Dual Therapy with Boosted Darunavir and Dolutegravir: A Review of the Literature

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INTRODUCTION

- Dual therapy with ritonavir- or cobicistat-boosted darunavir (bDRV) and dolutegravir (DTG) may be considered as a simplification ART strategy in cases of drug intolerance, toxicity, resistance or simplification of complex salvage regimens.
- The US DHHS guidelines recommend a bPI + an INSTI as a treatment option in certain patients with virologic failure *(Level III evidence- "Expert Opinion")*:[1]
  - Failure on NNRTI + 2 NRTIs- LPV/r + RAL or DTG + bPI
  - Failure on bPI + 2 NRTIs- use a different bPI + INSTI
  - Failure on INSTI + 2 NRTI- if resistance to RAL or EVG/c, but susceptible to DTG, use DTG BID dosing
- Proposed benefits are high barrier to resistance, potency, simple/convenient (2-3 pills once daily), well-tolerated

OBJECTIVES

- To summarize available evidence regarding the efficacy, resistance and tolerability of bDRV + DTG.

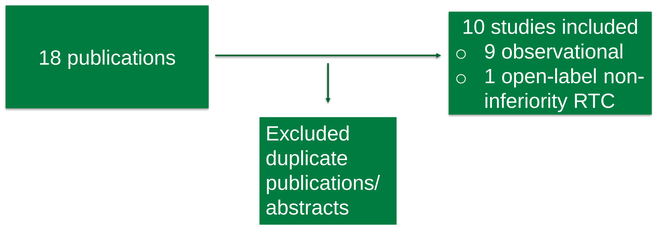
METHODS

Literature review
- Databases: Medline, Google scholar
- Recent HIV conference abstracts and posters

Search terms:
- "Dolutegravir, darunavir, dual therapy"

Inclusion:
- Both observational and experimental studies
- Date range: 1946 to end of September 2019

Exclusion:
- ART regimens containing additional ARVs along with bDRV + DTG



LEGEND

ART: antiretroviral treatment
ARV: antiretroviral
bDRV: boosted darunavir
bPI: boosted protease inhibitor
BID: twice daily
c/mL: copies/mL
DRV/c: darunavir/cobicistat
DRV/r: darunavir/ritonavir
DTG: dolutegravir
eGFR: estimated glomerular filtration rate
EVG/c: elvitegravir/cobicistat
INSTI: integrase strand transfer inhibitor
ITT: intention to treat analysis
LPV/r: lopinavir/ritonavir
NNRTI: non-nucleoside reverse transcriptase inhibitor
NRTI: nucleos(t)ide reverse transcriptase inhibitor
QD: once daily
RAL: raltegravir
RAMs: resistance associated mutations
RTC: randomized controlled trial
VL: viral load

RESULTS

Summary of Evidence:

Design:
- Table 1 summarizes the overall study results[2-11]
- 9 observational studies[3-7,9-11], 1 RCT[8]

Population:
- 3 studies in suppressed patients[2,8,10], 7 mix of suppressed/unsuppressed[3-7,9,11]
  - Baseline VL in unsuppressed patients often not reported
  - In 3 that reported baseline VL, average ranged from 1,259 – 31,623 c/mL[3,6,7]
- Studies ranged from 13 to 263 patients (611 patients total on DTG + bDRV)
- Large variability in pre-switch regimens
- Most patients had been on multiple previous regimens
- Mean CD4 ranged 148-598 cells/mm^3
- Many patients had resistance mutations, but detailed resistance information often not reported

Intervention/Control:
- Observational studies: single arm, switch (from wide variety of regimens) to DTG + bDRV
- RCT: DTG + bDRV vs. continuation of 2 NRTI + bDRV
- 3 studies used ritonavir[2-4], 2 cobicistat[5,6], 5 mixed[7-11]

Results:
- Follow-up ranged from 48 weeks – 29 months
- Viral suppression (range of <20 to <50 copies/mL) in 86-100%
  - Usually measured at week 48
- Viral failures: 0% - 8%[4,6-11]
  - Mean VL in patients with failure ranged from 79 - 39,200 copies/mL
- No patients reported to developed new RAMs

Adverse Effects:
- ART discontinuation due to adverse effects was 2.1% (n=13), including:
  - Neuropsychiatric effects (insomnia, headache, anxiety) (n=4)[10,11]
  - Decreased or no improvement in eGFR (n=2)[4,6]
  - Myalgias (n=1)[4]
  - Other, not specified (n=6)[8]
  - Non-significant increases in serum creatinine[9-11] and lipids[4] reported in some studies

Table 1. Summary of Studies using bDRV + DTG as Dual Therapy.

Study	Design	Regimen	Follow-up	Results
Wheeler et al (2018)[2]	Retrospective (suppressed)	DRV/r + DTG QD (n = 13)	12.8 months	Maintenance of VL <20 c/mL: **100%** (n=13/13)
Verna et al (2018)[3]	Retrospective (mixed)*	DRV/r + DTG QD (n = 20)	48 weeks	VL <50 c/mL at week 48: **95%** (n=19/20)
Jablonowska et al (2019)[4]	Retrospective (mixed)*	DRV/r + DTG QD (n = 76)	48 weeks	VL <50 c/mL at week 48: **92%** (n=65/71)
de la Fuente et al (2017)[5]	Retrospective (mixed)*	DRV/c + DTG QD (n = 44)	55 weeks	Undetectable VL at week 24 (non-treatment failure group): **93%** (n=26/28). Undetectable VL or "appropriate decline" at week 24 (treatment failure group): **100%** (n=16/16)
Lee et al (2018)[6]	Retrospective (mixed)*	DRV/c + DTG (n = 31); QD (28), BID (3)	48 weeks	VL <50 c/mL at week 48: **89%** (n=8/9)
Capetti et al (2018)[7]	Retro-/prospective cohort (mixed)*	DRV/r then DRV/c+ DTG (n = 130); QD (113), BID (15)	107 weeks	VL <50 c/mL at week 48: **91%** (n=118/130) VL <50 c/mL at week 96: **95%** (n=124/130)
Spinner et al (2019)[8]	Open-label non-inferiority RCT (suppressed)	DRV/r or DRV/c + DTG QD (n=131) vs. 2 NRTI + bDRV (n=132)	48 weeks	VL <50 c/mL at week 48: **86.3%** (n=113/131) vs. 87.9% (n=116/132); difference -1.6% (95.48% CI -9.9% - +6.7%). Met non-inferiority margin (△ -10%)
Hawkins et al (2019)[9]	Retrospective (mixed)*	DRV/r or DRV/c + DTG (n=65); QD (59), BID (6)	60 weeks	VL <50 c/mL, using last outcome carried forward: **94%** (n=62/65)
Navarro et al (2019)[10]	Retrospective (suppressed)	DRV/r or DRV/c + DTG QD (n=50)	25 months	VL <50 c/mL, using last outcome carried forward: **98%** (n=49/50)
Vizcarra et al (2019)[11]	Prospective, single-arm, cohort (mixed)*	DRV/r or DRV/c + DTG QD (n=51)	29 months	VL <37 c/mL at week 48: **90%** (ITT analysis) and 94% (per-protocol analysis)

* study involved a mix of virologically suppressed and unsuppressed patients

DISCUSSION

- Majority of studies retrospective
- Studies had small sample sizes
- Many studies did not give detailed information on:
  - Pre-switch regimens
  - What actual RAMs or level of resistance patients had
  - What the mean VL was at baseline in unsuppressed patients, or after treatment failure
- Significant heterogeneity in how results reported and analyzed
  - Handled missing data different
  - Snapshot analysis vs last outcome carried forward (or not described at all)
- Many studies did not report all data points of interest
  - Some were only conference posters or research letters, limited in what they can report

CONCLUSIONS

- Evidence on bDRV + DTG limited to 1 RCT and 9 observational studies
- Only studied in treatment experienced patients
- Was used in both virologically suppressed and unsuppressed patients
- Effective in most patients (86-100%)
- No reports of treatment emergent resistance
- Regimen was well tolerated with discontinuation rate of 2.1%
- Advantage of once daily dosing and low pill burden
- Consider this regimen as salvage therapy when NRTIs are not an option (toxicity, resistance)

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Conflict of Interest Disclosure: The authors have no conflicts.

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