Dual therapy with PI/r+3TC or PI/r+TDF shows non-inferior HIV RNA suppression and rates of discontinuation for adverse events, versus triple therapy. Meta-analysis of seven randomised trials in 1635 patients

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Background: Using fewer nucleos(t)ide analogues could improve safety, increase adherence and lower treatment costs. Generic versions of 3TC, tenofovir (TDF), atazanavir/r (ATVr), darunavir/r (DRV/r) and lopinavir/r (LPV/r) are becoming available worldwide. Several randomised trials have evaluated two drug combinations of a ritonavir boosted protease inhibitor (PI/r) in combination with lamivudine (3TC) or tenofovir (TDF) in naive patients or those with HIV RNA suppression at baseline.

Methods: A systematic search of PubMed, Embase, conference proceedings, and trial registries was conducted to identify all randomised controlled trials comparing PI/r+3TC or PI/r+TDF dual-therapy to triple-therapy in treatment-naïve and treatment-experienced, suppressed patients. Using Mantel-Haenszel weightings, pooled risk differences (RD) were calculated for virological suppression (FDA Snapshot), protocol-defined virological failure (PDVF), treatment-emergent resistance mutations and discontinuation due to adverse events. Virological suppression was assessed for non-inferiority (FDA non-inferiority margin delta=-4%).

Results: Seven studies were identified of three different ritonavir boosted PIs in 1,635 patients, 3 treatment-naïve: ANDES n=145, GARDEL n=306, Kalead n=152), and four treatment-experienced, supressed patient groups (ATLAS-M n=266, DUAL-GESIDA n=249, OLE n=250, SALT n=267). The pooled risk difference for viral suppression at the longest follow-up date of dual-therapy compared to triple-therapy was +2% (95%CI -2% to +6%) which met the FDA criteria for non-inferiority. Results were consistent in treatment naïve and switching studies (p=0.92). There were 5/752 patients on dual therapy with treatment-emergent major IAS NRTI drug resistance mutations, versus 5/802 on triple therapy (p=0.98). Results for treatment discontinuation for adverse events lower for dual-therapy. This was borderline significant(RD -2%, 95%CI -3% to 0%; p=0.06).

Conclusions: In this meta-analysis of 7 randomised trials in 1635 patients, rates of HIV RNA suppression < 50 copies/mL on PI/r+3TC or PI/r+TDF dual-therapy were non-inferior to triple-therapy by US FDA criteria, with fewer discontinuations for adverse events (borderline significance). Consistent results were seen in treatment naïve and suppressed patients. There was no increased risk of treatment-emergent drug resistance for dual therapy. Combination treatment with DRV/r+3TC costs < $900 per person year in low- and middle-income countries. Generic combinations of DRV/r + 3TC could save significant costs relative to branded triple therapy combinations including TDF/FTC or TAF/FTC.

Table 1: Study characteristics

Study	Follow Up Week	Dual	Triple	Treatment History
GARDEL (n=306)	96	LPV/r + 3TC	LPV/r + 2 NRTI	Naïve
KALEAD (n=152)	24	LPV/r + TDF	LPV/r + 2 NRTI	Naïve
ANDES (n=145)	48	DRV/r + 3TC	DRV/r + 3TC/TDF	Naïve
OLE (n=250)	48	LPV/r + 3TC	LPV/r + 2 NRTI	Switch
ATLAS-M (n=266)	96	ATV/r + 3TC	ATV/r + 2 NRTI	Switch
SALT (n=267)	96	ATV/r + 3TC	ATV/r + 2 NRTI	Switch
DUAL-GESIDA (n=249)	48	DRV/r + 3TC	DRV/r + 2 NRTI	Switch
Total (n=1635)				

Table 2: HIV RNA <50 copies/mL

Study	Follow Up Week	Dual	Triple	RD, 95% Confidence Interval
GARDEL (n=306)	96	90.3%	84.4%	+6% (-2%, +13%)
KALEAD (n=152)	24	69.4%	70.0%	-1% (-15%, +14%)
ANDES (n=145)	48	93.3%	94.2%	-1% (-9%, +7%)
OLE (n=250)	48	87.8%	86.6%	+1% (-7%, +9%)
ATLAS-M (n=266)	96	77.4%	65.4%	+12% (1 %, +23%)
SALT (n=267)	96	74.4%	73.4%	+1% (-10%, +11%)
DUAL-GESIDA (n=249)	48	88.9%	92.7%	-4% (-11% , +3%)
Total (n=1635)	**p=0.40**	**83.6%**	**80.6%**	**+2% (-2%, +6%)**

Table 3: PDVF and treatment-emergent resistance mutations

	Dual	Triple	RD, 95% Confidence Interval	P-value
PDVF	41/827 (5.0%)	36/808 (4.5%)	**0% (-2%, +2%)**	**0.98**
Resistance mutations	5/752 (0.7%)	5/738 (0.7%)	**0% (-1%, +1%)**	**0.89**

Table 4: Discontinuations due to adverse events for PI/r + 3TC

Study	Follow Up Week	Dual	Triple	RD, 95% Confidence Interval
GARDEL (n=306)	96	0.6%	2.8%	-2% (-5% – +1%)
OLE (n=250)	48	0.8%	3.1%	-2% (-6%, +1%)
ATLAS-M (n=266)	96	1.5%	2.3%	-1% (-4%, +3%)
SALT (n=281)	96	5.0%	7.1%	-2% (-8%, +3%)
DUAL-GESIDA (n=249)	48	0.8%	1.6%	-1% (-4%, +2%)
Total (n=1352)	**p=0.04**	**1.7%**	**3.5%**	**-2%**	**(-3%, 0%)**

*** PI/r + 3TC studies only**

Figure 1: Summary efficacy and safety of PI/r +3TC or TDF

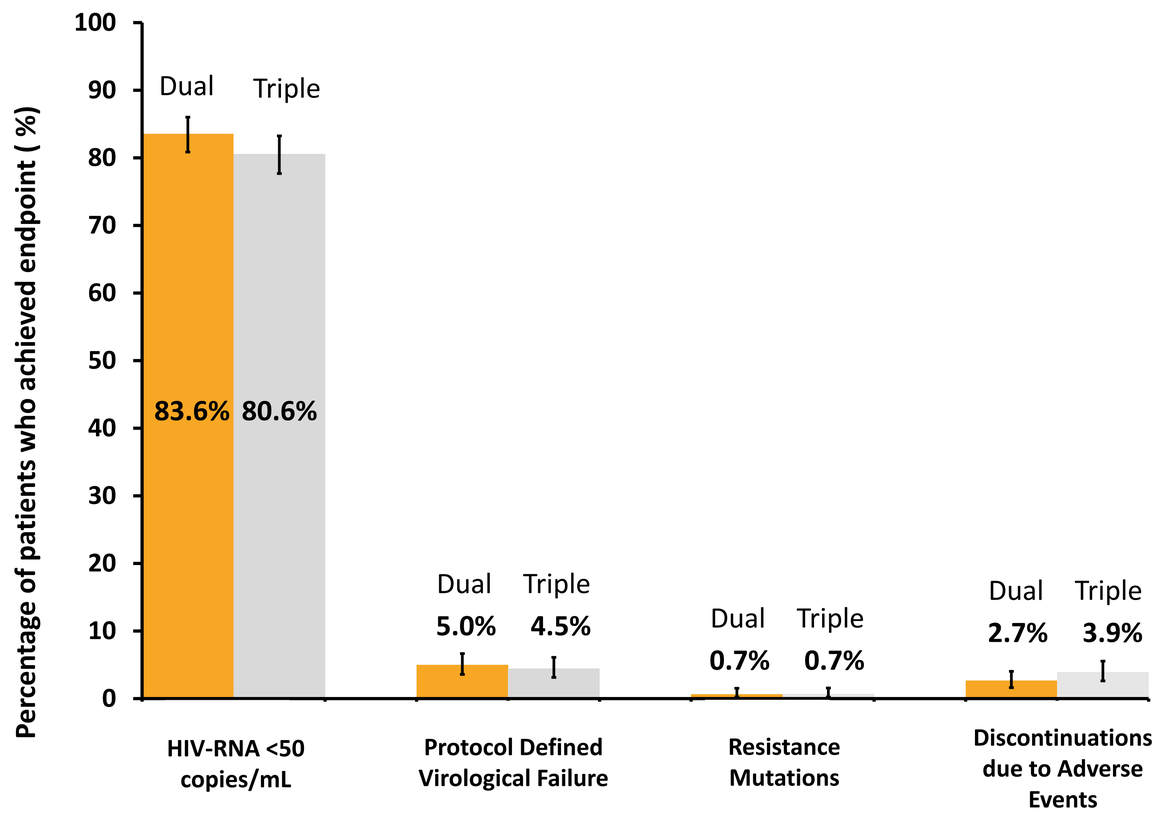

Table 5: Comparisons with DTG dual therapy

Dual therapy	DTG + 3TC	DTG + RPV	PI/r + 3TC/TDF
Clinical trials	GEMINI 1 + 2	SWORD 1+2	7 trials
Patients	1433	1024	1635
Naïve/switch	Naïve	Switch	Naïve + Switch
Non-inferior efficacy	Yes	Yes	**Yes**
Safety benefits	No	No	**No**
Discontinuations due to adverse events	Dual – 2.1% Triple – 2.2%	Dual – 3.3% Triple – 0.6%	Dual – 2.7% Triple – 3.9%
List price (per person per year in the UK)	**£6,186**	**£8,506**	**DRV/r + 3TC = £3942**