Raltegravir Based Therapy Non-inferior to Standard of Care in SECOND-LINE Therapy over 96 weeks

Name: Janaki Amin on behalf of the SECOND LINE study team

Affiliation: The Kirby Institute, University of New South Wales, Australia

Introduction

There is little evidence to inform treatment guidelines for second-line combination antiretroviral therapy (cART) recommendations.

The World Health Organization (WHO) recommends a boosted-protease inhibitor plus two nucleoside analogues (N(t)RTIs) as the first option for second-line therapy.

The Week 48 report of the SECOND-LINE trial and the Week 96 results of the EARNEST study, randomised trials of cART for treatment of people who were failing first line, demonstrated non-inferior outcomes for an experimental regimen of cART containing raltegravir plus ritonavir-boosted lopinavir (LPV/r) (RAL) compared to 2-3N(t)RTI + LPV/r (Control).

Aim:

To assess the durability of efficacy and safety of RAL compared to Control over 96 weeks.

Methods

Participants

- 541 HIV-1 infected adults virologically failing first-line NNRTI+2N(t)RTI

Randomisation

- **Control=2-3 N(t)RTI+LPV/r, n=271**
- **RAL=raltegravir+LPV/r, n=270**
- open-label

Eligibility

- no previous exposure to protease inhibitors (PI) or integrase strand transfer inhibitors (InSTI)

Statistical analysis

- differences between the proportion of participants with HIV-1 RNA (VL) <200 copies/mL and <50 copies/mL compared using X^2
- non-inferiority margin of -12% in intention to treat, per protocol and non-completion equals failure populations
- differences in biochemical, haematological and metabolic changes were assessed using T-tests
- clinical outcomes were assessed by Cox regression

Results

Disposition and demographics

- Participants were 55% male; 42% Asian; 36% African; and14% Hispanic; mean (sd) age was 38.8 (8.8) years, duration of 1st-line ART, 4.1 (2.8) years, VL, 4.2 (0.9) log copies/mL, and CD4+T-cells, 211 (157) cells/μL.
- 3.7% patients withdrew/lost to follow-up by week 96 (1.9% RAL vs 5.5% Control) (Figure 1)
- 19 participants died (8 RAL vs 11 Control)
- 83% of participants remained on the randomized regimen through 96 weeks.

Efficacy and outcomes

- VL < 200 copies/mL at 96 weeks was 80% in the RAL arm and 76% in the Control arm, difference: 4.4 [95% confidence interval -2.6, 11.3]) and met non-inferiority criteria for all populations and sub-groups (Figure 2).
- Of all virologic failures in RAL (53) and Control (65)
  - week 48: 47 (89%), and 52 (80%)
  - weeks 47-96: 6 (11%) and 13 (20%)
- Mean increases in CD4+ T lymphocyte count (cell/mm^3) were similar in both arms.
- The RAL arm was associated with a significantly higher mean change in haemoglobin, lymphocytes, total cholesterol, HDL-cholesterol and LDL-cholesterol (Table 1).
- There were no differences in number of participants experiencing an adverse or serious adverse (Table 2).

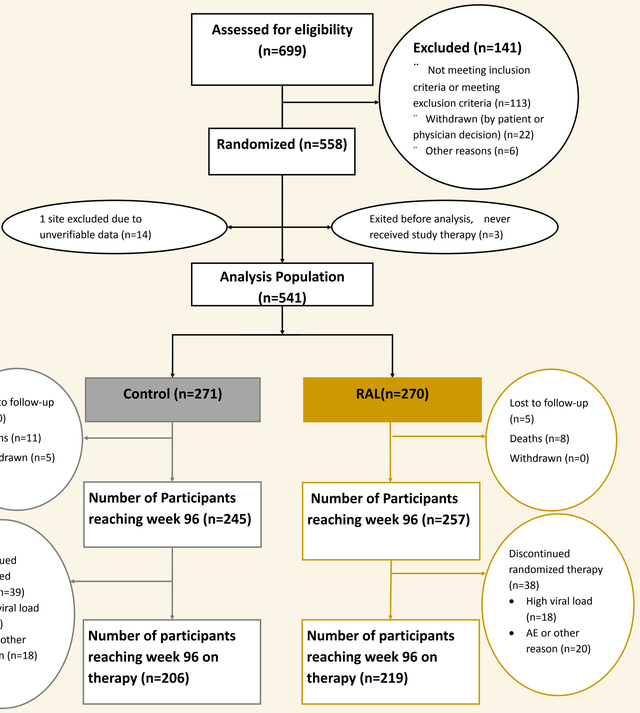


Figure 1. Participant disposition

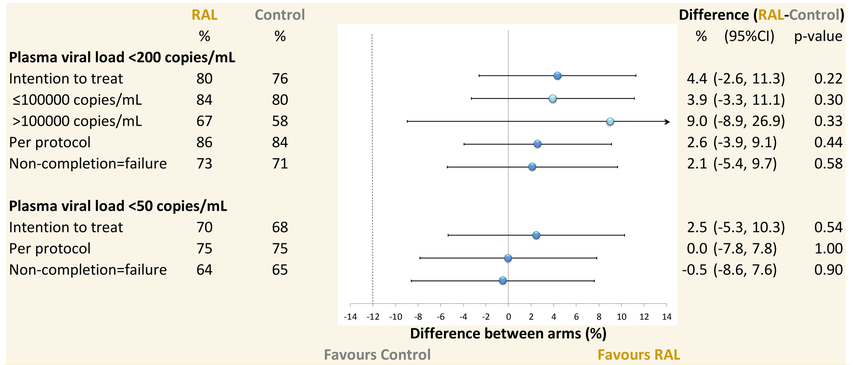


Figure 2. Virologic response at Week 96, by arm study population and screening strata

non- inferiority bound -12% indicated by dotted line ----

Table 2. Clinical outcomes, by arm

	Control		RAL				
	n	Rate/100py	n	Rate/100py	Hazard Ratio	95%CI	p-value
Deaths	11	2.4	8	1.6	0.7	(0.3, 1.8)	0.456
AIDS or death	29	6.6	34	7.6	1.2	(0.7, 1.9)	0.538
Serious adverse events	33	7.4	40	8.8	1.2	(0.8, 1.9)	0.456
Adverse events	1391	297.2	1387	285.0	0.9	(0.8, 1.1)	0.238
Time to loss of virologic response	104	26.9	111	28.1	1.06	(0.8, 1.4)	0.680

PY: person years

Table 1 Differences in mean change from baseline to Week 96

	Control Mean	RAL Mean	Difference (Control-RAL) Difference	95%CI	p-value
Immunology					
CD4+ T lymphocytes (cells/mm^3)	201.7	228.7	-27.0	(-59.0, 5.0)	0.100
Total lymphocytes (cells/mm^3)	0.5	0.7	-0.2	(-0.3, -0.0)	0.018
Neutrophils(cells/mm3)	0.8	0.9	-0.1	(-0.3, 0.2)	0.452
Haemoglobin (g/L)	5.5	8.3	-2.9	(-5.7, -0.1)	0.046
Biochemistry					
ALT (U/L)	-11.1	-6.6	-4.5	(-9.7, 0.7)	0.091
Creatine kinase (U/L)	-13.7	-14.9	1.3	(-33.8, 36.4)	0.943
eGFR (mL/min/1.73m^2)	-5.5	-5.2	-0.3	(-3.1, 2.5)	0.834
Metabolics					
Total cholesterol (mmol/L)	0.4	0.9	-0.5	(-0.8, -0.3)	<0.001
HDL cholesterol (mmol/L)	0.0	0.1	-0.1	(-0.1, -0.0)	0.003
Total:HDL cholesterol ratio	0.4	0.5	-0.2	(-0.4, 0.1)	0.204
LDL cholesterol (mmol/L)	0.2	0.5	-0.3	(-0.5, -0.2)	<0.001
Triglycerides (mmol/L)	0.8	1.0	-0.1	(-0.5, 0.2)	0.417
Glycaemic parameters					
Glucose (mmol/L)	-0.1	0.2	-0.3	(-0.5, 0.0)	0.090
Insulin (mU/L)	-0.9	0.6	-1.6	(-4.3, 1.2)	0.267
HOMA	-0.3	0.4	-0.7	(-1.6, 0.2)	0.128

eGFR: estimated glomerular filtration rate, LDL: low density lipoprotein, HDL: high density lipoprotein, HOMA: homeostasis model assessment, p<0.05 highlighted

Conclusion

At 96 weeks, an N(t)RTI-sparing second-line regimen of LPV/r+RAL continued to demonstrate similar efficacy, at over 75% in both arms, safety and tolerability compared to a regimen containing LPV/r+2-3N(t)RTIs. These results support the use of a combination LPV/r and RAL regimen as an option following failure of 1st line NNRTI+2N(t)RTIs

Acknowledgements

This study was funded by the Australian Government Department of Health and Ageing, Merck and AbbVie. The views expressed in this publication do not necessarily represent the position of the Australian Government. The Kirby Institute is affiliated with the Faculty of Medicine, University of New South Wales.