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Is it safe to stop Cotrimoxazole in adults on ART: COSTOP a non-inferiority RCT

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Disclosure

Jonathan Levin has no financial relationships with commercial entities to disclose

Background

Policy on Cotrimoxazole Preventive Therapy (CPT)

adopted in resource limited settings

follows WHO/UNAIDS recommendations

> Studies in Africa on **ART naïve HIV +ve patients** had demonstrated reduction in HIV-related mortality ranging from 25-46%, in hospitalization 21 – 53% and in malaria up to 72%. Other morbid events not characterized.

Benefit for patients stable on ART remained to be determined

Concerns: pill burden & haematological co-toxicity with ART

> In developed countries, primary CPT is not routinely practiced

Studies on CPT in ART treated populations

Adults on ART for a mean of 3.7 years who discontinued CPT
had a relative risk of malaria of 32.5 (95% CI 8.6–275.0)
and of diarrhea of 1.8 (95% CI, 1.3–2.4)
Campbell JD et al. CID 2012;54(8):1204-11

Adults on ART who continued CPT had a reduction in Malaria IRR = 33.2
no difference in pneumonia and diarrhea
Polyak CS et al. CROI 2014. Oral Abstract 98

ARROW trial, Children who stopped CPT after 96 weeks of ART had higher rates of hospitalisation/death HR=1.57, mainly due to malaria & bacterial RTI.
Bwakura-Dangarembizi et al. NEJM 2014;370:41-53

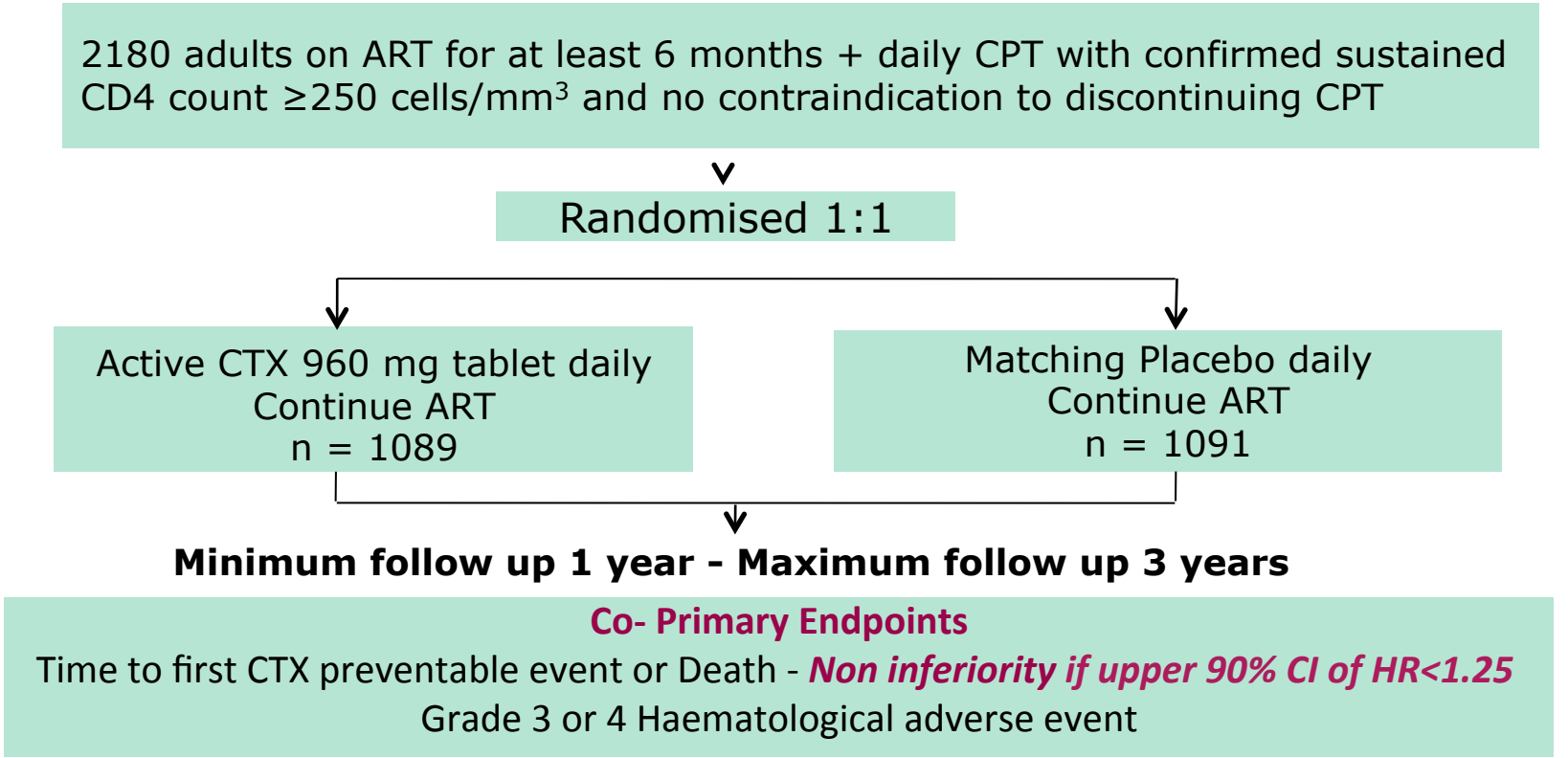
All of these were open-label trials

Objectives of COSTOP

A placebo controlled trial to asses whether,
in patients on ART with CD4 count ≥250cells/mm³,
discontinuation of CPT is

- not inferior to the control regimen in which CPT is continued
- superior with respect to the incidence of haematological adverse events

Study Design



Secondary endpoints

- Incidence of all CTX preventable events
- All cause mortality
- Incidence, severity & outcome of confirmed malaria episodes
  - asymptomatic & symptomatic
- Mean change in CD4 count & haematologic indices
  - after 12 months on the trial
- Incidence of all hospitalisations & SAEs

Baseline Characteristics

	CTX *(n=1089)*	Placebo *(n=1091)*
Entebbe Site	46.0%	45.9%
Masaka Site	54.0%	54.1%
Females	73.7%	74.1%
Age in years- Median (IQR)	41 (36-46)	40 (35-47)
Months on ART - Median (IQR)	48 (27-66)	47 (26-65)
CD4 cells/mm3 - Median IQR	518 (410-696)	519 (411-682)
WHO Clinical Stage III	57.4%	57.6%
WHO Clinical Stage IV	10.6%	9.7%
Sleeps under an ITN	62.1%	63.6%

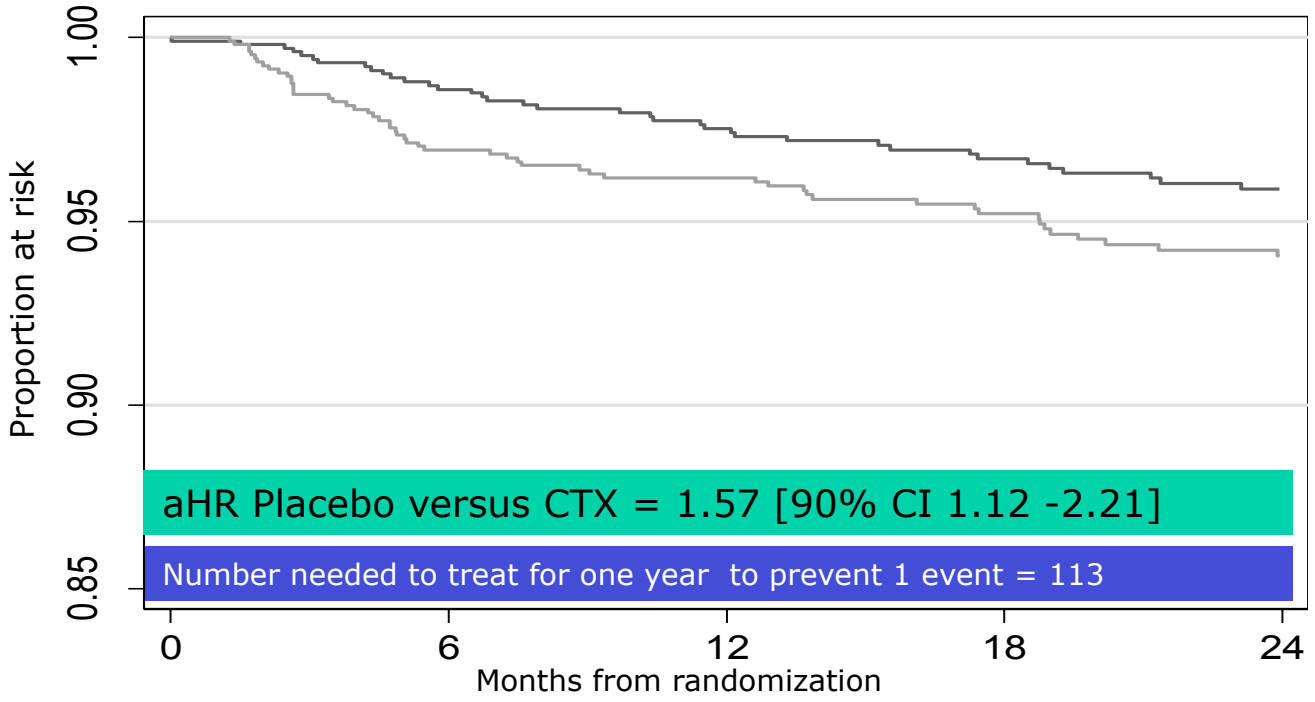
Results: ITT and PP populations

ITT: all participants who took at least one dose of study medication and who had at least one follow-up assessment (*no f/u in 5 participants*)

PP: participants whose adherence assessed by pill count or self-report remained above 80% for each period between study visits

Week	CTX ITT % retained	Placebo ITT % retained	CTX PP % retained	Placebo PP % retained
12	98.3	98.8	90.4	91.0
24	97.5	97.2	88.2	88.4
36	96.0	95.4	85.6	84.2
48	94.4	93.8	82.1	79.9
60	91.3	89.7	77.8	74.5

Time to first CTX preventable event – PP population



CTX arm
39 events (1.84 / 100PY)

59 events (2.94 / 100PY)
Placebo arm

CTX preventable events

The most common CTX preventable events were:

- *Bronchopneumonia (33 P ; 20 CTX)*
- *Recurrent Bacterial URTIs (4 P ; 5 CTX)*

6 deaths were deemed CTX preventable

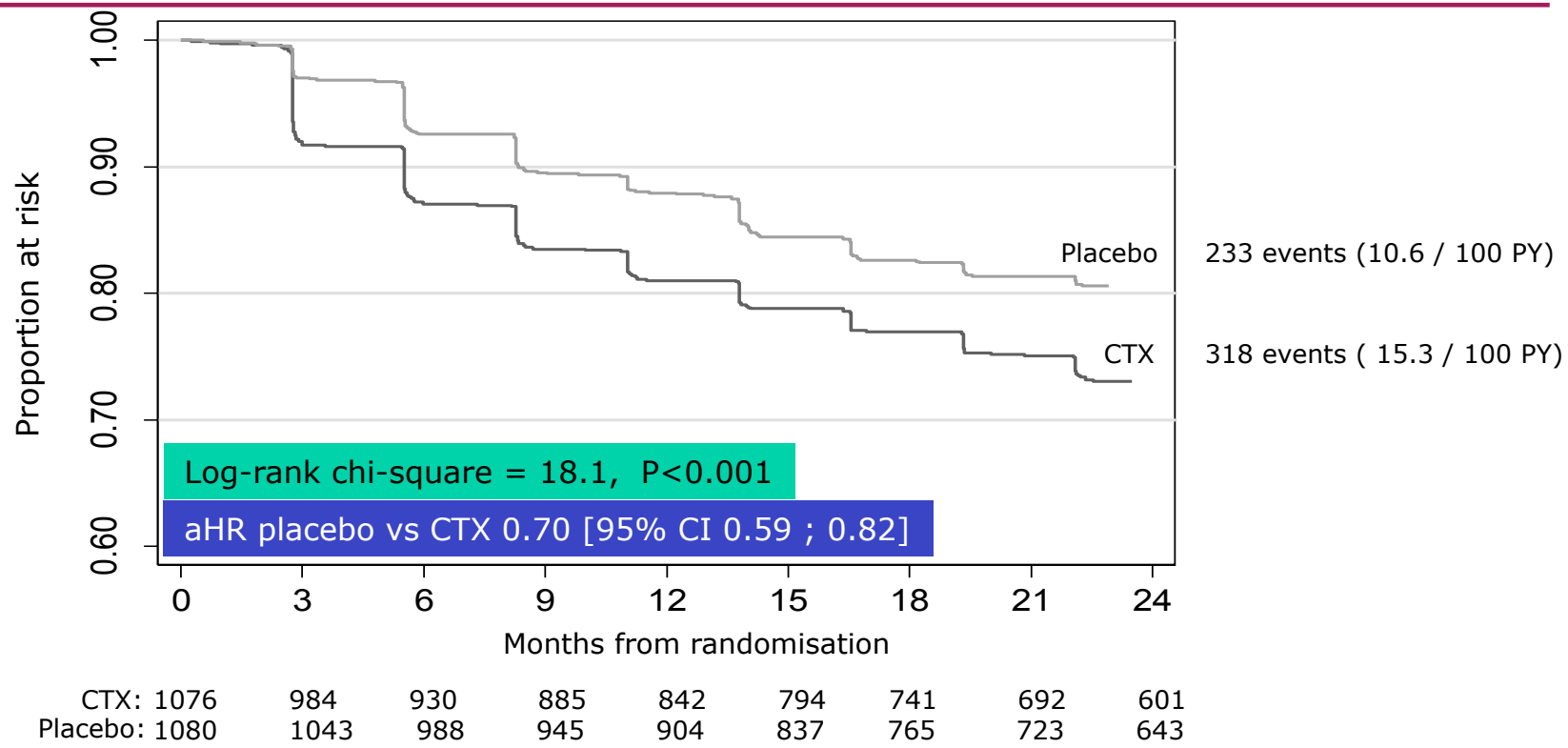
Placebo arm

1. *Klebsiella pneumonia*
2. *Septicaemic shock*
3. *Diarrhoea of unknown cause*
4. *KS with severe sepsis*

CTX arm

1. *Malaria w quinine toxicity*
2. *Pyogenic meningitis*

Time to first grade 3 / 4 haematological adverse event



Haematological adverse events

- Large number of grade 3 / 4 hematological adverse events
  Mainly grade 3 / 4 neutropenia

- Participants who experienced ≥ 1 grade 4 neutropenia
  8.2 % in CTX arm vs 5% in the Placebo arm

- Number of participants with grade 4 anaemia
  or grade 4 thrombocytopenia was very low & similar in two arms

Secondary endpoint: all cause mortality

A total of 37 deaths, 6 were deemed CTX-preventable by ERC, while 31 not CTX-preventable

	CTX	Placebo
Number of deaths	19	18
Stratified log-rank test $p = 0.91$		

Secondary endpoint: symptomatic malaria

In total 362 (16.6%) participants experienced 453 episodes of symptomatic malaria (parasitaemia + fever)

	CTX	Placebo
Number of episodes of symptomatic malaria	103	350
Rate	4.1 / 100 PY	13.9 / 100 PY
Log-rank chi-square = 137.3 ; P<0.001		
aHR placebo vs CTX 3.43 [95% CI 2.69 – 4.38]		

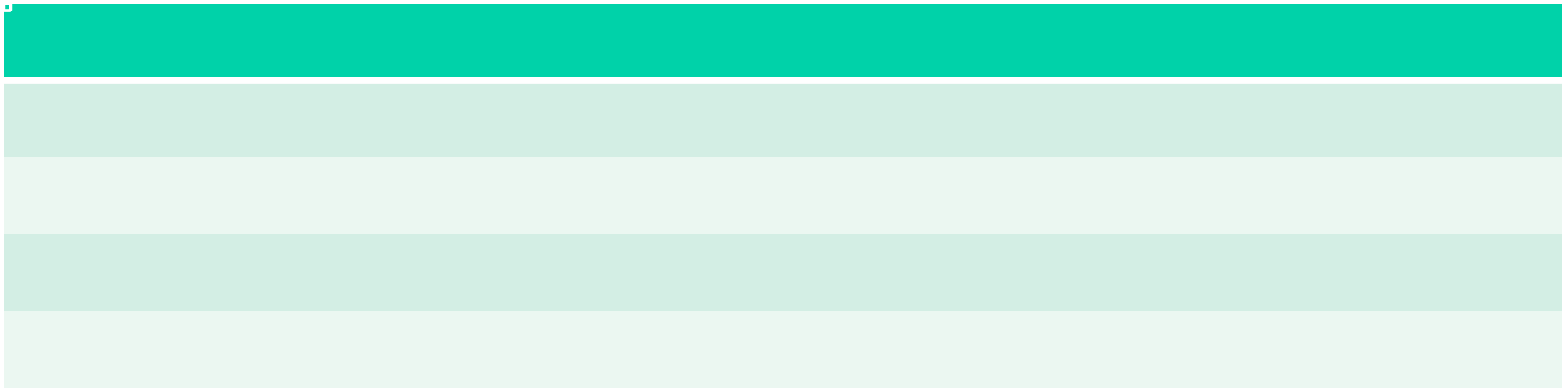
Secondary endpoint: CD4 count at week 48

Adjusting for baseline CD4 count and study site, CD4 count at week 48 was significantly higher in placebo arm than in CTX arm (P<0.001)

	CTX	Placebo
Back-transformed adjusted mean CD4 count at 48 weeks	469.5 cells/mm^3	495 cells/mm^3
% participants with **no** increase in CD4 count at 48 weeks	54.2%	45.7%

Secondary endpoint: hospitalisations

146 participants had a total of 175 hospital admissions



Reasons for admission

	CTX	Placebo
Malaria related	13	34
Anaemia	4	8
Bacterial pneumonia	2	4
Neutropenia	1	0
Unknown cause	9	5

Secondary endpoint: SAE's

155 SAE's reported

	CTX	Placebo
Total number of SAE's reported	61	94
Malaria related SAE's	8	29
Classified as "anaemia with clinical symptoms"	7	7

Time to 1st SAE: 122 participants had at least one SAE

	CTX	Placebo
Number with at least one SAE	47	75
Rate	21.92 / 100 PY	3.18 / 100 PY
log rank chi-square = 7.35 P=0.007		
aHR placebo versus CTX = 1.65 [95% CI 1.15 – 2.38]		

Conclusion

Discontinuing CPT:

- leads to a significant increase in CTX-preventable clinical events, mainly bacterial pneumonias
- significantly increases risk of Malaria and related hospitalisation
- is associated with a decrease in grade 3 / 4 haematological adverse events, mainly neutropenia
- has a small effect on change in CD4 counts on ART
- has no effect on all cause mortality

Implications

- Our results are in line with recently revised WHO guidelines on CPT in resource limited settings
- Number needed to treat with CPT (for one year) is 113 to prevent one event

  A cost effectiveness analysis is pending

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COSTOP Trial Monitors: M Akello & EACCR Monitors.
Independent Trial Steering Committee: EK Mbidde (Chair), A Kambugu, S Watiti, M Roberts (Observer)
Independent Data Monitoring Committee: T Peto (Chair), S Bahendeka, C Lombard.
Independent Endpoint Review Committee: F Semitala (Chair), R Parkes, F Kiweewa, L Ssebuyira.

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