PROGRAMMATIC EFFECTIVENESS OF TUBERCULOSIS PREVENTIVE TREATMENT FOR PEOPLE WITH HIV: A TARGET TRIAL EMULATION

771

N. Sarita Shah[1], Fadimatu Mishara[2], Seth Zissette[1], Nassir Kashmiri[2], Gerry Augustin[3], Herman Weyenga[4], Stephen Balogun[5], Deus Lukoye[6], Serhii Riabokon[7], Blessing Mushangwe[8], David Benkeser[1], Macarthur Charles[9], for the Preventing Occurrence of TB by Expanding Coverage of TPT among PLHIV (PROTECT) Study Group

[1]Emory Rollins School of Public Health, Atlanta, GA, USA, [2]National Foundation for the Centers for Disease Control and Prevention, Atlanta, GA, USA, [3]U.S. Centers for Disease Control and Prevention, Port-Au-Prince, Haiti, [4]U.S. Centers for Disease Control and Prevention, Nairobi, Kenya, [5]U.S. Centers for Disease Control and Prevention, Abuja, Nigeria, [6]U.S. Centers for Disease Control and Prevention, Kampala, Uganda, [7]Public Health Center of Ukraine, Kyiv, Ukraine, [8]Zimbabwe Technical Assistance Training and Education Center for Health, Harare, Zimbabwe, [9]U.S. Centers for Disease Control and Prevention, Atlanta, GA, USA

BACKGROUND

- Tuberculosis (TB) remains the leading cause of morbidity and mortality among people living with HIV (PLHIV)
- Clinical trials have shown TB preventive treatment (TPT) can reduce TB incidence and mortality among PLHIV
- By 2023, over 13 million PLHIV had received TPT through PEPFAR-supported clinics globally
- Effectiveness of TPT in real-world settings can be examined using routinely collected clinical data, but study design must address known biases of observational data
- A target trial framework can minimize these biases by defining parameters of a hypothetical clinical trial and aligning observational data to these criteria
- **We applied a target trial framework to observational data to determine the programmatic effectiveness of TPT among PLHIV in six high-TB-burden countries**

METHODS

- We emulated six separate clinical trials using individual-level electronic health records in **Haiti, Kenya, Nigeria, Uganda, Ukraine, and Zimbabwe**
- PLHIV initiating ART from 1/1/2018–12/31/2021 in PEPFAR-supported clinical sites were eligible and followed to 12/31/23
- **Target trial parameters were defined as:**
  - Intervention grace period: initiating a first course of TPT within 8 weeks of entering HIV care
  - Follow-up time: date of enrollment in HIV care to TB diagnosis, death, or right censoring after 2 years
  - Covariates: time-fixed (entry into HIV care year, age, sex) and time-varying (CD4 count, WHO clinical stage, ART adherence, TB symptoms)
- Estimation used a clone-censor-weight approach adjusted for covariates above
- Marginal structural models used to calculate hazard ratios and 2-year cumulative incidence of TB and all-cause mortality
- **Pooled meta-analysis** conducted to characterize overall TPT effectiveness across all 6 countries, using inverse variance weighting, and heterogeneity assessed using I^2

Initiating TPT within 8 weeks of entering HIV care was associated with a ***61% reduction in TB incidence and 45% reduction in mortality***. These findings reinforce support for TPT as an essential component of HIV care, even in an era of universal test-and-treat and newer ART regimens.

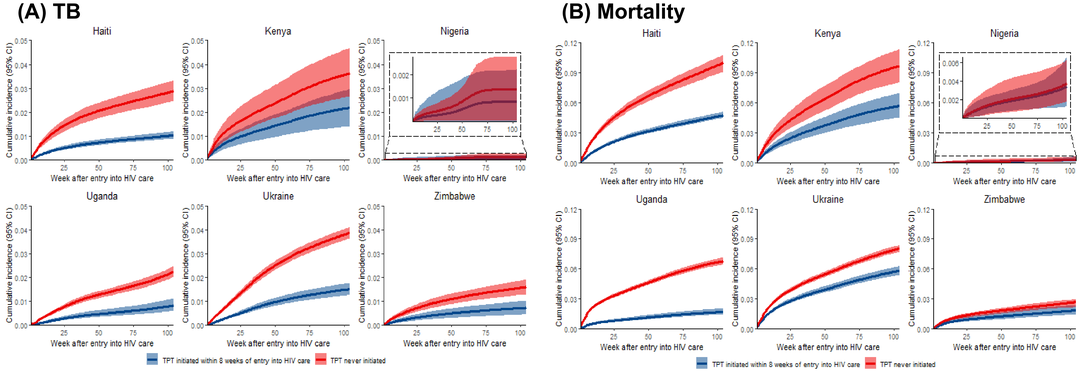
RESULTS

Table 1. Demographic and clinical characteristics (N = 235,424)

	Haiti (n=69,936)	Uganda (n=65,936)	Ukraine (n=57,851)	Zimbabwe (n=24,099)	Kenya (n=9,549)	Nigeria (n=8,053)*
Age: Median (IQR)	34 (27, 43)	30 (24, 37)	38 (32, 44)	32 (25, 40)	32 (26, 39)	29 (24, 35)
Sex: Female	42,557 (61%)	42,526 (64%)	22,414 (39%)	15,478 (64%)	6,555 (69%)	4,052 (50%)
Year of care entry: 2018	18,943 (27%)	21,512 (33%)	13,945 (24%)	3,277 (14%)	2,171 (23%)	657 (8.2%)
2019	19,334 (28%)	15,595 (24%)	14,742 (25%)	7,555 (31%)	3,127 (33%)	872 (11%)
2020	17,752 (25%)	11,219 (17%)	14,889 (26%)	4,780 (20%)	2,532 (27%)	3,921 (49%)
2021	13,907 (20%)	9,332 (14%)	14,275 (25%)	4,412 (18%)	1,719 (18%)	2,603 (32%)
ART regimen: DTG-based	53,857 (87%)	26,942 (42%)	32,633 (56%)	11,738 (49%)	7,004 (77%)	6,740 (90%)
EFV-based	6,255 (10%)	31,497 (49%)	20,009 (35%)	9,070 (38%)	1,756 (19%)	563 (7.5%)
TPT within 8 weeks	48,175 (69%)	7,174 (11%)	25,650 (44%)	6,214 (26%)	6,363 (67%)	3,677 (46%)
TB during follow-up	851 (1.2%)	775 (1.2%)	1,741 (3.0%)	235 (1.0%)	178 (1.9%)	19 (0.2%)
Died during follow-up	2,854 (4.1%)	2,333 (3.5%)	3,607 (6.2%)	386 (1.6%)	324 (3.4%)	28 (0.3%)

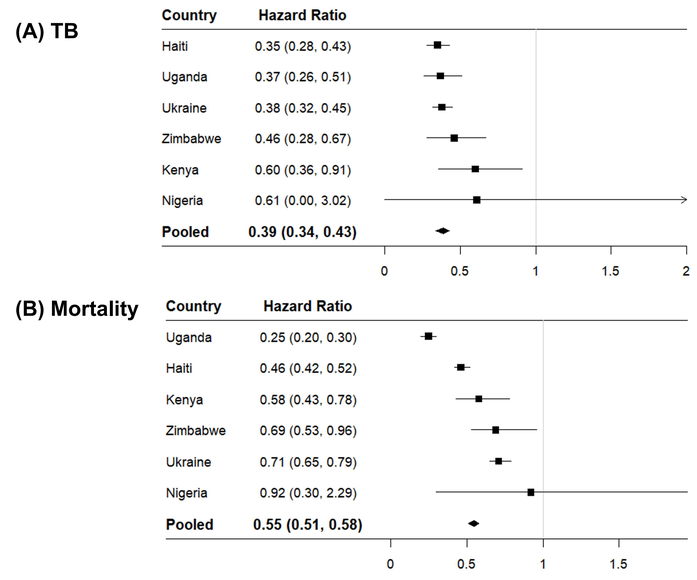
* Nigeria did not meet protocol-specified target sample size, so was underpowered for country-specific analysis, but data were retained in the pooled meta-analysis

Figure 1. Two-year cumulative incidence (95% CI) of TB (panel A) and mortality (panel B), comparing TPT initiation within 8 weeks of entry into HIV care to never initiating TPT



RESULTS (CONT.)

Figure 2. Adjusted hazard ratios of TB (panel A) and mortality (panel B), comparing TPT initiation within 8 weeks of enrollment into HIV care to never initiating TPT, pooled and by country



CONCLUSIONS

- Large, real-world evaluation of TPT effectiveness, using an innovative analytic approach for causal inference to minimize biases of observational data
- Across diverse epidemiologic and programmatic settings, showed consistent association between TPT initiation and lower TB incidence and mortality
- Findings support data from earlier clinical trials conducted before universal test-and-treat and dolutegravir-based ART

PROTECT Study team acknowledges the patients, PEPFAR implementing partners, Ministries of Health, CDC country offices and headquarters teams, and CDC Foundation staff who contributed to this work.

For more information:
Sarita.shah@emory.edu