

1. BACKGROUND & AIMS

- Randomised controlled trials (RCTs) are the gold standard for estimating treatment effect, but recruitment can be challenging in **small populations such as paediatrics**.
- Real-world data (RWD) from observational cohorts are increasingly used as **external controls (ECs)** when conventional RCTs are infeasible or difficult to conduct.
- ECs can be incorporated in different ways, including **partial replacement of concurrent controls or Bayesian borrowing while retaining the full control arm**, potentially reducing recruitment requirements and improving trial efficiency.
- However, the validity of ECs depends on how comparable the external and trial populations are, particularly when there are differences in baseline characteristics or clinical setting.

AIM: To compare two approaches to incorporating paediatric HIV real-world data into a completed Phase III RCT: frequentist partial replacement of trial controls and Bayesian borrowing while retaining the full trial control arm.

2a. METHODS: Data Sources

RCT

- ODYSSEY** was a **Phase III non-inferiority (NI) RCT** comparing **dolutegravir (DTG)-based antiretroviral therapy (ART) to standard of care (SOC)** ¹ in children starting first-line (ODYSSEY A) or second-line ART (ODYSSEY B).
 - Primary outcome:** 96-week risk difference (RD) in virological or clinical treatment failure; NI margin = 10%.
 - Setting:** 88% sub-Saharan Africa, 9% Thailand, 3% Europe.
 - Result:** DTG was superior to SOC; RD -8% (95% CI -13% to -2%; p=0.006).
- External data source**
- Epidemiology of Pregnancy and Paediatric Infections International Cohort Collaboration (EPPICC)** pools routine-care data from **17 paediatric HIV cohorts** across Europe and Thailand.
 - Children in EPPICC were included if they were:
 - aged <18 years, weighed ≥14 kg,
 - initiated first- or subsequent-line ART* on a SOC regimen (SOC was defined as in ODYSSEY)
 - had complete data for analysis covariates, and
 - had ≥1 VL measurement every 24 weeks to ensure adequate outcome ascertainment.
 - ODYSSEY B included second-line ART only; EPPICC B also included second or subsequent ART to increase the eligible sample
 - 1 Turkova A, et al. N Engl J Med. 2021;385(27):2531-43.**

3a. RESULTS: Population Characteristics

Table 1. Baseline characteristics of SOC populations		
	EPPICC SOC (n = 193)	ODYSSEY SOC (n = 357)
N(%), median [IQR]		
Age (years)	11.9 [8.9, 14.3]	12.1 [8.8, 14.7]
Sex, female	105 (54%)	171 (48%)
Ethnicity: Black	145 (75%)	315 (88%)
White	25 (13%)	1 (0.3%)
Other	23 (12%)	41 (11.7%)
Region: Europe	190 (98%)	13 (4%)
Sub-Saharan Africa	0 (0%)	311 (87%)
Thailand	3 (2%)	33 (9%)
BMI-for-age z-score	0.32 [-0.42, 1.04]	-0.58 [-1.39, 0.10]
Log VL (copies/mL)	4.5 [3.8, 4.9]	4.4 [3.7, 4.9]
CD4 count (cells/mm ³)	401 [283, 626]	486 [254, 751]
Previous AIDS	16 (8%)	32 (9%)
ART-naïve	152 (79%)	157 (44%)
NRTI: ABC/3TC	107 (55%)	235 (66%)
TDF/3TC;TDF/FTC	68 (35%)	81 (23%)
Other	18 (9%)	41 (11%)

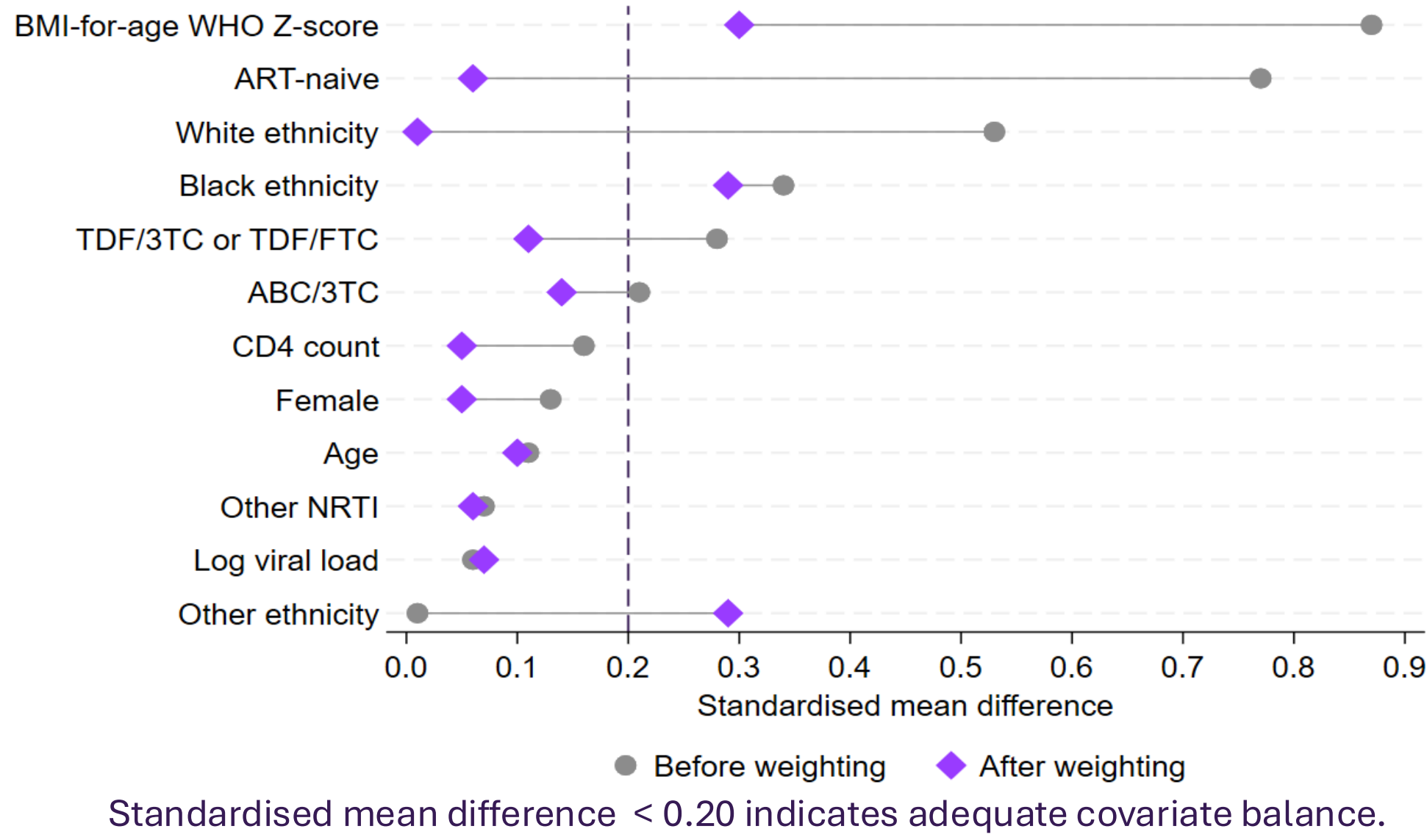


Figure 2. Covariate balance between EPPICC and ODYSSEY SOC before and after weighting

- Weighting improved balance amongst the SOC populations** across most measured characteristics, although **residual balance remained for ethnicity and BMI-for-age** (Figure 2).
- These differences may be explained by **markedly different geographical distributions** which couldn't be fully accounted for.

3b. RESULTS: Frequentist Approach

Table 2: Estimated 96-week treatment failure probability in ODYSSEY and EPPICC controls

Group	ODYSSEY SOC	EPPICC unweighted	EPPICC weighted
Overall	22%	20%	33%
ART-naïve (A)	22%	16%	20%
ART-experienced (B)	21%	36%	33%

- After weighting, the **overall probability of treatment failure was higher in EPPICC than ODYSSEY overall** (Table 2)
- This was **driven by a higher failure rate in ART-experienced patients in EPPICC** than ODYSSEY; this group represented 21% in the unweighted EPPICC cohort and increased to 53% in the weighted EPPICC cohort.
- When replacing proportions of the ODYSSEY SOC arm with EPPICC SOC this translated into **larger treatment effects overall and in the ART-experienced subgroup**. For the **ART-naïve subgroup, findings were similar to the original ODYSSEY result**. (Figure 3)

4. KEY FINDINGS & CONCLUSIONS

- Replacing ODYSSEY SOC participants with EPPICC controls had little impact on results in ART-naïve children but led to larger estimated treatment effects in ART-experienced children and overall in frequentist analysis.
- Due to sample size limitations, ART experienced children were those on second or subsequent line ART, who may have more complex treatment histories on average than in ODYSSEY which included second line only.
- These findings highlight that while external controls may be suitable when populations are closely comparable, slight differences in treatment history and patient mix can materially affect estimated treatment effects in frequentist approaches and must be carefully considered when constructing external control arms.
- In the Bayesian approach, dynamic borrowing from EPPICC resulted in a treatment effect estimate that was almost identical to the original ODYSSEY result, indicating limited influence of the external control data.

LIMITATIONS: EPPICC and ODYSSEY differed substantially in geographical setting, and region could not be adjusted for because of limited overlap. Residual imbalance remained after weighting for some measured characteristics, particularly ethnicity and BMI-for-age, and unmeasured differences between trial and RWD populations may also remain. Bayesian subgroup analyses were not conducted because of the small number of EPPICC events within ART history subgroups. Bayesian borrowing was restricted to the SOC outcome model because EPPICC contributed external controls only; therefore, external information could not directly inform the treatment effect parameter.

3c. RESULTS: Bayesian Approach

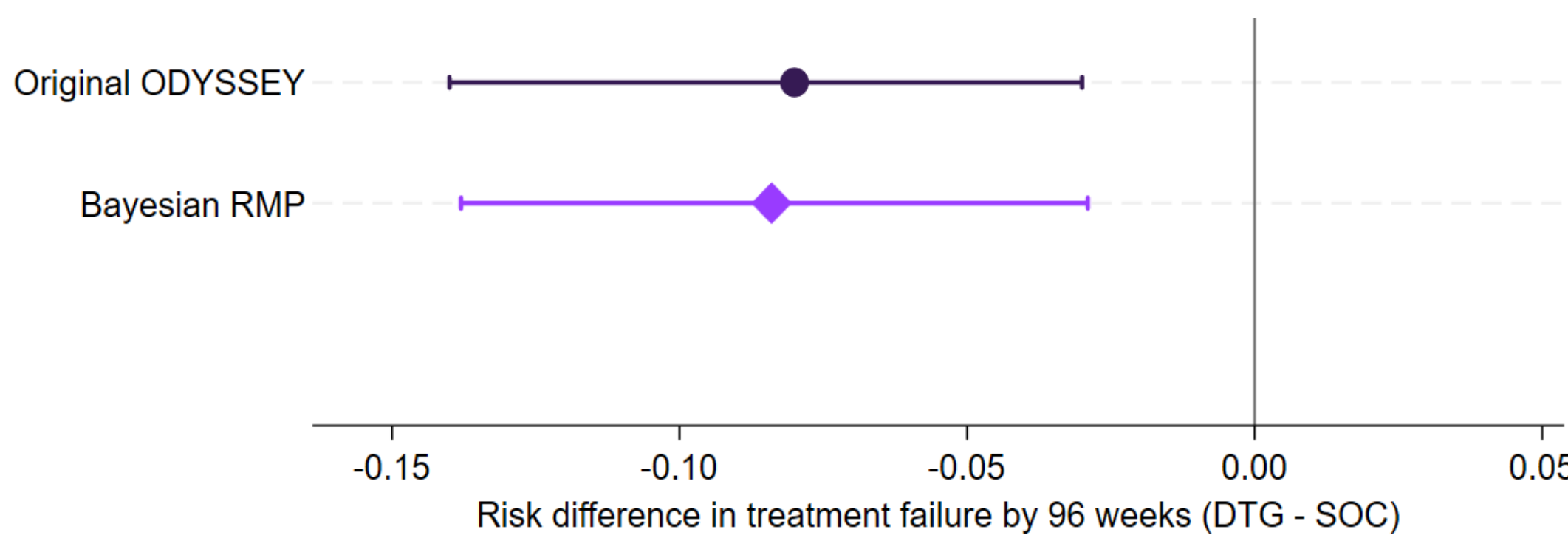


Figure 4. Treatment effect in ODYSSEY and Bayesian analysis combining ODYSSEY and EPPICC SOC

- The robust mixture prior dynamically weighted the EPPICC-informed prior according to its compatibility with ODYSSEY SOC, limiting the influence of discrepant external information.
- The EPPICC-informed prior was given a posterior mean weight of 65% (95% CrI; 11%-99%), indicating compatibility of the EPPICC cohort, although the degree of borrowing was very uncertain.
- The **Bayesian treatment effect was very similar to ODYSSEY alone** (RD ≈ -8%), with little change in precision (Figure 4).

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