Does Trimethoprim-Sulfamethoxazole Prophylaxis for HIV Induce Bacterial Resistance to Other Antibiotic Classes?: Results of a Systematic Review

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Background. Trimethoprim-sulfamethoxazole (TMP-SMX) prophylaxis has long been recommended for immunosuppressed HIV-infected adults and children born to HIV-infected women. Despite this, many resource-limited countries have not implemented this recommendation, partly because of fear of widespread antimicrobial resistance not only to TMP-SMX, but also to other antibiotics. We aimed to determine whether TMP-SMX prophylaxis in HIV-infected and/or exposed individuals increases bacterial resistance to antibiotics other than TMP-SMX.

Methods. A literature search was conducted in Medline, Global Health, Embase, Web of Science, ELDIS, and ID21.

Results. A total of 501 studies were identified, and 17 met the inclusion criteria. Only 8 studies were of high quality, of which only 2 had been specifically designed to answer this question. Studies were classified as (1) studies in which all participants were infected and/or colonized and in which rates of bacterial resistance were compared between those taking or not taking TMP-SMX and (2) studies comparing those who had a resistant infection with those who were not infected. Type 1 studies showed weak evidence that TMP-SMX protects against resistance. Type 2 studies provided more convincing evidence that TMP-SMX protects against infection.

Conclusion. There was some evidence that TMP-SMX prophylaxis protects against resistance to other antibiotics. However, more carefully designed studies are needed to answer the question conclusively.
million children eligible for TMP-SMX received it [8]. In Zimbabwe in 2007, only 10.5% of children eligible for TMP-SMX received it [9].

In Africa, barriers to implementation include shortages of trained staff, stock-outs of TMP-SMX, and failure of health care systems to identify individuals eligible for TMP-SMX prophylaxis [7]. In addition, there is anxiety that it may not be cost-effective. However new evidence of the intervention’s cost-effectiveness may alleviate these concerns [10, 11].

Furthermore, there has been a concern that this intervention will not work in areas where resistance to TMP-SMX is thought to be high [7]. Fortunately, there is now convincing evidence from South Africa and Zambia that it is effective even in these settings, and indeed the beneficial effects persist even as resistance to TMP-SMX increases [7, 12, 13].

Of great importance has been the fear that blanket TMP-SMX prophylaxis may lead to an increase in resistance to other drugs besides TMP-SMX among common microbial pathogens [7, 14, 15]. There is evidence that TMP-SMX prophylaxis does not increase resistance of Plasmodium falciparum to pyrimethamine-sulfadoxine [14, 16]. However, it remains unclear whether TMP-SMX prophylaxis increases bacterial resistance to other classes of antibiotics [7]. Biologically, when TMP-SMX causes multidrug resistance, this is thought to be a result of coselection and transference of antibiotic resistance genes between bacteria [17]. Conversely and indirectly, TMP-SMX prophylaxis may reduce development of multidrug resistance by preventing infections and, thereby, hospitalizations and exposure to other antibiotics [7].

The aim of this systematic review was to evaluate the available evidence with regard to whether TMP-SMX prophylaxis causes an increase in bacterial resistance to other classes of antibiotics. From a public health perspective, an increase in resistance would reduce the usefulness of current first-line antibiotics and result in reduced options for treating common bacterial infections in developing countries. From an individual perspective, patients receiving TMP-SMX prophylaxis may be at increased risk of treatment failure when they acquire a bacterial infection, although this has not been demonstrated in trials evaluating the effectiveness of TMP-SMX.

METHODS

Publications were eligible for review if the study outcome included a comparison of bacterial resistance to antibiotics other than TMP-SMX between HIV-infected individuals or HIV-exposed children receiving TMP-SMX prophylaxis and those who were not.

Computer searches were conducted in the following databases on the Ovid Platform: Medline 1950 through week 4 June 2009, Embase 1980 through week 27 2009, and Global Health 1910 through June 2009. Searches were also conducted in Web of Science database (accessed 7–22 July 2009), ELDIS (accessed on 6 July 2009), and ID21 (accessed on 6 July 2009). Three concepts derived from the research question were used for the literature search: TMP-SMX prophylaxis, HIV infection, and antibiotic resistance. The first part of the search was an iterative process by which the terms and synonyms that were relevant for the search were determined. The search terms used on the Ovid Platform are shown in Table 1. The search terms for Web of Science were:

| Topic | Search Terms |
|-------|-------------|
| HIV/AIDS | (human immunodeficiency virus) |
| - | and |
| HIV | or |
| AIDS | and |
| | and |
| Enteric fever | and |
| Streptococcus pneumoniae | and |
| Pseudomonas aeruginosa | and |
| MRSA | and |

The findings from the studies were synthesized, with more credence being placed on studies that had fared better in the quality assessment process. In theory, it would have been possible to meta-analyze the results from studies reporting methicillin-resistant Staphylococcus aureus (MRSA) and studies reporting pneumococcal resistance to penicillin. In practice, however, the studies that examined penicillin resistance reported differing outcomes; thus, it was not possible to combine them. It was possible to conduct separate meta-analyses for case-control, cross-sectional, and cohort studies of infection and/or colonization with MRSA.
RESULTS

A total of 501 studies were identified, of which 17 remained eligible for inclusion. Figure 1 shows the elimination process for the reviewed studies.

Description of Studies

Six cohort studies [16, 17, 20–23], 4 case-control studies [24–27], 6 cross-sectional studies [28–33], and 1 before-after study [34] met the eligibility criteria (Table 2). Six studies were conducted in the United States, 4 in South Africa, 2 in Italy, and 1 in each of the following countries: Kenya, Zambia, Singapore, Spain, and France.

Only 2 studies [16, 17] were designed to determine whether TMP-SMX prophylaxis increases antibiotic resistance. The remainder examined the question as subanalyses of studies which had been designed to answer a different question.

There were 2 comparison groups for bacterial resistance to antibiotics other than TMP-SMX: studies in which all participants were infected and/or colonized and in which rates of bacterial resistance were compared between those taking or not taking TMP-SMX. Most type 1 studies reported on pneumococcal resistance to penicillin. Type 2 studies compared those who had a resistant infection/colonization with those who were not infected/colonized. Most type 2 studies reported on infection and/or colonization with MRSA.

Description of the Quality of Studies

Studies that did not control for confounders of interest (stage of HIV disease, prior hospitalization, and previous antibiotic use) were considered to be of poorer quality. Only 8 [16, 17, 20, 23, 25, 26, 29, 31] of the 17 studies were considered to have protection from bias and confounding. The rest of the studies were not necessarily poorly conducted, but they had not been designed to primarily answer the question of this review. Only 4 studies [17, 22, 30, 32] involved children: 3 involved HIV-infected children and 1 involved HIV-exposed infants [17].

Synthesis of Findings From the Studies

When looking at the study findings according to type of comparison group, 10 studies [16, 17, 21, 22, 26, 27, 30, 32–34] were considered to have type 1 comparisons, and 7 [20, 23–25, 28, 29, 31] were considered to be type 2. Of type 1 studies, 4 [16, 17, 30, 33] were colonization studies (1 MRSA and 3 pneumococcal), 4 [21, 22, 27, 32] investigated infection (1 MRSA, 2 pneumococcal, and 1 various organisms), and 2 [26, 34] investigated both colonized and infected patients. Two of the 4 colonization studies [30, 33], neither of which were considered to be good quality (1 pneumococcal and 1 MRSA), reported increased colonization with drug-resistant bacteria. One good-quality study [16] reported no change, and another good-quality study [17] reported mixed findings; among HIV-exposed infants, TMP-SMX prophylaxis increased pneumococcal resistance to clindamycin but had no effect on pneumococcal resistance to penicillin, tetracycline, erythromycin, and chloramphenicol. Of the 4 infection studies, 2 [22] (1 MRSA and 1 pneumococcus, neither considered to be good quality) reported no difference in rate of infection with drug-resistant pneumococcus, and 1 [21] (not considered to be good quality) reported an increase. One study [32] had too few isolates to allow meaningful interpretation of the results despite presenting the number of drug-resistant isolates in each group (TMP-SMX vs no TMP-SMX). The 2 studies (1 good quality [26]) that investigated both colonized and infected patients reported increases in infection and/or colonization with drug-resistant bacteria.

The 2 studies (both type 1) [16, 17] that had been designed specifically to answer the question of this review showed no change in pneumococcal resistance to penicillin. However, one of these studies reported resistance to clindamycin among HIV-exposed infants, as described above [17].

Of type 2 studies, 4 investigated MRSA infection [20, 23–25], 2 investigated colonization with MRSA [29, 31], and 1 reported on colonization with vancomycin-resistant
enterococci [28]. Three (all considered to be good quality) [20, 23, 25] of the 4 MRSA infection studies reported a reduction in infection with MRSA, and 1 (not considered to be good quality) reported an increase in MRSA infection. The type 2 colonization studies reported no change [31] and reduced colonization [29] for 2 MRSA studies, whereas there was reported increase in colonization with vancomycin-resistant enterococcus [28].

Of the type 2 MRSA studies, there was significant heterogeneity among both the cross-sectional and case-control studies, and thus, no meta-analyses are presented. However, for cohort studies, the meta-analysis showed a protective effect of TMP-SMX prophylaxis on MRSA (relative risk, .29; 95% confidence interval, .12 - 0.7) (Figure 2); the test for heterogeneity among cohort studies was not significant ($P = .92$).

In an analysis of results according to whether the study outcome was colonization or infection, no trends were seen in the data, possibly because there were small numbers in each of the categories. In addition, no trends were noted in analysis of whether the study population comprised adults or children, because only 3 child studies were included in the synthesis, and they all had different results.

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**Figure 1.** Process for identification of eligible publications.
### Table 2. Summary of Studies that Met the Inclusion Criteria

| Author                        | Study location | Study design | Study population and size | Comparison group (Type 1 or Type 2) | Reported outcomes | Prevalence of antibiotic resistance by group or Relative Risk/Odds Ratio (95% CI) | Study conclusions |
|-------------------------------|----------------|--------------|----------------------------|-------------------------------------|-------------------|----------------------------------------------------------------------------------|-------------------|
| Crum-Cianflone et al 2007     | USA Cohort     | Cohort       | HIV-positive adult         | Type 2                              | Community-acquired infection with Methicillin-Resistant Staphylococcus Aureas (MRSA) | CTX=0/29 (0%) CNTL=49/404 (12%) P=.06 RR not reported | CTX ↓ MRSA       |
| Mathews et al 2005            | USA Cohort     | Cohort       | HIV-positive adult patients who had been on CTX for at least 120 days. Controls had been on CTX for less than 120 days (reference in RR calculation). N=3,455 | Type 2                              | Initial episode of clinically significant MRSA infection during the study period | Prevalence not reported Unadjusted RR 0.4 \( ^a \) Adjusted RR .3 (0.1–.7) \( ^b \) \(^a\)No confidence interval given for unadjusted effect  \(^b\)Adjusted for race, HIV disease progression, and antiretroviral drug therapy | CTX ↓ MRSA infection |
| Jordano et al 2004            | Spain Cohort   | Cohort       | HIV-positive adult patients (duration on CTX not given), with controls who were not on CTX. N=57 | Type 1                              | Infection with pneumococcal bacterial strains with resistance to penicillin | CTX=60%\(^c\) CNTL=38.5% P=.09 RR not reported \(^d\)No numbers given | CTX ↑ pneumococcal resistance to penicillin |
| Hamel et al 2008\(^e\)        | Kenya Cohort   | Cohort       | HIV-positive adults with low CD4+ cells. Exposed to CTX for six months. N=1,160 | Type 1                              | Among patients colonized with pneumococcus, comparison of prevalence of pneumococcal resistance to penicillin at baseline with that at 6 months after initiation of CTX prophylaxis | CTX=85% CNTL=85% RR not reported | No change in pneumococcal resistance to penicillin |
| Gill et al 2008\(^f\)         | Zambia Cohort  | Cohort       | Infants born to HIV-positive mothers who were given CTX from six weeks of age and followed up to age 18 months (HIV-exposed infants) with HIV-unexposed infants as controls. N=260 | Type 1                              | Among infants colonized by *S. Pneumoniae* comparison of resistance levels to each of the following drugs: clindamycin, penicillin, erythromycin, tetracycline, chloramphenicol | Prevalence not reported Unadjusted RR\(^g\): 1.6 (1.0–2.6)\(^d\) 1.1 (0.7–1.7) 1.0 (0.6–1.7) 0.9 (0.6–1.5) 0.8 (0.3–2.3)\(^d\)RR are for each of the following drugs respectively: Clindamycin, penicillin, erythromycin, tetracycline, Chloramphenicol RR remained the same after adjusting for confounders | ↑ resistance to clindamycin but no change in pneumococcal resistance to penicillin, erythromycin, tetracycline, and Chloramphenicol |

\( ^{a} \) No numbers given

\( ^{b} \) Adjusted for race, HIV disease progression, and antiretroviral drug therapy

\( ^{c} \) No numbers given

\( ^{d} \) Confidence interval given for unadjusted effect

\( ^{e} \) Adjusted for race, HIV disease progression, and antiretroviral drug therapy

\( ^{f} \) No numbers given

\( ^{g} \) Confidence interval given for unadjusted effect
| Author                  | Study location          | Study design     | Study population and size | Comparison group (Type 1 or Type 2) | Reported outcomes                                                                 | Prevalence of antibiotic resistance by group or Relative Risk/Odds Ratio (95% CI) | Study conclusions                        |
|------------------------|-------------------------|------------------|---------------------------|------------------------------------|----------------------------------------------------------------------------------|---------------------------------------------------------------------------------|------------------------------------------|
| Madhi et al 2000 [22]  | South Africa cohort     |                  | HIV-positive children. Controls were also HIV-positive who were not on CTX for unspecified reasons. Duration on CTX not given. N=146. | Type 1                             | Infection with *S. Pneumoniae* resistant to penicillin, cefotaxime, TMP-SMX, tetracycline, chloramphenicol, erythromycin, clindamycin, rifampicin | Cotrimoxazole prophylaxis had no impact on resistance to other antibiotics, no other data given | CTX had no impact on pneumococcal resistance to other antibiotics               |
| Drapeau et al 2007 [24]| Italy case-control      |                  | HIV-positive patients admitted to a hospital in Italy. Duration on CTX not given. N=81 | Type 2                             | Cases were defined as HIV-positive patients who developed clinically significant MRSA infection. Controls were HIV-positive patients who did not develop MRSA | Prevalence not applicable Unadjusted OR 3.06 (.99–9.41) Adjusted OR not given | CTX ↑ MRSA                               |
| Lee et al 2005 [25]    | USA case-control        |                  | HIV-positive MSM receiving care at three participating clinics in Los Angeles County. Duration on CTX not given. N=111 | Type 2                             | A case was the onset of a culture-positive MRSA skin infection in an HIV-positive MSM. A control was an HIV-positive MSM without skin symptoms | Prevalence not applicable Unadjusted OR .3 (0.1–.9) Adjusted OR .2 (0.1–.8)↑ | CTX ↓ MRSA                               |
| Meynard et al 1996 [26]| France case-control     |                  | Hospitalised HIV-positive patients. Duration on CTX not given. N=46 | Type 1                             | Cases were patients with *S. Pneumoniae* isolates that were intermediately or fully resistant to penicillin; and controls were patients with *S. Pneumoniae* isolates that were susceptible to penicillin | Prevalence not applicable Unadjusted OR 5.0 (1.9–13.3) Adjusted OR: 4.4 (1.6–7.0)↑ 4.9 (2.1–11.7)h | CTX ↑ pneumococcal resistance to penicillin                                      |
| Tumbarello et al 2002 [27]| Italy case-control     |                  | HIV-infected patients aged >18 years with *S. aureus* bacteremia. Duration on CTX not given N=129 | Type 1                             | Cases were HIV-positive patients with MRSA bacteremia and controls were defined as HIV-positive patients with MSSA bacteremia | Prevalence not applicable Unadjusted OR .76 (.36–1.60) Adjusted OR not given | CTX had no impact on MRSA                |
| Author                  | Study location          | Study population and size | Comparison group (Type 1 or Type 2) | Reported outcomes                                                                 | Prevalence of antibiotic resistance by group or Relative Risk/Odds Ratio (95% CI) | Study conclusions                                           |
|-------------------------|-------------------------|---------------------------|-------------------------------------|-----------------------------------------------------------------------------------|---------------------------------------------------------------------------------|------------------------------------------------------------|
| Achenbach et al 2006    | USA cross-sectional     | HIV-positive adults, some on CTX and some not. Duration on CTX not given. N=85 | Type 2                             | Prevalence of colonization with vancomycin resistant enterococcus                  |                                                                                 | CTX † resistance of enterococcus to penicillin             |
| Cenizal et al 2008      | USA cross-sectional     | HIV-positive adults, some on CTX and some not. Duration on CTX not given. N=146 | Type 2                             | Prevalence of nasal colonization with MRSA                                         | CTX=0/29 (0%) CNTL=15/102 (15%) P=.04                                          | CTX † MRSA                                                  |
| Cotton et al 2008       | South Africa cross-sectional | HIV-positive children, some on CTX and some not. Duration on CTX not given. N=203 | Type 1                             | Nasal colonization with S. Aureus                                                 | CTX: 87% CNTL: 70% P=.002 RR not reported                                     | CTX † MRSA                                                  |
| Pemba et al 2008        | South Africa cross-sectional | HIV-positive mine workers, some on CTX and some not. Duration on CTX not given. N=856 | Type 1                             | Prevalence of penicillin resistant Pneumococcus among patients who were colonized | CTX=7/23 (30%) CNTL=4/49 (8%) Unadjusted RR 4.92 (1.27–19.7) Adjusted RR not given | CTX † pneumococcal resistance to penicillin                |
| Villacian et al 2004    | Singapore cross-sectional | HIV-positive adults, some on CTX and some not. Duration on CTX not given. N=195 | Type 2                             | Prevalence of colonization with MRSA                                              | Prevalence not reported Unadjusted RR 19.4 (1.2–347.4) Adjusted RR values not given, but after adjustment for confounders TMP-SMX was not associated with MRSA | CTX had no impact on MRSA                                  |
| Zar et al 2003          | South Africa cross-sectional | HIV-positive children, some on TMP-SMX and some not. N=151 | Type 1                             | Five different bacterial pathogens were cultured: K. Pneumonia; S.Aureus H. Influenza, S. Pneumonia, M.Catarrhalis. Prevalence of resistance of each organism to 3 or 4 different drugs was determined. | Data not presented in a way that allowed interpretation for this review: Of the pneumococcal isolates from children taking prophylaxis, two were sensitive, three were intermediate resistant and one was resistant to penicillin. The single isolate from a child not on prophylaxis was penicillin-sensitive. |                                                           |
### Table 2. (Continued)

| Author          | Study location | Study design   | Study population and size                                                                 | Comparison group (Type 1 or Type 2) | Reported outcomes                                                                                   | Prevalence of antibiotic resistance by group or Relative Risk/Odds Ratio (95% CI) | Study conclusions |
|-----------------|----------------|----------------|-------------------------------------------------------------------------------------------|----------------------------------|------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------|-------------------|
| Martin et al 1999 [34] USA before-after | Hospital patients. Antibiotic resistance levels were compared between the period during (n=19,514, 30,886 cultures) and one before (n not given, 24,884 cultures) widespread implementation of TMP-SMX prophylaxis. | Type 1                           | Resistance of *E. Coli* and *S. Aureas* species among colonized or infected HIV-positive individuals were compared between two periods | CTX=72%; CNTL=41%<sup>l</sup>  
CTX=14%; CNTL=0%<sup>m</sup>  
CTX=21%; CNTL=0%<sup>n</sup>  
CTX=16%; CNTL=4%<sup>o</sup>  
CTX=14%; CNTL=0%<sup>p</sup>  
RR not reported |<sup>l,m</sup>Resistance of *E. Coli* to ampicillin and cephazolin respectively.  
<sup>n,o,p</sup>Resistance of *S. Aureas* to ciprofloxacin, nafcillin and gentamicin respectively.  
In *E. Coli* and *S. Aureas* HIV-infected patients with CTX resistance were significantly more likely to display resistance to other antibiotics. | CTX↑ Resistance of *E. Coli* and *S. Aureas* |

**NOTE.** CTX=Cotrimozaxole; CNTL=Control; MRSA=Methicillin Resistant *Staphylococcus Aureas*, MSSA=Methicillin Susceptible *Staphylococcus Aureas*, RR=Relative Risk, OR=Odds Ratio, MSM=Men having sex with men, CD4=CD4+ T lymphocyte count.

* The study was designed to look at the effect of TMP-SMX prophylaxis on resistance levels.

* Clinically significant infection—Generally described in the specified papers as clinician diagnosis of infection as opposed to colonisation, and isolation of bacteria from a normally sterile body site.

* 1=Comparison group is based on having sensitive bacterial infection/coloniisation; 2=comparison group is based on having no infection/coloniisation at all.
patients [22, 35, 36]. There is also evidence that HIV-infected individuals are more likely to be colonized and infected by antibiotic-resistant bacteria [30]. In accordance with this, comparison of HIV-exposed and nonexposed children should show that HIV-exposed children have higher antibiotic resistance levels. However, the findings by Gill et al do not show this expected difference in 4 of 5 classes of antibiotics that were investigated, possibly because TMP-SMX has a protective effect, which makes HIV-exposed children similar to HIV-unexposed children [17]. Carefully designed observational studies to test this theory should be conducted in low-income countries where TMP-SMX prophylaxis is recommended for HIV-exposed children.

In contrast to type 1 studies, for type 2 studies, there was stronger evidence that TMP-SMX prophylaxis protects against infection with drug-resistant bacteria. Four studies, all considered of good quality, reported reduced infection and/or colonization with MRSA, and 1 study, also of good quality, reported no change in colonization with MRSA. The 2 lower-quality studies in this group reported increased MRSA. The meta-analysis of MRSA cohort studies revealed a 70% protective effect of TMP-SMX prophylaxis from MRSA infection (relative risk, 0.29; 95% confidence interval, 0.12–0.7).

It is plausible that TMP-SMX prophylaxis protects against infection with drug-resistant bacteria. TMP-SMX may directly protect against colonization and/or infection with drug-susceptible bacterial pathogens [3], and indirect protection may arise as a result of this as the individual is less exposed to conditions that have been found to be risk factors for infection and/or colonization with drug-resistant bacteria. For example, the patient may no longer need frequent hospitalization or will be less likely to be exposed to intravenous catheters, conditions that have been shown to increase antibiotic resistance [31]. As a result, the patient may be less likely to receive other antibiotics for treatment of infections, and such exposure to antibiotics has been shown to increase antibiotic resistance [27].

The finding by Gill et al that pneumococcal resistance to 1 of 5 antibiotics increased whereas there was no change in the resistance levels for the other 4 drugs might mean that it is possible for TMP-SMX prophylaxis to increase bacterial resistance to some classes of antibiotics but not to others [17]. This may be possible if the mechanism of development of resistance to TMP-SMX is linked to that of the other antibiotic. Multidrug resistance can be horizontally transferred between bacterial species and genus borders if the genes that code for multidrug resistance are located on transferable plasmids or transposons [37]. It has been proposed that TMP-SMX prophylaxis may cause resistance to clindamycin or penicillin through co-selection of linked antibiotic resistance genes [17, 26].

The strength of the Hamel et al [16] study is that it was adjusted for baseline antibiotic resistance levels. Results from that study suggest that there is no effect of 6 months of
TMP-SMX prophylaxis on antibiotic resistance among similarly exposed HIV-infected adults. This may also be explained by possible protection of TMP-SMX from infections, as explained above. Of note, the 2 studies that were designed to answer the question of this review reported no change in pneumococcal resistance to penicillin.

The meta-analysis of studies relating to colonization and/or infection with MRSA shows the potential effect of differing study designs on resistance outcomes. The 2 cohort studies (ie, the most robust studies) clearly showed reduced MRSA colonization and/or infection, both individually and when combined, whereas the cross-sectional and case-control studies showed no effect.

This literature review had several limitations. Because TMP-SMX prophylaxis has long been proven to save lives of HIV-infected patients, only observational studies, which have more potential for bias and confounding, were available for review. Most studies did not control for factors that are known to independently increase antibiotic resistance. For example, only 3 studies adjusted for HIV disease progression or previous hospitalization. Previous hospitalization has been reported as an important risk factor for colonization or infection with MRSA [24, 25, 38].

Most studies did not provide data on the duration of exposure to TMP-SMX prophylaxis. Of the studies that did, the duration of exposure is shorter than expected in clinical practice in resource-limited settings. Because of the shortage of antiretroviral therapy in such settings, HIV-infected adults are likely to be receiving TMP-SMX prophylaxis for much longer periods than was evaluated in these studies. However, the finding from Gill et al may be more generalizable to HIV-exposed infants, because TMP-SMX was given according to guidelines used in many resource-limited settings [17].

Most studies only evaluated resistance to 1 antibiotic. This makes it difficult to know whether findings can be applied across different antibiotic classes.

The other limitation of the review was the heterogeneity of study designs, class of bacteria, and drug classes investigated, which makes comparing study findings problematic and makes it inappropriate to conduct a meta-analysis for all studies.

CONCLUSIONS AND RECOMMENDATIONS

After placing weight on good-quality studies and additional weight on studies that were specifically designed to determine whether TMP-SMX prophylaxis increases antibiotic resistance, the findings of this review offer suggestive evidence that TMP-SMX prophylaxis for opportunistic infections in HIV protects against development of bacterial resistance to other classes of antibiotics. More carefully designed studies should be conducted to answer this question. It is important to ensure that future studies evaluate the importance of duration of exposure to TMP-SMX on antimicrobial resistance.

Ideally, microbial resistance surveys should be included with TMP-SMX implementation in developing countries to alert providers to any changes in drug resistance patterns.

Of most importance, the fear of antibiotic resistance should not stop health care providers from giving TMP-SMX to individuals who need it.

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