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Exit interviews administered to patients participating in the COSTOP placebo controlled randomised trial in Uganda

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ABSTRACT

Introduction: COSTOP was a randomised controlled trial designed to assess the risks and benefits to HIV-infected participants stabilised on anti-retroviral treatment of stopping cotrimoxazole (CTX). In order to assess the extent to which patients may have had access to and used CTX other than that supplied as study drug it was decided to conduct an exit interview.

Methods: A structured interview was administered by interviewers who were not associated with the COSTOP trial team in order to make it easier for participants to respond truthfully to sensitive questions about adherence to the study protocol.

Results: A total of 1993 participants were interviewed. Only 29 (1.7%) said they had taken their left over CTX; 101 (6.1%) had kept supplies at home. When asked about obtaining open label CTX during the trial 92 (4.7%) participants said they had done so, in contrast to only 12 who admitted doing so when asked at trial visits. The questions participants found most difficult to answer honestly at clinic visits were those concerning adherence to trial drugs (15.6% of participants) and whether they had slept under the insecticide treated mosquito nets (14.9%).

Discussion: The exit interview demonstrated that there was some evidence of open label drug being taken by the participants. However, the results from the interview do not suggest that the trial results would have been seriously compromised. We would recommend the exit interview as a valuable way of assessing adherence to trial procedures.

1. Background

Cotrimoxazole (CTX) is widely used as prophylaxis against opportunistic infections among HIV-infected persons as recommended by the World Health Organisation [1]. The benefits of continuing to use CTX in patients in limited resource settings who have been stabilised on antiretroviral treatment are unknown. COSTOP was a double blind placebo controlled trial designed to evaluate the benefits and risks associated with stopping CTX in two sites in Uganda [2].

For intervention trials, like COSTOP, that include provider–client interactions, exit interviews with clients are recommended to monitor their understanding of the advice that was provided [3]. Laboratory based tests to detect the treatment under study are often non-existent or expensive, and therefore exit interviews conducted by independent research staff are an important way in which to evaluate adherence to study product [4] Findings from exit interviews have been reported in brief in many accounts of trial findings but the experience of using this technique has only occasionally been presented in standalone papers [5,6].

Because most patients entering the COSTOP would be expected

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to have unused supplies of CTX at home and the drug is relatively inexpensive and can readily be obtained over the counter in Uganda the investigators considered it important to assess the extent to which patients might have taken left over supplies or drugs from other sources while participating in the trial. Use of CTX outside of the study clinics could potentially render the results of the trial uninterpretable. A simple test to identify metabolites of CTX in randomly collected urine samples would have been the best way to identify patients allocated to placebo who were taking active drug and to assess whether those allocated to active drug were taking it. Unfortunately no such test is available and although participants were asked at each visit whether they been taking open-label CTX it would have been difficult for them to admit to the study team that they had not followed protocol instructions.

In order to assess the extent to which patients may have had access to and used CTX other than that supplied as study drug it was decided to conduct an exit interview to be administered to all participants by persons not directly associated with the COSTOP trial team in order to make it easier for the participants to respond truthfully to sensitive questions. The present paper reports on the conduct of the exit interview, the findings and the implications for the interpretation of the main trial results.

Only very few clinical trials provide a detailed report on the use and the results of exit interviews to measure adherence in placebo controlled studies. Our paper therefore also provides a contribution to clinical trial methodology.

2. Methods

The methods of the main COSTOP study (trial registration number: ISRCTN44723643) have already been reported in detail [2]. In brief, COSTOP was a randomised double blind placebo controlled non-inferiority trial conducted in two clinics in Entebbe and Masaka in Uganda. The study aims were to assess whether stopping CTX is not inferior to continuing with respect to the incidence of pre-defined CTX-preventable events and superior with respect to the reduced incidence of haematological adverse events. Eligible patients were adults aged 18 years or more, infected with HIV who had been receiving antiretroviral treatment (ART) for at least six months, who were clinically asymptomatic having had two CD4 counts (not more than 6 months apart) of $\geq$250 cells/mm3, the most recent no more than 4 weeks prior to enrolment. Participants were instructed to stop taking their regular supplies of CTX after which they were randomised in equal proportions to receive either CTX provided by the study or a matching placebo; all continued to receive ART as prescribed. Participants were provided with an insecticide treated mosquito net (ITN) and educated about the importance of using it. They were told that both they the study team were blinded to the treatment assignment and that it was important that they did not acquire CTX from any other source. Participants were told to present their COSTOP study appointment cards at the ART service points, private clinics or public health centres and to inform the staff not to prescribe or dispense CTX to them. They were seen monthly for the first three months and every three months thereafter for a minimum follow-up of one year post-randomisation. At each visit patients were seen by a study nurse and trial physician for protocol related assessments. A questionnaire to document adherence to ART and trial drug was administered on each occasion which included a question on whether participants had had access to open label CTX. The trial had 80% power to detect non-inferiority of placebo to CTX with respect to cotrimoxazole preventable events i.e. the upper limit of the one-sided 95% confidence interval of the hazard ratio (HR) for placebo relative to CTX should be no greater than 1.25 (a relative increase of 25%). A total of 2000 participants were required to be enrolled.

The trial was closed after the last randomised patient had completed one year in the study. At the final study visit all patients were requested to participate in an exit interview. They were randomised to be interviewed either by a field worker from the Social Science programme of the MRC/UVRI Uganda Research Unit or by a trained peer interviewer from TASO (The AIDS Support Organisation) in Entebbe or Kampala. A total of eight interviewers (four social scientists and four peers) conducted the interviews using a questionnaire with pre-defined options for answers to most of the questions (see Appendix for details).

3. Results

The results of the main study have been presented [7]. In brief they showed that among HIV-infected adults on ART with a CD4 count above 250 cells/mm^3, discontinuing CTX significantly increased the risk of CTX preventable bacterial infections (particularly pneumonia), and of malaria and led to an increase in hospital admission rates. However, discontinuing CTX also significantly reduced the risk of laboratory determined grade three or four haematological adverse events, in particular neutropenia. The trial found no evidence that discontinuing CTX led to an increase in mortality.

Of 2180 participants enrolled into the trial 37 died before the final visit, 95 were lost to follow-up, 49 had withdrawn consent and six were not interviewed at their final study visit. A total of 1993 remained (1001 allocated to CTX, 992 allocated to placebo) with whom the exit interview was conducted, in 1007 instances by social scientists and 986 by peer interviewers.

The majority of participants, 1667 (83.6%) of 1993, reported that they had supplies of CTX left over at the time they joined the study; 283 (14.2%) said they had none and 43 (2.2%) said they could not recall what they had. Of those with supplies left over at the beginning of the study the majority either submitted them to the study clinic or to their ART provider (Table 1); 101 (6.1%) kept them at home and 29 (1.7%) took them either before or at the same time as taking the study drug. There were minor differences according to the allocated treatment arm and who interviewed the participants.

Participants were asked how often they reported having taken the trial drug when they had actually missed some doses; 144 (7.2%) of them admitted to doing so regularly and a further 325 (16.3%) occasionally. In the course of discussions with other participants 430 (21.6%) reported that they were aware that others had found it difficult to admit that they had failed to take the trial drug. There were no differences between those receiving CTX or placebo.

Of 1963 participants who were not switched by clinic study staff to open-label CTX at some time during the trial, 92 (4.7%) admitted to having had access to the drug from other sources, half of them on a frequent basis. There was a slight excess among those prescribed placebo, 50 (5.1%) of 973 compared to 42 (4.2%) of 990 prescribed CTX. The commonest reported source of CTX from outside the study

Table 1
Response to question "What did you do with the left over cotrimoxazole at trial entry?".

	No.	%
Took to study clinic	705	42.3
Took to ART provider	270	16.2
Gave away	275	16.5
Thrown away	213	12.8
Kept at home	101	6.1
Forgotten	70	4.2
Took before or with trial drug	29	1.7
Other	4	0.2
Total with cotrimoxazole left over	1667	100.0