Comparative Efficacy and Safety of Dolutegravir and Lamivudine in Treatment-Naive HIV Patients

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Introduction
• Given the lifelong nature of HIV treatment, there is clinical interest in 2-drug antiretroviral therapy (ART) regimens that could minimise cumulative drug exposure while maintaining the efficacy of traditionally used 3-drug regimens (comprising a core agent + 2 nucleoside/nucleotide reverse transcriptase inhibitors).
• In randomised controlled trials (RCTs), the 2-drug regimen dolutegravir (DTG) plus lamivudine (3TC) had similar efficacy to the traditional 3-drug regimen DTG plus tenofovir disoproxil fumarate/lamivudine/emtricitabine (TDF/FTC) in treatment-naive patients with HIV-1. However, there are a number of other traditionally used 3-drug regimens for which no head-to-head study data are available.
• Objective: To conduct an indirect comparison of the efficacy and safety of DTG + 3TC with commonly used 3-drug regimens in treatment-naive patients with HIV-1, using a systematic review and network meta-analysis (NMA).

Methods
Systematic literature search and NMA
• A systematic review of the literature, clinicaltrials.gov and reimbursement documents was performed (4 December, 2018) to identify Phase III/IV RCTs for inclusion.
• Key inclusion criteria: studies in treatment-naive patients 13 years of age or older with HIV infection.
• Treatment regimens of interest were those containing recommended core agents (as of October 2018) plus the new core agent bictegravir (BIC). Efavirenz (EFV) + TDF/FTC was also included to facilitate the formation of a connected network.

Outcomes
• Efficacy: the proportion of patients with virological suppression (V5) at Week 48 and change from baseline in CD4+ cell count at Week 48.
• Safety: proportions of patients with adverse events (AEs), serious AEs (SAEs) and drug-related AEs by Week 48.

Statistical analysis
• A Bayesian NMA methodology was used to estimate relative treatment outcomes,1,4 using a regimen approach where each regimen represented a unique node in the network. A likelihood function was defined for each outcome and treatment effects were modelled using a link function.
• VS and change from baseline in CD4+ at Week 48 were analysed as continuous outcomes using normal distributions and are expressed as mean differences between the 3-drug regimens and DTG + 3TC with 95% credibility intervals (CrI). Safety outcomes were analysed as binary outcomes using binomial distributions and are expressed as odds ratios (OR) and 95% CrI for 3-drug regimens relative to DTG + 3TC.

Results
• The network contained 14 unique ART regimens, including DTG + 3TC (Figure 1), based on data from 12 publications including 10,043 treatment-naive patients with HIV-1.
• Fixed-effect models were chosen based on model fit diagnostics (Deviance Information Criterion, convergence criteria, total residual deviations)

Conclusion
• Safety
  - AEs, SAEs and drug-related AEs were assessed for the same 3 drug regimens as the efficacy endpoints relative to DTG + 3TC, except for drug-related AEs with EVG/c/ + TAF/FTC and EVG/c/ + TDF/FTC, for which no data were available.
  - The odds of having an AE were similar with all 3-drug regimens and DTG + 3TC, except for DTG + TDF/FTC, EVG/c/ + TAF/FTC and EFV + TDF/FTC for which the odds of having an AE were significantly higher (Figure 3).
  - The odds of having a SAE were similar with all 3-drug regimens and DTG + 3TC (Figure 3).
  - The odds of having a drug-related AE were significantly higher for most 3-drug regimens versus DTG + 3TC, except BIC + TAF/FTC, DTG + TAF/FTC and RAL + TDF/FTC, for which the odds were similar (Figure 3).

Figure 3. Safety outcomes by Week 48

AEs
SAEs
Drug-related AEs

OR (95% CrI) 0 1 2 3 4 5 6 7 8

OR (95% CrI) 0 1 2 3 4 5 6 7 8

OR (95% CrI) 0 1 2 3 4 5 6 7 8

References