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Safety of discontinuing cotrimoxazole prophylaxis among HIV infected adults on anti-retroviral therapy in Uganda (COSTOP trial): Design

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ABSTRACT

Introduction: Cotrimoxazole (CTX) prophylaxis is recommended by the World Health Organisation for HIV infected persons. However, once HIV infected patients have commenced ART in resource limited settings, the benefits of continued CTX prophylaxis are not known. The few studies that investigated the safety of discontinuing CTX prophylaxis in these settings had limitations due to their design.
Materials and methods: COSTOP is a randomised double blind placebo controlled non-inferiority trial among HIV infected Ugandan adults stabilised on anti-retroviral treatment (ART). Participants with CD4 count of 250 or more cells/mm^3 are randomised to two arms: the intervention arm in which CTX is discontinued and the control arm in which CTX prophylaxis is continued. The study aims to assess whether the intervention regimen is not inferior, with respect to the incidence of pre-defined CTX-preventable events, to the control regimen and superior with respect to the incidence of haematological adverse events.
Discussion: Studies that have previously evaluated the safety of discontinuing CTX prophylaxis among HIV infected adults in resource limited settings have provided moderate to low quality evidence owing in part to methodological limitations. COSTOP is designed and conducted with sufficient rigour to answer this question. The results of the trial will assist in guiding policy recommendations.
Conclusion: This paper describes the design and methodological considerations important for the conduct of CTX cessation studies.

1. Introduction

The use of cotrimoxazole (CTX) as prophylaxis against opportunistic infections among HIV-infected persons is part of the standard of care recommended by the World Health Organisation (WHO) [1,2]. In resource limited settings, once HIV infected patients have commenced ART, the benefits of continued prophylactic CTX medication are not known [1].

A few studies in resource limited settings [3–6] have investigated the effect of providing prophylactic CTX *versus* no CTX among patients concurrently taking ART. All these studies had limitations in that either they were observational [3], had small sample sizes [4,5] or followed participants for short periods as reviewed by Suthar et al. [6]. This systematic review also concluded that "cotrimoxazole significantly increased survival in HIV infected adults on ART. Further research is needed to determine the optimum duration of CTX treatment in these patients". Campbell and colleagues carried out a trial in a home based care setting in rural Eastern Uganda in which 836 patients who had been on ART for a median time of 3.7 years and who had a CD4 count above 200 cells/μl were randomised at household level to continue or discontinue CTX prophylaxis in an open label design [7]. The trial was stopped at the recommendation of the DSMB following the occurrence of significantly higher rates of asymptomatic and symptomatic malaria in the group which stopped CTX (RR = 27.7, 95% CI 6.8, 113.1, $p < 0.001$). There was also a significantly higher rate of self-reported diarrhoea, but no difference between the two arms in the incidence of AIDS-related opportunistic infections and no deaths were reported. Recently, a study conducted in Kisumu—Kenya compared the effect of CTX cessation *versus* continuation on a composite outcome of death, malaria, pneumonia and diarrhoea among HIV infected adults stabilised on ART [8]. None of these studies used a double-blind placebo controlled design.

A WHO Guideline Development Group on CTX Prophylaxis convened in 2013 recommended the continuation of CTX prophylaxis

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among patients stable on ART in settings with severe bacterial infections and high malaria prevalence; but that these guidelines should be adapted to 'national context' [2]. There is still uncertainty within resource limited settings and further research is needed to provide evidence based recommendations for or against stopping CTX. Garnering high quality evidence requires studies with robust designs, methodological and ethical considerations.

In this paper we present the design and methods used in the conduct of the CTX prophylaxis cessation trial among HIV infected adults on ART in Uganda (trial registration number: ISRCTN44723643).

2. Materials and methods

COSTOP is a randomised, double-blind, placebo controlled non-inferiority trial among HIV-infected adults in Uganda that have been immunologically stabilised on ART. The objective of the study is to assess whether, in patients with CD4 count of ≥250 cells/mm^3, a regime in which CTX prophylaxis is discontinued is:

(a) not inferior, with respect to the incidence of pre-defined CTX-preventable events to the control regimen in which prophylaxis with CTX is continued and
(b) superior to continuing CTX prophylaxis with respect to reducing the incidence of haematological adverse events.

The pre-defined CTX-preventable events (Table 1) are a subset of the WHO-staging events, namely those that are deemed to be CTX-preventable *a priori*.

2.1. Study setting and population

The study is being conducted in Uganda at the MRC/UVRI Unit clinics in Entebbe and Masaka. Patients on long-term CTX and ART care are recruited from local HIV treatment centres situated near-by.

The eligibility criteria used are as follows:

Inclusion criteria

- HIV-infected patient with documented intake of CTX for at least 6 months;
- age of ≥18 years;
- documented intake of ART for at least 6 months;
- clinically asymptomatic;
- 2 CD4 counts (not more than 6 months apart) of ≥250 cells/mm^3, the most recent no more than 4 weeks prior to enrolment; and
- able to attend study clinics at 3-monthly intervals and in the event of intercurrent illness.

Exclusion criteria

- acute illness (opportunistic infection or other co-morbidity);
- first trimester pregnancy;
- known hypersensitivity to cotrimoxazole; and
- grade 3/4 anaemia, neutropenia or thrombocytopenia.

Table 1
Cotrimoxazole preventable WHO staging events.

Cotrimoxazole preventable events
WHO clinical stage 4
Pneumocystis pneumonia
Recurrent severe bacterial pneumonia
Central nervous system toxoplasmosis
Chronic isosporiasis
Recurrent non-typhoidal salmonella bacteraemia
WHO clinical stage 3
Unexplained severe weight loss (>10% of presumed or measured body weight)
Unexplained chronic diarrhoea for longer than one month
Unexplained persistent fever (above 37.6 °C intermittent or constant, for longer than one month)
Severe bacterial infections (such as pneumonia, empyema, pyomyositis, bone or joint infection, meningitis or bacteraemia)
Acute necrotizing ulcerative stomatitis, gingivitis or periodontitis
Unexplained anaemia (<8 g/dl), neutropaenia (<0.5×10^9 per litre) or chronic thrombocytopaenia (<50×10^9 per litre)
WHO clinical stage 2
Moderate unexplained weight loss (<10% of presumed or measured body weight)
Recurrent respiratory tract infections (sinusitis, tonsillitis, otitis media and pharyngitis)

2.2. Ethical approval

Ethical permission was obtained from the Uganda Virus Research Institute Research and Ethics Committee (UVRI REC), the Uganda National Council for Science and Technology (UNCST) and the Ugandan National Drug Regulatory Authority (NDA). The trial is monitored by an Independent Data Monitoring Committee (IDMC).

2.3. Intervention

All participants are required to stop their regular CTX after which they are randomised to receive CTX tablets of 960 mg or a matching placebo tablet. All participants continue to receive ART from their routine providers. Trial medication is dispensed monthly for the first three months and three-monthly thereafter with a fixed number of extra tablets to allow for the possibility of late attendance. Participants are requested to return their trial medication packs with any unused tablets at scheduled clinic visits. Allocated trial treatment is discontinued in the event of the following: confirmed CD4 count drop to below 250 cells/mm^3, participants' consent withdrawal and intercurrent illness preventing further treatment with trial drug. No additional participants are recruited to replace those withdrawn. Participants withdrawn from trial treatment due to a confirmed CD4 count drop to below 250 cells/mm^3 or due to consent withdrawal are prescribed open label CTX. Follow-up of participants withdrawn from the study intervention continue unless the participant explicitly withdraws consent for follow-up.

2.4. Study schedule

A summary of the study schedule of visits and procedures is shown in Table 2. Participants are informed about the trial and provide informed consent before screening by signing the informed consent form. Illiterate participants sign by thumbprint in the presence of an independent literate witness.

At screening, potential participants are assessed for eligibility, sociodemographic and behavioural characteristics, and for their medical history (including ART use and past WHO clinical stage events). A clinical examination is conducted and Laboratory investigations include a full blood count, malaria slide and CD4 count.

The enrolment visit takes place within 2 to 4 weeks of screening; eligibility is confirmed and consent obtained for randomisation into the trial. At enrolment and each follow-up visit, routine trial procedures are performed as indicated in Table 2. Participants are seen monthly for the first three months and 3 monthly thereafter. All participants are provided with an insecticide treated mosquito net (ITN) and educated about the importance of using it. Other medications and investigations are provided as required for the management of the participant's reported disease condition. Participants are encouraged to report to the study clinics whenever they fall sick. All adverse events (AE) are