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[Intervention Review]

Cotrimoxazole prophylaxis for opportunistic infections in adults with HIV

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ABSTRACT

Background

The prevention and early treatment of infections are the mainstay of the medical management of the majority of people with HIV infection, who live in low income countries without access to antiretroviral drugs. Cotrimoxazole is cheap and effective against a wide range of organisms. However, routine prophylactic treatment is difficult to deliver in low-resource settings, and could also lead to increased resistance to the drug.

Objectives

To assess the effects of routinely administered cotrimoxazole on death and illness episodes in HIV infected adults.

Search methods

We searched the Cochrane HIV/AIDS Group register, the Cochrane Controlled Trials Register, MEDLINE, LILACS, AIDSLINE, AIDSTRIALS and AIDSDRUGS databases, and proceedings and abstracts from AIDS and tuberculosis (TB) conferences (search date July 2001). We checked reference lists for trials and other pertinent articles, and contacted pharmaceutical companies and experts in the field.

Selection criteria

Randomised or quasi randomised trials comparing routinely administered cotrimoxazole versus placebo or no treatment in adults (age greater than 13 years).

Data collection and analysis

Two reviewers independently assessed trial eligibility and quality, and extracted data. Where data were incomplete or unclear trial authors were contacted for further details.

Main results

Four trials involving 1476 people were identified. Three trials (1416 people) studied heterosexual men and women in West Africa. A fourth trial was of homosexual men on chemotherapy for Kaposi's sarcoma, in the United States. Meta-analysis of the three African trials showed a significant beneficial effect of cotrimoxazole for death: relative risk 0.69 (95% confidence interval 0.55 to 0.87); for morbid events: 0.76 (0.64 to 0.9); and for hospitalisation: 0.66 (0.48 to 0.92). There was no significantly greater risk of adverse effects: relative risk 1.28 (0.47 to 3.51). Effects were similar in people with early and advanced HIV disease. Insufficient evidence was found on effects in areas with higher bacterial resistance or in people on antiretroviral therapy.

Authors' conclusions

In the trials included in the review, cotrimoxazole prophylaxis had a beneficial effect in preventing death and illness episodes in adults with both early and advanced HIV disease. However, the wider applicability of these findings is unclear, in particular to areas with higher background bacterial resistance to cotrimoxazole. Further trials would be required in differing settings to widen applicability.

PLAIN LANGUAGE SUMMARY**A daily low dose of cotrimoxazole for preventing opportunistic infections in adults with HIV**

Cotrimoxazole helps to prevent infections in adults who are HIV-infected but may increase resistance to the drug and more trials are needed.

Human immunodeficiency virus (HIV) attacks the immune system, leaving people vulnerable to infections. Such infections often cause death or serious complications. Anti-viral drugs can slow HIV. However, most HIV-infected people live in developing countries without access to these treatments. Preventing infections is therefore the main aim of HIV treatment in developing countries. A daily low dose of cotrimoxazole, an antibiotic (a drug that fights bacterial infections), is used to try to prevent infections and improve survival, but with unknown effectiveness for HIV-infected people. The review found cotrimoxazole improved survival in some areas of Africa and found improvements in other outcomes, but adverse effects and possible drug resistance are unclear. More trials are needed.

BACKGROUND

Human immunodeficiency virus (HIV) damages the immune system, making secondary (or opportunistic) infections more common. Infected people may develop infections that are rare in those with normal immunity, such as *Pneumocystis carinii* pneumonia (PCP), toxoplasmosis and cryptococcosis. They may also suffer from common infections such as pneumococcal disease and non-typhi *Salmonella* septicaemia.

The spectrum of infections varies across the world. In the developed world, previously rare infections such as PCP are important (Gottlieb 1981). Soon after the start of the HIV epidemic the potential was recognised for altering the course of the disease by preventing opportunistic infections with antibiotic prophylaxis (Fischl 1988), and prophylactic antibiotics such as cotrimoxazole are widely used in conjunction with antiretroviral therapy. Antiretroviral therapy involves a combination of expensive drugs that have a direct action on HIV to slow down disease progression.

However, most of the HIV/AIDS burden is borne by people in the developing world (UNAIDS 2000), who are without access to antiretroviral drugs. Life expectancy is similar to that seen in the developed world without antiretroviral therapy (Morgan 2000), but the organisms causing opportunistic infections are quite different. Although PCP occurs, its importance and impact is much less (Abouya 1992). The main causes of mortality and morbidity are tuberculosis and bacterial and parasitic infections, particularly pneumococcus, non-typhi *Salmonella* and parasitic enteritis (Gilks 1990, Vugia 1993, Gilks 1996, Grant 1997). (The prophylaxis of tuberculosis is dealt with in another review [Wilkinson 2000].) This pattern of disease is related to high exposure to organisms that can cause illness in people with normal immunity, and to poor access to healthcare (Del Amo 1998). Because antiretroviral therapy is currently not available to the majority of people in the developing world, the mainstay of management is the treatment and prevention of such infections.

Cotrimoxazole (trimethoprim-sulphamethoxazole, Septrin®, Septra® or Bactrim®) is of particular interest for prophylactic treatment as it has a wide range of action against common bacteria, parasites including toxoplasmosis and those causing chronic diarrhoea, and fungi and yeasts such as PCP. Cotrimoxazole is cheap, costing less than one US dollar per month for prophylactic treatment with one 960 mg tablet daily (SA PMSC 2000) and is widely available. However, it is also frequently used in the treatment of acute infections and it shares a component with one of the most commonly used drugs for malaria (sulphadoxine-pyrimethamine). There is, therefore, the possibility of increased resistance to the drug, rendering it useless when required to treat infection. In addition, routine delivery of the drug in low-income settings is expensive and difficult in a practical sense. It is thus important to establish whether preventative measures are more cost-effective than alternatives such as prompt effective treatment of illness episodes when they occur.

Patients who have both HIV and tuberculosis have higher death rates than those with either infection on its own (Colebunders 1989, De Cock 1992, Perriens 1995). This is despite the fact that the standard tuberculosis treatment is as effective at curing TB in HIV positive and negative people (Colebunders 1989, Perriens 1995). The possible reasons for the higher death rate include the

dual effect of two infections that suppress the immune system, and the effect of tuberculosis in increasing the speed at which HIV progresses to a more advanced state (Del Amo 1999). The effect of cotrimoxazole prophylaxis in patients with both infections is thus of particular interest.

OBJECTIVES

To assess the effects of routinely administered cotrimoxazole on death and illness episodes in HIV infected adults (children are covered in a separate review).

METHODS

Criteria for considering studies for this review

Types of studies

Randomised and quasi-randomised controlled trials

Types of participants

People aged 13 years or more who are infected with HIV

Types of interventions

Intervention: cotrimoxazole, given routinely;

Control: placebo or no treatment.

Types of outcome measures

Primary Outcome

Mortality, expressed as number of deaths occurring during the follow up period

Secondary outcomes

- Serious morbid events as defined by the trial researchers
- Admissions to hospital
- Adverse events, defined as those causing cessation of the therapy or hospitalisation
- Type of infection:
 - Pneumocystis carinii pneumonia (PCP);
 - toxoplasmosis;
 - bacterial infections;
 - parasitic infections excluding toxoplasmosis;
 - fungal infections excluding PCP.

Search methods for identification of studies

Studies were identified through the Cochrane HIV/AIDS Group register, the Cochrane Controlled Trials Register (CENTRAL/CCTR), and using MEDLINE, EMBASE, AIDSLINE, AIDSTRIALS and AIDSDRUGS databases (search date July 2001). Proceedings and abstracts from AIDS and tuberculosis (TB) conferences were searched and experts in the field contacted in an attempt to identify unpublished research or trials still underway. Reference lists from reports of trials and other pertinent articles were searched.

Pharmaceutical companies were approached for any unpublished data on this topic.

Data collection and analysis

Eligibility

Study eligibility was judged independently by two reviewers who reviewed the abstracts identified in the above searches. If the title of a report was judged to be potentially relevant by either reviewer then the abstract was reviewed by both. If the abstract was judged by either reviewer to be potentially eligible the full article was then examined. Disagreements were resolved by discussion.

Data collection

Characteristics of included studies and data were extracted independently by two reviewers using a standard form. Data retrieved from the reports included study design and methodological quality, participant characteristics (age, concomitant TB, stage of disease), trial setting (including level of resistance to cotrimoxazole), interventions, co-interventions (including antiretroviral use) and outcomes.

Analysis

A quantitative analysis was performed using the intention to treat principle. The chi-square test for heterogeneity was used to assess the likelihood of heterogeneity in the three African trials. No statistical heterogeneity existed in any of the analyses (P-value greater than 0.10). Meta-analysis was performed using a fixed effects model.

Occurrence of the specified outcomes was compared between participants that received prophylactic antibiotics and those that did not. Relative risks (RR) with 95% confidence intervals (CI) were calculated.

Subgroup analyses

As part of the primary analysis, subgroup analysis were conducted for:

- Bacteriological resistance of the major pathogens to cotrimoxazole in the geographical area studied (greater than 30% ie high versus less than 30% ie low; resistance of Salmonella was used in the analysis because it was reported in all relevant studies and is a major cause of morbidity and mortality);
- Comorbidity with tuberculosis (TB) (TB versus no TB);
- CD4 cell count (CD4 greater than 200 taken to be synonymous with WHO stages 1 or 2 versus CD4 less than 200, or WHO stages 3 or 4, versus all levels of CD4 count and WHO stages [French 1999]);
- Concomitant antiretroviral use (yes or no);
- Dosage of cotrimoxazole (low dose ie 480 mg per day versus 960 mg per day).

RESULTS

Description of studies

Four studies were included. Three studies were randomised placebo controlled trials conducted in Africa, amongst heterosexual men and women, comparing cotrimoxazole to placebo and measuring mortality, morbidity and adverse events in both groups.

Anglaret (Anglaret 1999) randomly allocated 545 adults with HIV-1, stage 2 or 3 disease (WHO staging system), from Abidjan, Cote d'Ivoire, West Africa to 960 mg cotrimoxazole daily or matching placebo. There were slightly more women than men (57.8% women) and mean age was 33 years in both arms. Eleven per cent of participants had active tuberculosis at the time of inclusion in the study. Mean CD4 count was 322 cells/mm³ in the intervention group and 331 cells/mm³ in the control group, with 64.1% having a CD4 count of less than 200 cells/mm³ at enrolment. Mean duration of follow up was 9.5 months. The main outcome measurements were serious morbid events, defined by the investigators as death or hospital admission, where the latter could be admission to a day hospital. They also studied types of infection and adverse events. The rate of background resistance to cotrimoxazole was stated as 9% amongst Salmonella species, 53% for Shigella species, and 77% for E coli.

Wiktor (Wiktor 1999) also enrolled adults in Abidjan. They randomised 771 adults, with tuberculosis (sputum smear positive) and HIV-1 infection, to receive 960 mg cotrimoxazole per day or matching placebo. There were slightly more men than women (60% men) and the age range was 18 to 64 years with a median age of 33 years in the intervention arm and 31 years in the control arm. Median CD4 count was 311 cells/mm³ in the cotrimoxazole group and 325 cells/mm³ in the control group, with 30% of participants having a CD4 count of less than 200 cells/mm³ at enrolment. Mean duration of follow up was 10.4 months. The primary outcome was mortality with secondary outcomes of morbidity, types of infection and adverse events. The rate of background resistance to cotrimoxazole was stated as 14% amongst non-typhi Salmonella.

Maynard (Maynard 2001) reported a pilot study of 100 adults with HIV-1 infection in Senegal, West Africa. The trial was stopped when the results of the Abidjan studies were published. Therefore, the number of participants was small. They randomly allocated people with all stages of disease to 480 mg cotrimoxazole or matching placebo but excluded those who had poor performance scores (Karnofsky Performance Scale - score of activities of daily living). No participants had active tuberculosis at the time of enrolment. There were more women in the intervention arm than in the control arm (71% of the people randomised to cotrimoxazole versus 53% of those on placebo), although there were only 50 subjects randomised to each group. Age ranges in each group were comparable, with a median age of 37 years in the cotrimoxazole group and 35 in the placebo group. Median CD4 count was 150 cells/mm³ in the intervention arm and 153 cells/mm³ in the placebo arm. Sixty eight per cent of participants had a CD4 count of less than 200 cells/mm³ at enrolment. Mean duration of follow up was 7.8 months. Outcome measures were mortality, the occurrence of severe events (death and/or hospitalisation), type of infection and adverse events. The rate of background resistance to cotrimoxazole was 43% amongst Salmonella typhi.

The fourth study fulfilled the inclusion criteria but was judged by the authors to be sufficiently different to the other studies to be excluded from the meta-analysis (Fischl 1988); it is included in the Results. This study was conducted amongst 60 predominantly homosexual men in the United States (age range 21 to 57 years), all of whom were receiving chemotherapy for Kaposi's Sarcoma. The objective of the study was to examine the effect of cotrimoxazole in specifically preventing Pneumocystis carinii pneumonia. The intervention was compared to no treatment as opposed to placebo.

There was no blinding of subjects or trialists. Those participants who received cotrimoxazole were also given a second drug, leucovorin, a type of folic acid (a vitamin) intended to reduce side-effects to cotrimoxazole. The comparison was thus of cotrimoxazole and leucovorin versus no treatment. Adverse events were studied only in the intervention arm.

Risk of bias in included studies

The quality of included trials was assessed independently by two reviewers according to the following criteria.

1. Allocation Concealment

- Adequate measures to conceal allocations, such as central randomisation; serially numbered, opaque sealed envelopes; or other descriptions that contain convincing elements of concealment
- Unclearly concealed trials in which the authors either did not report an allocation concealment approach at all or reported an approach that did not fall into one of the categories above
- Inadequately concealed trials in which method of allocation is not concealed, such as alternation methods or use of case record numbers

2. Inclusion of all randomised participants

- Trials where an intention to treat analysis was possible and there were few losses to follow-up
- Trials which reported exclusions after randomisation, but exclusions were less than 10%
- No reporting on exclusions, exclusions greater than 10%, or wide differences in exclusions between groups

All four included studies were found to be of high methodological quality. The Fischl study stated that participants were randomly assigned to the intervention or control arm but did not state the method of randomisation. As the control was no treatment as opposed to placebo there was no blinding of subjects or investigators.

The other three studies all described in detail central randomisation with adequate allocation concealment. Only one study (Wiktor 1999) had a small number of exclusions following randomisation (7 participants out of a total of 771).

Effects of interventions

Four trials involving 1476 people were included. One trial was in a very different setting to the others and was excluded from the meta-analysis, but the findings are reported below (see 'Description of Studies' for reasons).

Meta-analysis of the three remaining studies (1416 participants) found significant beneficial effect from cotrimoxazole on death, morbid events and hospitalisation. Compared with placebo, the relative risk for death in those taking cotrimoxazole was 0.69 (95% CI 0.55 to 0.87), for morbid events: 0.76 (95% CI 0.64 to 0.9) and for hospitalisation: 0.66 (confidence intervals 0.48 to 0.92). In one study the definition of morbid events included admission to a day hospital (Anglaret 1999), leading to a proportionally greater

number of morbid events in this trial and consequent greater weighting in the meta-analysis. A sensitivity analysis excluding that study found a similar beneficial effect from cotrimoxazole but that did not reach statistical significance: relative risk 0.82 (95% CI 0.60 to 1.13).

Cotrimoxazole prophylaxis significantly reduced the occurrence of bacterial infections (RR 0.48, 95% CI 0.37 to 0.62), parasitic infections excluding toxoplasmosis (RR 0.37, 95% CI 0.24 to 0.58), and Pneumocystis carinii pneumonia (PCP) (in men on chemotherapy for Kaposi's sarcoma) (RR 0.31, 95% CI 0.13 to 0.74). Insufficient data were available for toxoplasmosis and fungal infections.

There was a small non-significant trend to increased adverse effects in the cotrimoxazole group compared to placebo: relative risk 1.28 (CI 0.47 to 3.51). An adverse effect was defined in all studies as a reaction requiring withdrawal of treatment. All adverse effects resolved once treatment was withdrawn.

Sub-group analyses

Pre-specified sub-group analysis found a similar significant reduction of mortality in participants with CD4 counts above and below 200 cells/mm³: relative risk 0.58 (95% CI 0.43 to 0.78) versus 0.68 (95% CI 0.55 to 0.83) respectively.

In three sub-group analyses, by level of bacterial resistance, comorbidity with tuberculosis and dose of cotrimoxazole, the only available data for areas with high levels of bacterial resistance to cotrimoxazole, participants without tuberculosis (TB) and for a lower cotrimoxazole dose (480 mg/day) were from a single small trial in which all participants shared all three characteristics. No effect of cotrimoxazole was detected in these sub-groups but the 95% confidence intervals did not exclude meaningfully different effects: relative risk 0.68 (95% CI 0.54 to 0.87) for bacterial resistance less than 30% versus 0.80 (95% CI 0.38 to 1.68) for resistance more than 30%; 0.57 (95% CI 0.42 to 0.78) for participants with tuberculosis versus 0.80 (95% CI 0.38 to 1.68) for those without tuberculosis; 0.68 (95% CI for 0.54 to 0.87) for cotrimoxazole 960 mg daily versus 0.80 (95% CI 0.38 to 1.68) for 480 mg daily. No trials included participants on antiretroviral therapy.

Insufficient data were available for meaningful sub-group analyses of the effects of cotrimoxazole on hospitalisation. Unsuccessful attempts were made to obtain unpublished data from authors on number of hospitalisation episodes, the breakdown of mortality and morbidity according to the presence or absence of TB infection at enrolment, and cause of death or hospitalisation.

A protective effect of cotrimoxazole (plus leucovorin) was found in the single trial of cotrimoxazole in men in the United States receiving chemotherapy for Kaposi's sarcoma: relative risk for death 0.64 (95% CI 0.40 to 1.03), and for PCP infection 0.31 (95% CI 0.13 to 0.74).

DISCUSSION

Cotrimoxazole prophylaxis in adults with HIV infection appears to have a beneficial effect with an estimated reduction of 31% in mortality, 27% in morbid events and 55% in patients being hospitalised. Significant reductions in specific infection were detected for bacterial and parasitic infections (excluding toxoplasmosis) and for Pneumocystis carinii pneumonia (PCP). The

beneficial effect appears to be similar for early and advanced HIV infection. Insufficient evidence was found in the included trials to draw confident conclusions about the magnitude of adverse effects.

Many questions remain unanswered. Other sub-group analyses were largely unhelpful because one small trial provided the only data from a setting with bacterial resistance above 30%, the only extractable data on people without tuberculosis, and the only data on lower dose (480 mg/day) cotrimoxazole. It is thus not possible to deduce which, if any, of these factors contributed to an apparent reduced effect in this trial. This review was limited to comparisons with placebo or no treatment and did not include direct comparisons of different doses. Two meta-analyses of studies comparing high dose to low dose cotrimoxazole prophylaxis conducted in developed countries found no significant difference in prophylactic effect between dosages ([Ioannidis 1996](#)[Bucher 1997](#)). However, as this review has shown, there is limited evidence of the efficacy of cotrimoxazole alone at any dose in that setting.

Attempts to obtain unpublished subgroup data from the single trial including people with and without tuberculosis were unsuccessful. We thus found insufficient evidence to exclude either a meaningfully beneficial or moderately harmful effect of prophylactic cotrimoxazole in areas with resistance above 30%, or in people without tuberculosis, or with a dose of 480 mg daily. We found no randomised evidence at all on the effect of cotrimoxazole in people also receiving antiretroviral therapy. Although unpublished subgroup data for people with and without tuberculosis may throw some light on the effect of prophylaxis in people without tuberculosis, there appears to be no way of reaching rigorous conclusions about its effect in the other subgroups mentioned above without conducting further randomised controlled trials. A randomised placebo controlled trial currently underway in Zambia, where cotrimoxazole resistance is much higher than in West Africa ([Nunn Personal Comm](#)), will provide important further information.

This review is not designed to provide information regarding the effect of widespread use of cotrimoxazole prophylaxis on bacterial resistance.

AUTHORS' CONCLUSIONS

Implications for practice

Cotrimoxazole prophylaxis appears to be effective in preventing death and illness episodes in adults with HIV infection. Similar benefit was seen in both early and advanced HIV disease. Insufficient evidence exists of the effect of cotrimoxazole in areas with high bacterial resistance, in people without tuberculosis, and in people on antiretroviral therapy. This lack of evidence should be kept in mind when balancing the beneficial effects of cotrimoxazole against the cost and feasibility of implementation in specific settings and against the potential for the development of bacterial resistance.

Implications for research

Further evidence is needed on the effect of cotrimoxazole prophylaxis in areas of high bacterial resistance, in people without tuberculosis, and in people on antiretroviral therapy. Objections to such trials, on ethical grounds, need to be weighed against the lack of evidence in the above mentioned sub-groups, in which meaningful harmful effects have not been excluded.

Given the limited resources available for any intervention in low income countries, there is also a need to evaluate the cost-effectiveness of this intervention against other potentially cheap interventions in such settings.

ACKNOWLEDGEMENTS

Elizabeth Pienaar helped develop the search strategy, performed the electronic search and supplied some of the articles.

REFERENCES

References to studies included in this review

Anglaret 1999 {published data only}

* 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. *Lancet* 1999;**353**(9163):1463-8.

Fischl 1988 {published data only}

* Fischl MA, Dickinson GM, La Voie L. Safety and efficacy of sulphamethoxazole and trimethoprim chemoprophylaxis for *Pneumocystis carinii* pneumonia in AIDS. *JAMA* 1988;**259**(8):1185-9.

Maynard 2001 {published and unpublished data}

* Maynard M, Lievre L, Sow P. S, Kony S, Gueye N. F, Bassene E, Metro A, Ndoye I, Ba D. S, Coulaud J. P, Costagliola D. Primary prevention with cotrimoxazole for HIV-1-infected adults: results of the pilot study in Dakar, Senegal. *J Acquir Immune Defic Syndr* 2001;**26**(2):130-6.

Wiktor 1999 {published data only}

* Wiktor S. Z, Sassan-Morokro M, Grant A. D, Abouya L, Karon J. M, Maurice C, Djomand G, Ackah A, Domoua K, Kadio A, Yapi A, Combe P, Tossou O, Roels T H, Lackritz E M, Coulibaly D, De Cock K M, Coulibaly I. M, Greenberg A. E. 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;**353**(9163):1469-75.

References to studies excluded from this review

Haller {published data only}

* Haller L, Sossouhounto R, Coulibaly IM, Dosso M, Kone M, Adom H, Meyer UA, Betschart B, Wenk M, Haefeli WE, Lobognon LR, Porquet M, Kabore G, Sorenson F, Reber-Liske R, Sturchler D. Isoniazid plus sulphadoxine-pyrimethamine can reduce morbidity of HIV-positive patients treated for TB in Africa: a controlled clinical trial. *Chemotherapy* 1999, (45):452-465.

References to ongoing studies

Nunn Personal Comm {unpublished data only}

Nunn AJ. A randomized placebo controlled trial of trimethoprim-sulphamethoxazole as prophylaxis against opportunistic infections in patients with M.tuberculosis and HIV-1 infection in Zambia. Personal communication.

Additional references

Abouya 1992

Abouya YL, Beaumel A, Lucas S, Dago - Akribi A, Coulibaly G, N'Dhatz M, Konan JB, Yapi A, De Cock KM. *Pneumocystis carinii* pneumonia. An uncommon cause of death in African patients

with acquired immunodeficiency syndrome. *American Review of Respiratory Diseases* 1992;**145**(3):617-20.

Bucher 1997

Bucher HC, Griffith L, Guyatt GH, Opravil M. Meta-analysis of prophylactic treatments against *Pneumocystis carinii* pneumonia and *Toxoplasma encephalitis* in HIV-infected patients. *Journal of Acquired Immunodeficiency Syndrome and Human Retrovirology* 1997, (15):104-14.

Colebunders 1989

Colebunders RL, Ryder RW, Nzilambi N, Dikulu K, Willame JC, Kaboto M, Bagala N, Jeugmans J, Meupu K, Francis HL, et al. HIV infection in patients with tuberculosis in Kinshasa, Zaire. *American Review of Respiratory Diseases* 1989;**139**(5):1082-5.

De Cock 1992

De Cock KM, Soro B, Coulibaly IM, Lucas SB. Tuberculosis and HIV in sub-Saharan Africa. *Journal of the American Medical Association* 1992;**268**(12):1581-7.

Del Amo 1998

Del Amo J, Petrukevitch A, Phillips A, Johnson AM, Stephenson J, Desmond N, Hanscheid T, Low N, Newell A, Obasi A, Paine K, Pym A, Theodore CM, De Cock KM. Disease progression and survival in HIV-1 infected Africans in London. *AIDS* 1998;**12**(10):1203-9.

Del Amo 1999

Del Amo J, Malin AS, Pozniak A, De Cock KM. Does tuberculosis accelerate the progression of HIV disease? Evidence from basic science and epidemiology. *AIDS* 1999;**13**(10):1151-8.

Fischl 1988

Fischl MA, Dickinson GM, La Voie L. Safety and Efficacy of sulfamethoxazole and trimethoprim chemoprophylaxis for *Pneumocystis carinii* pneumonia in AIDS. *Journal of the American Medical Association* 1988;**259**(8):1185-9.

French 1999

French N, Mujugira, Nakiyingi J, Mulder D, Janoff EN, Gilks CF. Immunologic and clinical stages in HIV-1 infected Ugandan adults are comparable and provide no evidence of rapid progression but poor survival with advanced disease. *Journal of AIDS* 1999;**22**:509-16.

Gilks 1990

Gilks CF, Brindle RJ, Otieno LS, Simani PM, Newnham RS, Bhatt SM, Lule GN, Okelo GB, Watkins WM, Waiyaki PG, et al. Life-threatening bacteraemia in HIV - 1 seropositive adults admitted to hospital in Nairobi, Kenya. *Lancet* 1990;**336**(8714):545-9.

Gilks 1996

Gilks CF, Ojoo SA, Ojoo JC, Brindle RJ, Paul J, Batchelor BI, Kimari JN, Newnham R, Bwayo J, Plummer FA, et al. Invasive pneumococcal disease in a cohort of predominantly HIV - 1 infected female sex-workers in Nairobi, Kenya. *Lancet* 1996;**347**(9003):718-23.

Gottlieb 1981

Gottlieb MS, Schroff R, Schanker HM, Weisman JD, Fan PT, Wolf RA, Saxon A. Pneumocystis carinii pneumonia and mucosal candidiasis in previously healthy homosexual men: evidence of a new acquired immunodeficiency. *New England Journal of Medicine* 1981;**305**(24):1425-31.

Grant 1997

Grant AD, Djomand G, Smets P, Kadio A, Coulibaly M, Kakou A, Maurice C, Whitaker JP, Sylla-Koko F, Bonard D, Wiktor SZ, Hayes RJ, De Cock KM, Greenburg AE. Profound immunosuppression across the spectrum of opportunistic disease among hospitalized HIV-infected adults in Abidjan, Cote d'Ivoire. *AIDS* 1997;**11**(11):1357-64.

Ioannidis 1996

Ioannidis JPA, Cappelleri JC, Skolnik PR, Lau J, Sacks HS. A meta-analysis of the relative efficacy and toxicity of Pneumocystis carinii prophylactic regimens. *Archives of Internal Medicine* 1996, (156):177-88.

Morgan 2000

Morgan D, Muwonge D, Mahe C, Whitworth J. Natural History of HIV infection in rural Uganda - results after 10 years. Abstract Number TuOrC428 XIII International AIDS Conference. 2000.

Perriens 1995

Perriens JH, St Louis ME, Mukadi YB, Brown C, Prignot J, Pouthier F, Portaels F, Willame JC, Mandala JK, Kaboto M, et al. Pulmonary tuberculosis in HIV-infected patients in Zaire. A controlled trial of treatment for either 6 or 12 months. *New England Journal of Medicine* 1995;**332**(12):779-84.

SA PMSC 2000

South African Provincial Medical Supply Centre price list. 2000.

UNAIDS 2000

UNAIDS. Report on the global HIV / AIDS epidemic. June 2000.

Vugia 1993

Vugia DJ, Kiehlbauch JA, Yeboue K, N'Gbichi JM, Lacina D, Maran M, Gondo M, Kouadio K, Kadio A, Lucas SB, et al. Pathogens and predictors of fatal septicaemia associated with human immunodeficiency virus infection in Ivory Coast, West Africa. *Journal of Infectious Diseases* 1993;**168**(3):564-70.

Wilkinson 2000

Wilkinson D. Drugs for preventing tuberculosis in HIV infected persons. *The Cochrane Library* 2000, Issue 2.

* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Anglaret 1999

Methods	Randomised double blinded placebo controlled trial Blocked pre-established randomisation, sequentially numbered sealed packages of tablets prepared centrally Intention to treat analysis 3.1% loss to follow up	
Participants	541 West African adults infected heterosexually with HIV 1 with or without HIV 2 infection, Mean age 33 years 11% TB infected at enrolment 65.1% with CD4 count <200 No patients on antiretroviral therapy	
Interventions	980mg cotrimoxazole daily vs matching placebo	
Outcomes	Primary outcome: Serious clinical events defined as death or hospital admission (including admission to day hospital) Secondary outcomes: Morbidity with particular attention on morbidity preventable by cotrimoxazole, adverse drug reactions	
Notes	Bacterial resistance to cotrimoxazole: 9% Salmonella sp. 0% Streptococcus pneumoniae, 53% Shigella sp. 77% E. coli	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Fischl 1988

Methods	Randomised unblinded trial Randomisation and allocation concealment not described Analysis not consistently by intention to treat - losses to follow up included but adverse events occurring in patients having stopped treatment not included
Participants	60 white American males, predominantly infected through homosexual route (93.3%), HIV 1 only, all on chemotherapy for Kaposi's Sarcoma Mean age 35.35 All WHO stage 4 by virtue of KS No patients on antiretroviral therapy
Interventions	980mg cotrimoxazole twice daily plus leucovorin 5mg daily vs no treatment
Outcomes	Outcomes: PCP infection, death, adverse drug reactions (although only looked for in intervention group)
Notes	All patients on chemotherapy for Kaposi's Sarcoma: Interferon alpha, vincristine or vinblastine regimes

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Maynard 2001

Methods	Randomised double blinded placebo controlled trial Pre-established block randomisation preparation and packaging by and independent pharmacist Intention to treat analysis performed, 5% loss to follow up
Participants	100 West African adults infected heterosexually with HIV 1 with or without HIV2 Median age 36 years No TB at enrolment 68% CD4 count <200 No patients on antiretroviral therapy
Interventions	480mg cotrimoxazole daily vs matching placebo
Outcomes	Primary outcome: death Secondary outcomes: clinical events, particularly looking at morbidity preventable by cotrimoxazole, adverse drug reactions
Notes	Bacterial resistance to cotrimoxazole: 43% S typhi (others to follow) Pilot study - full study stopped prematurely following release of Abidjan results

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Wiktor 1999

Methods	Randomised double blinded placebo controlled trial Pre-established block randomisation Allocation centralised. Drug and placebo identical and unlabelled No intention to treat analysis, loss to overall follow up 0.9%, loss to mortality follow up 12.2%
Participants	771 West African adults with sputum positive TB, infected heterosexually with HIV 1 with or without HIV 2 Median age 32 years 30% CD4 count <200 No patients on antiretroviral therapy
Interventions	980mg cotrimoxazole daily vs matching placebo
Outcomes	Outcomes: death, serious adverse events, hospitalisation, adverse drug reactions
Notes	Bacterial resistance to cotrimoxazole: 14% non-typhi Salmonellae

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Haller	Intervention isoniazid plus cotrimoxazole .

Characteristics of ongoing studies [ordered by study ID]

Nunn Personal Comm

Trial name or title	A randomized placebo controlled trial of trimethoprim-sulphamethoxazole as prophylaxis against opportunistic infections in patients with M.tuberculosis and HIV-1 infection in Zambia.
Methods	
Participants	1000 people with sputum smear-positive tuberculosis and HIV-1 infection.
Interventions	960mg cotrimoxazole versus matching placebo.
Outcomes	Mortality, adverse drug reactions, hospitalisation, infections, resistance patterns to cotrimoxazole amongst common pathogens.
Starting date	April 2000
Contact information	Prof Andrew Nunn CTU MRC London

Nunn Personal Comm (Continued)

Notes

DATA AND ANALYSES

Comparison 1. Cotrimoxazole vs Control

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death	3	1318	Risk Ratio (M-H, Fixed, 95% CI)	0.69 [0.55, 0.87]
2 Serious morbid events	3	1384	Risk Ratio (M-H, Fixed, 95% CI)	0.76 [0.64, 0.90]
3 Hospitalisation	3	764	Risk Ratio (M-H, Fixed, 95% CI)	0.66 [0.48, 0.92]
4 Adverse events	3	1405	Risk Ratio (M-H, Fixed, 95% CI)	1.28 [0.47, 3.51]
5 Type of infection	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.1 PCP	3	1405	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
5.2 Toxoplasmosis	3	1405	Risk Ratio (M-H, Fixed, 95% CI)	0.30 [0.08, 1.08]
5.3 Bacterial infections	3	1405	Risk Ratio (M-H, Fixed, 95% CI)	0.48 [0.37, 0.62]
5.4 Parasitic infections excluding toxoplasmosis	3	1405	Risk Ratio (M-H, Fixed, 95% CI)	0.37 [0.24, 0.58]
5.5 Fungal infections excluding PCP	3	1405	Risk Ratio (M-H, Fixed, 95% CI)	1.49 [0.25, 8.91]
5.6 TB	3	1405	Risk Ratio (M-H, Fixed, 95% CI)	0.72 [0.46, 1.12]

Analysis 1.1. Comparison 1 Cotrimoxazole vs Control, Outcome 1 Death.

Analysis 1.2. Comparison 1 Cotrimoxazole vs Control, Outcome 2 Serious morbid events.

Analysis 1.3. Comparison 1 Cotrimoxazole vs Control, Outcome 3 Hospitalisation.

Analysis 1.4. Comparison 1 Cotrimoxazole vs Control, Outcome 4 Adverse events.

Analysis 1.5. Comparison 1 Cotrimoxazole vs Control, Outcome 5 Type of infection.

Comparison 2. Cotrimoxazole and leucovorin vs control

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death	1	120	Risk Ratio (M-H, Fixed, 95% CI)	0.64 [0.40, 1.03]
2 PCP infection	1	60	Risk Ratio (M-H, Fixed, 95% CI)	0.31 [0.13, 0.74]

Analysis 2.1. Comparison 2 Cotrimoxazole and leucovorin vs control, Outcome 1 Death.

Analysis 2.2. Comparison 2 Cotrimoxazole and leucovorin vs control, Outcome 2 PCP infection.

Comparison 3. Sub-group analysis: Level of bacterial resistance

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Bacterial resistance less than 30%	2	1218	Risk Ratio (M-H, Fixed, 95% CI)	0.68 [0.54, 0.87]
1.2 Bacterial resistance more than 30%	1	100	Risk Ratio (M-H, Fixed, 95% CI)	0.80 [0.38, 1.68]

Analysis 3.1. Comparison 3 Sub-group analysis: Level of bacterial resistance, Outcome 1 Death.

Comparison 4. Sub-group analysis: Co-morbidity with tuberculosis

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Tuberculosis	1	677	Risk Ratio (M-H, Fixed, 95% CI)	0.57 [0.42, 0.78]
1.2 No tuberculosis	1	100	Risk Ratio (M-H, Fixed, 95% CI)	0.80 [0.38, 1.68]

Analysis 4.1. Comparison 4 Sub-group analysis: Co-morbidity with tuberculosis, Outcome 1 Death.

Comparison 5. Sub-group analysis: Severity of HIV illness

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 CD4 count < 200	3	508	Risk Ratio (M-H, Fixed, 95% CI)	0.68 [0.55, 0.83]
1.2 CD4 count >200	3	850	Risk Ratio (M-H, Fixed, 95% CI)	0.58 [0.43, 0.79]
2 Hospitalisation	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 CD4 count <200	2	299	Risk Ratio (M-H, Fixed, 95% CI)	0.76 [0.53, 1.10]
2.2 CD4 count >200	2	520	Risk Ratio (M-H, Fixed, 95% CI)	0.61 [0.28, 1.29]

Analysis 5.1. Comparison 5 Sub-group analysis: Severity of HIV illness, Outcome 1 Death.

Analysis 5.2. Comparison 5 Sub-group analysis: Severity of HIV illness, Outcome 2 Hospitalisation.

Comparison 6. Sub-group analysis: Dose of cotrimoxazole

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Cotrimoxazole 480 mg daily	1	100	Risk Ratio (M-H, Fixed, 95% CI)	0.80 [0.38, 1.68]
1.2 Cotrimoxazole 960 mg daily	2	1218	Risk Ratio (M-H, Fixed, 95% CI)	0.68 [0.54, 0.87]

Analysis 6.1. Comparison 6 Sub-group analysis: Dose of cotrimoxazole, Outcome 1 Death.

Comparison 7. Sub-group analysis: Concomitant antiretroviral use

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Antiretroviral use	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.2 No antiretroviral use	3	1318	Risk Ratio (M-H, Fixed, 95% CI)	0.69 [0.55, 0.87]

Analysis 7.1. Comparison 7 Sub-group analysis: Concomitant antiretroviral use, Outcome 1 Death.

WHAT'S NEW

Date	Event	Description
11 November 2008	Amended	Converted to new review format.

HISTORY

Protocol first published: Issue 2, 2001

Review first published: Issue 3, 2003

Date	Event	Description
25 March 2003	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

Both reviewers participated in development of the protocol, reviewing of abstracts, data extraction, analysis of results, interpretation of the findings and writing of the final report.

DECLARATIONS OF INTEREST

KCG is supported by DFID (Department for International Development) to investigate the effectiveness of cotrimoxazole prophylaxis when implemented in a rural resource poor setting.

DFID is the British government aid and development agency.

GS: None declared

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- Department for International Development, UK.

INDEX TERMS

Medical Subject Headings (MeSH)

AIDS-Related Opportunistic Infections [*drug therapy]; Anti-Infective Agents [*therapeutic use]; HIV Infections [complications]; Randomized Controlled Trials as Topic; Trimethoprim, Sulfamethoxazole Drug Combination [*therapeutic use]

MeSH check words

Female; Humans; Male