Increase in trimethoprim-sulphamethoxazole (co-trimoxazole) resistance at Chris Hani Baragwanath Hospital, Soweto, in the AIDS era

To the Editor: As prophylaxis, trimethoprim-sulphamethoxazole (co-trimoxazole) is mainly used for prevention of *Pneumocystis jiroveci* (previously *carinii*) pneumonia (PCP) and toxoplasmosis in AIDS patients. Co-trimoxazole may also prevent other opportunistic infections, such as salmonellosis, bacterial pneumonia, nocardiosis and isosporiasis. It is inexpensive and widely available, rendering it suitable as a general prophylactic agent against a range of opportunistic infections.

In 2000, the joint United Nations Programme on HIV/AIDS (UNAIDS) and the World Health Organisation (WHO) published provisional recommendations on the use of co-trimoxazole prophylaxis in HIV/AIDS patients, stating that it should be used for prophylaxis in adults and children living with HIV/AIDS in Africa as part of a minimum package of care. It should be offered to HIV-positive adults with symptomatic HIV disease (stages 2, 3 or 4 of the WHO classification of HIV infection and disease), asymptomatic individuals with a CD4 cell count ≤ 500/µl, and pregnant women after the first trimester.[1] The recommendations were based on the findings of two randomised controlled trials on adults in Côte d'Ivoire — the first showed that co-trimoxazole prophylaxis significantly decreased hospitalisation and death in patients with tuberculosis;[2] the second showed reduced rates of bacterial pneumonia, malaria, isosporiasis and acute unexplained fever in early HIV infection.[3]

The South African HIV/AIDS Policy Guidelines for adults recommend co-trimoxazole for PCP prophylaxis, and in all symptomatic HIV-infected individuals (WHO clinical stages 2, 3 or 4) or patients with a CD4 count below 200/µl.[4] Guidelines for managing HIV infection in children recommend that any infant born to an HIV-positive woman, symptomatic HIV-infected children and asymptomatic HIV ELISA-positive children receive co-trimoxazole prophylaxis from 4 - 6 weeks to at least 15 months of age.[5]

Several recent studies have investigated the efficacy of prophylactic co-trimoxazole. In Cape Town, use of prophylactic low-dose co-trimoxazole in HIV-infected adults resulted in a survival benefit consistent with previous trials, except in patients who were WHO stage 2 or who had CD4 counts of 200 - 500/µl.[6] In contrast, a study in Dakar, Senegal,[7] did not show a beneficial effect of chemoprophylaxis on survival or occurrence of opportunistic infections. In an 11-site USA study,[8] co-trimoxazole prophylaxis for PCP was associated with significantly decreased risk of toxoplasmosis, salmonellosis, *Haemophilus* and staphylococcal infections but not pneumococcal, *Klebsiella* and *Pseudomonas* infections.

Elsewhere, in Ohio, chronic prophylactic administration of co-trimoxazole led to less frequent isolation of *Staphyloccocus aureus* and enterobacteriaceae.[9] However, in San Francisco, a marked increase in co-trimoxazole resistance was observed in HIV-infected patients, from 6.3% in 1988 to 53% in 1995, particularly in *Escherichia coli* and *S. aureus* isolates. The increase was greater in sterile-site isolates from HIV care units compared with non-HIV units. Co-trimoxazole resistance was associated with a rise in multidrug resistance. A rapid increase in the use of co-trimoxazole for PCP prophylaxis was implicated.[10]

Co-trimoxazole susceptibility was investigated retrospectively among isolates from invasive bloodstream and cerebrospinal fluid (CSF) infections in adults and children, regardless of HIV status, at Chris Hani Baragwanath (CHB) Hospital during the periods 1 October 1998 - 30 September 1999 and 1 January 2000 - 31 December 2002. The study was confined to selected organisms commonly causing respiratory and urinary tract infections and septicaemia in HIV-infected patients. Blood cultures were processed using the BacT/Alert system; CSF specimens were analysed using routine methodology. Antimicrobial susceptibility tests were performed using agar disk diffusion according to National Committee for Clinical Laboratory Standards (NCCLS) criteria. A minority of strains interpreted as intermediate were included in the resistant category.

Results showed that co-trimoxazole resistance increased in most invasive organisms tested during the 4-year period and rates were usually higher in children than in adults. Tables I and II show co-trimoxazole resistance rates in selected Gram-positive cocci and Gram-negative bacilli respectively. Among *Streptococcus pneumoniae* isolates, there was a significant increase in resistance in adult and paediatric isolates. A significant increase in resistance occurred in adult and total isolates of *S. aureus*. Among non-typhoidal salmonellae, there was a significant progressive increase in resistance in adult and paediatric isolates, with consistently higher rates in children. Resistance was initially high in *E. coli* strains, and remained high throughout. *H. influenzae* resistance increased significantly in adults and children. Among *Klebsiella* spp., the rise in resistance varied over time, but was significant in adult and total isolates.

Further analysis of co-trimoxazole resistance in *S. pneumoniae* isolates in 2001 - 2002 showed that 24% (60/246) versus 15% (4/27) ($p = 0.265$) of HIV-infected compared with non-infected adults and 54% (81/151) v. 15% (6/39) ($p < 0.001$) of children respectively, were resistant.

Table I. Co-trimoxazole resistance in Gram-positive cocci

		Year								
		1999		2000		2001		2002		
Organism	Patients	%	*N*	%	*N*	%	*N*	%	*N*	*p*-value
Steptococcus	Adult	16.9	60/355	19.8	67/339	23.2	103/444	32.1	117/364	< 0.001
pneumoniae	Paediatric	32.3	40/124	50.0	73/146	47.0	117/249	52.1	111/213	0.003
	Total	20.9	100/479	28.9	140/485	31.7	220/693	39.5	228/577	< 0.001
Staphylococcus	Adult	17.6	66/374	35.8	93/260	40.0	94/235	32.9	125/380	< 0.001
aureus	Paediatric	41.5	22/53	29.0	31/107	34.0	32/94	43.4	46/106	0.298
	Total	20.6	88/427	33.8	124/367	38.3	126/329	35.2	171/486	< 0.001

Table II. Co-trimoxazole resistance in Gram-negative bacilli

		Year								
		1999		2000		2001		2002		
Organism	Patients	%	*N*	%	*N*	%	*N*	%	*N*	*p*-value
Non-typhoidal	Adult	5.0	5/101	7.0	8/114	23.1	31/134	40.9	65/159	< 0.001
Salmonella	Paediatric	18.4	7/38	35.3	18/51	38.9	14/36	49.1	27/55	0.009
	Total	8.6	12/139	15.8	26/165	26.5	45/170	43.0	92/214	< 0.001
Escherichia	Adult	66.0	165/250	75.6	170/225	76.4	191/250	72.3	204/282	< 0.120
coli	Paediatric	88.6	101/114	77.4	103/133	79.2	103/130	82.2	125/152	0.348
	Total	73.1	266/364	76.3	273/358	77.4	294/380	75.8	329/434	0.366
Haemophilus	Adult	42.9	3/7	25.0	3/12	50.0	6/12	87.5	7/8	0.034
influenzae	Paediatric	22.2	12/54	40.0	14/35	44.4	12/27	69.2	18/26	< 0.001
	Total	24.6	15/61	36.2	17/47	46.2	18/39	73.5	25/34	< 0.001
Klebsiella spp.	Adult	33.0	70/212	37.7	52/138	33.1	52/157	58.3	91/156	< 0.001
	Paediatric	53.8	63/117	61.0	89/146	38.8	52/134	59.1	68/115	0.609
	Total	40.4	133/329	49.6	141/284	35.7	104/291	58.7	159/271	0.002

Since co-trimoxazole resistance rates increased significantly during the study period in *S. pneumoniae*, *S. aureus*, non-typhoidal *Salmonella*, *H. influenzae* and *Klebsiella* spp., and remained high among *E. coli* strains, co-trimoxazole prophylaxis for opportunistic infections caused by these bacteria may often be suboptimal or ineffective in our setting. There were limitations to our study however. It was not possible to separate nonsocomial from community-acquired infections, therefore resistance levels may be lower in the community. Except for *S. pneumoniae*, we did not compare isolates from HIV-positive and HIV-negative individuals. However, HIV-infected patients often yield isolates with higher resistance levels than those of HIV-uninfected patients.

Currently, co-trimoxazole is frequently used in a range of health care settings as a first-line agent, mainly in the treatment of respiratory and urinary tract infections. We are concerned that widespread use of co-trimoxazole may greatly increase resistance and that the efficacy of this agent for the general population will wane rapidly. If significant resistance develops, co-trimoxazole may not easily be replaced by another effective, cheap and available compound. Another concern regarding widespread use is the occurrence of adverse reactions. Sulphonamide therapy among children in the general population is safe, with an overall adverse reaction rate of 5%, but in HIV-positive children this may reach 40%, involving neutropenia, erythema multiforme, and Stevens-Johnson syndrome.[11] In adults with AIDS treated with high-dose co-trimoxazole for PCP in our hospital, rashes were seldom observed, but haematological side-effects were relatively common.[12]

In conclusion, the current high and increasing levels of resistance in invasive opportunistic bacteria, important in HIV disease, are of great concern. The WHO recommendation that co-trimoxazole be prescribed broadly as a prophylactic agent in HIV/AIDS-infected individuals cannot therefore be fully endorsed. We would recommend review of guidelines and a more restrictive approach, taking into consideration the higher background resistance to co-trimoxazole. Guidelines should focus on those who are likely to benefit most from prophylaxis. When co-trimoxazole is prescribed it should be administered to patients who are under medical care and who are followed up regularly to monitor compliance and side-effects.

Epidemiological studies on the extent of co-trimoxazole resistance are also necessary in various urban and rural centres in South Africa and resistance levels should be monitored on a continuous basis.

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