# Cotrimoxazole use and immune system recovery among newly initiating HIV-infected patients in an urban outpatient HIV clinic in Johannesburg, South Africa

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## ABSTRACT

**Background**: Previous research has shown that cotrimoxazole (CTX) use reduces mortality among patients initiating antiretroviral therapy (ART). We investigated whether CTX also accelerates immune recovery and reduces loss to follow-up (LTF) at an outpatient HIV clinic in South Africa.

**Methods**: We included all adult (≥18) ART-naïve patients initiating standard first-line treatment between April 2004 and March 2012 at Themba Lethu Clinic in Johannesburg. Patients were followed from ART initiation until death, transfer, LTF (≥3 months late for a scheduled visit with no subsequent visit), or close of the dataset (July 31, 2013). As per the South African National ART Guidelines, patients were eligible to receive CTX if their CD4 count was <200 cells/mm$^3$ or they had a WHO Stage II, III, or IV condition. The exposure was defined as being on CTX at the time of ART initiation or starting within 3 months of initiation. Immune system recovery was defined as achieving a CD4 count >200 cells/mm$^3$. A modified Poisson regression model was used to examine associations between CTX use and LTF by 12 months.

**Results**: 13392 patients initiated ART between April 2004 and March 2012, were eligible to receive CTX, and were included in the analysis. 59.0% of patients were female, the median (IQR) age was 36.9 (31.6-43.6) years, and the median (IQR) baseline CD4 count was 90 (35-155) cells/mm$^3$. Patients who did not receive CTX (14.3%) were similar to patients who did receive CTX although they did have a slightly higher, though not clinically significant, median baseline CD4 count (105 vs 89).

Patients with a baseline CD4 count from 25-49 cells/mm$^3$ who did not receive CTX took a median of 399 days to achieve immune system recovery while patients who received CTX recovered in a median of 358 days. Likewise, patients in the 50-99 cells/mm$^3$ category who did not receive CTX reached immune recovery in 331 days while those who received CTX recovered their immune system in a median of 281 days (Table 2).

Upon completion of 12 months of follow-up, patients who did not receive CTX were more likely to be LTF (15.6% vs 10.3%) than patients who received CTX. However, in a model adjusted for baseline clinical characteristics, only a slight increased risk for loss remained (aRR: 1.13; 95% CI: 0.95, 1.35) (Table 3).

**Conclusions**: Lack of provision of CTX to newly initiating HIV-infected patients results in delayed immune recovery of up to 8 weeks. Further research is needed to determine the impacts of such delays in immune recovery on treatment outcomes.

## BACKGROUND

Previous research has shown that cotrimoxazole (CTX) use reduces mortality for patients initiating antiretroviral therapy (ART).

## OBJECTIVE

We sought to investigate whether CTX use accelerates immune system recovery and reduces loss to follow-up (LTF) among ART-naïve, HIV-infected adult patients in Johannesburg, South Africa

## METHODS

We conducted a retrospective cohort analysis among HIV-infected patients who initiated ART at a large public-sector HIV clinic in Johannesburg, South Africa from April 2004 – March 2012

### Study Population

- We included all HIV-infected patients at the Themba Lethu Clinic who were eligible to receive CTX and met the following inclusion criteria:
  - Treatment naïve adults (≥18 years old)
  - Initiated onto ART between April 2004 and March 2012
  - Initiated a standard first-line ART regimen (d4T-3TC-EFV/NVP, AZT-3TC-EFV/NVP, TDF-3TC/FTC-EFV/NVP)
- Patients were followed from the date of ART initiation until death, transfer, LTF, or dataset closure (July 31, 2013)

### Exposure

- Guidelines for prescribing CTX:
  - CD4 count <200 cells/mm$^3$
  - WHO Stage II, III, or IV condition
- Exposed to CTX defined as being on CTX at the time of ART initiation or starting within 3 months of initiation
- Excluded patients with a recorded allergy to sulfa, those with grade 3 or 4 neutropenia, and those with severe anemia

### Outcomes

- **Primary outcome**: immune system recovery defined as achieving a CD4 count >200 cells/mm$^3$
- **Secondary outcome**: LTF defined as being ≥3 months late for a scheduled visit with no subsequent visit

### Statistical Methods

- Medians with corresponding interquartile ranges (IQR) are presented for continuous variables while proportions are used for categorical variables
- We present the median (IQR) time to immune recovery
- Utilized a modified Poisson regression model with robust error estimation to examine the association between CTX use and LTF at 12 months

## RESULTS

- 13392 patients were included: 59.0% were female, the median (IQR) age was 36.9 (31.6-43.6) years, and the median (IQR) baseline CD4 count was 90 (35-155) cells/mm$^3$
- 14.3% (n=1914) of eligible patients did not receive CTX
- Patients who did not receive CTX were similar to those who did although they were more likely to be prescribed TDF-3TC-EFV (36.6% vs 20.0%) and they did have a slightly higher, though not clinically significant, median baseline CD4 count (105 vs 89)

**Table 1 – Baseline demographic and clinical characteristics**

| Characteristic | Total | Received CTX | Did not receive CTX |
|---|---|---|---|
| **TOTAL** | 13392 (100%) | 11478 (100%) | 1914 (100%) |
| **Sex** | | | |
| Male | 5493 (41.0%) | 4711 (41.0%) | 782 (40.9%) |
| Female | 7899 (59.0%) | 6767 (59.0%) | 1132 (59.1%) |
| **Age at initiation** | | | |
| Median (IQR) | 36.9 (31.6-43.6) | 36.9 (31.6-43.5) | 37.1 (31.4-44.2) |
| **CD4 Count (cells/mm$^3$)** | | | |
| Median (IQR) | 90 (35-155) | 89 (34-151) | 105 (37-194) |
| **BMI** | | | |
| Median (IQR) | 21.5 (19.1-24.7) | 21.5 (19.0-24.6) | 22.0 (19.5-25.5) |
| **WHO Stage** | | | |
| I/II | 6246 (46.6%) | 5391 (47.0%) | 855 (44.7%) |
| III/IV | 7146 (53.4%) | 6087 (53.0%) | 1059 (55.3%) |
| **Hemoglobin (g/dL)** | | | |
| Median (IQR) | 11.1 (9.8-12.5) | 11.1 (9.8-12.5) | 11.1 (9.8-12.5) |
| **TB at ART Initiation** | | | |
| Yes | 2094 (15.6%) | 1803 (15.7%) | 291 (15.2%) |
| **Pregnant at ART Initiation** | | | |
| Yes | 134 (1.7%) | 101 (1.5%) | 33 (2.9%) |
| **First ART Regimen** | | | |
| d4T-3TC-EFV | 9043 (67.5%) | 8083 (70.4%) | 960 (50.2%) |
| AZT-3TC-EFV | 345 (2.6%) | 267 (2.3%) | 78 (4.1%) |
| TDF-3TC-EFV | 3000 (22.4%) | 2300 (20.0%) | 700 (36.6%) |
| Other | 1004 (7.5%) | 828 (7.2%) | 176 (9.2%) |

- Patients in the 50-99 cells/mm$^3$ category who did not receive CTX reached immune recovery in 331 days while those who received CTX recovered their immune system in a median of 281 days (Table 2).
- In an adjusted model, there was a slight increased risk for LTF for patients who did not receive CTX compared to those who did (aRR: 1.13; 95% CI: 0.95, 1.35) (Table 3).

**Table 2 – Time to immune recovery (in days) by CTX use at each CD4 count (cells/mm$^3$) level**

| | Received CTX | | Did not receive CTX | | |
|---|---|---|---|---|---|
| **Baseline CD4 count** | N (%) | Median (IQR) time to immune recovery | N (%) | Median (IQR) time to immune recovery | Change |
| Total | 7365 (100%) | 240 (161-468) | 889 (100%) | 302 (182-545) | 62 |
| <25 | 1239 (16.8%) | 458 (317-643) | 146 (16.4%) | 494 (299-705) | 36 |
| 25-49 | 914 (12.4%) | 358 (178-580) | 143 (16.1%) | 399 (236-644) | 41 |
| 50-99 | 1679 (22.8%) | 281 (162-503) | 198 (22.3%) | 331 (184-542) | 50 |
| 100-149 | 1668 (22.6%) | 202 (154-354.5) | 182 (20.5%) | 236.5 (169-434) | 34.5 |
| 150-199 | 1865 (25.3%) | 181 (150-243) | 220 (24.7%) | 213 (162-340.5) | 32 |

**Table 3 – Association between CTX use and LTF at 12 months**

| Characteristic | LTF/N (%) | Unadjusted RR (95% CI) | Adjusted RR (95% CI)* |
|---|---|---|---|
| **On CTX at ART Initiation** | | | |
| Yes | 1114/10848 (10.3%) | Reference | Reference |
| No | 275/1768 (15.6%) | 1.51 (1.34, 1.71) | 1.13 (0.95, 1.35) |
| **CD4 Count (cells/mm$^3$)** | | | |
| <25 | 305/2275 (13.4%) | 1.44 (1.15, 1.79) | 1.25 (0.96, 1.62) |
| 25-49 | 185/1609 (11.5%) | 1.23 (0.97, 1.56) | 1.17 (0.89, 1.55) |
| 50-99 | 267/2644 (10.1%) | 1.08 (0.86, 1.36) | 1.10 (0.84, 1.43) |
| 100-149 | 262/2393 (11.0%) | 1.17 (0.94, 1.47) | 1.29 (0.99, 1.68) |
| 150-199 | 209/2457 (8.5%) | 0.91 (0.72, 1.15) | 1.07 (0.82, 1.40) |
| ≥200 | 93/997 (9.3%) | Reference | Reference |
| **BMI** | | | |
| <18.5 | 302/2154 (14.0%) | 1.53 (1.34, 1.74) | 1.44 (1.26, 1.65) |
| 18.5-24.9 | 613/6670 (9.2%) | Reference | Reference |
| 25-29.9 | 135/1901 (7.1%) | 0.77 (0.65, 0.92) | 0.84 (0.69, 1.01) |
| ≥30 | 47/868 (5.4%) | 0.59 (0.44, 0.79) | 0.68 (0.50, 0.92) |
| **WHO Stage** | | | |
| I/II | 575/6000 (9.6%) | Reference | Reference |
| III/IV | 814/6616 (12.3%) | 1.28 (1.16, 1.42) | 0.99 (0.87, 1.12) |
| **Anemia** | | | |
| No anemia | 276/3050 (9.1%) | Reference | Reference |
| Mild anemia | 290/3150 (9.2%) | 1.02 (0.87, 1.19) | 0.93 (0.78, 1.10) |
| Moderate anemia | 685/5621 (12.2%) | 1.35 (1.18, 1.54) | 1.22 (1.05, 1.43) |
| **First ART Regimen** | | | |
| d4T-3TC-EFV | 871/8507 (10.2%) | Reference | Reference |
| AZT-3TC-EFV | 41/321 (12.8%) | 1.25 (0.93, 1.67) | 1.45 (1.03, 2.04) |
| TDF-3TC-EFV | 380/2823 (13.5%) | 1.31 (1.17, 1.47) | 1.24 (1.08, 1.42) |
| Other | 97/965 (10.1%) | 0.98 (0.80, 1.20) | 0.98 (0.78, 1.24) |

*Also adjusted for age at ART initiation, sex, and pregnancy at ART initiation

## CONCLUSIONS

Lack of provision of CTX to newly initiating HIV-infected patients results in delayed immune recovery of up to 8 weeks and may increase the risk of LTF after ART initiation. Further research is needed to determine the impacts of such delays in immune recovery on treatment outcomes.

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