Reduced bacterial skin infections in HIV-infected African children randomized to long-term cotrimoxazole prophylaxis

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INTRODUCTION

Recurrent skin infections are common during childhood in developing countries[1, 2], leading to frequent clinic attendances, risk of complications and reduced quality of life[3]. In HIV-infected children, skin infections are more severe and atypical, respond less well to treatment and relapse more frequently compared to HIV-uninfected children[4].

Cotrimoxazole prophylaxis reduces death and hospitalization from serious bacterial infections in HIV-infected children on antiretroviral therapy (ART) in sub-Saharan Africa[5], despite high rates of resistance among common bacterial isolates[6]. It is unclear whether long-term cotrimoxazole reduces common conditions such as skin infections, although its potential antimicrobial activity against methicillin-sensitive and methicillin-resistant *Staphylococcus aureus* and *Streptococcus pyogenes* suggests prophylaxis may have benefits[7-10]. We therefore investigated the frequency of skin complaints among HIV-infected children enrolled in the ARROW trial in Zimbabwe and Uganda, who were randomized to stop or continue cotrimoxazole prophylaxis.

METHODS

Of 1206 children in the ARROW trial in Uganda/Zimbabwe, 758 meeting eligibility criteria were randomized to stop (n=382) or continue (n=376) daily cotrimoxazole (open-label) after median(IQR) 2.1(1.8,2.2) years on ART[5]. Eligible children were aged >3 years, had been receiving ART for >96 weeks, were currently on cotrimoxazole, using insecticide-treated bednets if living in malaria-endemic areas and had no previous *Pneumocystis jirovecii* pneumonia. All children were followed to ARROW trial closure (16 March 2012). The co-primary endpoints were hospitalization or death and grade 3 or 4 adverse events, as previously reported[5]. Caregivers and older children (≥18 years) gave written consent; those 7-18 years gave assent depending on knowledge of their HIV status. The trial was approved by Research Ethics Committees in Uganda, Zimbabwe and the UK.

This post-hoc analysis compared skin complaints and other routinely solicited signs and symptoms between randomized groups. These were identified at 6-weekly visits, when nurses screened for 25 pre-specified signs/symptoms using a standardized checklist (fever; weight loss; weakness/tiredness; pallor; jaundice/yellow eyes; rash; new bruises/masses/bumps; muscle aching/pain; abdominal aching/pain; poor appetite; difficulty feeding; sore mouth /throat/ulcers/thrush; vomiting/nausea; chronic, bloody or moderate-severe diarrhoea; dehydration; cough; difficult/fast breathing; ear discharge/pain; difficulty walking; delayed developmental milestones; new visual problems; poor sleep/bad dreams; funny feeling/numbness/pain in hands or feet; depression/withdrawn; severe headache) and also solicited any other symptoms. Skin complaints were reported as 'other symptoms' and categorized blind to randomization (by AJP) by their clinical description, as bacterial (boils, abscesses, sores, impetigo, pustules, infected wounds), fungal (tinea, ringworm, fungal infection, scalp lesions) viral (varicella, warts, molluscum contagiosum, verrucae planae, herpes labialis, herpes zoster), pruritic papular eruptions (PPE), dermatitis (eczema, itching or pruritus without PPE), or other (blisters, desquamation, ulcers and urticaria); microbiological and histopathological data were not available. During 12-weekly examinations, doctors recorded any

clinical findings. A socioeconomic questionnaire was completed at trial enrolment and every 2 years subsequently; the closest questionnaire completed up to 60 days post-cotrimoxazole randomization was used (517(68%) within 1 year of randomization).

Proportions of children ever reporting each sign/symptom were compared across randomized groups using exact tests and logistic regression, and across visit weeks using generalized estimating equations (independent correlation structure), taking $P<0.01$ as the significance threshold, since these were not primary or secondary endpoints. Univariable associations between proportions reporting bacterial skin infections and demographic and clinical factors pre-ART and at randomization to stop versus continue cotrimoxazole were assessed using rank-sum and exact tests for continuous and categorical variables, respectively. A multivariable model for ever presenting with a bacterial infection was constructed using backwards elimination (exit $P=0.1$ to fit an explanatory model) on all factors except household income/expenditure (missing for 30 children), allowing for non-linearity in continuous factors using fractional polynomials. Interactions between randomized group and other factors were tested and retained where interaction $P<0.1$, and the additional impact of household income and expenditure estimated. All analyses used Stata 14.0.

RESULTS

At randomization to stop versus continue cotrimoxazole, children were median(IQR) 7(4,11) years old and had spent 2.1(1.8,2.2) years on ART. Median CD4 was 33%(26,39), compared to pre-ART CD4 of 13%(8,18); 59% and 14% children had WHO stage 3 and 4 disease, respectively (Supplementary Table 1). There was no difference in the prevalence of different skin complaints or other signs/symptoms at randomization (Supplementary Table 2). Children were followed for median(IQR) 108(97,117) weeks post-randomization and seen at a total of 12,747 scheduled nurse visits. Adherence to randomized cotrimoxazole strategy was high, as previously reported[5].

Fewer children continuing compared to stopping cotrimoxazole ever reported bacterial skin infections (56(15%) versus 125(33%), respectively; P<0.001; Figure 1A). Effects were in a similar direction for PPE (P=0.06) and other skin complaints (p=0.11). There was no evidence of a difference in fungal (P=0.45) or viral (P=0.23) infections or dermatitis (P=1.00). Bacterial skin infections were also reported at significantly fewer nurse clinic visits between 6-120 weeks post-randomization in those continuing cotrimoxazole (1.2% versus 3.0% stopping; P<0.001; Figure 1B), but there was no evidence of a difference between randomized groups in the proportion of clinic visits at which other skin complaints were reported (all P>0.15). Furthermore, fewer children continuing cotrimoxazole ever had clinically significant bacterial skin infections recorded by the doctor at examination (24(6%) versus 49(13%) stopping; P=0.003); there were no differences between groups for non-bacterial skin complaints as recorded by clinicians (all P>0.15).

Seven of the 25 solicited signs/symptoms (fever; weight loss; tiredness/weakness; bruises; poor appetite; nausea and cough) also occurred significantly less commonly in children continuing versus stopping cotrimoxazole (Supplementary Figure 1A) and were reported at significantly fewer scheduled visits (Supplementary Figure 1B). Effects were in a similar direction for rash, difficulty feeding, sore mouth, diarrhoea and headache (0.04<P<0.08, Supplementary Figure 1C, 1D). No

sign/symptom was reported more frequently in children continuing cotrimoxazole.

Independent of cotrimoxazole, in a multivariable model bacterial skin infections were more common in children aged 6-8 years, with current CD4<500 cells/mm^3, WHO stage 3/4, less time on ART at cotrimoxazole randomization, and with lower socioeconomic status as measured both by a household asset score and getting water from a well; and were less common in those receiving efavirenz (all P<0.05; Table 1). Reductions in bacterial skin infections with cotrimoxazole were greater in children with CD4<500 than CD4>500 cells/mm^3 (heterogeneity/interaction P=0.06) and smaller in those on efavirenz (heterogeneity/interaction P=0.02). In the 726 children with household income/expenditure data, risk of bacterial skin infections was independently lower in those spending a greater percentage of their household income on school (odds ratio per 5 percentage points higher 0.97(95%CI 0.95-1.00), P=0.03; effects of other factors similar to Table 1).

DISCUSSION

HIV-infected children continuing long-term cotrimoxazole in Uganda and Zimbabwe had fewer bacterial skin infections than children stopping cotrimoxazole, despite good immune reconstitution on ART. There was also a marginal reduction in pruritic papular eruptions and a significant reduction in other important signs/symptoms such as cough, fever and weight loss among those continuing cotrimoxazole. Collectively, these data highlight several previously unrecognized benefits of daily prophylaxis, despite high-level microbial resistance to cotrimoxazole in sub-Saharan Africa[6].

We previously reported reduced hospitalization for serious bacterial infections such as sepsis, meningitis and pneumonia among children continuing cotrimoxazole[5]. The current study highlights additional benefits of cotrimoxazole for HIV-infected children on ART. Skin complaints are frequent, associated with stigma and reduce quality of life[4]; they often necessitate clinic attendance and antibiotic prescriptions and are associated with complications such as sepsis and post-streptococcal glomerulonephritis[11-13]. Skin infections remain common among HIV-infected children in sub-Saharan Africa despite ART[14]. In ARROW, one-third of children stopping cotrimoxazole developed bacterial skin infections during 2 years of follow-up; cotrimoxazole prophylaxis led to 64% lower odds of reported skin infections. Independent of cotrimoxazole, bacterial skin infections were more common in children aged 6-8 years and in those with more advanced HIV (CD4<500 and WHO stage 3/4 disease); consistent with this, longer duration of ART was associated with lower risk of bacterial skin infections. It is notable that there were consistent reductions in bacterial skin infections as assessed both by caregiver recall during nurse visits and on examination by physicians; by contrast, there were no reductions in viral or fungal infections, giving plausibility to our hypothesis that cotrimoxazole would prevent bacterial skin infections due to its antimicrobial spectrum of activity.

The global burden of bacterial skin infections has generally been under-appreciated; a recent systematic review estimated that 162 million children are affected at any time by impetigo,

predominantly in tropical, low-income countries[15]. In tropical regions, *Streptococcus pyogenes* is the predominant pathogen causing impetigo[9]; despite previous uncertainty, *S. pyogenes* is susceptible to cotrimoxazole *in vitro*[7]. A trial among indigenous Australian children with impetigo showed non-inferiority of short-course oral cotrimoxazole compared to intramuscular benzathine benzylpenicillin for treatment[8]. There is increasing recognition that *Staphylococcus aureus* is also an important cause of skin infections in tropical settings[10], and that *S. pyogenes* and *S. aureus* co-infection is common[9]. Published cotrimoxazole resistance rates among *Staphylococcus aureus* isolates from sub-Saharan Africa are 25-100%[16-22], suggesting that cotrimoxazole has limited efficacy for staphylococcal skin infections; however, high intracellular concentrations may facilitate its antibacterial activity[23]. It has been noted in many previous studies that cotrimoxazole retains prophylactic activity against a range of infections despite high rates of resistance among causative organisms[5, 24-27]. It is also plausible that the benefits of cotrimoxazole for skin infections are particularly driven by its activity against *Streptococcus pyogenes*[7]; there are few published data on cotrimoxazole resistance among *S. pyogenes* isolates in sub-Saharan Africa[6].

Pruritic papular eruptions are one of the most frequent and troublesome skin complaints among HIV-infected individuals and can cause disfiguring and stigmatizing scarring[28-30]. The histopathology of PPE lesions is characterized by perivascular and interstitial lymphocytic and eosinophilic infiltration with epidermal hyperplasia, and likely arises from an exaggerated, Th2-skewed immune response to arthropod bites[30]. PPE has been related to higher viral loads[31, 32] and to lower CD4 counts in some[30, 33] but not all[32, 34] studies. We found a trend towards lower reports of PPE among children continuing cotrimoxazole, which is difficult to explain, but could plausibly be due to reduced frequency of impetiginized PPE lesions, immunomodulatory properties of cotrimoxazole[35-38], or miscategorization of PPE. Scabies frequently co-exists with bacterial skin infections and, in this context, cotrimoxazole may have useful activity[39]; since scabies was not specifically diagnosed in this study, some cases of PPE may in fact have been due to underlying

scabies with or without bacterial co-infection. In addition to our primary findings regarding skin complaints, children continuing cotrimoxazole were less likely to have caregiver-reported episodes of fever, weight loss, tiredness or weakness, bruises, poor appetite, nausea and cough, suggesting that cotrimoxazole has broader benefits than previously recognized [6]. Since cotrimoxazole is now recommended lifelong for HIV-infected children, it is likely to improve health and quality of life beyond the important reductions in mortality and hospitalization that underpinned the change in WHO guidance[40].

The main study strength is the randomization to continuing versus stopping cotrimoxazole, reducing bias from confounding, and the fact that children were enrolled across a range of ages. However, the main limitation is that the trial was open-label, so carers and clinicians knew whether children were receiving cotrimoxazole, which may have led to over-reporting of symptoms in those stopping. However, caregivers had been asked to recall this symptom list at every visit for 2 years pre-randomization and for 2 years subsequently; since many symptoms were common, it would be hard to explain all effects as bias, particularly as only bacterial skin infections were reported significantly less frequently in those continuing. Furthermore, clinicians recorded bacterial skin infections (but not other skin complaints) less commonly on examination, corroborating caregiver reports. All events were diagnosed clinically; confirmatory microbiological and histopathological investigations were not available, which may have led to some misclassification of skin conditions. Longitudinal viral loads were not available in this study.

In summary, HIV-infected children continuing cotrimoxazole after ART-mediated immune reconstitution had fewer bacterial skin infections, which may reduce clinic attendances, prevent infectious and autoimmune complications and improve quality of life. Together with reductions in other important signs and symptoms, such as cough, fever, weight loss and pruritic papular eruptions, these findings highlight additional benefits to long-term cotrimoxazole prophylaxis in sub-

Saharan Africa.

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Table 1 Characteristics at randomization to stop versus continue cotrimoxazole and impact on subsequent reported bacterial skin infections

Factor (at randomization to stop versus continue cotrimoxazole)		Without bacterial skin infection N (%) or median (IQR)	With bacterial skin infection N (%) or median (IQR)	Multivariable model* Odds ratio	(95% CI)	P (adjusted)
Age (years)		8 (4,11)	7 (4,9)	4yr: 0.36	(0.18,0.72)	0.004
				7yr: 1.00	-	
				10yr: 0.37	(0.22,0.60)	<0.001
				13yr: 0.20	(0.09,0.42)	<0.001
Randomized to	Stop cotrimoxazole	257 (67%)	125 (33%)	1.00	-	
	Continue cotrimoxazole†	320 (85%)	56 (15%)	0.26	(0.15,0.46)	<0.001
	<500 cells/mm3 & continue cotrimoxazole			0.09	(0.03,0.29)	Heterogeneity p=0.06
	3TC ABC EFV** & continue cotrimoxazole			0.86	(0.38,1.98)	Heterogeneity p=0.02
	ZDV 3TC ABC & continue cotrimoxazole			0.34	(0.17,0.68)	Heterogeneity p=0.57
CD4	<500 cells/mm3	105 (72%)	40 (28%)	2.69	(1.46,4.97)	0.002
	>=500 cells/mm3	472 (77%)	141 (23%)	1.00	-	
ART	3TC ABC EFV**	173 (83%)	35 (17%)	0.26	(0.14,0.49)	<0.001
	3TC ABC NVP	212 (71%)	86 (29%)	1.00	-	
	ZDV 3TC ABC	192 (76%)	60 (24%)	0.59	(0.35,1.02)	0.06
Years on ART	(per year longer)	2.1 (1.8,2.3)	2.1 (1.8,2.3)	0.53	(0.27,1.02)	0.06
WHO stage (worst)	1 or 2	169 (83%)	34 (17%)	1.00	-	
	3 or 4	408 (72%)	147 (28%)	1.70	(1.08,2.68)	0.02
Water	Domestic tap	350 (79%)	93 (21%)	1.00	-	
	Standpipe	97 (78%)	27 (22%)	1.14	(0.67,1.94)	0.62
	Well	128 (68%)	61 (32%)	1.76	(1.14,2.72)	0.01
Household asset score***	(per unit higher)	-0.7 (-0.9,+1.1)	-0.9 (-1.3,-0.0)	0.88	(0.77,0.99)	0.04

*See supplementary Table 1 for all characteristics considered. P>0.25 for all other factors in Supplementary Table 1

** Including 4 children on lopinavir/ritonavir containing second-line therapy, none of whom developed a bacterial skin infection.

*** Calculated as the first principal component of 9 household items (refrigerator, radio, television, video player, landline telephone, mobile phone, motorbike, bicycle, car)
† At reference category; receiving 3TC ABC NVP at cotrimoxazole randomization with CD4>=500 cells/mm^3.
3TC=lamivudine, ABC=abacavir, ZDV=zidovudine, NVP=nevirapine, EFV=efavirenz.

FIGURE LEGENDS

Figure 1 – Skin complaints among HIV-infected children randomized to stop or continue cotrimoxazole. (A) Proportion of children who ever reported skin complaints at nurse visits during median 2 years of follow-up and (B) the proportion of scheduled nurse clinic visits where skin complaints were reported. Grey bars show proportions among children randomized to continue cotrimoxazole; white bars show proportions among children randomized to stop cotrimoxazole after median 2.1 years of ART. Percentages with corresponding P value and odds ratios with 95% confidence intervals are shown.

Supplementary Figure 1 - Reported signs and symptoms among HIV-infected children randomized to stop or continue cotrimoxazole. (A, C, E) Proportion of children who ever reported a pre-specified list of solicited signs and symptoms to nurses during median 2 years of follow-up and (B, D, F) the proportion of scheduled nurse clinic visits where signs and symptoms were reported. Grey bars show proportions among children randomized to continue cotrimoxazole; white bars show proportions among children randomized to stop cotrimoxazole after median 2.1 years of ART. Percentages with corresponding P value and odds ratios with 95% confidence intervals are shown.