Comparing low-dose efavirenz to standard-dose efavirenz and dolutegravir: A systematic literature review and network meta-analysis

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Background
The ENCORE-1 trial suggested that low-dose efavirenz (EFV400) may be a more tolerable and as efficacious alternative to standard dose efavirenz (EFV600). With dolutegravir (DTG) now the anchor treatment drug of the preferred first-line regimen, results of the NAMSAL trial could provide further insights into the therapeutic landscape.

Methods
We updated the evidence base obtained from a systematic literature review conducted on February 2018 by adding recently presented results of the NAMSAL trial. This was the same evidence base used to update the interim WHO consolidated HIV guidelines in 2018. Outcomes extracted from the NAMSAL trial were: viral suppression at 48 weeks, change in CD4 cell count at 48 weeks, discontinuations, mortality, AIDS defining illnesses (ADI), and treatment-related adverse events. Data were analyzed using network meta-analyses (NMA) in the Bayesian framework. We defined nodes by the anchor treatment drug and adjusted for differences in backbone therapies using arm-specific meta-regression adjustments. Given that the NAMSAL trial was seen as an outlier with respect to baseline HIV RNA levels, two adjustment strategies were employed. First, meta-regression was used with adjustments on HIV RNA levels, as well as baseline CD4 cell count, proportion of males and age. Second, analyses restricted to patients with baseline viral load > 100,000 copies/ml were conducted. Given the large number of outcomes, radar plots were also used to compare the treatment rankings across a variety of outcomes simultaneously.

Results
A total of 71 trials reporting on 163 arms and containing 33,764 patients were included in the analysis (Figure 1). The random-effects unadjusted model was selected throughout. Meta-regression adjustments did not change estimate sizes. Figure 2a presents the comparison of EFV400 relative to EFV600 and DTG. At 48 weeks, EFV400 had a slightly higher estimated odds of suppression (odds ratio [OR]: 1.20; 95% credible interval [Crl]: 0.90, 1.63) and was now statistically significantly differentiable from DTG (OR: 0.74; 95% Crl: 0.56, 0.98). Among patients with high viremia, the differences were similar; however, the comparison to DTG was only marginally significant in favor of DTG. EFV400 was differentiable from EFV600 with respect to improvement in CD4 cell count (mean difference: 25 cells/ml; 95% Crl: 6.57, 43.43), discontinuation due to adverse events OR: 0.42; 95% Crl: 0.23, 0.77 (Figure 2b) and treatment related adverse events OR: 0.70; 95% Crl: 0.61, 0.96(Figure 2b). There were too few deaths and ADIs for meaningful differences to be found.

The radar plot for ranking the major efficacy outcomes (Figure 3), clearly shows that DTG was consistently ranked first, or close to first, among the 12 treatments in the network of evidence. It also shows a substantially better ranking for EFV400 relative to EFV600. Figure 4 displays the rankings in the tolerability and safety outcomes, where both ranked well in terms of tolerability (DTG being the most tolerable drug) and had mixed results for safety.

Conclusion
The addition of the NAMSAL trial did not alter the results of the 2018 NMA. DTG is superior to both EFV600 and EFV400 and appears to be non-inferior to EFV600 with notably improved tolerability.