Comparative Efficacy of Dolutegravir Relative to Common Core Agents in Treatment-Naïve HIV-1–Infected Patients: A Systematic Review and Network Meta-Analysis

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Introduction

- Advances in antiretroviral therapy (ART) have dramatically improved outcomes for patients with HIV.[1,2] Evaluation of the comparative efficacy/safety of increasing numbers of treatment choices can be helped by the use of methods such as network meta-analysis (NMA), which has recently been used to inform World Health Organization treatment guidelines[3]
- Dolutegravir (DTG) is an integrase inhibitor approved for the treatment of HIV-1 disease in combination with other antiretroviral agents.[4] A previous NMA conducted in 2013 showed that DTG had similar or superior efficacy to other guideline-recommended agents.[5] To reflect changes in the treatment landscape, we updated this NMA to include recently published data
- **Objective**: To compare the efficacy of commonly used and emerging core agents and fixed-dose regimens in treatment-naïve HIV-1–infected patients via systematic review and NMA

Methods

Systematic literature search and NMA

- A systematic search of the literature was performed in September 2017 to identify randomized controlled trials (RCTs) for inclusion in the analysis. Key inclusion criteria included phase III/IV RCT, HIV-1 infection, age ≥13 years, treatment-naïve population
- Treatments of interest were boosted protease inhibitors (PIs: ritonavir-boosted atazanavir [ATV/r], ritonavir-boosted darunavir [DRV/r], ritonavir-boosted lopinavir [LPV/r]), non-nucleoside reverse transcriptase inhibitors (NNRTIs: efavirenz [EFV], rilpivirine [RPV]), and integrase strand inhibitors (INSTIs: dolutegravir [DTG], raltegravir [RAL], elvitegravir/cobicistat [EVG/c], bictegravir [BIC]). Trials comparing any two of these treatments were included in the analysis

Outcomes

- Virologic suppression (VS) of HIV RNA <50 copies/mL at Week 48 and CD4 cell change from baseline to Week 48 (modified or exposed intention-to-treat [ITT] populations)
- Subgroup analyses of the VS outcome included baseline viral load (VL) ≤100,000, ≥100,000, and ≥500,000 copies/mL, and baseline CD4 <200 and >200 cells/µL

Statistical analysis

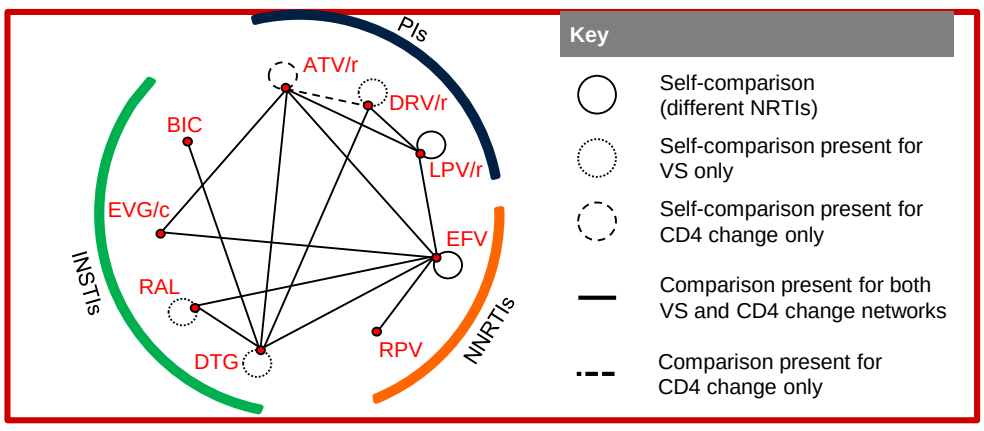
- VS and CD4 change from baseline were estimated using the Bayesian fixed effect network meta-analysis methodology[6,7] and expressed as point estimates (median) and 95% credibility intervals (CrI), using the posterior distribution to estimate the range, with 95% probability, that the parameter's point estimate falls. This methodology additionally allowed probabilities of treatments being better than others to be calculated using the posterior distribution of the treatment difference.
- Fixed effect model was chosen after considerations of population comparability (homogeneity) and fixed and random effect model fit diagnostics (residual deviance)
- Analyses were adjusted for type of NRTIs used in the treatment combination (tenofovir disoproxil fumarate/emtricitabine [TDF/FTC], abacavir/lamivudine [ABC/3TC], or any other NRTIs [Other])
- Sensitivity analysis was conducted to assess the impact of alternate model specifications (i.e., random effects and no NRTIs adjustment) on efficacy outcomes

Results

Studies included

- A total of 61 unique trials were identified. After data extraction, 22 trials were included in the analyses with the available number varying by outcome/subgroup
- The network of treatment comparisons for each outcome is shown in Figure 1

Figure 1. NMA network



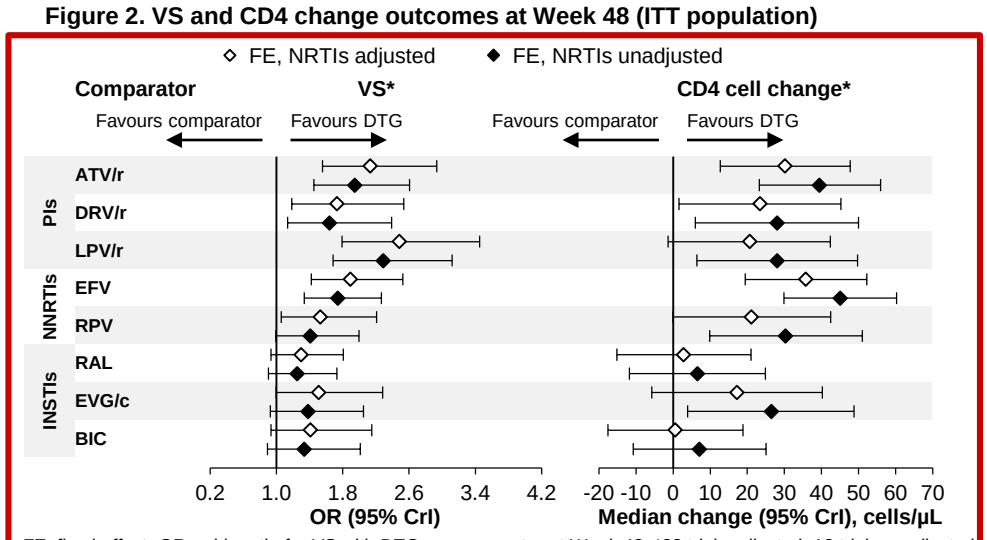
VS at Week 48

- Adjusting for NRTIs, DTG was statistically superior to NNRTIs and PIs for VS at Week 48 (Figure 2). Model results without adjusting for NRTIs (Figure 2) were overall consistent with the adjusted model
- DTG had high probabilities of being better than other treatments for VS at Week 48 in all patients, including difficult-to-treat patients (baseline VL ≥100,000 copies/mL or baseline CD4 <200 cells/µL) (Table 1)
- In the baseline VL ≥100,000 copies/mL subgroup, DTG was statistically superior to most comparators except RAL and BIC. In the VL ≥500,000 copies/mL subgroup, DTG was statistically superior to ATV/r (data not shown). In the VL ≤100,000 copies/mL subgroup, DTG was statistically superior to EFV and ATV/r. In the baseline CD4 <200 cells/µL subgroup, DTG was statistically superior to ATV/r and LPV/r (Figure 3)

CD4 cell change from baseline to Week 48

- Increases in CD4 cells were statistically higher with DTG than EFV; ATV/r and DRV/r in both models; and LPV/r, RPV, and EVG/c in the NRTI-unadjusted model (Figure 2)
- Although fixed effect models resulted in better overall fit, random effect results were consistent with fixed effect results for both outcomes (data not shown)

Figure 2. VS and CD4 change outcomes at Week 48 (ITT population)



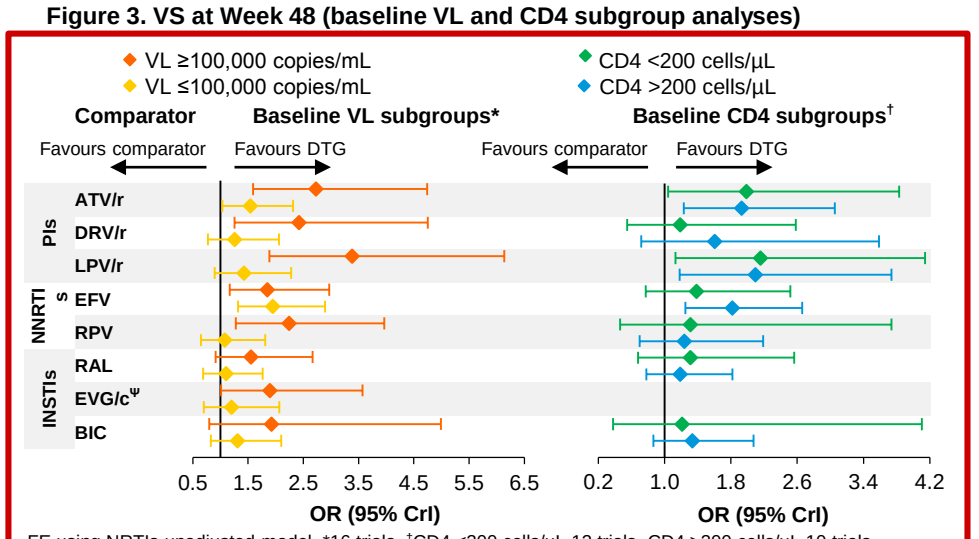
FE, fixed effect; OR, odds ratio for VS with DTG vs comparator at Week 48. *22 trials adjusted, 18 trials unadjusted

Table 1. Probability of DTG having higher VS at Week 48 versus comparators

	ATV/r	DRV/r	LPV/r	EFV	RPV	RAL	EVG/c*	BIC
All patients	100%	100%	100%	100%	97%	91%	94%	92%
Baseline VL ≥100,000 copies/mL	100%	100%	100%	100%	100%	95%	98%	93%
Baseline CD4 <200 cells/µL	98%	67%	99%	86%	70%	79%	–	62%

FE using NRTIs-unadjusted model; *Data not available for CD4 <200 cells/µL subgroup

Figure 3. VS at Week 48 (baseline VL and CD4 subgroup analyses)



FE using NRTIs-unadjusted model. *16 trials, †CD4 <200 cells/µL 12 trials, CD4 >200 cells/µL 10 trials
Ψ Data not available for CD4 <200 cells/µL subgroup

Conclusions

- In treatment-naïve patients, the odds of achieving VS with DTG were higher than all PIs and NNRTIs and similar to other INSTIs
- Irrespective of the NRTIs, DTG had higher probability of VS compared with all core agents and all patient subgroups, including difficult-to-treat patients with high VL or low CD4 cell counts
- These results suggest DTG is among the most effective treatments available for the initial treatment of HIV-1 infection

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