**Table 1: Quality of evidence of individual studies**

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| **STUDY CHARACTERISTICS** | | | | **Key Findings** | **Quality of evidence for individual studies** | | | **Evidence from Economic Evaluation** | **COMMENTS** |
| **External and Internal Validity (1=Good; 2=Fair; 3=Poor)** | | **Overall**  **Quality**  **of Evidence**  **Rating** |
| **Citation** | **Study design** | **Study**  **period**  **(Country)** | **No. participants** | **Internal Validity  (Bias)** | **External**  **Validity** |
| **MORTALITY** | | | | | | | | | |
| **Alemu et al 2010 1** | OS | 2006, **Ethiopia** | 271 | . CG: “On CTX”: 240; “Off CTX”: 31  . aHR= for death CTX: 0.14 (95% CI: 0.05–0.37) | **Fair** | **Fair** | **Medium** | **No** | . ART: Yes . SP: GP  . No information on WHO stage and CD4 count distribution in the CTX and no CTX CG  . 85% of enrollees : CD4 count below 200 cells/µL with a median CD4 count of 103 cells/µL |
| **Amuron et al 2011 2** | OS | 2005-2009, **Uganda** | 1453 | . CG: “On CTX”: 1403 “Off CTX”: 50  . Risk of death for no-CTX group: 2.2 times the risk for on CTX group | **Fair** | **Fair** | **Weak** | **No** | . ART: Yes . SP: GP  . WHO stage I: 1.4%, II: 44.2%, III: 46.3%, IV: 8.1% . CD4 count: below 50: 30%, 50-99: 16%, 100-200: 45%, above 200: 9%, Median (IQR) cells/μL 108 (35-165) |
| **Anglaret et al 1999 3** | RCT | 1996-1998, **Cote d'Ivoire** | 545 | . CG: CTX arm: 271; Placebo arm: 270 . No difference in survival between CTX and placebo arms  . HR= 0·87 (0·57–1·32), p=0·51 | **Fair** | **Fair** | **Strong** | **No** | . ART: No . SP: GP  . WHO stage: CTX group (stage II: 34 %); stage III: 59 %; stage IV: 7 %) - Placebo group: (stage II: 36 %; stage III: 59 %; stage IV: 5 %) . CD4 count: CTX group (mean: 322)- placebo group (mean: 331) |
| **Badri et al 2001 4** | OS | 1992-1996, **South Africa** | 562 | . CG: “CTX-group”: 155  “No CTX group”: 407  . aHR: 0.40; 95% CI, 0.22-0.75; P< 0.001) | **Fair** | **Fair** | **Medium** | **No** | . ART: No . SP: GP . CD4 count: CTX group below 200: 86.5%, 200-500: 13.5%, above 500: NA; comparison CG <200: (65%), 200-500: (23%), above 500: 12% . WHO stage: CTX group: stage I: 14.2%, stage II: 14.8%, stage III: 44.5%, IV=26.5%; Comparison group: stage I: 34%, stage II:19.2%, stage III: 29.5%, stage IV: 16.9% |
| **Boeree et al 2005 5** | OS | 1998-2001**, Malawi** | 767 (Analyzed: Received CTX 480 mg, n=272); Received CTX 960 mg, n=307); NTP: 1999 (n=8185), Zomba 1995 (n=255) | .CG: “On CTX 480 mg”: 272;on CTX 960 mg: 307); off CTX: NTP 1999 (8185), Zomba 1995 (255)  . No significant difference in mortality between the 2 doses groups (480 vs. 960) HR= 1.11 (95% : 0.72–1.71)  . Survival in the study’s enrollees and the 2 historical cohorts significantly different (P < 0.001): lower in the current cohort (on CTX group) | **Fair** | **Fair** | **Medium** | **No** | . ART: No . SP: HIV-positive new smear-positive PTB patients . CD4 count: available for the RCT participants (those on 480/960 mg CTX) included for the comparison of doses of CTX, but not for the historical cohorts i.e. participants not on CTX (from the Zomba and the NTP cohorts), used as comparator for CTX effect assessment |
| **Fairall et al 2008 6** | OS | 2004-2005, **South Africa** | 14267 | . CG: 14267 patients (“on-CTX” and “off-CTX”)  . HR mortality “on CTX”: 0.37; 95% CI, 0.32-0.42) | **Fair** | **Fair** | **Medium** | **No** | . ART: Yes  . SP: GP  . WHO stage: stage 1 (3.2%); stage 2 (9.3%); stage 3 (18.0%); stage 4 (3.6); Non-staged (65.9%)  . CD4 count: <50: 14.8%; 50-200: 33.5%; 200-350: 16.5%; >350: 16.5%; Unknown: 18.8% |
| **Grimwade et al 2003 7** | SRM | 1995-1998, **Cote d'Ivoire, Sénégal** | 1416 | . CG: see individual studies information elsewhere in this table  . RR for death 0.69 (95% CI: 0.55 to 0.87) | **Fair** | **Fair** | **Medium** | **No** | . ART: No  . SP: in 2 studies, enrollees from the GP, and one study enrolled TB smear-positive participant  . CD4 count and WHO stage: See individual studies’ information elsewhere in this table |
| **Grimwade et al 2005 8** | OS | 1998-2002, **South Africa** | 3325 (HIV status was known in  < 10% of participants) | . CG: Intervention group: adults who started TB treatment between June 2001 and June 2002; CTX 960 mg/day for 6 months during TB treatment Control group: All adult TB on treatment from Jan1998 to Dec 2000 (2004 patients)  . At 6 months: 29% decrease in death rate (95% CI: 13–45; P < 0.001) | **Fair** | **Fair** | **Medium** | **No** | . ART: No . SP: adults with active TB, irrespective of HIV status . WHO stage: not reported . CD4 count: not reported |
| **Hoffmann et al 2014 9** | OS | 2003-2009**, South Africa** | 2590 | . CG: On CTX: 1294 (total number of enrollees: 2393)  . HR for death: 0.48, 95% CI: 0.21, 1.1). | **Good** | **Good** | **Medium** | **No** | . ART: Yes  . SP: GP  . WHO stage 3 or 4: 29%.  . Median CD4 count at entry was 209 cells/µL (IQR: 115, 292) |
| **Hoffmann et al 2010 10** | OS | 2003-2008, **South Africa** | 14097 | . CG: Comparison of mortality in the “12 months following the start of ART” between “on-CTX” and “off-CTX” patients  . aHR for death on CTX: 0.64 (95% CI: 0.57–0.72 P < 0.001) | **Fair** | **Fair** | **Medium** | **No** | . ART: Yes  . SP: GP  . WHO stage: Stage 1 or 2: CTX (35%), NO CTX (41%) Stage 3: CTX (29%), NO CTX (25%)  Stage 4: CTX (36%) NO CTX (34%)  . Median CD4: 132 cells/ µL, No CTX: 153 (IQR:70–236); Received CTX: 118 (IQR: 53-184) |
| **Khoza et al.2010 11** | OS | 2004, **Zimbabwe** | 234 | . CG: “on-CTX” vs. “off- CTX” (records of 234 HIV infected patients were reviewed, of whom 19% were on CTX)  . Prophylaxis significantly Reduced mortality (p=0.0017) (no measure reported in the abstract) | **Poor** | **Poor** | **Weak** | **No** | . ART: No . SP: GP  . CD4 count: not reported |
| **Lim et al 2012 12** | OS | 2003-2009,  **12 countries throughout the Asia-Pacific region** | 4050 | . CG: Prophylaxis vs. no prophylaxis: Of those with CD4 counts below 200 cells/µL, 58% to 72% in any given year received “PCP prophylaxis”, mainly CTX  . More than 10 times higher mortality risk (aIRR 10.8, p < 0.001) | **Fair** | **Fair** | **Medium** | **No** | . ART: Yes  . SP: GP  . No specific information on the distribution of WHO stage and CD4 count among the 2 CGs (those who ever started and those who never did)  . Overall: median CD4 counts (IQR): 163 (89- 261) cells/µL when patients started prophylaxis |
| **Lowrance et al 2007 13** | OS | 2005, **Malawi** | 1052 | . CG: Comparison of “6-month mortality rate” at 11 clinics that were or were not providing CTX  . aRR of death on CTX: 0.59 (95% CI: 0.43– 0.82) “6-month mortality” risk reduction: 40.7% (P=0.0013) | **Poor** | **Fair** | **Medium** | **No** | . ART: Yes . SP: GP  . WHO stage:  . CTX Sites (%): stage III (60), stage IV (21), CD4 <200 cells/µL (19); Non-CTX Sites (%): stage III (66), stage IV (27), CD4 count< 200 cells/µL (7) |
| **Madec et al 2007 14** | OS | 2001-2005**, Cambodia** | 1735 started ART but no number of patients on CTX has been reported in the article | . CG: 1599.1 person-years of FU on CTX, 205.4 person-years of FU without CTX  . HR for death on CTX: 0.15 (95% CI: 0.11–0.21) | **Fair** | **Fair** | **Medium** | **No** | . ART: Yes  . SP: GP  . WHO stage: at ART initiation: stage I: 3.1%, stage II: 5.8%, stage III: 45.5%, stage IV: 45.6% . Median CD4 count cell count at ART initiation: 20 cells/µL (IQR, 6–78) |
| **Maynart et al 2001 15** | RCT | 1996-1998, **Sénégal** | 100 | . CG: CTX: 51; Placebo: 49  . HR=0.84 (0.36-1.94) “Severe events” (deaths and/or hospitalizations): HR= 1.52 (0.76-3.07). No difference between CTX and placebo | **Fair** | **Fair** | **Medium** | **No** | . ARV: No . SP: GP  . CDC classification: CTX/placebo respectively A (14%/12%), B (55%/49%), and C (31%/39%)  . CD4 count: CTX group: 150 (1-398); Placebo: 153 (2-385) |
| **Mermin et al 2004 16** | OS | 2001-2003, **Uganda** | 509 individuals with HIV-1 infection and their 1522 HIV-negative household members | . CG: before vs. after CTX  . 46% reduction in mortality among the HIV infected enrollees (HR=0·54 [95% CI: 0·35–0·84], p=0·006) | **Fair** | **Fair** | **Medium** | **No** | . ART: No . SP: HIV-1 infected individuals and their HIV-negative household members . WHO stage information reported for enrollees who died or developed malaria or diarrhea, before and after CTX prophylaxis  . CD4 count: baseline, 27% of enrollees had CD4 below 200 cells/µL, 37%: 200–500 per µL, and 36% above 500/µL; Median CD4 count: 82 cells/µL lower before the start of prophylaxis (p=0·03) |
| **Mwaungulu et al 2004 17** | OS | 1999-2000, **Malawi** | 717 (70% HIV +) | . CG: TB patients registered in 1999 and patients registered in 2000  . No change in “case fatality rates” between the 2 years in HIV-negative patients, HIV-positive: from 43% to 24% (1999 vs. 2000) | **Fair** | **Fair** | **Medium** | **No** | . ART: No . SP: TB patients (PTB and EPTB; smear positive and smear negative) CD4 count not reported |
| **Nunn et al.2008 18** | RCT | 2000-2004, **Zambia** | 835 | . CG: CTX: 416; Placebo: 419  . “All-cause mortality” reduced by 21% (HR=0.79, 95% CI 0.63 to 0.99; P=0.04) | **Good** | **Fair** | **Medium** | **No** | . ART: No . SP: HIV infected adults being treated for TB . CD4 count: Only 42% of enrollees had CD4 counts information available, of which 55% had counts below 200 cells/μL |
| **Nunn et al 2011 19** | RCT | 2000-2004, **Zambia** | 600 women randomized, FU information was available from 355 (180 CTX, 175 placebo) participants | . CG: CTX180; Placebo: 179  . No difference in “death or hospital admission”: unadjusted HR=0.82, 95% CI: (0.46, 1.45), P = 0.49 | **Fair** | **Fair** | **Medium** | **No** | . ART: No . SP: GP  . WHO stage 2 or 3 (no precise distribution among the 2 CG)  . CD4 count not in most of participants |
| **Polyak et al 2014 20** | RCT | 2012-2013, **Kenya** | 500 | . CG: 250 enrollees in each arm continue or discontinue CTX, FU every 3-months for one year  . Better “primary endpoint” in On-CTX; No differences in mortality | **Good** | **Good** | **Strong** | **No** | . ART: Yes . SP:GP  . WHO stage: not reported . Median enrollment CD4 count: 595 cells/µL |
| **Suthar et al.2012 21** | SRM | Articles published in 2007-2008-2009-2010, **Cambodia, Ethiopia, Malawi, South Africa, Uganda and Zimbabwe** | 7 studies included in the meta-analysis:19192  Fairall et al and Madec et al studies did not report on the specific "On-CTX" and "Off-CTX" proportions | . CG: see individual studies description elsewhere in this table  .“Summary estimate” 0.42 (95% CI: 0.29–0.61) | **Good** | **Good** | **Medium** | **No** | See individual studies |
| **Van Oosterhout et al 2010 22** | OS | 2005-2007**, Malawi** | 593 | . CG: “Ready-to-use fortified spread”: 244, of whom 61% were on CTX; Of 245 who received “corn/soy blended flour” 56% were on CTX. Of 104 enrollees who received no “supplementary food” 33 32% were on CTX  . “aOR for death” on CTX: At 14 weeks: 0.61 (95% CI: 0.38–0.96). At 26 weeks: 0.71 (95% CI: 0.46–1.11) | **Fair** | **Fair** | **Medium** | **No** | . ART: Yes . SP: GP  . WHO clinical stage III or IV or a CD4 count below 250 cells/µL irrespective of clinical stage) with a BMI < 18.5 kg/m2 were included  . No information on the distribution of WHO stage and CD4 count the 2CG |
| **Walker et al 2010 23** | OS | 2003-2004, **Uganda and Zimbabwe** | 3179 | . CG: On CTX at ART initiation 61.6%  Off CTX at ART initiation 38.4%  Total number enrollees n=3,179)  . “aOR for death” on CTX: 0.65 (95% CI: 0.50–0.85) | **Fair** | **Fair** | **Medium** | **No** | . ART: Yes . SP: GP . WHO stage 2 to 4 . CD4 cell count ≤ 200 cells/μL  ART naïve; Median CD4 count: 83 (29–137) |
| **Watera et al.2006 24** | OS | 2000- 2002,  **Uganda** | 1268 | . CG: Before CTX 933  After CTX 936  . Mortality IRR: 0.76 (95% CI, 0.60-0.96; P=0.020), a 24% decrease in mortality | **Fair** | **Fair** | **Medium** | **Yes** | . ART: No . SP: GP  WHO stage: before CTX (Stage 1: 12%; stage 2: 48%; stage 3: 38%; stage 4: 2%), After CTX (stage 1: 17%, stage 2: 47%, stage 3: 35%; stage 4: 3%)  . CD4 count: Median (IQR): before CTX: 269 (103-481), after CTX: 252 (104-435) P=0.3 |

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| **Wiktor et al 1999 25** | | | RCT | | 1995-1998**, Cote d'Ivoire** | | 771 | . CG: On CTX: 386  Placebo: 385  . “Risk of death” reduced by 46% [95% CI 23–62], p<0·001) | **Good** | | **Fair** | | **Strong** | | **No** | | . ART: No . SP: patients with sputum-smear-positive PTB . WHO: III and IV (distribution not reported) . Median CD4 count-cell count cells/µL(n %):=317; 0–99 : 12%; 100–199: 18%; 200–349: 22%; 350: 42%; Missing: 6% |
| **Zachariah et al 2003 26** | | | OS | | 1998- 2000, **Malawi** | | 1986 | . CG: CTX: 1061 (77% HIV positive)  Control group: No CTX  . “aRR of death” : 0.81 (P < 0.001) | **Fair** | | **Fair** | | **Medium** | |  | | . ART: No . SP: TB patients . WHO stages III and IV; precise distribution in the 2 CG not reported.  . CD4 count: not reported |
| **Yazdanpanah et al 2005 27** | | | CE study | | **Cote d'Ivoire** | | NA | CTX prophylaxis is “most effective” and “reasonably cost-effective” when initiated at WHO stage 2 | **NA** | | **NA** | | **NA** | | **YES** | | CE : simulation model |
| **Goldie et al 2006 28** | | | CE study | | **Cote d'Ivoire** | | NA | More “economically beneficial option”, in resource-constrained settings, when using the strategy consisting of CTX prophylaxis and ART provision | **NA** | | **NA** | | **NA** | | **YES** | | Computer-based simulation |
| **Abimbola et al 2012 29** | | | CE study | | NA | | NA | CE of the CTX coverage expansion: preferable strategy to improve survival among HIV-infected individuals who newly register in programs and get started with ART | **NA** | | **NA** | | **NA** | | **Yes** | | Decision-analytic model |
| **Pitter et al 2007 30** | | | CE study | | 2001-2003, **Uganda** | | NA | ‘Universal prophylaxis’ vs. ‘Non-CTX prophylaxis’ option:  Production of 7.3 life-years and 7.55 DALYs per 100 persons over 1 year vs. “no prophylaxis”. “Universal CTX”: cost savings of $2.50 per person-year | **NA** | | **NA** | | **NA** | | **Yes** | | Four CTX algorithms examined |
| **MORBIDITY** | | | | | | | | | | | | | | | | | |
| **Anglaret et al 1999 3** | | RCT | | 1996-1998,  **Cote d'Ivoire** | | | 545 | . CG:CTX:271); Placebo : 270  . HR “severe events”: 0·57 [95% CI 0·43–0·75], p=0·0001); Benefit irrespective of CD4 | | **Fair** | **Fair** | **Strong** | | **No** | | See Mortality | |
| **Badri et al 2001 4** | | OS | | 1992- 1996, **South Africa** | | | 562 | . CG: CTX 155 No CTX: 407  . “Severe HIV-related illnesses” AHR= 0.52; 95% (CI), 0.38-0.68; P <0.001]; No evidence of efficacy in patients with WHO stage 2 or CD4 count 200-500 cells/µL | | **Fair** | **Fair** | **Medium** | | **No** | | See Mortality | |
| **Bulabula et al 2009 31** | | OS | | 2009**, DRC** | | | 345 | . CG: HIV positive “on CTX” and HIV negative “off CTX”  . Malaria prevalence: 6.9% in on-CTX group vs. 4.8% in off-CTX group (95 % CI 3.1 - 7.9); OR = 1.5 (95% CI 0.58 - 3.81) | | **Poor** | **Fair** | **Weak** | | **No** | | . ART: Unknown status . SP: HIV infected and non-infected individuals . No information on CD4 counts in HIV positive or WHO stage | |
| **Campbell et al 2012 32** | | RCT | | 2007-2008, **Uganda** | | | 836 | . CG: “Continuing CTX”:452 vs. “discontinuing CTX”: 384) CTX  . “At least one episode of malaria”: “Continuing. CTX” vs “Discontinuing.CTX”: 0.4% and 12.2%; P<0.001)  . Diarrhea: “continuing CTX” vs “discontinuing”: 14% and 25% (P < .001) | | **Fair** | **Fair** | **Strong** | | **No** | | . ART: Yes . SP: GP  . WHO stage: not reported  . Median CD4 count of 489 cells/µL | |
| **Denoeud-Ndam et al 2014 33** | | RCT | | 2009- 2011, **Benin** | | | 432 | . CG: “CNM trial”: 140 ( CTX: 72 or MQ-IPTp: 68)  “CM trial”: 292 CTX: 146 or CTX+ MQ-IPTp: 146  . 5% less placental malaria in the CTX group as compared to CTX + MQ-IPTp group | | **Good** | **Good** | **Strong** | | **No** | | . ART: Yes . SP: HIV-infected pregnant women  . WHO stage distribution: not reported . . CD4 count: In the CM trial: CD4below 350 cells/µL. In the CNM trial: CD4 count above 350/µL) | |
| **Dow et al 2013 34** | | OS | | 2004- 2009, **Malawi** | | | 1236 | . CG: 468 “CTX-exposed” and 768 “CTX-unexposed” women  . CTX protects against malaria vs IPTp (HR=0.35, 95% (CI): 0.20, 0.60) | | **Poor** | **Fair** | **Medium** | | **No** | | . ART: Yes . SP: HIV-infected pregnant women  . CTX-unexposed (N=468): median CD4 count=350 (IQR: 276−421); CTX-exposed (N=768): median CD4 count: 362 (IQR: 303−429); Total population (N=1236): median CD4 count: 357 (IQR: 295−427) CD4 count at screening (cells/µL) | |
| **Grimwade et al 2003 7** | | SRM | | 1995-1998,  **Cote d'Ivoire, Sénégal** | | | 1416 | . CG: see individual studies description  . Significant beneficial effect of CTX for morbid events: 0.76 (0.64 to 0.9); and for admission: 0.66 (0.48 to 0.92) | | **Fair** | **Fair** | **Medium** | | **No** | | See Mortality | |
| **Hoffmann et al 2014 9** | | OS | | 2003- 2009**, South Africa** | | | 2590 | . CG: all enrollees: 2393  . No association between CTX and TB incidence nor with diagnosis of TB | | **Good** | **Good** | **Medium** | | **No** | | See Mortality | |
| **Kapito-Tembo et al 2011 35** | | OS | | 2005-2009, **Malawi** | | | 1142 | . CG: SP & CTX (n=173); CTX only (n=334); SP only (n=557); None (n=57)  . SP-IPTp vs. SP-IPTp plus CTX, and vs. CTX  . OR, [95%CI]: 0.09, [0.01-0.66]  . OR: SP-IPTp vs. CTX 0.43, [0.19-0.97]) | | **Good** | **Good** | **Medium** | | **No** | | . ART: Yes; 554 (48.5%) of 1,142 of the women reported ART uptake . SP: HIV-infected pregnant women  . Median CD4 count cell count of 423 cells/µL (range, 11–1528 cells/µL) | |
| **Klement et al 2013 36** | | RCT | | 2009-2011, **Togo** | | | 264 | . CG: 264 (CTX or IPT-SP)  . No non-inferiority to IPT-SP for preventing maternal malaria | | **Good** | **Good** | **Strong** | | **No** | | . ART: Yes . SP: HIV type 1– infected pregnant women  . WHO HIV clinical stage distribution: CTX (n=126) vs. IPT-SP (n=124) = Stage 1 (91.3%) vs. (92.7%), Stage 2 (4.8%) vs. (4.0%), Stage 3 (4.0%) vs. (3.2%) Stage 4 (0.0%) vs. (0.0%); No significant difference in terms of WHO stage at baseline | |
| **Lim et al 2012 12** | | OS | | 2003-2009  **12 countries throughout the Asia-Pacific region** | | | 4050 | . CG: Prophylaxis vs. no prophylaxis: Of those with CD4 counts< 200 cells/µL, 58% to 72% in any given year received PCP prophylaxis, mostly CTX  . During FU, No-CTX : no higher risk of PCP, | | **Fair** | **Fair** | **Medium** | | **No** | | See Mortality | |
| **Maynart et al. 2001 15** | | RCT | | 1996-1998  Senegal | | | 100 | . CG: CTX: 51; Placebo: 49  . HR “deaths” or “hospital admission”: 1.10; 95% CI: 0.57-2.13) | | **Fair** | **Fair** | **Medium** | | **No** | | See mortality | |
| **Manyando et al 2013 37** | | SR | | SR | | | SR | CTX prophylaxis: 46%–97% reduction of clinical malaria  (see individual studies elsewhere in this table) | | **Fair** | **Fair** | **Medium** | | **No** | | See individual studies | |
| **Mermin et al 2004 16** | | OS | | 2001- 2003, **Uganda** | | | 509 individuals with HIV-1 infection and their 1522 HIV-negative household members | . CG: Comparison “before/after CTX implementation” . Malaria “Incidence rate” ratio 0·28 [0·19–0·40], p<0·0001  . CTX: “diarrhea incidence rate”: (0·65 [0·53–0·81], p< 0·0001) | | **Fair** | **Fair** | **Medium** | | **No** | | See Mortality | |
| **Newman et al 2009 38** | | OS | | 2008-2009, **Uganda** | | | 517 | . CG: HIV-infected mothers: 89% on CTX  HIV-uninfected mothers 94% on IPT-SP)  . No increased risk of placental malaria | | **Fair** | **Fair** | **Medium** | | **No** | | . ART: Yes  . SP: HIV-infected and infected pregnant women . WHO stage: not reported . CD4: not reported | |
| **Polyak et al 2014 20** | | RCT | | 2012-2013, **Kenya** | | | 500 | . CG: 250 enrollees in each arm continue or discontinue CTX, FU every 3-months for one year  . CTX enrollees had better outcomes (Combined morbidity/mortality)  . No significant differences in diarrhea or pneumonia | | **Good** | **Good** | **Strong** | | **No** | | See mortality | |
| **Walker et al 2010 23** | | OS | | 2003-2004, **Uganda and Zimbabwe** | | | 3179 | . CG: On CTX at ART initiation: 61.6%); Off CTX at ART initiation 38.4%  . Malaria OR: 0·74, 0·63–0·88; p=0·0005) | | **Fair** | **Fair** | **Medium** | | **No** | | . ART: Yes . SP: GP  . WHO stages 2 to 4 CD4 cell count ≤ 200 cells/μL  Median CD4 count of all participants (n=3179) = 83 (29–137) | |
| **Watera et al 2006 24** | | OS | | 2000-2001, **Uganda** | | | 353 | . CG: number of patients included in the analysis 933 before CTX and 936 after CTX introduction  . No change in “overall febrile events” and “morbidity rates” on CTX, Malaria incidence:  rate ratio, 0.31; 95% CI: ( 0.13-0.72) | | **Fair** | **Fair** | **Medium** | | **No** | | . ART: No . SP: GP . WHO stage information for participants enrolled in morbidity analysis: not specified. | |
| **Wiktor et al 1999 25** | | RCT | | 1995-1998,  **Cote d'Ivoire** | | | 771 | . CG:CTX: 386; Placebo : 385  . 43% (10–64) decrease in “risk of admissions” on CTX (p=0·02) | | **Fair** | **Fair** | **Strong** | | **No** | | See Mortality | |
| **RETENTION IN CARE** | | | | | | | | | | | | | | | | | |
| **Auld et al 2011 39** | OS | | | 2004-2007, **Mozambique** | | 2596 | | . CG: CTX at baseline: 821; No CTX: 1775  . “Lack of CTX prescription” is one of “attrition predictors”: (aHR=1.4; 95% CI: 1.0–1.8) | **Fair** | | **Fair** | **Medium** | | **No (not for CTX)** | | . ART: Yes . SP: GP  . Median CD4 count at ART initiation: 153  (Below 50: 16%; 50-200: 50%) | |
| **Clouse et al 2012 40** | OS | | | 2010,  **South Africa** | | 755 | | . CG: “On-CTX”: 78.3%  “No CTX”: 21.7%  . 96.4% of enrollees who were prescribed CTX at baseline, initiated ART within 1 year; 9.1% initiated ART within 1 year among those who were not | **Poor** | | **Fair** | **Weak** | | **No** | | . ART: Yes . SP: GP  . First CD4 count value (cells/μL): median (IQR) Total enrollees 96 (46, 146); “on CTX”: 95 (49, 142); Did “off-CTX”: 103 (41,158) | |
| **Kohler et al 2010 41** | OS | | | 2005-2007, **Kenya** | | 1,024 | | . CG: comparison of those who started CTX with those who did not, among non-eligible patients for ART)  . 84% retention rate with “CTX free provision”; 63% retention rate “before CTX free provision”; P < 0.001) | **Poor** | | **Fair** | **Medium** | | **No** | | . ART: No . SP: GP  . ART: No  . Median CD4 cell count 412 cells/μL before “free CTX” vs 441 cells/μL after “free CTX”, P=0.36) | |
| **Msellati et al 2003 42** | OS | | | 1999-2000,  **Cote d'Ivoire** | | 711 | | . CG: “On CTX”: 35%)  “Not on CTX”: 65%  . “Enrollees Not in “Drug Access Initiative” and not ARV-treated were more likely to be off CTX: aOR (95%CI)=2.0 (1.5–2.7)” | **Poor** | | **Fair** | **Weak** | | **No** | | . ART: Yes (Of 711 enrollees , 77% were not on ART SP: GP . CD4 count below 500 cells/µL: 87.1%, and below 200 cells/µL: 49.8% | |

***Abbreviations:***

*AHR: adjusted hazard, ART: antiretroviral therapy, CDC: Centers for Disease Control and Prevention, CE: cost-effectiveness, CG: comparison group CI: confidence interval, CM trial: co-trimoxazole mandatory trial, CNM trial: co-trimoxazole non-mandatory trial, CSS: cross-sectional study, CTX: co-trimoxazole, DALY: disability adjusted life years, EPTB: extra-pulmonary tuberculosis, FU: follow-up, SP: study population, GP: general population tuberculosis, HR: hazard ratio, IRR: incidence rate ratio, NTP: national TB program, OR: odds, OI: opportunistic infection, OR: odds ratio, OS: observational study, PTB: pulmonary tuberculosis, RCT: randomized controlled trial, SR: systematic review, SRM: systematic review meta-analysis, RR: relative risk, WHO: World Health Organization*.

1. Alemu AW, Sebastian MS. Determinants of survival in adult HIV patients on antiretroviral therapy in Oromiyaa, Ethiopia. *Glob Health Action*. 2010;3.

2. Amuron B, Levin J, Birunghi J, et al. Mortality in an antiretroviral therapy programme in Jinja, south-east Uganda: a prospective cohort study. *AIDS Res Ther*. 2011;8:39.

3. Anglaret X, Chene G, Attia A, et al. Early chemoprophylaxis with trimethoprim-sulphamethoxazole for HIV-1-infected adults in Abidjan, Cote d'Ivoire: a randomised trial. Cotrimo-CI Study Group. *Lancet*. 1999 May 1;353(9163):1463-8.

4. Badri M, Ehrlich R, Wood R, et al. Initiating co-trimoxazole prophylaxis in HIV-infected patients in Africa: an evaluation of the provisional WHO/UNAIDS recommendations. *AIDS* (London, England). 2001 Jun 15;15(9):1143-8.

5. Boeree MJ, Sauvageot D, Banda HT, et al. Efficacy and safety of two dosages of cotrimoxazole as preventive treatment for HIV-infected Malawian adults with new smear-positive tuberculosis. *Trop Med Int Health*. 2005 Aug;10(8):723-33.

6. Fairall LR, Bachmann MO, Louwagie GM, et al. Effectiveness of antiretroviral treatment in a South African program: a cohort study. *Arch Intern Med*. 2008 Jan 14;168(1):86-93.

7. Grimwade K, Swingler G. Cotrimoxazole prophylaxis for opportunistic infections in adults with HIV. *Cochrane Database Syst Rev*. 2003(3):CD003108.

8. Grimwade K, Sturm AW, Nunn AJ, et al. Effectiveness of cotrimoxazole prophylaxis on mortality in adults with tuberculosis in rural South Africa. *AIDS* (London, England). 2005 Jan 28;19(2):163-8.

9. Hoffmann CJ, Chaisson RE, Martinson NA. Cotrimoxazole prophylaxis and tuberculosis risk among people living with HIV. *PLoS One*. 2014;9(1):e83750.

10. Hoffmann CJ, Fielding KL, Charalambous S, et al. Reducing mortality with cotrimoxazole preventive therapy at initiation of antiretroviral therapy in South Africa. *AIDS* (London, England). 2010 Jul 17;24(11):1709-16.

11. Khoza S, Mkudu V, Mthethwa J, et al. Use of cotrimoxazole prophylaxis in HIV infected in patients at a referral hospital. *Cent Afr J Med*. 2010 May-Aug;56(5-8):26-30.

12. Lim PL, Zhou J, Ditangco RA, et al. Failure to prescribe pneumocystis prophylaxis is associated with increased mortality, even in the cART era: results from the Treat Asia HIV observational database. *J Int AIDS Soc*. 2012;15(1):1.

13. Lowrance D, Makombe S, Harries A, et al. Lower early mortality rates among patients receiving antiretroviral treatment at clinics offering cotrimoxazole prophylaxis in Malawi. *J Acquir Immune Defic Syndr* (1999). 2007 Sep 1;46(1):56-61.

14. Madec Y, Laureillard D, Pinoges L, et al. Response to highly active antiretroviral therapy among severely immuno-compromised HIV-infected patients in Cambodia. *AIDS* (London, England). 2007 Jan 30;21(3):351-9.

15. Maynart M, Lievre L, Sow PS, et al. Primary prevention with cotrimoxazole for HIV-1-infected adults: results of the pilot study in Dakar, Senegal. *J Acquir Immune Defic Syndr* (1999). 2001 Feb 1;26(2):130-6.

16. Mermin J, Lule J, Ekwaru JP, et al. Effect of co-trimoxazole prophylaxis on morbidity, mortality, CD4-cell count, and viral load in HIV infection in rural Uganda. *Lancet*. 2004 Oct 16-22;364(9443):1428-34.

17 . Mwaungulu FB, Floyd S, Crampin AC, et al. Cotrimoxazole prophylaxis reduces mortality in human immunodeficiency virus-positive tuberculosis patients in Karonga District, Malawi. *Bull World Health Organ*. 2004 May;82(5):354-63.

18. Nunn AJ, Mwaba P, Chintu C, et al. Role of co-trimoxazole prophylaxis in reducing mortality in HIV infected adults being treated for tuberculosis: randomised clinical trial. *BMJ*. 2008;337:a257.

19. Nunn AJ, Mwaba PB, Chintu C, et al. Randomised, placebo-controlled trial to evaluate co-trimoxazole to reduce mortality and morbidity in HIV-infected post-natal women in Zambia (TOPAZ). *Trop Med Int Health*. 2011 Apr;16(4):518-26.

20. Polyak C, Yuhas K, Singa B. et al. CTX Prophylaxis discontinuation among ART-treated adults: a randomised non-Inferiority trial [Oral abstract 98]. Presented at XXI Conference on Retroviruses and Opportunistic Infections; 2014; Boston.

21. Suthar AB, Granich R, Mermin J, et al. Effect of cotrimoxazole on mortality in HIV-infected adults on antiretroviral therapy: a systematic review and meta-analysis. *Bull World Health Organ*. 2012 Feb 1;90(2):128C-38C.

22. Van Oosterhout JJ, Ndekha M, Moore E, et al. The benefit of supplementary feeding for wasted Malawian adults initiating ART. *AIDS Care*. 2010 Jun;22(6):737-42.

23. Walker AS, Ford D, Gilks CF, et al. Daily co-trimoxazole prophylaxis in severely immunosuppressed HIV-infected adults in Africa started on combination antiretroviral therapy: an observational analysis of the DART cohort. *Lancet*. 2010 Apr 10;375(9722):1278-86.

24. Watera C, Todd J, Muwonge R, et al. Feasibility and effectiveness of cotrimoxazole prophylaxis for HIV-1-infected adults attending an HIV/AIDS clinic in Uganda. *J Acquir Immune Defic Syndr* (1999). 2006 Jul;42(3):373-8.

25. Wiktor SZ, Sassan-Morokro M, Grant AD, et al. Efficacy of trimethoprim-sulphamethoxazole prophylaxis to decrease morbidity and mortality in HIV-1-infected patients with tuberculosis in Abidjan, Cote d'Ivoire: a randomised controlled trial. *Lancet*. 1999 May 1;353(9163):1469-75.

26. Zachariah R, Spielmann MP, Chinji C, et al. Voluntary counselling, HIV testing and adjunctive cotrimoxazole reduces mortality in tuberculosis patients in Thyolo, Malawi. *AIDS* (London, England). 2003 May 2;17(7):1053-61.

27. Yazdanpanah Y, Losina E, Anglaret X, et al. Clinical impact and cost-effectiveness of co-trimoxazole prophylaxis in patients with HIV/AIDS in Cote d'Ivoire: a trial-based analysis. *AIDS* (London, England). 2005 Aug 12;19(12):1299-308.

28. Goldie SJ, Yazdanpanah Y, Losina E, et al. Cost-effectiveness of HIV treatment in resource-poor settings- the case of Cote d'Ivoire. *N Engl J Med*. 2006 Sep 14;355(11):1141-53.

29. Abimbola TO, Marston BJ. The cost-effectiveness of cotrimoxazole in people with advanced HIV infection initiating antiretroviral therapy in sub-Saharan Africa. *J Acquir Immune Defic Syndr* (1999). 2012 May 1;60(1):e8-e14.

30. Pitter C, Kahn JG, Marseille E, et al. Cost-effectiveness of cotrimoxazole prophylaxis among persons with HIV in Uganda. *J Acquir Immune Defic Syndr* (1999). 2007 Mar 1;44(3):336-43.

31. Bulabula AM, Mayanga, Mafwila, et al. Malaria prevalence in HIV patients under cotrimoxazole. Case of Kindu, Maniema, D.R. Congo. Preliminary results. *Italian Journal of Tropical Medicine*. 2009 Jan - Dec 2009;14(1-4):1-2.

32. Campbell JD, Moore D, Degerman R, et al. HIV-infected ugandan adults taking antiretroviral therapy with CD4 counts >200 cells/muL who discontinue cotrimoxazole prophylaxis have increased risk of malaria and diarrhea. *Clin Infect Dis*. 2012 Apr;54(8):1204-11.

33. Denoeud-Ndam L, Zannou DM, Fourcade C, et al. Cotrimoxazole prophylaxis versus mefloquine intermittent preventive treatment to prevent malaria in HIV-infected pregnant women: two randomized controlled trials. *J Acquir Immune Defic Syndr* (1999). 2014 Feb 1;65(2):198-206.

34. Dow A, Kayira D, Hudgens MG, et al. The effect of cotrimoxazole prophylactic treatment on malaria, birth outcomes, and postpartum CD4 count in HIV-infected women. *Infect Dis Obstet Gynecol*. 2013;2013:340702.

35. Kapito-Tembo A, Meshnick SR, Van Hensbroek MB, et al. Marked reduction in prevalence of malaria parasitemia and anemia in HIV-infected pregnant women taking cotrimoxazole with or without sulfadoxine-pyrimethamine intermittent preventive therapy during pregnancy in Malawi. *J Infect Dis*. 2011 Feb 15;203(4):464-72.

36. Klement E, Pitche P, Kendjo E, et al. Effectiveness of co-trimoxazole to prevent Plasmodium falciparum malaria in HIV-positive pregnant women in sub-Saharan Africa: an open-label, randomized controlled trial. *Clin Infect Dis*. 2014 Mar;58(5):651-9.

37. Manyando C, Njunju EM, D'Alessandro U, et al. Safety and efficacy of co-trimoxazole for treatment and prevention of Plasmodium falciparum malaria: a systematic review. *PLoS One*. 2013;8(2):e56916.

38. Newman PM, Wanzira H, Tumwine G, et al. Placental malaria among HIV-infected and uninfected women receiving anti-folates in a high transmission area of Uganda. *Malar J*. 2009;8:254.

39. Auld AF, Mbofana F, Shiraishi RW, et al. Four-year treatment outcomes of adult patients enrolled in Mozambique's rapidly expanding antiretroviral therapy program. PLoS One. 2011;6(4):e18453.

40. Clouse K,Shearer K, Bassett J, et al. Reduced loss to ART initiation among patients initiating cotrimoxazole prophylaxis therapy in Johannesburg, South Africa. AIDS 2012, TUPE737; 2012.

41. Kohler PK, Chung MH, McGrath CJ, et al. Implementation of free cotrimoxazole prophylaxis improves clinic retention among antiretroviral therapy-ineligible clients in Kenya. *AIDS* (London, England). 2011 Aug 24;25(13):1657-61.

42. Msellati P, Juillet-Amari A, Prudhomme J, et al. Socio-economic and health characteristics of HIV-infected patients seeking care in relation to access to the Drug Access Initiative and to antiretroviral treatment in Cote d'Ivoire. *AIDS* (London, England). 2003 Jul;17 Suppl 3:S63-8.