Cotrimoxazole preventive therapy in adults and pregnant women with HIV: a systematic review and meta-analysis
Introduction

Global efforts to scale-up antiretroviral therapy (ART) averted an estimated 4.2 million deaths in low- and middle-income countries from 2002-2012 [1]. All United Nations member states endorsed this important impact and agreed to continue scale-up of ART to 15 million people by 2015 [2]. In 2012, 9.7 million (65% of the United Nations target) were receiving ART [1]. While limited access to ART contributed to the 1.6 million deaths among the 35.3 million people with HIV in 2012, concomitant infections are also an important cause of death [3]. Cotrimoxazole is a fixed-dose combination of two antimicrobial agents (sulfamethoxazole and trimethoprim) that prevents a wide spectrum of infections among people with HIV.

WHO recommends cotrimoxazole preventive therapy in HIV-infected adults and pregnant women with CD4 counts below 350 cells/µL [4]. Discontinuation can be considered in individuals with CD4 counts above 350 cells/µL after at least six months of ART. Despite policies for cotrimoxazole preventive therapy in most countries, nationwide implementation remains problematic [5]. The reasons for the incomplete implementation of national policies are various and include service, patient, and demographic barriers. For example, in Malawi nationwide implementation only occurred after (1) completion of local cotrimoxazole operational research, (2) nationwide dissemination of findings through the Ministry of Health, (3) changes in national policy, and (4) the development of monitoring tools, drug procurement and distribution, and training packages [6].

Previous systematic reviews have reviewed *Pneumocystis jirovecii* pneumonia (PCP) prophylaxis among people not receiving ART [7-9], discontinuation of PCP prophylaxis after ART-induced CD4 recovery [10], cotrimoxazole initiation in people not receiving ART with advanced disease [11], cotrimoxazole initiation in people receiving ART with advanced disease [12], and PCP prophylaxis dosing [8]. Given these reviews only included a few studies conducted in low- and middle-income countries, The objective of this article is to systematically review cotrimoxazole initiation, discontinuation, and dosing in adults and pregnant women with HIV globally.

Methods

Conduct of systematic review
This systematic review will be conducted in accordance with PRISMA guidelines [13]. The PubMed, Embase, African Index Medicus, Index Medicus for the Eastern Mediterranean Region, Index Medicus for the Southeast Asia Region, Western Pacific Region Index Medicus, and Latin American and Caribbean Health Science Literature databases will be systematically searched without language, publication, date, or any other limits. The WHO International Clinical Trials Registry Platform, the Cochrane Central Register of Controlled Trials, the International Standard Randomised Controlled Trial Number Register, and ClinicalTrials.gov will be searched for future and on-going studies. Experts in the field will be contacted to identify unpublished research and on-going studies.

**Search strategy and selection criteria**

The search strategies (Table 1) were designed to identify studies including people with HIV using cotrimoxazole. Per recommendations from the PRISMA Group, eligibility criteria were based on key study characteristics: population, intervention, comparator, outcome, and design [13]. For issues related to initiation or discontinuation of cotrimoxazole, studies will be included when (1) the study population included adults, pregnant women, or breastfeeding women with HIV, (2) the intervention was daily cotrimoxazole, (3) the comparator was no cotrimoxazole (except in settings with moderate-high malaria transmission, where pregnant women ineligible for cotrimoxazole should receive intermittent preventive treatment [14]), (4) the outcomes were death, new WHO clinical stage 3 or 4 event, diarrhoea, pneumonia, malaria, severe bacterial infections, tuberculosis, treatment limiting adverse event, hospitalisation rates, cost or cost-effectiveness, acceptability, retention in care, or adherence to ART, and (5) the study design was a randomised trial or observational cohort study. For cotrimoxazole dosing, the study population will remain the same, the intervention will be 480 mg of cotrimoxazole daily, the comparator will be 960 mg of cotrimoxazole daily, and the outcomes and study designs will remain the same. Two investigators will independently screen abstracts of all identified articles and then match the full texts of all articles selected during screening against the inclusion criteria. Articles meeting the inclusion criteria will be included in this review.

**Data extraction**

Two investigators will complete the data extraction using a standardised extraction spreadsheet comprising four tables. The first table will summarise the characteristics of study
participants. The second table will summarise study methods. The third table will summarise the reported outcomes. The final table will focus on quality assessment.

**Statistical analyses**

Studies meeting eligibility criteria will be stratified by (1) pregnancy/breastfeeding status, (2) clinical stage or level of immunodeficiency, and/or (3) viral suppression. If there are an adequate number of studies meeting eligibility criteria for key analyses, a funnel plot with the effect measures on the x-axis and standard error of the log for the effect measures on the y-axis will be created to assess publication bias and the Egger and Begg tests will be used to test the funnel plot’s symmetry. If studies are similar enough to combine after stratification, meta-analyses will be performed and statistical heterogeneity will be assessed. Effect measures will be entered as the natural log of the effect measure and standard error as the natural log of \((95\% \text{ upper limit} ÷ 95\% \text{ lower limit}) ÷ 3.92\) [15]. Since it is possible that the magnitude and direction of cotrimoxazole’s impact could differ for reasons other than chance, random-effects models will be used for all analyses. For non-inferiority and equivalency analyses, a 10% margin will be used to compare the risk of outcomes [16, 17]. An I-squared statistic will be used to measure heterogeneity in the magnitude of pooled estimates [18]. I-squared statistics near 25% indicate low heterogeneity, values near 50% indicate moderate heterogeneity, and those above 75% indicate high heterogeneity [19]. If there is moderate to significant heterogeneity in estimates, potential causes, including clinical stage at cotrimoxazole initiation, study design, and the burden of infectious diseases in the country where studies were conducted may be explored using sensitivity analyses. STATA version 12.0 will be used for all analyses.

**Quality assessment**

For the quality assessment, studies will be stratified based on study design (i.e. randomised controlled trial or observational study). Per recommendations from the Cochrane Collaboration, the Collaboration’s ‘Risk of bias’ tool will be used to assess bias in randomised trials [20]. This tool rates studies based on six criteria in four sources of bias. The presence of random sequence generation for allocation into intervention and comparator arms, and attempts to conceal this allocation, will be used to gauge selection bias. Blinding of study participants, personnel, and outcome assessment during the conduct and analysis of the studies will be used to gauge performance and detection bias. Incomplete outcome data, through review of participants excluded from outcome analyses or lost to follow-up, will be
used to gauge attrition bias. Selective reporting of outcomes, time-points, subgroups, or analyses, will be used to gauge reporting bias. A criterion for other forms of bias will also be used. Based on these criteria, studies will be scored out of 100%.

Per recommendations from the Cochrane Collaboration [20], the *Newcastle-Ottawa Quality Assessment Scale* will be used to assess bias in observational studies [21]. This scale rates studies based on eight criteria in three sources of bias. Each criterion is worth one point except confounding, which is worth two points. Selection bias will be assessed using four criteria: (1) representativeness of the cohort on cotrimoxazole to the average person on cotrimoxazole in the community in which study participants were drawn, (2) representativeness of the cohort off cotrimoxazole to the cohort on cotrimoxazole, (3) ascertainment of cotrimoxazole use, and (4) demonstration that the outcome was not present at the start of follow up. Adjustment for CD4 count will be used to judge whether appropriate methods were used to address confounding. Measurement bias will be assessed using three criteria: (1) assessment of outcome, (2) adequate follow-up to detect the outcome, and (3) ≤ 30% of participants lost to follow up during the study.

The quality of evidence will be assessed using the *Grades of Recommendation, Assessment, Development, and Evaluation* (GRADE) system to guide HIV programme managers and other policy makers on appropriate cotrimoxazole use (Appendix, [22]).
Table 1. Search strategy for all databases.

<table>
<thead>
<tr>
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<tr>
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<td>HIV</td>
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<td>4</td>
<td>1 or 2 or 3</td>
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<td>5</td>
<td>cotrimoxazole</td>
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<td>6</td>
<td>co-trimoxazole</td>
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<td>7</td>
<td>CPT</td>
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<tr>
<td>8</td>
<td>bactrim</td>
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REFERENCES


APPENDIX

For systematic reviews, the GRADE approach defines the quality of a body of evidence as the extent to which one can be confident that an estimate of effect or association is close to the quantity of specific interest. The quality rating across studies has four levels: high, moderate, low, or very low. High quality indicates that further research is very unlikely to change our confidence in the estimate of effect. Moderate quality indicates that further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Low quality indicates that further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. Very low quality indicates that any estimate of effect is very uncertain. By default randomised trials are categorised as high quality and can be downgraded while cohort studies are categorised as low quality and can be upgraded or downgraded. The GRADE Profiler software will be used for performing the GRADE assessment (GRADEprofiler version 3.2.2).

There are five factors that can decrease the quality of a body of evidence. The first factor is major limitations in study design or execution that are likely to result in a biased assessment of the effect estimate. This factor will be gauged by assessing the risk of bias across studies. When the proportion of information from studies at high risk of bias is sufficient to affect the interpretation of results, the risk of bias across studies will be ‘high’. When most data included in the GRADE review is insufficient to affect the interpretation of results, the risk of bias across studies will be ‘low’. When most information included in the GRADE review is from studies at an unclear risk of bias, the risk of bias across studies will be ‘unclear’. ‘Low’ risk of bias will indicate ‘no limitation’, an ‘unclear’ risk of bias will indicate ‘no limitation’ or ‘serious limitation’, and a ‘high’ risk of bias will indicate ‘serious limitation’ or ‘very serious limitation.’ The second factor that can decrease the quality of a body of evidence is indirectness of evidence. Indirectness of evidence refers to bodies of literature that do not correspond to the population, intervention, comparator, and outcome specified in the inclusion criteria. The third factor that can decrease the quality of a body of evidence is inconsistency of study results. This would primarily be when studies yield widely different estimates of effect in terms of heterogeneity or variability in results. The fourth factor that can decrease the quality of a body of evidence is imprecision of results, i.e. when there are few participants, few events, and wide confidence intervals. The fifth and final factor that can decrease the quality of a body of evidence is high probability of publication bias. This would be when investigators fail to publish studies or outcomes on the basis of their results.
There are three factors that can increase the quality level of a body of evidence. The first factor is a large magnitude of effect. In the absence of plausible confounders, a large effect (i.e. RR > 2 or RR < 0.5) increases the quality one level while a very large effect (i.e. RR > 5 or RR < 0.2) increases the quality two levels. The second factor is plausible confounding that reduces the effect demonstrated in the included studies. The third factor is the presence of a dose-response gradient.