Prophylaxis of opportunistic infections in HIV-infected adults in sub-Saharan Africa: opportunities and obstacles

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Introduction

In industrialized countries the introduction of highly active antiretroviral therapy (HAART) has led to a dramatic reduction in morbidity and mortality among HIV-infected patients [1] and has made prophylaxis of opportunistic infections of less concern. At the same time, in developing countries, there has been an increased interest in prophylaxis of HIV-associated infections.

It is not an overstatement to say that, so far, care of HIV-infected patients in developing countries has received less than optimal attention. Commendable efforts have been made to organize palliative care, home care and psychosocial support, but – apart from trials of prophylactic treatment of tuberculosis – the evaluation of low-cost biomedical interventions to improve life expectancy and quality of life has lagged behind. HAART will become more accessible to HIV-infected people in developing countries but it is a long process and large sections of the population, in particular rural populations, will likely remain deprived of it. Prophylaxis of infections may be an affordable option to improve the life expectancy and quality of life of those who will not have access to HAART in a foreseeable future. In this paper we will present an overview of what is known about prevention of HIV-associated infections in sub-Saharan Africa. We will focus on primary prophylaxis, aiming to prevent first episodes of infections, as feasibility and access to secondary prophylaxis cannot be separated from the treatment of opportunistic infections.

Prophylaxis of opportunistic infections in industrialized countries

According to the Prevention of Opportunistic Infections Working Group in the US opportunistic infections are infections for which the incidence and/or severity are increased in patients with HIV-related immunosuppression [2]. Prevention of opportunistic infections consists of prevention of exposure to the pathogen and prevention of disease by prophylactic treatment. Table 1 gives the US recommendations for the primary prevention of opportunistic infections.

Recommendations for the prevention of exposure include avoiding the consumption of undercooked red meat and exposure to cats to prevent *Toxoplasma* infection; avoiding contact with patients with tuberculosis (TB); and not drinking water directly from a river or lake because of cryptosporidiosis [3–5]. In many instances however prevention of exposure is not feasible, in particular if the pathogen is ubiquitous as is the case for *Pneumocystis carinii* and *Mycobacterium avium*

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Table 1. Prophylaxis to prevent first episode of opportunistic infections in adults with HIV infection: main recommendations for the US [4]

Selected pathogens	First choice
1. Strongly recommended as standard of care	
*Pneumocystis carinii**	TMP-SMX 80/400 mg q.d. or 160/800 mg q.d.
*Toxoplasma gondii**	TMP-SMX 160/800 mg q.d.
Mycobacterium avium complex *	azithromycin 1200 mg q.w. or clarithromycin 500 mg b.i.d.
Mycobacterium tuberculosis	isoniazid 300 mg q.d. × 9 mo; or rifampicin 600 mg +pyrazinamide 20 mg/kg q.d. × 2 mo
2. Generally recommended	
Streptococcus pneumoniae	pneumococcal vaccine 0.5 ml intramuscular
3. Not routinely indicated	
Cytomegalovirus (CMV)	no treatment but regular check-up, or oral ganciclovir 1g t.i.d.
Candida	not recommended
Cryptococcus neoformans	not recommended
Herpes simplex virus	not recommended
Cryptosporidium	not available

TMP-SMX, trimethoprim-sulfamethoxazole (= cotrimoxazole); q.d., daily; q.w., weekly; b.i.d., twice a day; t.i.d., three times a day; mo, months.
* Discontinuation of prophylaxis will be considered according to the immune restoration and the level of the viral load while under highly active antiretroviral therapy.

complex (MAC) [5]. Moreover the environmental sources of pathogens are often not known [3], and evidence for the efficacy of measures to avoid exposure is missing [4]. Consequently, most recommendations for the prevention of exposure remained optional.

Before HAART became available the introduction of chemoprophylaxis against *Pneumocystis carinii* pneumonia (PCP), toxoplasmosis, MAC and other pathogens has contributed to the improvement of the quality of life and life expectancy of HIV-infected persons in industrialized countries [4]. Death rates among patients with primary PCP prophylaxis were reduced by 40% to 21% [6–8]. The widespread use of preventive therapy against *Pneumocystis carinii* has led to a decrease in the incidence of primary PCP [9,10] and a shift in the clinical manifestations of HIV-1 infection, PCP being replaced by infections such as MAC disease and cytomegalovirus infection that occur in more advanced immunosuppression. Occurrence of the first AIDS-defining illness was delayed for 6 to 12 months [10]. The use and impact of other prophylactic treatments such as for TB [11] and MAC infection are less well documented, but there are reports that TB preventive therapy has been underutilized [12,13].

HAART has dramatically changed the patterns of occurrence of opportunistic infections. Marked reductions have been seen in the incidence of PCP, MAC, cytomegalovirus infection and TB [1,14,15]. More and more data are becoming available from prospective studies that suggest that prophylaxis can be safely discontinued in patients responding to HAART [4,5,16–22] and HAART has become the most effective approach to preventing opportunistic infections in industrialized countries [4].

The spectrum of HIV-associated infections in adults in sub-Saharan Africa

Results from several studies suggest that in Africa opportunistic diseases in HIV-infected adults occur at the same level of immunosuppression as in industrialized countries [23,24]. However death seems to occur at higher levels of CD4 cell counts than in industrialized countries [25,26].

Weight loss, minor mucocutaneous conditions, chronic diarrhoea, chronic fever and severe bacterial infections have been found to be early manifestations of HIV infection in a population-based cohort study in a rural area in Uganda [27].

In hospitalized, HIV-1-infected patients, TB and bacterial infections have been found to be the two most common causes of morbidity and mortality [25,28]. In clinical surveys and autopsy studies, up to 54% of patients had TB [28,29]. Indirect evidence for the importance of TB as HIV-associated infection is provided by the dramatic increases in reported cases of tuberculosis in Africa associated with the spread of HIV [29].

Bacteremia by organisms other than *M. tuberculosis* has been reported in 15 to 26% of HIV-positive patients that are admitted to hospital [25,30]. The predominant organisms are Gram-negative bacilli, particularly non-typhoid salmonella, and *Streptococcus pneumoniae*.

Streptococcus pneumoniae is the second most common bacterial aetiology of respiratory infections, after *M. tuberculosis* [25,26]. PCP is less common in HIV-infected patients in Africa but does occur. At first it

was estimated that between zero and 22% of patients with respiratory symptoms had PCP [31]. More recently, studies from Zimbabwe [32] and South Africa [33], found that 33 and 27% respectively, of HIV-positive patients with pulmonary disease and sputum negative for acid-fast bacilli, had PCP. In Abidjan PCP affected almost one-third of HIV-infected children under 15 months [34], a rate similar to that found in industrialized countries. Shorter survival in HIV-infected patients is unlikely to fully explain the lower incidence of PCP in Africa compared to industrialized countries, since many hospitalized patients do have profound immunosuppression [24,35]. However, lack of diagnostic facilities and access to care may – at least in part – explain the differences.

Cryptosporidium, *Isospora belli*, non-typhoid salmonella and *Shigella* species are the most frequently identified pathogens associated with diarrhoea in HIV-infected patients in Africa [25]. In many cases of diarrhoea, however, no cause is found.

Cerebral toxoplasmosis accounted for 10% of deaths of HIV-infected patients in Abidjan and ranked among the three most common causes of death [28]. However the seroprevalence of *Toxoplasma* infection varies widely in Africa, from 11 to 78%, and the incidence of cerebral toxoplasmosis may therefore be very different between different regions in Africa [28].

For a long time there has been controversy about the interaction between malaria and HIV infection. Studies in pregnant women found that the prevalence of malaria was higher in HIV-infected women than in HIV-negative women [36,37], but other studies failed to find convincing evidence for an association between the incidence and /or severity of malaria and HIV infection [38,39]. A recently published adult cohort study in Uganda found that HIV-1 infection was associated with an increased frequency of clinical malaria and parasitemia [40].

The association between severe forms of leishmaniasis and HIV infection is well documented in Europe. This could have implications for the control of leishmaniasis in African regions where it is endemic, but so far few data are available from Africa [41,42].

In conclusion, more than half of HIV-related infections and deaths in sub-Saharan Africa are caused by treatable and potentially preventable infections [25,28,43]. The spectrum of infections associated with HIV in adults in Africa differs from the one in industrialized countries. Reasons for this are differences in the background prevalence of pathogens [3,44,45], such as *M. tuberculosis*, and probably also the shorter life expectancy of HIV-infected people in sub-Saharan Africa due to limited access to care. In addition, in high HIV prevalence populations, transmission of certain pathogens, such as herpes simplex virus-2 may be enhanced [46].

Prevention of HIV-associated infections in sub-Saharan Africa: opportunities

Chemoprophylaxis of TB

Chemoprophylaxis of TB is the best-studied intervention against opportunistic infections in HIV-infected individuals in developing countries. In randomized controlled trials, daily isoniazid for 6 or 12 months had a protective effect ranging between 30 and 83%, in tuberculin skin test (TST)-positive subjects [47–50]. This effect was statistically significant in all studies but one [49]. In Uganda [50], also a shorter regimen of a daily combination of rifampicin and isoniazid for 3 months was protective. In TST-negative persons and in anergic patients no statistically significant effect was found of daily isoniazid [47,49–51]. Twice weekly isoniazid for 6 months or a combination of rifampicin and pyrazinamide for 3 months had a non-statistically significant effect [52] on a group of TST-positive and TST-negative HIV-infected patients combined.

Survival was not improved in any of the studies, but the studies were not designed to evaluate the effect of preventive therapy on mortality. However one meta-analysis [53] showed a moderate reduction of the risk of death [relative risk, 0.73; 95% confidence interval (CI), 0.57–0.95] in TST-positive subjects.

Chemoprophylaxis with cotrimoxazole

Until recently no data were available from randomized controlled trials, of cotrimoxazole prophylaxis for the prevention of bacterial and parasitic infections in developing countries. Anglaret *et al.* [54] found that the rate of severe events, defined as death or hospital admission for any cause, was 43% lower (hazard ratio 0.57; 95% CI, 0.43–0.75) in adults in the early stages of HIV-1 infection, taking cotrimoxazole (160mg/800mg) daily compared with a placebo group. The benefit was apparent in all CD4 cell count subgroups but overall survival did not differ significantly between the cotrimoxazole and placebo group.

In Africa morbidity and mortality are increased in TB patients with HIV infection compared with those without HIV infection [29] and this may be partly due to other concomitant opportunistic infections. This prompted Wiktor *et al.* [55] to assess the safety and efficacy of daily cotrimoxazole (160mg/800mg) in HIV-1-infected patients with sputum-smear-positive pulmonary TB. In a randomized controlled trial they found a 46% (95% CI, 23–62%) decrease in mortality and a 43% (95% CI, 10–64%) decrease in hospitaliza-

tions in patients taking cotrimoxazole with their TB treatment, compared to a control group. The effect was mainly seen in patients with CD4 cell counts below 350×10^6 cells/l.

In another randomized controlled trial, in Dakar, Senegal, enrolment had to be stopped after the results of the two previous studies became available. No statistically significant difference in survival and clinical events was found between the cotrimoxazole (80mg/400mg) and the placebo group [56], but sample sizes were small.

Pneumococcal vaccine

Vaccination against pneumococci has been recommended for HIV-infected patients in the US and in UK [4]. These recommendations are not supported by efficacy data but are based on immunogenicity data, and the low cost and safety of the vaccine. In Uganda a randomized controlled trial was conducted with a 23-valent pneumococcal polysaccharide vaccine, which showed no protective effect of the vaccine in HIV-1-infected adults in the early stages of the disease [57]. In fact pneumonia from all causes was significantly more frequent in the vaccinated group than in the placebo group. The reasons for this apparently harmful effect are unclear.

Malaria prevention

Studies on HIV-infected pregnant women showed that prophylaxis with chloroquine or intermittent treatment with sulfphadoxine-pyrimethamine had a lesser effect on *Plasmodium falciparum* infections than in HIV-uninfected women [37,58,59]. A WHO Expert Committee on Malaria has suggested to increase the frequency of sulphadoxine-pyrimethamine intermittent treatments for pregnant women with HIV living in areas where malaria is endemic [60]. Further studies are needed to determine the practical implications of the recently published data on the association between malaria and HIV-1 infection in Ugandan adults [40].

Supply of safe water for the prevention of HIV-associated diarrhoea

Measures to prevent exposure to pathogens causing diarrhoea, such as the supply of safe water, may have a positive impact in developing countries where sanitation is poor. Research is ongoing on *Cryptosporidium* infection.

Prevention of HIV-associated infections in sub-Saharan Africa: challenges

In 1993, WHO and the International Union Against Tuberculosis and Lung Disease (IUATLD) first recommended TB prophylaxis for HIV-infected people as an individual health measure [61]. Five years later, WHO and UNAIDS strongly recommended preventive therapy for TB in HIV-infected individuals with positive TST [62]. Recently recommendations on cotrimoxazole prophylaxis in adults and children living with HIV/AIDS in Africa have been issued by the same organizations [63]. Cotrimoxazole prophylaxis is recommended as part of a minimum package of care and should be proposed to adults with symptomatic HIV infection (WHO clinical stages 2, 3 or 4), asymptomatic patients with CD4 cell count below 500×10^6 cells/l, and children meeting certain criteria. Some African countries, including Côte d'Ivoire, have already decided to recommend cotrimoxazole prophylaxis for HIV-infected patients. However there are still many unresolved questions and non-negligible operational problems that need to be addressed.

Unresolved questions

A major concern about the large-scale implementation of chemoprophylaxis for HIV-associated infections is the emergence of drug resistance. There is no evidence from the efficacy studies of a higher rate of drug resistance in those who developed tuberculosis despite having received isoniazid preventive therapy, but the situation may change when preventive therapy is implemented on a large scale [64].

With regards to prophylaxis with cotrimoxazole, resistance to cotrimoxazole in non-typhi salmonella was low (14%) in Abidjan where the two efficacy trials have been conducted [65]. However, resistance rates may be higher in other parts of Africa. For instance in Kenya resistance rates of 39 to 46% have been found [66,67]. Therefore, the results of the Côte d'Ivoire studies can not be generalized. Studies on the feasibility and/or the efficacy of cotrimoxazole for prophylaxis are ongoing in Malawi [68] and in South Africa [69], where the resistance profiles are different. However, because of ethical problems, further randomized controlled trials to assess the efficacy of cotrimoxazole prophylaxis are unlikely to be conducted in the near future.

In settings where bacterial resistance against cotrimoxazole is high, this antibiotic could still prevent parasitic infections, such as cerebral toxoplasmosis, but the impact is likely to be limited [70].

In HIV-infected patients in industrialized countries, cotrimoxazole prophylaxis has been implicated in the development of cotrimoxazole bacterial resistance [71,72]. Anglaret *et al.* [54] found no significant difference in susceptibility to cotrimoxazole of pathogens isolated during the study, between the prophylaxis group and the control group, but follow-up was rather short and the groups were small. The possibility of emergence of resistance induced by the large-scale use of cotrimoxazole remains a concern and bacterial

susceptibility to cotrimoxazole should be monitored where cotrimoxazole prophylaxis is implemented on a large scale. In addition, in areas where both HIV infection and malaria are endemic, there is the threat of the emergence of cross-resistance between trimethoprim and pyrimethamine in *P. falciparum* which may accelerate the development of *P. falciparum* resistance against sulphadoxine-pyrimethamine [73].

In the absence of HAART, prophylactic treatment with cotrimoxazole, once initiated, is taken for life, but there are still doubts about the optimal duration of TB preventive therapy. The mean duration of follow-up in the randomized controlled trials did not exceed 36 months. Some data suggest that the protective effect of preventive therapy diminishes over time, but that there is an effect in the first 2.5 years [74]. Re-infection may occur in HIV-infected patients [75] and it has been suggested that high-risk populations take preventive treatment for a longer time, possibly life-long, or repeat the chemoprophylaxis. The relevance, efficacy, cost and feasibility of such strategies need to be carefully assessed. In addition the benefits of TB preventive therapy in HIV-infected patients in advanced stages of the disease, have not been properly evaluated.

Operational issues

It is obvious that chemoprophylaxis of HIV-associated infections can never be a substitute for a failing care system. We contend that the implementation of a programme of prophylaxis, for instance for TB, only makes sense if there is a proper treatment programme in place for active TB.

There are several steps to be considered in the delivery of chemoprophylaxis, each with their own problems (Table 2). The first problem to be overcome is the identification of HIV-infected patients in the early stages of the infection when they are likely to benefit most from preventive therapy. In addition, patients in late-stage disease pose problems for TB chemoprophylaxis, as ruling out active TB becomes more difficult [76,77].

Voluntary counselling and testing centres (VCT centres) allow the recruitment of patients in earlier stages of the disease. They could be used as entry points for the delivery of preventive therapies. Newly diagnosed HIV-infected individuals however, may decline preventive therapy or may initially accept it and fail to go through the complete process, because of psychological adjustment and the need to first cope with the test result.

In settings where cotrimoxazole prophylaxis is recommended, offering HIV counselling and testing to all newly diagnosed TB patients should be considered. Several studies from Africa have found that acceptance of HIV testing by TB patients was high [55,68,78].

Before prescribing chemoprophylaxis against TB to an HIV-infected person, active TB needs to be excluded. Sputum examination should be carried out in patients who are coughing for more than 3 weeks. Experts also recommend a chest X-ray for all potential recipients before considering preventive therapy [62], as smear-negative pulmonary TB is more common in HIV-infected patients [29]. However, chest X-rays are costly and patients may default if they are referred for additional tests. The use of chest X-ray in asymptomatic individual needs further evaluation [79,80].

Whether prophylaxis should be provided only to patients who test positive on TST or to all HIV-infected patients needs to be assessed carefully in each context.

Table 2. Operational issues related to preventive therapies in Africa: effective strategies and validated selection criteria from clinical trials and (in italics) issues or other options that need validation

Delivery process	Cotrimoxazole prophylaxis	Tuberculosis prophylaxis:
(Early) identification of HIV-infected patients through	Health services (HIV clinic) TB clinic *VCT services*	Health services *VCT services*
Selection criteria	WHO stage 2, 3 TB patients *Asymptomatic and advanced stage patients* *Other criteria: CD4, total lymphocyte count*	To select patients who benefit most: TST + *Anergic HIV patients* *All HIV-positive patients* To exclude active TB: Chest X-ray + sputum (if cough) *Clinical criteria only*
Ensuring adherence	(lifelong treatment) Education and follow-up *Other strategies to ensure adherence*	(time limited treatment) Education and follow-up *Other strategies to ensure adherence, e.g.: link with DOT programme*
Monitoring adverse events	Clinical follow up and patient information Management of adverse reactions *Monitoring of haematological disorders*	Clinical follow up and patient information Management of adverse reactions

TB, tuberculosis; VCT, voluntary counselling and testing; TST, tuberculin skin test; DOT, directly observed treatment

In some settings it may not be feasible to do a TST. Moreover, there is a high rate of anergy in HIV-infected patients with advanced disease and these patients are at higher risk of TB [81–83]. Some argue that, in countries with high TB prevalence, preventive therapy should be offered to all patients after exclusion of active TB. Not including TST in screening procedures may also increase participation. However, as the benefits of TB prophylaxis have not been proven in anergic patients, large numbers of clients may be unnecessarily treated, thus increasing the costs [62]. On the other hand, lack of a TST is not considered a reason for not implementing TB preventive therapy. It may still be considered without skin test in certain groups of patients with HIV infection, such as those living in populations with a high prevalence of TB infection (estimated to be $> 30\%$), health care workers, household contacts of TB patients, prisoners, miners and other selected groups at high risk of acquisition or transmission of TB [62].

Selection of patients for cotrimoxazole prophylaxis poses completely different problems. The efficacy of cotrimoxazole prophylaxis has been assessed in HIV-infected patients in the early stages of disease and in TB patients with HIV infection. However there is still uncertainty about the optimal time for starting cotrimoxazole prophylaxis and on how to reliably assess the stage of HIV infection if facilities for assessing the CD4 cell count are not available.

Adherence with prophylaxis under trial conditions was good but is likely to be less good in routine settings (Table 3). Strategies and techniques that are used to promote adherence to TB treatment may be applied to preventive therapies, and could be tested in feasibility studies.

Patients should be informed of potential adverse reactions of the drugs. Routine monitoring of liver enzymes for hepatitis in patients taking isoniazid is not recommended in developing countries. In the two efficacy trials on cotrimoxazole prophylaxis [54,55], the frequency of cutaneous reactions was low and the incidence of severe anaemia and neutropenia was not higher in the cotrimoxazole group. But the risk may increase with time, and will be difficult to monitor in areas with limited access to laboratory facilities.

Cost

There are a few studies on the cost-efficacy and cost-benefit of TB preventive therapy, but so far no studies have been carried out on the cost-efficacy of cotrimoxazole prophylaxis. One study modelled the costs and benefits of a TB preventive therapy programme in Zambia using daily isoniazid for 6 months [84]. TST was not included in the model. The benefit/cost ratio was 0.86 if preventing one case of TB prevents one additional case, and 1.71 if preventing one case of TB prevented an additional five cases. It was suggested that TB prophylaxis be targeted at HIV-infected individuals whose occupation or living situation exposes them to large numbers of other people. However the feasibility of such a strategy is doubtful. Bell *et al.* [85] found that when medical care and social costs are considered together, 6 months of isoniazid treatment will save money. In an operational study carried out in Uganda in 1992, the estimated cost per patient successfully completing a 6-month course of isoniazid prophylaxis, was US$ 18 [86]. Prophylaxis with a combination of isoniazid and rifampicin for 3 months is more costly (US$ 37) [85].

Lessons from feasibility studies

Table 3 summarizes published feasibility studies on the chemoprophylaxis of TB in Africa. The settings are very different but valuable lessons can be learned from these studies.

Table 3. Feasibility studies on TB preventive therapy in Africa: proportion of subjects dropping out of preventive therapy (PT) service[a] [76,77,79,85,86]

	Recruitment through				
	VCT centre		HIV clinic		Hospitalization
Studies	Aisu *et al.* (1995) Uganda [86]	Ayles *et al.* (2000) Zambia [80]	Godfrey-Fausset *et al.* (1995) Zambia[b] [87]	Lugada *et al.* (2000) Uganda [76]	Anglaret *et al.* (1995) Rwanda [77]
No. of HIV patients (prevalence in study population)	9862 (23%)	1059 (23%)	225 (47%)	1640 (100%)	146 (53%)
No. of HIV patients entering PT inclusion process (%)	*1524 (15%)*	*804 (76%)*	*95 (42%)*	*1640 (100%)*	*146 (100%)*
No. of patients who completed inclusion process (%)	1094 (72%)	NA	NA	NA	NA
No. of patients eligible (%)	520 (48%)	NA[c]	85 (89%)[c]	100 (6%)	43 (29%)[c]
No. of patients entering inclusion process who started PT (%)	*520/1524 (34%)*	*365/804 (45%)*	*77/95 (81%)*	*100/1640 (6%)*	NA
No. of patients who completed (adherence) (%)	322 (62%)	123 (33.6%)	NA	75 (75%)	NA

[a]Adapted and updated from WHO global tuberculosis programme and UNAIDS [62]. [b]Other study that has reported on feasibility (data from PT trial). [c]Positive tuberculin skin test was not included in eligibility criteria. PT, preventive therapy; VCT, Voluntary counselling and testing; NA, not available.

Recruitment was poor at a VCT centre in Uganda [86]. Only 15% of HIV-positive persons were seen by a physician and entered the preventive therapy process, and among them one-third only started treatment. In a recent study on the feasibility of provision of isoniazid prophylaxis in Lusaka [80], any client testing positive for HIV at a VCT centre was offered prophylaxis. Main reasons for not starting treatment included late stage of presentation for HIV test and loss during the screening process. The largest losses, in another study in Zambia [87], were among those who declined referral to the preventive therapy trial or accepted referral but did not reach the hospital clinic. In an operational assessment of isoniazid prophylaxis in a community-based HIV/AIDS clinic in Uganda [76], a very low proportion (6%) of patients who were screened, were eventually put on prophylaxis, mainly due to the low proportion of eligible patients.

Preliminary results of an operational study in Malawi showed that it was possible to effectively implement counselling, HIV testing and cotrimoxazole prophylaxis in HIV-positive patients with TB in a rural district [68]. The vast majority of TB patients accepted to be tested (90%), 77% were HIV positive and 98% started cotrimoxazole prophylaxis. Compliance was good.

Conclusions

In analogy to the successes of chemoprophylaxis in industrialized countries in the era before HAART, prophylaxis of TB and cotrimoxazole preventive therapy may open up opportunities for the improvement of the quality of life and the life expectancy of HIV-infected patients in developing countries. However it would be erroneous to extrapolate what was done in industrialized countries to sub-Saharan Africa. First of all the spectrum of infections is quite different. Secondly, there are a number of unresolved issues and obstacles that call for some caution. More research is needed, in particular more randomized trials (especially on cotrimoxazole prophylaxis) and more operational research.

In the meanwhile however we can move forwards and learn by doing. In a country or setting where conditions that are required for such interventions to work are fulfilled – i.e. capacity for HIV counselling, trained health care staff, adequate drug supply, capacity to ensure adequate monitoring and follow-up – preventive therapy must be considered. VCT services and health services should merge in order to provide more comprehensive care. In the same way, HIV/AIDS care and TB control services should be linked. Prior to considering TB prophylaxis, TB treatment services should ensure that they successfully treat most cases of active TB [62], which remains the priority for TB control programmes. In addition, TB prophylaxis should only be used when it is possible to exclude active TB cases.

Preventive therapy is not a panacea. It is only one component of a care package [88], that should be made available for people living with HIV/AIDS. Thus in settings where there is no wide-spread resistance against cotrimoxazole, chemoprophylaxis with this antibiotic should be included in the minimum package of care for HIV-infected people [88]. Delivery of TB prophylaxis requires more conditions to be fulfilled, as previously mentioned, and may be part of a more sophisticated package.

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