143–1148.
- Barker RD, Nthangeni ME & Millard FJ (2002) Is the distance a patient lives from hospital a risk factor for death from tuberculosis in rural South Africa? *International Journal of Tuberculosis and Lung Disease* **6**(2), 98–103.
- Bell JC, Rose DN & Sacks HS (1999) Tuberculosis preventive therapy for HIV-infected people in sub-Saharan Africa is cost-effective. *AIDS* **13**, 1549–1556.
- Brou H, Desgrees-du-Lou A, Souville M, Moatti JP & Msellati P (2003) Prophylactic use of cotrimoxazole against opportunistic infections in HIV-positive patients: knowledge and practices of health care providers in Cote d'Ivoire. *AIDS Care* **15**(5), 629–637.
- Buekens P, Kusch G, Belizan J & Bhutta ZA (2004) Evidence-based global health. *JAMA* **291**(21), 2639–2641.
- Castetbon K, Anglaret X, Attia A *et al.* (2001) Effect of early chemoprophylaxis with co-trimoxazole on nutritional status evolution in HIV-1-infected adults in Abidjan, Cote d'Ivoire. *AIDS* **15**(7), 869–876.
- Chariyalertsak S, Supparatpinyo K, Sirisanthana T & Nelson KE (2002) A controlled trial of itraconazole as primary prophylaxis for systemic fungal infections in patients with advanced human immunodeficiency virus infection in Thailand. *Clinical Infectious Diseases* **34**(2), 277–284.
- Chetchotisakd P, Sungkanuparph S, Thinkhamrop B, Mootsikapun P & Boonyaprawit P (2004) A multicentre, randomized, double-blind, placebo-controlled trial of primary cryptococcal meningitis prophylaxis in HIV-infected patients with severe immune deficiency. *HIV Medicine* **5**(3), 140–143.
- Chlebowski RT, Grosvenor M, Lillington L, Sayre J & Beall G (1995) Dietary intake and counseling, weight maintenance, and the course of HIV infection. *Journal of the American Dietetic Association* **95**(4), 428–432.
- Coutsoudis A, Bobat RA, Coovadia HM, Kuhn L, Tsai WY & Stein ZA (1995) The effects of vitamin A supplementation on the morbidity of children born to HIV-infected women. *American Journal of Public Health* **85**(8 Pt 1), 1076–1081.
- Coutsoudis A, Pillay K, Spooner E, Kuhn L & Coovadia HM (1999) Randomized trial testing the effect of vitamin A supplementation on pregnancy outcomes and early mother-to-child HIV-1 transmission in Durban, South Africa. South African Vitamin A Study Group. *AIDS* **13**(12), 1517–1524.
- Fawzi WW, Mbise RL, Hertzmark E *et al.* (1999) A randomized trial of vitamin A supplements in relation to mortality among human immunodeficiency virus-infected and uninfected children in Tanzania. *Pediatric Infectious Disease Journal* **18**(2), 127–133.
- Fawzi WW, Msamanga GI, Hunter D *et al.* (2002) Randomised trial of vitamin supplements in relation to transmission of HIV-1 through breastfeeding and early child mortality. *AIDS* **16**(14), 1935–1944.
- Fawzi WW, Msamanga GI, Spiegelman D *et al.* (2004) A Randomized trial of multivitamin supplements and HIV disease progression and mortality. *New England Journal of Medicine* **351**, 23–32.
- French N, Gray K, Watera C *et al.* (2002) Cryptococcal infection in a cohort of HIV-1-infected Ugandan adults. *AIDS* **16**(7), 1031–1038.
- Gibert CL, Wheeler DA, Collins G *et al.* (1999) Randomized, controlled trial of caloric supplements in HIV infection. Terry Bein Community Programs for Clinical Research on AIDS. *Journal of Acquired Immune Deficiency Syndrome and Human Retrovirology* **22**(3), 253–259.

J. Mermin *et al.* **Preventive care package for persons with HIV**

- Grant AD, Kaplan JE & de Cock KM (2001) Preventing opportunistic infections among human immunodeficiency virus-infected adults in African countries. *American Journal of Tropical Medicine and Hygiene* 65(6), 810–821.
- Grimwade K, French N, Mbatha DD, Zungu DD, Dedicoat M & Gilks CF (2004) HIV infection as a cofactor for severe falciparum malaria in adults living in a region of unstable malaria transmission in South Africa. *AIDS* 18(3), 547–554.
- Grubb I, Perriens J & Schwartzlander B (2003) *World Health Organization. A Public Health Approach to Antiretroviral Treatment: Overcoming Constraints*. <http://whqlibdoc.who.int/publications/2003/9241590858.pdf>, pp. 1–10.
- Haggerty PA, Muladi K, Kirkwood BR, Ashworth A & Manunabo M (1994) Community-based hygiene education to reduce diarrhoeal disease in rural Zaire: impact of the intervention on diarrhoeal morbidity. *International Journal of Epidemiology* 23(5), 1050–1059.
- Hawken M, Ng'ang'a L, Meme H, Chakaya J & Porter J (2001) Is cough alone adequate to screen HIV-positive persons for tuberculosis preventive therapy in developing countries? *International Journal of Tuberculosis and Lung Disease* 3(6), 540–541.
- Hays RB, McKusick L, Pollack L, Hilliard R, Hoff C & Coates TJ (1993) Disclosing HIV seropositivity to significant others. *AIDS* 7(3), 425–431.
- Holmes CB, Losina E, Walensky RP, Yazdanpanah Y & Freedberg KA (2003) Review of human immunodeficiency virus type 1-related opportunistic infections in sub-Saharan Africa. *Clinical Infectious Diseases* 36(5), 652–662.
- Ioannidis JP, Collier AC, Cooper DA *et al.* (1998) Clinical efficacy of high-dose acyclovir in patients with human immunodeficiency virus infection: a meta-analysis of randomized individual patient data. *Journal of Infectious Diseases* 178(2), 349–359.
- Jiamton S, Pepin J, Suttent R *et al.* (2003) A randomized trial of the impact of multiple micronutrient supplementation on mortality among HIV-infected individuals living in Bangkok. *AIDS* 17(17), 2461–2469.
- Kabatesi D, Ransom R, Lule JR, Coutinho A, Baryarama F & Bunnell RE (2002) *HIV Prevalence Among Household Members of Persons Living with HIV in Rural Uganda*. XIV International Aids Conference, Barcelona, abstract TuPeD4910.
- Kamenga M, Ryder RW, Jingu M *et al.* (1991) 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* 5(1), 61–67.
- Kaplan JE, Janoff EN & Masur H (1999) Editorial response: do bacterial pneumonia and *Pneumocystis carinii* pneumonia accelerate progression of human immunodeficiency virus disease? *Clinical Infectious Diseases* 29(3), 544–546.
- Kaplan JE, Masur H & Holmes KK (2002) Centers for Disease Control and Prevention. Guidelines for preventing opportunistic infections among HIV-infected persons—2002. Recommendations of the U.S. Public Health Service and the Infectious Diseases Society of America. 2002.MMRW 51 (RR-8), 1–23.
- Keithley JK, Swanson B, Zeller JM *et al.* (2002) Comparison of standard and immune-enhancing oral formulas in asymptomatic HIV-infected persons: a multicenter randomized controlled clinical trial. *Journal of Parenteral and Enteral Nutrition* 26(1), 6–14.
- Kilewo C, Massawe A, Lyamuya EF *et al.* (2001) HIV counseling and testing of pregnant women in sub-Saharan Africa: experiences from a study on prevention of mother-to-child HIV-1 transmission in Dar es Salaam, Tanzania. *Journal of Acquired Immune Deficiency Syndrome and Human Retrovirology* 28(5), 458–462.
- Kumwenda N, Miotti PG, Taha TE *et al.* (2002) Antenatal vitamin A supplementation increases birth weight and decreases anemia among infants born to human immunodeficiency virus-infected women in Malawi. *Clinical Infectious Diseases* 35(5), 618–624.
- Lengeler C (2004) Insecticide-treated bed nets and curtains for preventing malaria. *Cochrane Database System Review* 2004(2), CD000363.
- Luby SP, Agboatwalla M, Painter J, Altar A, Billhimer WL & Hoekstra RM (2004) Effect of intensive handwashing promotion on childhood diarrhea in high-risk communities in Pakistan: a randomized controlled trial. *JAMA* 291(21), 2547–2554.
- Lugada ES, Watera C, Nakiyingi J *et al.* (2002) Operational assessment of isoniazid prophylaxis in a community AIDS service organisation in Uganda. *International Journal of Tuberculosis and Lung Disease* 6(4), 326–331.
- de Luis Roman DA, Bachiller P, Izaola O *et al.* (2001) Nutritional treatment for acquired immunodeficiency virus infection using an enterotropic peptide-based formula enriched with n-3 fatty acids: a randomized prospective trial. *European Journal of Clinical Nutrition* 55, 1048–1052.
- Lule JR, Mermin JH, Malamba S *et al.* (2004) *Effect of safe water and cotrimoxazole on diarrhea among people with HIV and their family*. 13th International Conference on AIDS and STIs in Africa (ICASA), Nairobi, abstract no. 776099.
- Lule JR, Mermin J, Ekwaru JP *et al.* (2005) Effect of home-based water chlorination and safe storage on diarrhea among persons with HIV in Uganda. *American Journal of Tropical Medicine and Hygiene* (in press).
- Lurie MN, Williams BG, Zuma K *et al.* (2003) Who infects whom? HIV-1 concordance and discordance among migrant and non-migrant couples in South Africa. *AIDS* 17(15), 2245–2252.
- Maman S, Mbwambo JK, Hogan NM, Weiss E, Kilonzo GP & Sweat MD (2003) High rates and positive outcomes of HIV-serostatus disclosure to sexual partners: reasons for cautious optimism from a voluntary counseling and testing clinic in Dar es Salaam, Tanzania. *AIDS and Behavior* 7(4), 373–382.
- McNaghten AD, Hanson DL, Jones JL, Dworkin MS & Ward JW (1999) Effects of antiretroviral therapy and opportunistic illness primary chemoprophylaxis on survival after AIDS diagnosis. Adult/Adolescent Spectrum of Disease Group. *AIDS* 13(13), 1687–1695.
- Mermin J, Lule J, Ekwaru JP *et al.* (2004) Effect of cotrimoxazole prophylaxis on morbidity, mortality, CD4 cell count, and HIV viral load among persons with HIV in rural Uganda. *Lancet* 364, 1428–1434.

J. Mermin *et al.* Preventive care package for persons with HIV

- Mermin J, Lule JR, Ekwaru JP & Pitter C (2005a) Should cotrimoxazole prophylaxis be taken by all adults with HIV in Africa? *AIDS* 19(8), 845-846.
- Mermin J, Lule J, Ekwaru JP *et al.* (2005b) Cotrimoxazole prophylaxis by HIV-infected persons in Uganda reduces morbidity and mortality among HIV-uninfected family members. *AIDS* 19, 1035-1042.
- Mole L, Ripich S, Margolis D & Holodny M (1997) The impact of active Herpes Simplex virus infection on human immunodeficiency virus load. *Journal of Infectious Diseases* 176, 766-770.
- Mosimaneotsile B, Talbot EA, Moeti TL *et al.* (2003) Value of chest radiography in a tuberculosis prevention programme for HIV-infected people, Botswana. *Lancet* 362(9395), 1551-1552.
- Newton JA Jr, Tasker SA, Bone WD *et al.* (1995) Weekly fluconazole for the suppression of recurrent thrush in HIV-seropositive patients: impact on the incidence of disseminated cryptococcal infection. *AIDS* 9(11), 1286-1287.
- Nightingale SD, Cal SX, Peterson DM *et al.* (1992) Primary prophylaxis with fluconazole against systemic fungal infections in HIV-positive patients. *AIDS* 6, 191-194.
- Peterson S, Nsungwa-Sabiti J, Were W *et al.* (2004) Coping with paediatric referral-Ugandan parents' experience. *Lancet* 363, 1955-1956.
- Pichard C, Sudre P, Karsegard V *et al.* (1998) A randomized double-blind controlled study of 6 months of oral nutritional supplementation with arginine and omega-3 fatty acids in HIV-infected patients. Swiss HIV Cohort Study. *AIDS* 12(1), 53-63.
- Powderly WG, Finkelstein D, Feinberg J *et al.* (1995) A randomized trial comparing fluconazole with clotrimazole troches for the prevention of fungal infections in patients with advanced human immunodeficiency virus infection. NIAID AIDS Clinical Trials Group. *New England Journal of Medicine* 332(11), 700-705.
- Quick RE, Kimura A, Thevos A *et al.* (2002) Diarrhea prevention through household-level water disinfection and safe storage in Zambia. *American Journal of Tropical Medicine and Hygiene* 66(5), 584-589.
- Rabeneck L, Palmer A, Knowles JB *et al.* (1998) A randomized controlled trial evaluating nutrition counseling with or without oral supplementation in malnourished HIV-infected patients. *Journal of the American Dietetic Association* 98(4), 434-438.
- Reller ME, Mong YJ, Hoekstra RM & Quick RE (2001) Cholera prevention with traditional and novel water treatment methods: an outbreak investigation in Fort-Dauphin, Madagascar. *American Journal of Public Health* 91(10), 1608-1610.
- Schacker T, Zeh J, Hu H, Shaughnessy M & Corey L (2002) Changes in plasma human immunodeficiency virus type 1 RNA associated with herpes simplex virus reactivation and suppression. *Journal of Infectious Diseases* 186(12), 1718-1725.
- Semba RD, Lyles CM, Margolick JB *et al.* (1998) Vitamin A supplementation and human immunodeficiency virus load in injection drug users. *Journal of Infectious Diseases* 177(3), 611-616.
- Spira R, Lepage P, Msellati P *et al.* (1999) Natural history of human immunodeficiency virus type 1 infection in children: a five-year prospective study in Rwanda. Mother-to-Child HIV-1 Transmission Study Group. *Pediatrics* 104(5), e56.
- The Voluntary HIV-1 Counseling and Testing Efficacy Study Group (2000) Efficacy of voluntary HIV-1 counselling and testing in individual and couples in Kenya, Tanzania, and Trinidad: a randomised trial. *Lancet* 356, 103-112.
- Trask SA, Derdeyn CA, Fideli U *et al.* (2002) Molecular epidemiology of human immunodeficiency virus type 1 transmission in a heterosexual cohort of discordant couples in Zambia. *Journal of Virology* 76(1), 397-405.
- UNAIDS (2004a) *Factsheet: Sub-Saharan Africa*, available at: <http://www.unaids.org>.
- UNAIDS (2004b) *Epidemiology of HIV/AIDS Among Children and Adults*, available at: http://www.unaids.org/html/pub/topics/epidemiology/slides02/epicore2003_en_ppt.ppt.
- Villamor E, Mbise R, Spiegelman D *et al.* (2002a) Vitamin A supplements ameliorate the adverse effect of HIV-1, malaria, and diarrheal infections on child growth. *Pediatrics* 109(1), 1-10.
- Villamor E, Msamanga G, Spiegelman D *et al.* (2002b) Effect of multivitamin and vitamin A supplements on weight gain during pregnancy among HIV-1-infected women. *American Journal of Clinical Nutrition* 76(5), 1082-1090.
- Weller S & Davis K (2001) Condom effectiveness in reducing heterosexual HIV transmission. *Cochrane Database System Review* 2001(3), CD003255.
- Whitworth J, Morgan D, Quigley M *et al.* (2000) Effect of HIV-1 and increasing immunosuppression on malaria parasitaemia and clinical episodes in adults in rural Uganda: a cohort study. *Lancet* 356(9235), 1051-1056.
- WHO (2004) *Choosing Interventions That Are Cost Effective: Who Statistical Information System (WHOSIS)*, available at: <http://www3.who.int/whosis/menu.cfm>.
- WHO, UNAIDS (2000) *Provisional WHO/UNAIDS Secretariat Recommendations on the Use of Cotrimoxazole Prophylaxis in Adults and Children Living with HIV/AIDS in Africa*, available at: <http://www.unaids.org>.
- Wiktor SZ, Sassin MM, Grant AD *et al.* (1999) 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* 353(9163), 1469-1475.
- Wiseman V, Hawley WA, ter Kuile FO *et al.* (2003) The cost-effectiveness of permethrin-treated bed nets in an area of intense malaria transmission in western Kenya. *American Journal of Tropical Medicine and Hygiene* 68(4), 161-167.
- Yazdanpanah Y, Losina E, Anglaret X *et al.* (2004) *Clinical Impact and Cost-Effectiveness of Co-Trimoxazole Prophylaxis in Patients Living with HIV/AIDS in Cote d'Ivoire: A Trial-Based Analysis*. 15th International Aids Conference, Bangkok, Thailand.
- Zachariah R, Spielmann MP, Harries AD, Gomani P & Bakali E (2002) Cotrimoxazole prophylaxis in HIV-infected individuals after completing anti-tuberculosis treatment in Thyolo, Malawi. *International Journal of Tuberculosis and Lung Disease* 6(12), 1046-1050.

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Authors

Jonathan Mermin, Rebecca Bunnell, John Lule and Jonathan Kaplan, CDC-Uganda, Uganda Virus Research Institute, PO Box 49, Entebbe, Uganda. Tel.: +256-41-320776; Fax: +256-41-3321457; E-mail: jhm7@cdc.gov (corresponding author).

A. Opio, Uganda Ministry of Health, Kampala, Uganda.

A. Gibbons, United States Agency for International Development, Washington DC, USA.

M. Dybul, Office of the US Global AIDS Coordinator, United States Department of State, Washington DC, USA.