



## CLINICAL PRACTICE

## Co-trimoxazole prophylaxis in HIV: The evidence

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Human immunodeficiency virus (HIV) damages the body's immune system, making secondary (or opportunistic) infections more common. Treatment and prevention of such infections is integral to the management of patients with HIV infection. Co-trimoxazole is a prophylactic treatment that has a wide range of action against common bacteria, parasites, fungi and yeasts. As part of a minimum care package, UNAIDS/WHO recommends co-trimoxazole prophylaxis for HIV-infected adults with symptomatic disease (WHO stage II, III or IV), or asymptomatic individuals with CD4 counts  $\leq 500$  cells/ $\mu$ l, and for all HIV-positive pregnant women after the first trimester.<sup>1</sup> Co-trimoxazole is also recommended for use in children with proven HIV infection and infants exposed to HIV (from 4 - 6 weeks of age until infection with HIV is ruled out).<sup>2</sup>

The object of this report is to summarise the effects of co-trimoxazole prophylaxis on morbidity and mortality among HIV-infected individuals.

### Beneficial effects

In HIV-positive adults not receiving antiretroviral therapy (ARV), a Cochrane Review (including three randomised controlled trials (RCTs)) found that co-trimoxazole prophylaxis reduced the risk of death by almost a third (Table I).<sup>3</sup> The beneficial effect was similar for early (CD4  $\geq 200$  cells/ $\mu$ l) and advanced (CD4  $< 200$  cells/ $\mu$ l) disease. The frequency of admissions to hospital and the incidence of bacterial, parasitic and *Pneumocystis carinii* pneumonia (PCP) infections were also significantly reduced (Table I). A further RCT among HIV-positive adults in Malawi newly diagnosed with tuberculosis<sup>4</sup> found no significant difference in bacterial pneumonia (hazard

Table I. Effects of co-trimoxazole v. placebo (Cochrane Review)<sup>3</sup>

Outcome	No. of trials	No. of participants	RR (95% CI)
Death	3	1 318	0.69 (0.55 - 0.87)
Hospital admissions	3	764	0.66 (0.48 - 0.92)
Serious morbid events	3	1 384	0.76 (0.64 - 0.90)
Bacterial infections	3	1 405	0.48 (0.37 - 0.62)
Parasitic infections	3	1 405	0.37 (0.24 - 0.58)
<i>Pneumocystis carinii</i> pneumonia (PCP)	1	60	0.31 (0.13 - 0.74)
Adverse events	3	1 405	1.28 (0.47 - 3.51)

RR = relative risk

ratio (HR) 1.07 (95% confidence interval (CI) 0.56 - 2.06)) and the probability of survival (HR 1.11 (95% CI 0.72 - 1.71)) between participants allocated 480 mg v. 960 mg of co-trimoxazole.

In children, support for co-trimoxazole prophylaxis came from a randomised placebo-controlled trial (N=541) conducted in an area in Zambia with high levels (60 - 80%) of *in vitro* resistance to this antibiotic.<sup>5,6</sup> Children  $\leq 5$  years were given a daily dose of 240 mg co-trimoxazole while those  $> 5$  years received a daily dose of 480 mg. Co-trimoxazole significantly reduced mortality by 33% (RR 0.67; 95% CI 0.53 - 0.85) and hospital admission rates by 23% (RR 0.77; 95% CI 0.62 - 0.95). Follow-up was reported to be excellent and few patients stopped their medication. The beneficial effect was seen across all ages and CD4 counts, and effectiveness of the drug did not diminish during periods of use up to 18 months' administration.

### Harmful effects

The Cochrane Review found a higher risk of adverse effects in adults on co-trimoxazole compared with placebo, but this difference was not statistically significant (Table I). The RCT in Zambian children found no difference between treatment and control groups in the incidence of one or more grade 3 or 4 adverse drug reactions (HR 0.76; 95% CI 0.39 - 1.5). No allergic reactions to co-trimoxazole occurred in this study. In HIV-infected patients with a previous history of mild or moderate hypersensitivity to co-trimoxazole who required prophylaxis, desensitisation (stopping treatment and recommencing treatment with dose escalation over a period of days) compared with co-trimoxazole rechallenge (stopping treatment and starting at the full dose) resulted in fewer treatment

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discontinuations before 6 months (RR 0.64; 95% CI 0.45 - 0.91) and overall adverse reactions (RR 0.51; 95% CI 0.36 - 0.73).<sup>7</sup>

### Comments

No randomised studies provide information on the optimal time for initiating prophylaxis in adults, or on when to stop prophylaxis. None of the trials included in the review focused on patients receiving treatment with antiretrovirals. Current studies neither report on the effects of prolonged co-trimoxazole use on bacterial resistance nor evaluate whether co-trimoxazole affects resistance of malaria parasites to sulfadoxine pyrimethamine (with which co-trimoxazole shares a component).

### Conclusions

Co-trimoxazole is highly effective in reducing mortality and morbidity in HIV-infected adults and children not receiving antiretroviral treatment. Similar benefits are seen in early and advanced HIV disease. Co-trimoxazole is well tolerated,

with minimal side-effects. Further research is required on the optimal time for commencement of co-trimoxazole prophylaxis and to evaluate its use in patients on antiretrovirals.

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## ISSUES IN PUBLIC HEALTH

# HPV vaccines: Bring me your daughters!

Carol Thomas

Our approach to cervical cancer prevention is set to change dramatically over the next decade with the advent of human papillomavirus (HPV) DNA typing, the probable demise of the PAP smear as we know it, and the registration of two highly effective vaccines against the two main HPV types (16 and 18). The latter account for about 70% of all cervical cancer cases globally and for 63% of those in South African women.<sup>1</sup> HPV-45 and HPV-31 account for another 10% of cases.<sup>2,3</sup>

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Except for a minority of non-mainstream, but remarkably visible and vocal, groups and individuals the general consensus worldwide is that HPV vaccines herald a new era and a phenomenal advance in the fight against cervical cancer, the most common cancer to affect women in South Africa and sub-Saharan Africa, where the established co-factors of smoking, long-term oral contraceptive use, HIV co-infection and high parity are also operative.<sup>4</sup> Lesotho has the unfortunate claim of the highest rate of cervical cancer in the world, with an age-standardised incidence rate of 61.6 (versus our 37.5) per 100 000 women.<sup>5</sup>

Women and health care providers have had to make two paradigm shifts around cervical cancer: firstly, although most HPV infections clear naturally, persistent infection with particular genotypes of a virus are responsible for most cases of cervical cancer (including the less common adenocarcinoma),<sup>6</sup> and secondly, close contact (as in both penetrative and non-penetrative sex) is the main mode of infection.