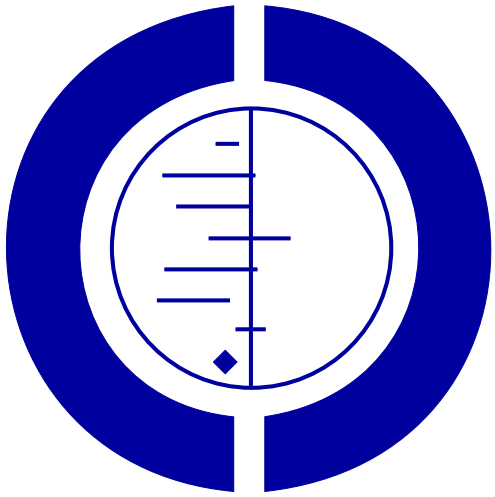
Cotrimoxazole for prophylaxis or treatment of opportunistic infections of HIV/AIDS in patients with previous history of hypersensitivity to cotrimoxazole (Review)

Lin D, Li WK, Rieder MJ



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ABSTRACT

Background
Opportunistic infections continue to cause a significant amount of morbidity and mortality worldwide in patients infected with HIV. Trimethoprim-sulfamethoxazole (cotrimoxazole) is used in the treatment and prophylaxis of several opportunistic infections. In patients with HIV/AIDS, cotrimoxazole use can cause a higher rate of adverse drug reactions than in the general population. Given the cost-effectiveness of cotrimoxazole, the management of these adverse reactions has included continuing the drug (treating-through) and reintroducing the drug at a later date, either using dose-escalation (desensitization), or rechallenge at full dose. This systematic review is the first to examine the differences in patient outcomes between these strategies.

Objectives
To compare the rate of discontinuation of cotrimoxazole and adverse reactions among the three strategies of treating-through, desensitization, and rechallenge in patients living with HIV who previously had an adverse reaction to cotrimoxazole.

Search strategy
We searched MEDLINE, EMBASE, LILACS, *The Cochrane Library*, Meeting Abstracts, AIDSTRIALS, ACTIS, Current Controlled Trials, The National Institutes of Health Clinical Trials Registry, and CenterWatch (search date May 2006).

Selection criteria
Randomised trials comparing treating-through, rechallenge, or desensitization of cotrimoxazole treatment or prophylaxis in adults (age 18 years or over) and/or children (age 17 years or under).

Data collection and analysis
Two reviewers independently assessed trial eligibility and quality, and extracted data. Where data were incomplete or unclear, a third reviewer resolved conflicts and/or trial authors were contacted for further details.

Main results
Three trials that examined cotrimoxazole prophylaxis and involving 268 adults were included. Meta-analysis of these studies found a beneficial effect of using a desensitization protocol over a rechallenge protocol at six months of follow-up for preventing discontinuation of cotrimoxazole (number needed to treat (NNT) 7.14, 95% confidence interval (CI) 4.0-33.0), and for lower incidence of overall hypersensitivity (NNT 4.55, 95% CI 3.03-9.09). No severe hypersensitivity reactions occurred for either protocol in the three studies.

Authors' conclusions
In the small trials included in this review, when compared to cotrimoxazole rechallenge for prophylaxis of opportunistic infections, cotrimoxazole desensitization resulted in fewer treatment discontinuations and overall adverse reactions in HIV-infected patients with

a previous history of mild or moderate hypersensitivity to cotrimoxazole. Paediatric data and trials in resource-poor settings are urgently required. Further randomised controlled trials are also needed for the treatment of opportunistic infections, treating-through, adjunctive medications, and different desensitization-dosing schedules.

PLAIN LANGUAGE SUMMARY

This review examines strategies to enable the continued use of the antibiotic cotrimoxazole in patients with HIV/AIDS to treat or prevent opportunistic infections in patients who previously experienced hypersensitivity to this drug.

Opportunistic infections are a threat to the lives and health of people living with HIV. Cotrimoxazole, an antibiotic also known as trimethoprim-sulfamethoxazole, is used in the treatment and prevention of several opportunistic infections. In patients with HIV/AIDS, cotrimoxazole can cause more drug-related side effects than in the general population. However, there are not many effective alternatives for this drug, which is also by far the cheapest option available. When a patient with HIV experiences a side effect related to cotrimoxazole, often the drug is continued (treating-through) or reintroduced at a later date, either using increasingly larger doses (desensitization), or immediately starting at the full dose (rechallenge). This systematic review is the first to examine the differences in how patients are able to tolerate these strategies.

Three trials examining the use of cotrimoxazole in preventing opportunistic infections were included in the review. When compared to rechallenge, desensitization appeared to result in fewer treatment stoppages and side effects in HIV-infected adult patients who had a previous mild or moderate reaction to cotrimoxazole. However, more data are needed for these results to be conclusive. It is important to note that reintroduction of cotrimoxazole was usually successful using either desensitization or rechallenge, with 44.4% to 79.4% of patients still on cotrimoxazole after six months in the three studies. Furthermore, in the studies reviewed, no strategy resulted in severe hypersensitivity reactions. Severe limitations of this review included the absence of data in paediatric populations and the minimal data from resource-poor populations.

BACKGROUND

Opportunistic infections continue to cause a significant amount of morbidity and mortality in patients infected with Human Immunodeficiency Virus (HIV) worldwide (Benson 2004). In resource-rich countries, diseases that are rare in the general population, such as *Pneumocystis jiroveci* pneumonia (PCP, formerly known as *pneumocystis carinii* pneumonia), are the most common opportunistic diseases in patients with HIV (Phair 1990, Klatt 1994). In resource-poor nations, where most HIV infection occurs (UNAIDS 2004), highly prevalent diseases such as tuberculosis, parasitic enteritis, and bacterial infections are the main causes of death and illness in these patients (Gilks 1990; Abouya 1992; Grant 1997; Wannamethee 1998; Joshi 2002).

In both settings, trimethoprim-sulfamethoxazole (cotrimoxazole) is used in the treatment and prophylaxis of several opportunistic infections. While highly active antiretroviral therapy has greatly reduced the incidence of opportunistic infections in resource-rich nations, PCP still remains a common and life-threatening disease best treated and prevented by cotrimoxazole (McNaghten 1999, Kaplan 2000, Benson 2004). Cotrimoxazole is also effective for the treatment of isosporiasis, salmonella and Shigella gastroenteritis and paracoccidioidomycosis, as well as the prevention of *Toxoplasma gondii* encephalitis (Kaplan 2002, Benson 2004). In a meta-analysis of three African studies, routine cotrimoxazole prophylaxis appears to have a beneficial effect on preventing death, illness, and hospitalization in adults with HIV infection (Grimwade 2003). In Africa, adjunctive cotrimoxazole has been shown to reduce mortality in HIV-positive tuberculosis patients by up to 53% (Wiktor 1999; Chintu 2004; Mwaungulu 2004; Grimwade 2005). The World Health Organization has issued guidelines that recommend that in resource-limited settings, all adults and adolescents living with symptomatic HIV and all infants born to mothers living with HIV should receive cotrimoxazole (WHO 2006).

For patients without HIV, adverse drug reactions to cotrimoxazole occur at a rate of 8% (Jick 1982). In patients with AIDS, cotrimoxazole treatment of PCP much more commonly causes adverse drug reactions (20%-100%), and can lead to a change of therapy in up to 57% of individuals (Kovacs 1984; Wharton 1986; Medina 1990; Hughes 1993). These adverse effects are usually idiosyncratic hypersensitivity reactions, typically occurring between 7and 10 days after the start of therapy. They most often include rash, fever, peripheral blood cell abnormalities, and kidney and liver damage, although life-threatening mucocutaneous reactions occasionally occur (Jaffe 1983; Gordin 1984; Small 1985). In cotrimoxazole prophylaxis, adverse reactions requiring treatment discontinuation also occur at a rate of approximately 15-25% (Fischl 1988; Hardy 1992; Schneider 1992). In the meta-analysis of three African studies, however, adverse effects of cotrimoxazole prophy-

laxis did not cause a significant increase in discontinuation compared to placebo (Grimwade 2003).

Treatment failure due to an adverse drug reaction to cotrimoxazole represents a serious issue, because cotrimoxazole is the most cost-effective medication for many opportunistic infections, and in some settings no affordable or efficacious alternative exists (Freedberg 1998; Goldie 2002). Even after an adverse drug reaction has occurred due to cotrimoxazole, an attempt is usually made to continue the drug or reintroduce the drug at a later date (Kaplan 2002). Continuing therapy despite adverse reactions (also known as treating-through) was shown to be effective in several case series, especially with the addition of antihistamines, antipyretics, prednisone, or therapeutic drug monitoring (Fischl 1988; Sattler 1988; Shafer 1989). Reintroducing the cotrimoxazole after stopping treatment includes either desensitization using various protocols of dose-escalation over a period of days, or rechallenge at full dose. In many uncontrolled studies, both desensitization and rechallenge were usually successful in a majority of patients and rarely cause serious reactions (Carr 1993; Absar 1994; Gluckstein 1995; Belchi 1996; Caumes 1997; Gompels 1999). The World Health Organization guidelines on the use of cotrimoxazole in resource-limited settings do not cite level 1evidence when recommending desensitization after an adverse reaction has interrupted the use of cotrimoxazole (WHO 2006). This paper is the first systematic review to examine these three strategies.

OBJECTIVES

To compare the rate of discontinuation and adverse reactions among the three strategies of treating-through, desensitization, and rechallenge, when using cotrimoxazole for prophylaxis or treatment of opportunistic infections in adult and/or paediatric patients with HIV who previously had an adverse reaction to cotrimoxazole.

CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW

Types of studies

Randomised trials, irrespective of language and publication status.

Types of participants

Adults (age 18 and older) and children (age 17 years and younger) with HIV infection who previously had a treatment-limiting and/or mild to moderate (grade 1 or 2) adverse reaction to trimethoprim-sulfamethoxazole.

Types of intervention

Interventions in which one of the following strategies is compared with a placebo or another strategy:

1.Treating through the adverse reaction by continuing therapy
2.Rechallenge at full dose after a recovery from an adverse reaction
3.Desensitization by introducing very low dosages of the therapeutic agent and subsequently increasing the dosage over a period of days

Types of outcome measures

1.Proportion successfully continuing cotrimoxazole for duration of treatment
2.Proportion of overall adverse reactions
3.Proportion with fever as an adverse reaction
4.Proportion with cutaneous adverse reaction
5.Proportion with an adverse reaction requiring hospitalization
6.Proportion of severe adverse reaction

SEARCH METHODS FOR IDENTIFICATION OF STUDIES

See: Cochrane HIV/AIDS Group methods used in reviews.

See: Cochrane HIV/AIDS Group methods used in reviews.

Electronic searches

We searched the following databases filtering for randomised controlled trials (search date May 2006):
·MEDLINE
·EMBASE
·LILACS
·*The Cochrane Library* (CENTRAL)
·Meeting Abstracts (http://gateway.nlm.nih.gov/meetingabstracts.html), searching HIV/AIDS abstracts including *International Conference on AIDS, Retrovirus and Opportunistic Infection Conference, Conference on Antimicrobial Agents and Chemotherapy, Australasian Society for HIV Medicine*.

We used the following keywords:
Acquired Immunodeficiency Syndrome, HIV Seropositivity, HIV, human immunodeficiency virus, drug hypersensitivity, adverse effects, drug eruptions, HIV infections, rechallenge, desensitization, Cotrimoxazole, Trimethoprim-Sulfamethoxazole, Trimethoprim-Sulfamethoxazole Combination/administration & dosage, recurrence, continued therapy, treating through, treat through, dose escalation, drug hypersensitivity/therapy.

We searched the following databases for ongoing randomised controlled trials:
·AIDSTRIALS (http://aidsinfo.nih.gov/clinical_trials/);
·ACTIS (AIDS Clinical Trials Information Service at http://www.actis.org/);
·Current Controlled Trials (http://www.controlled-trials.com/);
·The National Institutes of Health Clinical Trials Registry (http://clinicaltrials.gov/);
·CenterWatch (http://www.centerwatch.com/).

Other sources

We also checked the citations of included trials and major reviews for additional studies. We contacted the authors of published studies for information about additional published or unpublished studies.

METHODS OF THE REVIEW

Selection of Studies

Two reviewers (DL, WL) independently reviewed the titles and potentially relevant abstracts retrieved by the search strategy. They obtained full articles of the relevant trials that fulfilled the inclusion criteria. Relevant articles were inspected independently by these two reviewers and disagreements were solved by discussion with a third reviewer (MJR).

Data extraction and management

Two reviewers (DL, WL) independently extracted the data using a data-extraction form. For each of the studies, they extracted publication status, year, trial sponsor, duration of study follow-up, study setting, number of randomised patients in each group, age of patients, type of previous reactions to cotrimoxazole, purpose of cotrimoxazole use, number of female patients, HIV risk factors, and HIV disease severity as measured by CD4-positive lymphocyte count. They crosschecked data and solved discrepancies by discussion of the entire review group. In cases of unclear or missing data, study authors were contacted for clarification.

Assessment of methodological quality of included studies

Two reviewers (DL, WL) independently assessed the methodological quality of each trial in terms of allocation concealment, blinding, and inclusion of all randomised participants. Allocation concealment was classified as grade A (low risk of bias; adequate allocation concealment), grade B (possible risk of bias; unclear about allocation concealment), grade C (moderate risk of bias; inadequate allocation concealment), or grade D (high risk of bias; allocation concealment not used). Blinding was described as open (all parties are aware of treatment), single (participant or care provider is aware of the treatment given), or double (neither the participant nor care provider know which treatment is given). Inclusion of all randomised participants was rated as grade A (intention-to-treat analysis was possible and there were few losses to follow-up), grade B (exclusions after randomisation were less than 10%), or grade C (exclusions were greater than 10% or were widely different between groups).

Measure of treatment effect

Data were analysed using Review Manager 4.2.8. Mantel-Haenszel methods risk ratios with 95% confidence intervals using fixed-effects models were employed for dichotomous outcomes.

Assessment of heterogeneity

Heterogeneity among trials was assessed using the chi-squared test with a 10% level of statistical significance. Where heterogeneity was detected, investigation of heterogeneity was planned *a priori*, if needed, using the DerSimonian and Laird random-effects model, and/or excluding outlying trials.

Sensitivity analysis

After including all eligible studies in the primary analysis, sensitivity analyses were planned *a priori* for each of the methodological quality factors. Funnel plots were planned *a priori*, if needed, to estimate the treatment effect against the precision of trials, in order to estimate asymmetry because of selection bias or methodological flaws.

Subgroup analysis

Subgroup analyses were planned *a priori,* if sufficient number of studies and data exist, to be conducted for subsets of studies (resource-poor versus resource-rich), and subgroups of patients (gender, ethnicity, AIDS status).

DESCRIPTION OF STUDIES

Three published studies (Bonfanti 2000; Leoung 2001; Straatmann 2002) were identified that compared desensitization versus rechallenge of cotrimoxazole prophylaxis in adults with HIV infection who previously had a mild or moderate adverse reaction to trimethoprim-sulfamethoxazole, and now required cotrimoxazole daily prophylaxis. An ongoing registered clinical trial (COTOX 2005) was identified that compares treating-through versus desensitization versus rechallenge. A published trial was identified that compared two dosing schedules of desensitization (Picketty 1995), but was later excluded because it did not use true randomisation. No paediatric studies were found that matched the inclusion criteria.

Included Studies

Bonfanti (Bonfanti 2000) enrolled 73 HIV-seropositive adults with a previous history of mild or moderate hypersensitivity to cotrimoxazole in a randomised, multi-centre open study between January 1 and December 31, 1997 in a resource-rich setting. These patients had no serious infections and were not on antihistamines and/or corticosteroids. Prior to randomisation, all patients received 200mg of trimethoprim per day for 15 days and the 14 patients who had a hypersensitivity reaction to trimethoprim were not randomised. Fifty-nine patients were randomised to either rechallenge using 40 graduated doses over 36 hours or full-dose rechallenge. After the reintroduction of therapy, patients began home treatment on 800mg sulfamethoxazole/160mg trimethoprim daily. The mean age was similar between groups, at 35.18 (desensitization) and 34.84 (rechallenge). The percentage of female patients was also similar, at 65% (desensitization) and 72% (rechallenge). No data on ethnicity were presented. Both groups had 56% of patients with AIDS status. The desensitization group had a longer time interval since the previous hypersensitivity reaction (mean 17.8 months compared to mean 12.6 months). The

primary outcome was the presence of a hypersensitivity reaction during the six-month follow-up using intention-to-treat analysis.

Leoung (Leoung 2001) enrolled 191 HIV-infected adults with previous non-life-threatening hypersensitivity reactions to cotrimoxazole between October 1995 and June 1997 in a resource-rich setting. Patients were excluded if they received any cotrimoxazole since their hypersensitivity reaction or if they had taken cotrimoxazole within 8 weeks before allocation. Patients were randomised to a reintroduction phase of six days of either a paediatric suspension in five escalating doses plus one placebo tablet, or placebo suspensions plus one cotrimoxazole single-strength tablet (400mg sulfamethoxazole/160mg trimethoprim). After the introduction phase, both groups took one single-strength cotrimoxazole tablet daily. All patients began antihistamine therapy one day before the initiation of therapy and took the medication throughout the reintroduction phase. The use of non-steroidal agents and corticosteroids were encouraged during both the introduction and maintenance phases. Patients who missed more than two doses during the reintroduction phase were declared to have treatment failure. Median age was similar in both groups: 38.8 (desensitization) and 38.5 (rechallenge). Significantly more females were in the desensitization group (22.3%) than the rechallenge group (10.3%). The CD4 cell count was similar between groups: desensitization (125.5) and rechallenge (130.7). Ethnicity of patients was not significantly different between groups: desensitization (Native 1%, Black 16.5%, White 65.0%, Latino 16.5%, Other 1%) and rechallenge (Native 1%, Black 16.5%, Latino 19.2%, White 61.7%, Other 2%). The primary endpoint was the ability of patients to take one single-strength cotrimoxazole tablet daily for six months using intention-to-treat analysis. The enrolment for the trial was discontinued early due to significant differences in hypersensitivity reactions between the two groups.

Straatmann (Straatmann 2002) enrolled 18 HIV-infected adults who had a complete resolution of a previous hypersensitivity reaction to cotrimoxazole or sulfadiazine between August 1998 and October 1999 in a resource-limited setting. Patients were excluded if they had an active opportunistic infection. Patients were randomly assigned to escalating doses of cotrimoxazole over eight days or full-dose cotrimoxazole (800mg sulfamethoxazole/160mg trimethoprim) three times per week. Patients in the desensitization group were younger (38.3 versus 41.3), had fewer females (11% versus 22%), and had a lower CD4 cell count (mean 136 versus 107). No data on ethnicity were published. After the reintroduction phase, all patients received full-dose cotrimoxazole three times per week. The primary endpoint was the lack of an allergic reaction by six months.

METHODOLOGICAL QUALITY

Bonfanti (Bonfanti 2000) used central allocation with separate lists for each centre and allocation was appropriately concealed (Grade A). The trial was an open-label study (Grade C). Intention-to-treat analysis was performed (Grade A).

Leoung (Leoung 2001) did not explain how allocation was concealed (Grade B). The trial was double-blinded (Grade A). Intention-to-treat analysis was performed (Grade A).

Straatmann (Straatmann 2002) used a computer-generated list to assign allocation (Grade A). The trial was an open-label study (Grade C). Intention-to-treat analysis was performed (Grade A).

RESULTS

Three trials that examined cotrimoxazole prophylaxis involving 268 people were included. Meta-analysis of these studies at six months of follow-up found a beneficial effect from using a desensitization protocol over a rechallenge protocol on discontinuation of cotrimoxazole, overall rate of adverse reactions, and rate of fever.

Compared to rechallenge, desensitization had a risk ratio (RR) of 0.64 (95% confidence interval (CI) 0.45, 0.91) for discontinuation before six months of follow-up. The number needed to treat (NNT) to prevent one discontinuation was 7.14 (95% CI 4, 33). Compared to rechallenge, desensitization had a RR of 0.51 (95% CI 0.36, 0.73) for any adverse reaction after the introduction of cotrimoxazole. The NNT to prevent one adverse reaction was 4.55 (95% CI 3.03, 9.09). Desensitization had a RR of 0.41 (95% CI of 0.20, 0.83) for presence of fever, but no significant benefit was seen for cutaneous reactions or hospitalization (95% CI includes 1). None of the studies reported severe hypersensitivity events.

Since there were only three studies with fewer than 268 subjects, sensitivity analyses, funnel-plot analysis, and subgroup analyses of study setting were not done because they would be difficult to meaningfully interpret. The studies did not provide individual data for subgroups of patients based on gender, ethnicity, or AIDS status. None of the meta-analyses studies met the criteria for heterogeneity (range, p=0.14 to p=0.90).

None of the authors responded to our requests for missing information from their studies or data (published and unpublished) not found using our search methods.

DISCUSSION

Summary of benefits and harms

Significant reductions in treatment discontinuation, overall rate of hypersensitivity, and rate of fever were detected for desensitization protocols in adults. The meta-analyses did not show a difference between the two strategies in terms of cutaneous adverse reactions, serious adverse reactions, or adverse reactions requiring hospitalization.

Overall completeness and applicability of evidence

The evidence was not complete and further research is needed to conclusively favour one combination of strategies over another in all settings. All the included studies investigated the role of desensitization versus rechallenge for prophylaxis of opportunistic infections, but no randomised controlled trials were available to demonstrate the role of these interventions in the treatment of opportunistic infections. There were no paediatric data in the literature and studies in this patient population are urgently needed. Only 18 of the patients in this systematic review were from one of the resource-limited settings where the 2006 WHO guidelines are aimed. More studies in resource-limited countries would allow analysis between subgroups of studies according to resource setting. Furthermore, given previously described differences in adverse reactions to cotrimoxazole in patients living with HIV based on differences in gender, CD4 count, and ethnicity (Hennessy 1995; Pakianathan 1999), raw data from the three studies would have allowed for analyses for subgroups of patients. However, none of the authors responded to our requests for additional data. This review was limited to comparisons with desensitization protocols versus rechallenge, because no other randomised controlled trials were available to compare the third strategy of treating-through. All three studies used different desensitization protocols and no randomised controlled trials comparing different escalating dosing schedules were available. More data are needed regarding the effectiveness and safety of different desensitization protocols. Only one study included antihistamines, non-steroidal anti-inflammatory agents, and corticosteroids in its protocol. The influence of these adjunctive treatments in desensitization, rechallenge, or treating-through is still unclear.

Quality of the evidence

There were three studies and 268 participants included in this meta-analysis. Two of the studies had adequate allocation concealment. One study (Leoung 2001) did not and this study had a significant difference in gender between groups. Only one study was blinded, and the other two were open label. All three studies used intention-to-treat.

Agreements and disagreements with other studies

The conclusions of the three studies were not consistent. The results of two of the reviewed studies found no significant difference between protocols, and the authors suggested both protocols are equally feasible, with rechallenge being faster and easier (Bonfanti 2000; Straatmann 2002). The difference in results could have been due to actual differences in interventions among the studies. One study (Leoung 2001) used a maximum dose of single-strength cotrimoxazole daily, whereas the other studies used a maximum dose of double-strength cotrimoxazole, with either daily dosing (Bonfanti 2000) or dosing three times per week (Straatmann 2002). It has been shown elsewhere that efficacy is similar and tolerance may be better with a single-strength tablet daily or double-strength tablet three times per week than with a double-strength tablet (Kaplan 2002), although the differences in dosing schedules among these studies do not clearly correspond to differences between their results (e.g., discontinuation for rechallenge patients was 43% in Leoung 2001 but only 28% in Bonfanti 2000). One study (Leoung 2001) also used antihistamines, non-steroidal anti-inflammatory agents and corticosteroids in the study protocol, whereas the other studies did not. Insufficient studies are currently available for a sub-group analysis that could determine the role of these different dosing schedules or adjunctive agents in improving tolerance when reintroducing cotrimoxazole. The difference in the conclusions of the studies could also have been due to the two smaller studies being underpowered; no power analyses were made in these two studies *a priori*. The results of one of these studies (Bonfanti 2000) showed a trend towards favouring desensitization. The one study (Leoung 2001) did calculate the required sample size *a priori* to detect a success rate difference of 20% in 200 patients, although the study was ended early because of the significant benefit seen in the desensitization group.

AUTHORS' CONCLUSIONS

Implications for practice

When compared to rechallenge, cotrimoxazole desensitization appears to result in fewer treatment discontinuations and adverse reactions in HIV-infected adult patients with a previous history of mild or moderate hypersensitivity to cotrimoxazole, although more data are needed to for these results to be conclusive. The number needed to treat to prevent treatment discontinuation after six months was approximately seven patients, and to prevent any adverse reaction was approximately five patients. It is important to note that reintroduction of cotrimoxazole was generally successful using any protocol, with 44.4% to 79.4% of patients still on cotrimoxazole after six months in the three studies. Furthermore, no protocol resulted in severe hypersensitivity reactions in the studies reviewed.

Implications for research

The research in this area is far from complete. Trials in resource-poor settings are urgently needed, as are trials involving paediatric patients. Further evidence is needed to determine the role of these interventions in the treatment of opportunistic infections, the most effective desensitization protocol, and whether antihistamines, non-steroidal anti-inflammatory agents, and corticosteroids improve treatment continuation. The effectiveness of treating-through, compared to either desensitization or rechallenge, has not yet been examined in a controlled trial. Data to complete subgroup analysis of patient characteristics are also missing.

POTENTIAL CONFLICT OF INTEREST

None.

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- Robarts Research Institute CANADA

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TABLES

Characteristics of included studies

Study	Bonfanti 2000
Methods	Randomized, open-label
Participants	59 HIV seropositive adults; Previously diagnosed mild or moderate hypersensitivity to cotrimoxazole; Life expectancy of at least 1 year; Absence of active infections; No patients on antihistamines and/or steroids; Mean age 35 years; Mean CD4 cell count 117; 56% patients CD4 <200; Mean 15.6 month interval between previous reaction and treatment; 32.2% female.
Interventions	Desensitization (40 graduated doses over 36 hours) vs. double-strength dose rechallenge (800mg sulphamethoxazole plus 160mg trimethoprim).
Outcomes	Ability to continue receiving double strength cotrimoxazole daily for 6 months without hypersensitivity reactions; serious adverse reactions.
Notes	A group of 72 patients were given 200mg of trimethoprim for 14 days and only those who did not react were randomized to treatment. Follow up period was six months.
Allocation concealment	A – Adequate

Study	Leoung 2001
Methods	Randomized, double-blind
Participants	191 HIV seropositive adult patients requiring primary or secondary PCP prophylaxis; History of mild or moderate rash or fever resulting in discontinuation of cotrimoxazole in their medical records; Mean age 38.6 years; 16.2% female; Mean baseline CD4 cell count 128.
Interventions	Desensitization (cotrimoxazole pediatric suspension in 5 incrementally increasing amounts over 5 days, plus placebo cotrimoxazole tablet) vs. (placebo pediatric suspension in 5 incrementally increasing amounts over 5 days, plus single-strength 400mg/80mg cotrimoxazole tablet).
Outcomes	Ability to continue receiving single strength cotrimoxazole daily for 6 months; serious adverse reactions.
Notes	Patients were required to take an antihistamine each day during dose escalation.
Allocation concealment	B – Unclear

Study	Straatmann 2002
Methods	Randomized, open-label
Participants	18 HIV seropositive adults; Recent diagnosis of allergic reaction to cotrimoxazole or sulfadiazine with complete resolution; Absence of active opportunistic infections; Mean age 40.5 years; Mean CD4 count 130;

	79% CD4 count <200; 16.6% female.
Interventions	Desensitization protocol (initial dose of 75mg of sulphamethoxazole/15mg trimethoprim doubled every 48h until full dose was reached) vs. double-strength cotrimoxazole (800mg sulfamethoxazole and 160mg of trimethoprim).
Outcomes	Ability to continue receiving single strength cotrimoxazole three times per week for 6 months; serious adverse reactions.
Notes	
Allocation concealment	A – Adequate

Characteristics of excluded studies

Study	Reason for exclusion
Picketty 1995	Nonrandomized controlled trial. Comparison of two different desensitization protocols.

Characteristics of ongoing studies

Study	COTOX 2005
Trial name or title	Randomized, open-label
Participants	388 HIV seropositive adults who require PCP prophylaxis; Have or have had a mild or moderate reaction to co-trimoxazole; Not have or have had a severe reaction to co-trimoxazole.
Interventions	Treating through cotrimoxazole reaction vs. cotrimoxazole desensitisation (graduated doses over 10 days) vs. direct rechallenge.
Outcomes	Tolerability, safety and efficacy of each intervention.
Starting date	October 3, 2000
Contact information	Dr M Waugh, Leeds General Infirmary Great George Street, Leeds LS1 3EX 0113 392 3238
Notes	

ANALYSES

Comparison 01. Desensitization vs. Rechallenge

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Discontinuation before completion of 6 month follow up	3	268	Relative Risk (Fixed) 95% CI	0.64 [0.45, 0.91]
02 Presence of any hypersensitivity reactions after introduction of cotrimoxazole	3	268	Relative Risk (Fixed) 95% CI	0.51 [0.36, 0.73]

03 Presence of fever after reintroduction of cotrimoxazole	2	250	Relative Risk (Fixed) 95% CI	0.41 [0.20, 0.83]
04 Presence of cutaneous reactions (rashes, hives, exthanems and erythema) after reintroduction	2	250	Relative Risk (Fixed) 95% CI	0.88 [0.51, 1.53]
05 Presence of hypersensitivity event requiring hospitalization	3	268	Relative Risk (Fixed) 95% CI	2.23 [0.09, 52.54]
06 Presence of severe hypersensitivity event after reintroduction of cotrimoxazole	3	268	Relative Risk (Fixed) 95% CI	Not estimable

COVER SHEET

Title	Cotrimoxazole for prophylaxis or treatment of opportunistic infections of HIV/AIDS in patients with previous history of hypersensitivity to cotrimoxazole
Authors	Lin D, Li WK, Rieder MJ
Contribution of author(s)	Daren Lin searched for titles, obtained full articles, assessed the methological quality of studies, extracted data, analysed data and helped draft the review manuscript. Wing-Ki Li searched for titles, obtained full articles, assessed the methological quality of studies and helped to draft the review manuscript. Michael Rieder coordinated the review, solved study discrepencies, and helped to draft the review manuscript.
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Date new studies sought but none found	28 May 2006
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Contact address	Dr Michael Rieder Professor Department of Paediatrics Children's Hospital of Western Ontario 800 Commissioner's Rd. E London Ontario N6C 2V5 CANADA E-mail: mrieder@uwo.ca Tel: +1 519 685 8293

Fax: +1 519 685 8156

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GRAPHS AND OTHER TABLES

Analysis 01.01. Comparison 01 Desensitization vs. Rechallenge, Outcome 01 Discontinuation before completion of 6 month follow up

Review: Cotrimoxazole for prophylaxis or treatment of opportunistic infections of HIV/AIDS in patients with previous history of hypersensitivity to cotrimoxazole

Comparison: 01 Desensitization vs. Rechallenge

Outcome: 01 Discontinuation before completion of 6 month follow up

Study	Desensitization n/N	Rechallenge n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Bonfanti 2000	7/34	7/25		15.0	0.74 [0.30, 1.83]
Leoung 2001	24/97	40/94		75.7	0.58 [0.38, 0.88]
Straatmann 2002	5/9	5/9		9.3	1.00 [0.44, 2.29]
Total (95% CI)	140	128		100.0	0.64 [0.45, 0.91]

Total events: 36 (Desensitization), 52 (Rechallenge)

Test for heterogeneity chi-square=1.40 df=2 p=0.50 I^2 =0.0%

Test for overall effect z=2.48 p=0.01

Analysis 01.02. Comparison 01 Desensitization vs. Rechallenge, Outcome 02 Presence of any hypersensitivity reactions after introduction of cotrimoxazole

Review: Cotrimoxazole for prophylaxis or treatment of opportunistic infections of HIV/AIDS in patients with previous history of hypersensitivity to cotrimoxazole

Comparison: 01 Desensitization vs. Rechallenge

Outcome: 02 Presence of any hypersensitivity reactions after introduction of cotrimoxazole

Study	Desensitization n/N	Rechallenge n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Bonfanti 2000	7/34	7/25		13.5	0.74 [0.30, 1.83]
Leoung 2001	20/97	46/94		78.1	0.42 [0.27, 0.66]
Straatmann 2002	5/9	5/9		8.4	1.00 [0.44, 2.29]
Total (95% CI)	140	128		100.0	0.51 [0.36, 0.73]

Total events: 32 (Desensitization), 58 (Rechallenge)

Test for heterogeneity chi-square=3.87 df=2 p=0.14 I^2 =48.4%

Test for overall effect z=3.65 p=0.0003

Analysis 01.03. Comparison 01 Desensitization vs. Rechallenge, Outcome 03 Presence of fever after reintroduction of cotrimoxazole

Review: Cotrimoxazole for prophylaxis or treatment of opportunistic infections of HIV/AIDS in patients with previous history of hypersensitivity to cotrimoxazole

Comparison: 01 Desensitization vs. Rechallenge

Outcome: 03 Presence of fever after reintroduction of cotrimoxazole

Study	Desensitization n/N	Rechallenge n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Bonfanti 2000	3/34	5/25		25.0	0.44 [0.12, 1.68]
Leoung 2001	7/97	17/94		75.0	0.40 [0.17, 0.92]
Total (95% CI)	131	119		100.0	0.41 [0.20, 0.83]

Total events: 10 (Desensitization), 22 (Rechallenge)

Test for heterogeneity chi-square=0.02 df=1 p=0.90 I^2 =0.0%

Test for overall effect z=2.47 p=0.01

Analysis 01.04. Comparison 01 Desensitization vs. Rechallenge, Outcome 04 Presence of cutaneous reactions (rashes, hives, exthanems and erythema) after reintroduction

Review: Cotrimoxazole for prophylaxis or treatment of opportunistic infections of HIV/AIDS in patients with previous history of hypersensitivity to cotrimoxazole

Comparison: 01 Desensitization vs. Rechallenge

Outcome: 04 Presence of cutaneous reactions (rashes, hives, exthanems and erythema) after reintroduction

Study	Desensitization n/N	Rechallenge n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Bonfanti 2000	7/34	7/25		36.2	0.74 [0.30, 1.83]
Leoung 2001	14/97	14/94		63.8	0.97 [0.49, 1.92]
Total (95% CI)	131	119		100.0	0.88 [0.51, 1.53]

Total events: 21 (Desensitization), 21 (Rechallenge)

Test for heterogeneity chi-square=0.23 df=1 p=0.63 I^2 =0.0%

Test for overall effect z=0.44 p=0.7

Analysis 01.05. Comparison 01 Desensitization vs. Rechallenge, Outcome 05 Presence of hypersensitivity event requiring hospitalization

Review: Cotrimoxazole for prophylaxis or treatment of opportunistic infections of HIV/AIDS in patients with previous history of hypersensitivity to cotrimoxazole

Comparison: 01 Desensitization vs. Rechallenge

Outcome: 05 Presence of hypersensitivity event requiring hospitalization

Study	Desensitization n/N	Rechallenge n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Bonfanti 2000	1/34	0/25		100.0	2.23 [0.09, 52.54]
× Leoung 2001	0/97	0/94		0.0	Not estimable
× Straatmann 2002	0/9	0/9		0.0	Not estimable
Total (95% CI)	140	128		100.0	2.23 [0.09, 52.54]

Total events: 1 (Desensitization), 0 (Rechallenge)

Test for heterogeneity: not applicable

Test for overall effect z=0.50 p=0.6

Analysis 01.06. Comparison 01 Desensitization vs. Rechallenge, Outcome 06 Presence of severe hypersensitivity event after reintroduction of cotrimoxazole

Review: Cotrimoxazole for prophylaxis or treatment of opportunistic infections of HIV/AIDS in patients with previous history of hypersensitivity to cotrimoxazole

Comparison: 01 Desensitization vs. Rechallenge

Outcome: 06 Presence of severe hypersensitivity event after reintroduction of cotrimoxazole

Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
× Bonfanti 2000	0/34	0/25		0.0	Not estimable
× Leoung 2001	0/97	0/94		0.0	Not estimable
× Straatmann 2002	0/9	0/9		0.0	Not estimable
Total (95% CI)	140	128		0.0	Not estimable
Total events: 0 (Treatment), 0 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable