Cotrimoxazole Prophylaxis Discontinuation among ARV-Treated HIV-1-Infected Adults in Kenya: A Randomized Non-inferiority Trial

BACKGROUND:

- Discontinuation of cotrimoxazole prophylaxis following initiation of antiretroviral (ARV) therapy in HIV-infected-individuals is undefined in resource-limited countries such as Kenya.
- Minimal research has been conducted on the effects of cotrimoxazole prophylaxis discontinuation in those with HIV on ARV therapy.

OBJECTIVE:

- To assess the effect of cotrimoxazole prophylaxis discontinuation on malaria, pneumonia, and diarrhea in ARV-treated, immune reconstituted, HIV-1-infected adults in Kenya.

METHODS

- **Design:** Randomized, parallel, unblended, non-inferiority trial
- **Duration of study:** 12 months
- **Inclusion criteria:** At least 18 years old, HIV-positive, taking first-line ARV therapy with evidence of immune reconstitution, currently taking cotrimoxazole, and willing to return to clinic every 3 months for the 12-month study follow-up period.
- **Exclusion criteria**: Pregnant/breastfeeding, taking second-line ARV therapy, or documented allergy to cotrimoxazole
- 500 patients total (250 per group) either:
    - Continued cotrimoxazole 800 mg/160 mg once daily
      OR
    - Discontinued cotrimoxazole
- **Primary outcome measures:** Composite of malaria, pneumonia, and diarrhea and non-trauma mortality events.
- **Secondary outcomes measures:** 12-month CD4 change and clinical, immunological, or virological ARV treatment failure
- 500 individuals (250 in each group) was required to calculate a power of 80%
- Data handling method was intent-to-treat and per-protocol where appropriate.

RESULTS

- 490 patients completed the study (245 in each group)
- **Primary outcome measure:** A significant difference was detected in the combined outcome of malaria, pneumonia, diarrhea, and mortality: 13.4/100 person-years in the continuation group and 30.4/100 person-years in the discontinuation group (IRR = 2.27, 90% CI 1.62 – 3.17).
- **Secondary outcome measure:** No significant difference was detected in the 12-month CD4 change between groups: 28.8 cells/mm^3/year in the continuation group and 31.6 cells/mm^3/year in the discontinuation group ($p = 0.85$). No significant difference was detected in ARV treatment failure between the two groups: 5 failures in the continuation group and 4 failures in the discontinuation group ($p = 0.73$).
- **Authors' conclusion**: Cotrimoxazole prophylaxis discontinuation among ARV-treated adults results in an increased incidence of clinical malaria but not diarrhea or pneumonia. Though the implications are broad, cotrimoxazole prophylaxis should continue in regions with endemic malaria.

STRENGTHS

- High retention rate
- Randomized controlled trial design
- Baseline demographics were similar between groups

LIMITATIONS

- Unblinded
- No placebo
- Side effects for both groups were not clearly reported
- Cause of death was not reported for the death that occurred in the cotrimoxazole continuation group
- Single site study
- Disproportionate number of women to men in each group
- Water filters and mosquito bednets were donated for participants in the study
- Participants chosen for the study were described as an "elite subgroup" and may not accurately represent the community as a whole
- Reporting of confidence intervals was not consistent throughout
- Adherence was self-reported

CONCLUSIONS

- Discontinuation of cotrimoxazole prophylaxis shows no significant increased incidence of pneumonia or diarrhea in ARV-treated, immune-reconstituted, HIV-1-infected adults.
- Continuation of cotrimoxazole prophylaxis seems to have a protective effect on malaria in ARV-treated, immune-reconstituted, HIV-1-infected adults.
- Cotrimoxazole is not routinely used for malaria prophylaxis or treatment. However, with these data and according to other studies, cotrimoxazole may have a role in malaria prophylaxis.
- Making use of cotrimoxazole for prophylaxis of many disease states, such as malaria, pneumocystis jiroveci pneumonia, and toxoplasma gondii, in HIV infected individuals may be financially beneficial in resource limited countries such as Kenya.
- Future research:
    - Since cost and medication attainment are issues in resource-limited countries, a cost-benefit analysis should be conducted on using the single drug cotrimoxazole for prophylaxis in HIV infected individuals.

Reference: Polyak, C., Yuhas, K., Singa, B., Khaemba, M., Walson, J., Richardson, B., & John-Stewart, G. (2016, January). Cotrimoxazole Prophylaxis Discontinuation among ARV-Treated HIV-1 Infected Adults in Kenya: A Randomized Non-inferiority Trial. *PLOS Medicine, 13*(1), 1-16.

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