South African National Essential Medicine List
Adult Hospital Level Medication Review Process
Component: HIV and AIDs

Executive Summary

Date: 16 May2017
Medicine (INN): Cotrimoxazole (CTx) , oral, 960 mg daily (800 mg sulfamethoxazole + 160mg Trimethoprim)
Medicine (ATC): J01EE01
Indication (ICD10 code): Z29.2
Patient population: HIV-1 infected adult patients
Prevalence of condition: An estimated 7.02 million people were living with HIV in South Africa in 2016, representing 12.7% of the national population or 19.1% of those aged 15-49 years(1)
Level of Care: Primary level of care
Prescriber Level: Nurse prescriber, doctor.
Current standard of Care: Cotrimoxazole is indicated for HIV-infected patients with CD4 below 200 cells/ml and/or advanced HIV disease (WHO stages 2, 3, and 4).
Efficacy estimates: Numbers needed to treat*(2)for Cotrimoxazole initiation at CD4 < 350 cells/ml on ART vs. control, based on estimates from the systematic review/meta-analysis by Suthar et al, 2015;

- Mortality: NNT = 9 (95%CI: 7 – 15) and WHO Stage 3 & 4 events: NNT = 22 (95%CI: 11 - 185)

*method by Altman et al, BMJ, 1999.
Motivator/reviewer name(s): Dr S Takuva, Mr NJ Nabyoma
PTC affiliation: N/A

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Introduction

Cotrimoxazole (CTX), fixed-dose trimethoprim-sulfamethoxazole, is a broad spectrum antibiotic used to prevent opportunistic infections in patients with HIV. Prophylaxis with CTX has been shown to decrease mortality, morbidity, and hospitalizations among HIV-infected adults and children, primarily by decreasing rates of malaria, pneumonia, and diarrhoea, as well as severe bacterial infections, even in settings with high prevalence of CTX resistance.(3–8) CTX is inexpensive and its clinical benefits outweigh pill burden and cost of hospitalizations/morbidity. As a result of expanded access and progressive movement towards earlier initiation of antiretroviral therapy (ART), the World Health Organization (WHO) issued updated guidelines for CTX prophylaxis in 2014. In summary, CTX prophylaxis is recommended for adults (including pregnant women)

with severe or advanced HIV clinical disease (WHO stage 3 or 4) and/or with a CD4 count of ≤350 cells/mm3 and timing of discontinuation of CTX prophylaxis differs by malarial/bacterial infection burden of the setting. (9) A recent systematic review and meta- analysis supported the provision of CTX prophylaxis with ART in people with CD4 counts of 350 cells/mm3 lower in low-income and middle-income countries and also that CTX prophylaxis should be provided irrespective of CD4 count in settings with a high burden of infectious diseases.(10)

Current recommendations for CTX prophylaxis in South Africa are based on a 2003 Cochrane review (*Grimwade et al*), supporting benefit of initiating prophylaxis at CD4<200cells/mm3 and those with stage 2, 3 or 4 HIV disease (including TB) and discontinuation once CD4 was above 200cells/mm3 for longer than 6 months. (11) In a South African cohort study by Hoffmann et al examining mortality risk by baseline CD4 strata, overall cotrimoxazole prophylaxis reduced mortality amongst all CD4 strata (<200, 200-350 and >350cells/ml) by 36% (hazard ratio (HR) 0.64, 95%CI 0.57-0.72).(12)No statistically significant association was found between CTX prophylaxis and survival in the subgroup of persons with both CD4 cell count above 200 cells per microliter and WHO stage 1 or 2.In this study it was speculated that bacterial infections were a major contributor of deaths (WHO stage 3-4 events). This observational study may also have been inadequately powered to detect differences in mortality at CD4 >350 cells/ml.

In this technical review, we appraise the current WHO recommendations for CTX prophylaxis and also evaluated a recent systematic review and meta-analysis to investigate whether the CD4 cut-off for CTX prophylaxis among HIV-infected persons in South Africa should be revised up to 350 cells/mm3 from 200cells/mm3.The mortality benefit among patients with HIV-TB is also explored from synthesis of RCTs and observational studies. Additionally, there was a review of evidence for increased risk and side-effects for cotrimoxazole if prophylaxis is prolonged to a CD4 of 350 cells/ml, rather than current recommendations of 200 cells/ml.

Question 1:

Cotrimoxazole prophylaxis is indicated for HIV-infected individuals with CD4<350 cells/mm3

PICO criteria;

Population	HIV-1 infected adult patients on ART
Intervention	Stop cotrimoxazole at CD4 > 200 cells/mm3 OR cotrimoxazole
Comparison	Continue cotrimoxazole till CD4 > 350 cells/mm3 OR Control
Outcomes	Morbidity, hospitalizations, bacterial infections, malaria, mortality

Search strategy and Selection of Studies:

An electronic literature search of the PubMed and EMBASE database from beginning of time till May 2017 was undertaken using:

Search ((((((HIV) OR Human immunodeficiency virus)) AND (((Mortality) OR Death) OR Hospitalization)) AND (((Cotrimoxazole) OR Trimethoprim-sulfamethoxazole) OR Sulfamethoxazole-trimethoprim))) AND prophylaxis

The search was further limited to Systematic reviews and Meta-analysispublished in the last 5 years evaluating at both observational and randomized clinical trial data. Reviews evaluating only malaria as an outcome were excluded as South Africa is not a high malaria burden area. Only adult population reviews were included.

Initially 528 studies were identified. After applying all above listed criteria, 2 systematic reviews were evaluated.

The 2014 update on cotrimoxazoleprophylaxis to the 2013 WHO HIV treatment guidelineswas evaluated separately as they are the most relevant recommendations to this setting.

Evidence Synthesis

Part A: systematic Reviews

Two well designed and rigorous systematic reviews of both observational data and randomised control trials published within the last 5 years were identified.

Suthar et al. Co-trimoxazole prophylaxis in adults, including pregnant women, with HIV: a systematic review and meta-analysis, Lancet 2015(10)- Studies were eligible if they reported death, WHO clinical stage 3 or 4 events, admittance to hospital, severe bacterial infections, tuberculosis, pneumonia, diarrhoea, malaria, or treatment-limiting adverse events. Infant mortality, low birthweight, and placental malaria were additional outcomes for the comparison of CTX prophylaxis and intermittent preventive treatment for malaria in pregnant women (IPTp).

19 articles, published from 1995 to 2014 and including 35,328 participants, met the inclusion criteria. CTX prophylaxis reduced rates of death (hazard ratio [HR] 0·40, 95% CI 0·26-0·64) when started at CD4 counts of 350 cells/mm3 or lower with antiretroviral therapy (ART) worldwide. CTX prophylaxis started at higher than 350 cells/mm3 without ART reduced rates of death (0·50, 0·30-0·83) and malaria (0·25, 0·10-0·57) in Africa. CTX prophylaxis continuation after ART-induced recovery with CD4 counts higher than 350 cells/mm3 reduced admittances to hospital (HR 0·42, 95% CI 0·22-0·80), pneumonia (0·73, 0·61-0·88), malaria (0·03, 0·01-0·10), and diarrhoea (0·61, 0·48-0·78) in Africa. Figure 1 below is a forest-plot from the systematic review and meta-analysis summarizing the impact on clinical outcomes of cotrimoxazole initiation at different CD4 strata.

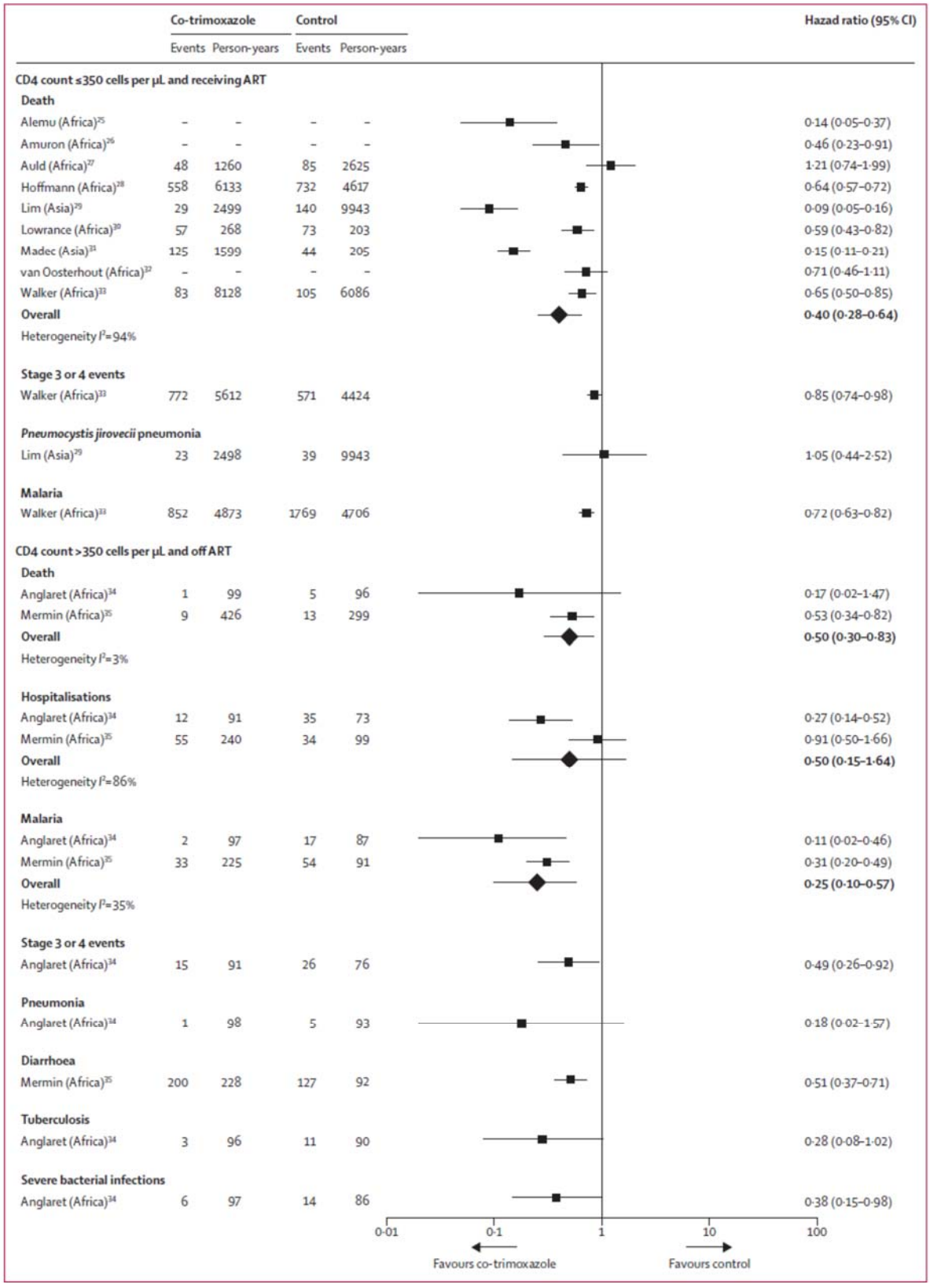


Figure 1: Cotrimoxazole initiation by CD4 count and clinical outcomes (adapted from Suthar et al, 2015)

Amongst its conclusions, this review which included RCTs from Asia and Africa supported that CTX prophylaxis should be given with ART in people with CD4 counts of 350 cells/mm3 or lower in low-income and middle-income countries and also CTX prophylaxis should be provided irrespective of CD4 count in settings with a high burden of infectious diseases. The authors also highlighted that there is need for more research on the use of CTX in the context of expanded ART in different epidemiological settings.

Critical appraisal:

Checklist (AMSTAR)(13)	**Score***	**Comments**
Was an 'a priori" design provided?	Yes	
Was there duplicate study selection and data extraction	Yes	More than one person conducted the search
Was a comprehensive literature search performed?	Yes	At least 2electronic sources were searched (PubMed, Embase, WHO Global Index Medicus, and clinical trial registries) and at least 1 supplementary strategy (experts in the specialty contacted to identify unpublished research and studies in progress)
Was the status of publication (i.e. grey literature) used as an inclusion criterion?	Yes	
Was a list of studies (included and excluded) provided?	Yes	
Were the characteristics of the included studies provided?	Yes	Data from the original studies provided on the participants, interventions, outcomes etc.
Was the scientific quality of the included studies assessed and documented?	Yes	Formal quality assessment process for each study is described. Used the Cochrane Collaboration's risk of bias method to assess bias in randomised trials
Was the scientific quality of the included studies used appropriately in formulating conclusions?	Yes	Cautious interpretation of findings stated due to a number of potential factors i.e. different epidemiological context like TB burden, malaria burden etc.
Were the methods used to combine the findings of studies appropriate?	Yes	They describe heterogeneity and how it was handled
Was the likelihood of publication bias assessed?	Yes	They used Egger and Begg statistics to test for publication bias
Was the conflict of interest included?	Yes	

*Score – either yes, no, can't answer or not applicable.

Hassani et al. Assessment of the impact of cotrimoxazole prophylaxis on key outcomes among HIV-infected adults in low- and middle-income countries: a systematic review. JAIDS, 2015(14) - Included articles addressed impact of CTX prophylaxis on the outcomes of mortality, morbidity, retention in care, quality of life, and/or prevention of ongoing HIV transmission.

These included 9 randomized controlled trials, 26 observational studies, 2 systematic reviews with meta-analysis, 1 other systematic review, and 4 cost-effectiveness (CE) studies. The overall quality of evidence was rated as "good" and the expected impact "high" for both mortality and morbidity. Evidence for impact was strongest for patients with CD4 <350 cells/mm3 or with WHO clinical stage 3 or 4 disease and data showing a mortality benefit are scarce for patients with higher CD4 counts. However, morbidity benefits, especially in preventing malaria, are consistently seen in persons with CD4 counts >350 cells/mm3. The overall quality of evidence from the 4 studies addressing retention in care was rated as "poor," and the expected impact on retention was rated as "uncertain." The 4 assessed CE studies showed that provision of CTX prophylaxis is cost effective and sometimes cost saving. No studies addressed impact on quality of life or HIV transmission.

The review concluded that CTX prophylaxis is a cost-effective intervention with expected high impact on morbidity and mortality reduction in HIV-infected adults in resource-limited settings. Benefits are seen in both pre-antiretroviral therapy and antiretroviral therapy populations.

Critical appraisal:

Checklist (AMSTAR)	Score*	Comments
Was an 'a priori" design provided?	Yes	The different outcomes are clearly defined
Was there duplicate study selection and data extraction	Yes	More than one person conducted the search
Was a comprehensive literature search performed?	Yeswith reservations	At least 2 electronic sources were searched (MEDLINE, Embase, Global Health, CINAHL, SOCA, and African Index Medicus (AIM). However the authors do not least any supplementary strategy to potentially identify unpublished research, conference proceedings and studies in progress.
Was the status of publication (i.e. grey literature) used as an inclusion criterion?	No	
Was a list of studies (included and excluded) provided?	Yes	Supplemental content
Were the characteristics of the included studies provided?	Yes	Data from the original studies provided on the participants, interventions, outcomes etc.
Was the scientific quality of the included studies assessed and documented?	Yes	They actively evaluated the quality of individual studies and the overall quality of evidence for each study was rated as "strong," "medium," or "weak."
Was the scientific quality of the included studies used appropriately in formulating conclusions?	Yes	The authors extensively highlight the quality of evidence for each of the conclusions they formulate i.e. poor quality for retention data.
Were the methods used to combine the findings of studies appropriate?	Yes	They did not attempt quantitative synthesis of study results overall. The authors grouped the studies by the outcome(s) addressed and rated the overall quality of the body of evidence for each outcome as good, fair, or poor.
Was the likelihood of publication bias assessed?	Can't answer	Not clear in the manuscript
Was the conflict of interest included?	Yes	

*Score – either yes, no, can't answer or not applicable.

Cotrimoxazole prophylaxis and impact on mortality among HIV-infected patients with TB

Findings from the meta-analysis by Suther et al(10)suggest cotrimoxazole benefit irrespective of CD4 count in settings in which the burden of infectious disease is high and a trend of mortality benefit to reduce tuberculosis. However, clear clinical benefit on reduction in TB incidence by cotrimoxazole status has not been shown in RCTs. One of the early randomized trials of cotrimoxazole among HIV-infected individuals reported 22 cases of TB among 271 participants in the placebo group and 17 cases among 270 participants in the cotrimoxazole group (p = 0.6).(15) Another large trial (DART) with over 200 cases of incident TB, also found no difference in TB incidence among participants who did and did not receive cotrimoxazole.(8)

In an observational study, Hoffman et al examined the impact of cotrimoxazole on TB incidence and "TB diagnostic yield" in a cohort of HIV-infected adults living in a high TB prevalence area.(16)Participants who received cotrimoxazole prophylaxis were found to be at an increased risk for TB (HR 1.7; 95% CI: 1.2 to 2.2). However, this association was believed to be due to confounding; no effect of CTX prophylaxis was found when analysis was based on data exclusively from laboratory-confirmed TB cases (HR: 0.97; 95% CI: 0.39 to 2.4).

Safety of long term cotrimoxazole among patients with higher CD4 cell counts

Question 2:
Cotrimoxazole prophylaxis is safe for HIV-infected adults and pregnant woman?

PICO criteria;

Population	HIV-1 infected adult patients
Intervention	Cotrimoxazole at various CD4 counts
Comparison	Control
Outcomes	Adverse events, neonatal adverse events, congenital abnormalities

Search strategy and Selection of Studies:
An electronic literature search of the PubMed and EMBASE database from beginning of time till August 2017 was undertaken:

Although, cotrimoxazole is well tolerated with low rates of toxicity, skin rash (including Stevens-Johnson syndrome), and the rate of treatment limiting adverse events is generally low (high-quality evidence), reactions of the blood and blood-forming organs and liver toxicity have been reported.A literature search reveals that data on cotrimoxazole safety is scanty for long term use and this is a research gap.It is noteworthy that trials in ART-naive participants have typically had little follow-up beyond 72 weeks. With regards to use in pregnancy among HIV-infected patients, there is still a possible association between first-trimester exposure to trimethoprim and an increased risk of congenital anomalies. Results from the evidence review suggest the benefits of prophylaxis outweigh the small safety concerns.

Below is a summary of the evidence reviewed.

Pubmed and Cochrane search

A search of Cochrane library yielded no results relevant to the research questions. Out of the 46 hits, only 2 systematic reviews & meta-analysis answered the research question.

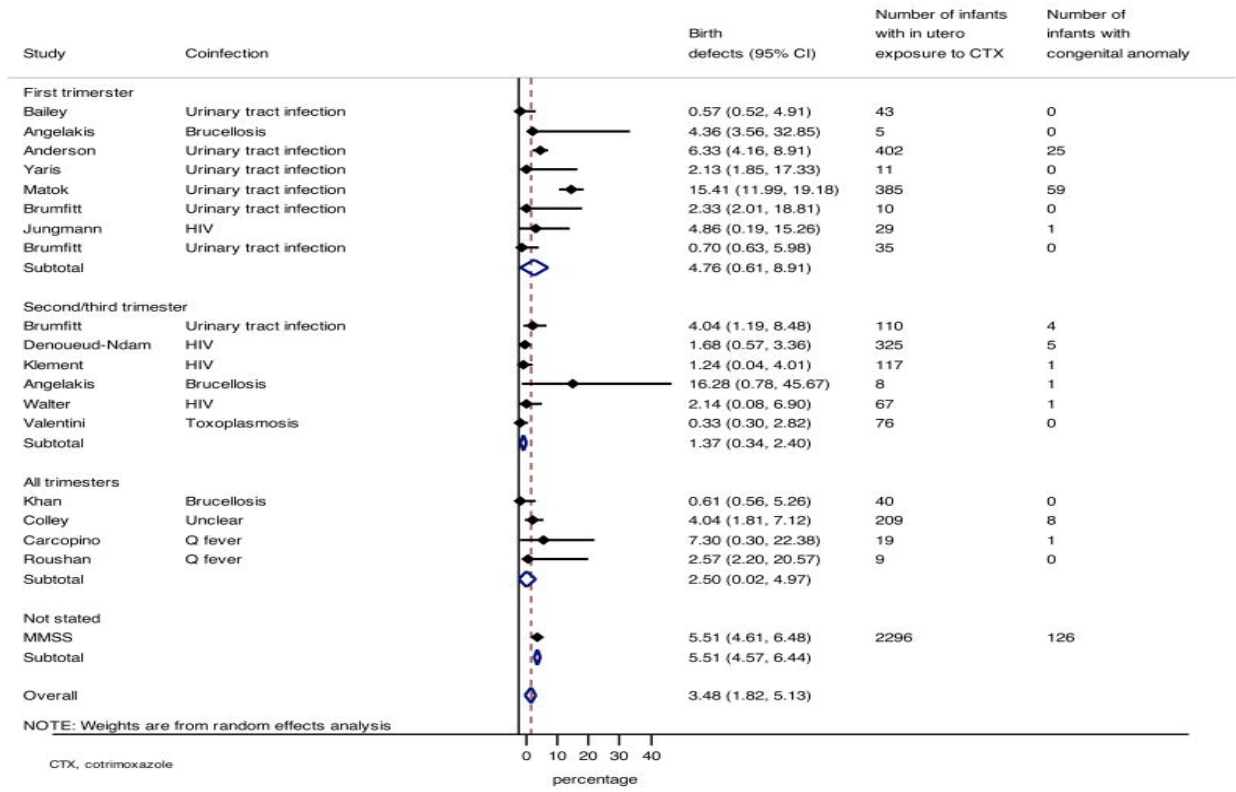
MeSH terms

((("trimethoprim, sulfamethoxazole drug combination"[MeSH Terms] OR ("trimethoprim"[All Fields] AND "sulfamethoxazole"[All Fields] AND "drug"[All Fields] AND "combination"[All Fields]) OR "sulfamethoxazole drug combination trimethoprim"[All Fields] OR "cotrimoxazole"[All Fields]) AND ("prevention and control"[Subheading] OR ("prevention"[All Fields] AND "control"[All Fields]) OR "prevention and control"[All Fields] OR "prophylaxis"[All Fields])) AND ("hiv"[MeSH Terms] OR "hiv"[All Fields])) AND ("safety"[MeSH Terms] OR "safety"[All Fields])

The search yielded **46** hits

Systematic reviews and meta- analysis: Existing data indicate that the risk of serious injury to neonates from maternal use of daily cotrimoxazole prophylaxis during pregnancy and breastfeeding is small.

Ford et al reviewed the safety of CXT in pregnancy. (17) Four studies included had cohorts who were HIV positive. The results of this review are inconclusive and may not draw us to a conclusion of cotrimoxazole safety in pregnancy due to the constraints that the authors eluded. Below is a forest plot summarizing these finding.



Forna et al examined the safety of cotrimoxazole vs SP use in pregnant women, both HIV + and HIV-.(18)Twenty-four studies were included for review. There were 232 infants with congenital anomalies among 4196 women receiving cotrimoxazole during pregnancy, giving an overall pooled prevalence of 3.5% (95% CI 1.8–5.1%). Three studies reported 31 infants with neural tube defects, giving a crude prevalence of 0.7% (95%CI 0.5–1.0%) with most data (29 neural tube defects) coming from a single study. The majority of adverse drug reactions were mild. The quality of the evidence was very low.

Part B: Guidelines

As WHO treatment guidelines are most relevant to this setting, the 2014 update on cotrimoxazole prophylaxis to the 2013 WHO HIV treatment guidelines update on cotrimoxazole prophylaxis was evaluated separately as they are the most relevant recommendations to this setting.(9)

AGREE II scoring sheet:

Guideline: Guidelines on Post-Exposure Prophylaxis for HIV and the Use of Co-trimoxazole Prophylaxis for HIV-Related Infections among Adults, Adolescents and Children: Recommendations for a Public Health Approach: December 2014 supplement to the 2013 consolidated guidelines. World Health Organisation, Geneva.

Domains	Criteria	Score 1=strongly disagree to 7= strongly agree	Comments
Domain 1: Scope and Purpose	The overall objective(s) of guideline is (are) specifically described	7	The objective is to make recommendations for the use of co-trimoxazole prophylaxis For HIV-related infections among adults, adolescents and children. The expanded access and progressive movement towards earlier initiation of ART warranted an update to existing WHO guidelines on cotrimoxazole prophylaxis.
	The health questions(s) covered by guideline is (are) specifically described	7	Very clear – when to start, when to start, among the different populations.
	Population (patients, public etc.) to whom guideline is meant to apply to is specifically described	5	Yes – adults including pregnant women, children, adolescents and infants. The population from the studies is mainly from resource limited settings. However the guideline understandably makes generalisations to the epidemiological context of resource limited settings i.e. the inferences of data on CTX impact on morbidity and mortality in areas with high malaria / parasitic burden maybe overestimated in areas with low/little malaria burden like South Africa.
Domain 2: Stakeholder Involvement	The guideline development group includes individuals from all relevant professional groups	7	A wide range of stakeholders are included
	The views and preferences of the target population (patients, public, etc.) have been sought	6	Patient groups included (not sure from guideline if from resource limited settings though)
	Target users of the guideline are clearly defined	7	Strongly agree
Domain 3: Rigour of Development	Systematic methods were used to search for evidence	6	These are very clear in the main HIV treatment guideline, however for the CTX supplement this is not adequately described. The assumption is that this was the same process?
	The criteria for selecting evidence are clearly described	6	Not clearly pre-defined
	The strengths and limitations of the body of evidence are clearly described	7	Strongly agree
	The methods for formulating the recommendations are clearly described	5	Not clearly described in this supplement

	The health benefits, side effects, and risks have been considered in formulating the recommendations	7	Strongly agree
	There is an explicit link between the recommendations and the supporting evidence	7	Strongly agree
	The guideline has been externally reviewed by experts prior to its publication	7	Strongly agree
	A procedure for updating the guideline is provided	1	No
Domain 4: Clarity of Presentation	The recommendations are specific and unambiguous	7	Strongly agree
	The different options for management of the condition or health issue are clearly presented	7	Strongly agree. Different scenarios are presented
	Key recommendations are easily identifiable	7	Strongly agree
Domain 5: Applicability	The guideline describes facilitators and barriers to its application	7	Strongly agree
	The guideline provides advice and/or tools on how recommendations can be put into practice	7	Strongly agree
	The potential resource implications of applying the recommendations have been considered	7	Strongly agree
	The guideline presents monitoring and/or auditing criteria	5	Not clear
Domain 6:Editorial independence	The views of the funding body have not influenced the content of the guideline	7	Strongly agree
	The competing interests of guideline development group members have been recorded and addressed.	7	Strongly agree

Overall Guideline Quality: Scores high - Good to Excellent.

EVIDENCE TO DECISION FRAMEWORK

	JUDGEMENT	SUPPORTING EVIDENCE & ADDITIONAL CONSIDERATIONS
QUALITY OF EVIDENCE	**What is the overall confidence in the evidence of effectiveness?** Confident [x] Not confident [ ] Uncertain [ ]	Observational and randomized control trial data demonstrates effectiveness.
BENEFITS & HARMS	**Do the desirable effects outweigh the undesirable effects?** Benefits outweigh harms [x] Harms outweigh benefits [ ] Benefits = harms or Uncertain [ ]	
THERAPEUTIC INTERCHANGE	Therapeutic alternatives available: Yes [ ] No [x]	Rationale for therapeutic alternatives included: n/a
VALUES & PREFERENCES / ACCEPTABILITY	**Is there important uncertainty or variability about how much people value the options?** Minor [x] Major [ ] Uncertain [ ] **Is the option acceptable to key stakeholders?** Yes [x] No [ ] Uncertain [ ]	
RESOURCE USE	**How large are the resource requirements?** More intensive [ ] Less intensive [x] Uncertain [ ]	Cost of medicines/ month: **Medicine** | **Cost (R)*** Cotrimoxazole 480 mg tabs (56) | R 9.35 * Average weighted price: Contract circular HP09-2015 AI **Additional resources:** Hassani et al, 2015(14)
EQUITY	**Would there be an impact on health inequity?** Yes [ ] No [x] Uncertain [ ]	
FEASIBILITY	**Is the implementation of this recommendation feasible?** Yes [x] No [ ] Uncertain [ ]	Cotrimoxazole is inexpensive and readily available.

Type of recommendation	We recommend against the option and for the alternative	We suggest not to use the option or to use the alternative	We suggest using either the option or the alternative	We suggest using the option	We recommend the option
	☐	☐	☐	☐	X

Recommendation

Based on the evidence gathered from the technical review, the Adult Hospital Level Expert Review Committee does not support the current recommendations by the WHO for cotrimoxazole prophylaxis among adult HIV-infected patients. The current recommendation be retained in the STGs and EML: Cotrimoxazole for HIV-infected patients with CD4 < 200 cells/ml and/or advanced HIV disease (WHO stages 2, 3, and 4).

Rationale: The impact and benefit of cotrimoxazole prophylaxis on morbidity and mortality among HIV-infected patients with CD4 ≤ 350 cells/mm3 and regions with high infectious disease (irrespective of CD4) has been demonstrated in a good quality systematic review and meta-analysis and individual randomized controlled trials. However, local South African data showed no benifit of cotrimoxazole prophylaxis when CD4 count >200 cells/mm3 in patients who were not WHO clinical stage III or stage IV.

Although cotrimoxazole is inexpensive, widely available and has been demonstrated to be cost-effective, long term safety data of cotrimoxazole use in adults and pregnant women are scanty.

Level of Evidence: I Systematic reviews and metaanalyses, Observational study

Review indicator:

Evidence of efficacy	Evidence of harm	Price reduction
x		

VEN status:

Vital	Essential	Necessary
	X	

NEMLC MEETING OF 29 JUNE 2017:

NEMLC accepted this evidence review and the proposal as recommended by the Adult Hospital Level Expert Review Committee, above.

The NEMLC also acknowledged that despite meta-analyses[10 19] and WHO Guidelines recommending cotrimoxazole prophylaxis in people on antiretroviral treatment (ART) with CD4 counts <350 cells/mm^{3}in low-income and middle-income countries, the majority of the studies (mix of observational and randomised controlled trials) were performed in countries with a high burden of malaria. The South African observational cohort study by Hoffman et al.[12], showed that cotrimoxazole prophylaxis reduced mortality overall (adjusted HR 0.64, 0.57 to 0.72; p<0.001), where CD4 count was <200 cells/mm^3 (adjusted HR 0.64, 0.56 to 0.72) or in those with WHO clinical stage 3 or 4 conditions. Mortality was not significantly reduced where CD4 count was >200 cells/mm3 (HR 0.92, 0.42 to 2.0, p=0.08) or in those with WHO clinical stage 1 or 2 conditions.

Monitoring and evaluation considerations

Research priorities

More data is needed on timing of cotrimoxazole cessation.

Impact of cotrimoxazole prophylaxis on morbidity and mortality in low malaria burden areas.

Role of cotrimoxazole prophylaxis in reducing TB incidence,morbidity and mortality.

Long-term safety profile of cotrimoxazole among HIV-infected patients.

Discontinuation of cotrimoxazole prophylaxis in TB patients.

Efficacy of cotrimoxazole prophylaxis in WHO stage II conditions.

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