Second-line treatment in sub-Saharan Africa: Week 144 follow-up of the EARNEST trial

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Abstract (updated)

Background: Trials to date have not shown any clear short-term benefit to replacing NRTIs with raltegravir (RAL) in PI-based second-line therapy. Longer-term efficacy and safety outcome data are needed to assess the potential value of this new combination for ART rollout programme settings.

Methods: 1277 patients aged ≥12 years who met WHO-defined treatment failure criteria after >12 months on NNRTI-based first-line ART were randomised in an open-label trial in 14 sub-Saharan African sites to receive bPI + 2/3 clinician-selected NRTIs (PI/NRTI), bPI plus RAL (400mg bd) (PI/RAL); or bPI monotherapy (+RAL induction for first 12 weeks; by DMC recommendation, treatment was re-intensified after week 96 (at median week 124), adding NRTIs only in 94% or by other treatment switch in 6%)(PI-mono). bPI was standardised to lopinavir/ritonavir, 400mg/100mg bd. Treatment was monitored clinically and by open CD4 count; VL and resistance testing were done annually blinded, reviewed by the DMC. The primary (composite) endpoint, good disease control, was defined as no new WHO stage 4 events or death after randomisation, CD4 count >250 cells/mm3, and VL < 10,000 copies/ml (or >10,000 copies/ml without major/minor PI resistance mutations) at week 96. Here we report final trial outcomes at week 144.

Results: Patients were 58% female, median baseline CD4=71 cells/mm^3, VL=69,782 copies/ml; 2% were withdrawn/lost to follow-up by week 144. There was no evidence of benefit of PI/RAL over PI/NRTI on any efficacy or safety outcome at week 144. Good disease control was met by 67%, 67%, and 63% in PI/NRTI, PI/RAL, and PImono respectively (p=0.29). In PI/RAL and PI/NRTI intermediate-high level resistance to lopinavir was low; in PI/NRTI, NRTI resistance was low (<3.5%); 6.7% of PI/RAL were estimated to have intermediate-high level RAL resistance. In PI-mono, clinical and CD4 outcomes were similar to other groups, and VL suppression recovered substantially at week 144 (up from 61% <400 c/ml at week 96 to 78% at week 144).

Conclusion: PI/RAL was not superior to PI/NRTI at week 144. NRTI re-initiation led to good re-suppression in PI-mono. PI+2NRTIs remains the optimal regimen for rollout programme settings.

Background

Millions of adults and children in sub-Saharan Africa are now taking first line ART. Most research looking at second line treatment has used relatively short-term outcomes. Here we assess the long term efficacy and safety of PI based second line therapies.

Methods

1277 patients aged ≥12 years who met WHO-defined treatment failure criteria after >12 months on NNRTI-based first-line ART were randomised in an open-label trial in 14 sub-Saharan African sites. Patients were randomised to:

- bPI + 2/3 clinician-selected NRTIs (PI/NRTI),
- bPI plus RAL (400mg bd) (PI/RAL),
- bPI monotherapy (+RAL induction for first 12 weeks) (PI-mono). The DMC recommended this arm be re-intensified (after median follow-up 124 weeks): NRTIs were added in 94%; 6% switched to other regimens.

bPI was standardised in all arms to lopinavir/ritonavir, 400mg/100mg bd

Treatment was monitored clinically and by CD4 count. VL and resistance testing were done annually blinded, reviewed by the DMC.

The primary (composite) endpoint, good disease control, was defined as no new WHO stage 4 events or death after randomisation, and CD4 count >250 cells/mm3 and VL < 10,000 copies/ml (or >10,000 copies/ml without major/minor PI resistance mutations

Week 96 primary endpoint results (previously reported) showed PI/RAL was not superior to PI/NRTI, and that PI-mono was inferior to PI/NRTI.

Results

Results- Characteristics

426 were randomised to PI/NRTI, 433 to PI/RAL and 418 to PI-mono. Patients were 58% female, median age 37, baseline CD4=71 cells/mm^3 (92%<250 cells/mm^3), VL=69,782 copies/ml; 2% were withdrawn/lost to follow-up.

Results- Good disease control

The primary outcome of good HIV disease control was similar in the 3 arms at week 144: 67% PI/NRTI, 67% PI/RAL, 63% PI-mono, p=0.29

Table 1: Primary endpoint components at week 144

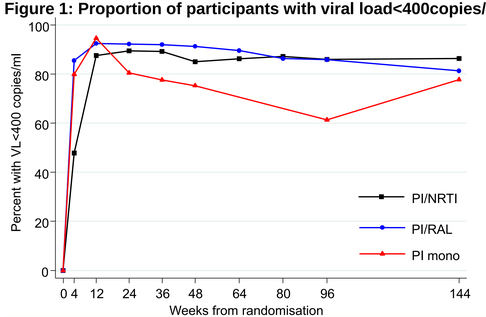
	PI/NRTI	PI/RAL	PI mono	Global P value
Good disease control	67%	67%	63%	0.29
Alive	90.1%	92.4%	92.6%	0.37
Alive and no new WHO stage 4 events	86.4%	88.9%	88.8%	0.57
CD4>250cells/mm^3	77%	77%	72%	0.15
VL<10,000 or no PI resistance mutations	98%	97%	94%	0.001

Results- Viral load

Suppression remained high in PI/NRTI (86% VL<400 copies/ml, 74% VL<50 copies/ml) and PI/RAL (81% VL<400 copies/ml, 72% VL<50 copies/ml). Suppression in PI-mono increased from week 96 to 144 (61% to 78% VL<400 copies/ml, 44% to 65% VL<50 copies/ml) following re-intensification.

Results- Viral load (cont)

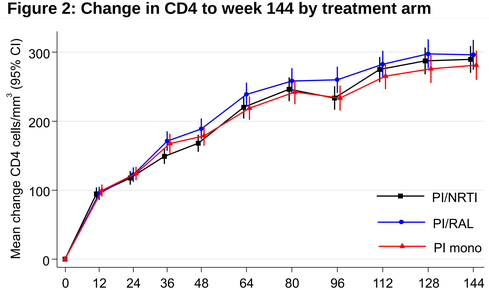
Figure 1: Proportion of participants with viral load<400copies/ml



Results- CD4

CD4 recovery was good in all arms. A substantial proportion (25%) of patients in all groups had not achieved a CD4>250cells/mm^3 up to 144 weeks on second line.

Figure 2: Change in CD4 to week 144 by treatment arm



Results- Resistance

Low levels of PI resistance were seen in those on PI/NRTI and PI/RAL, but higher levels in PI-mono. In PI/NRTI, NRTI resistance was low (<3.5%). 6.7% of PI/RAL were estimated to have intermediate-high level RAL resistance

Table 2: Prevalence of resistance by treatment arm

	PI/NRTI	PI/RAL	PI-mono
Int/high LPV resistance	2.4%	2.7%	11.0%
Int/high NRTI resistance (excl. 3TC/FTC)	3.4%	0.3%	2.5 %

Results- Adverse Events

Rates of adverse events were low throughout the trial and there was no difference between the arms.

Table 3: Prevalence of adverse events to week 144 by treatment arm

	PI/NRTI	PI/RAL	PI mono	Global P value
Grade 3 or 4 AEs	27.5%	27.3%	28.5%	0.93
Grade 4 AEs	15.0%	15.7%	15.8%	0.92
SAEs	26.5%	24.5%	23.7%	0.63

CONCLUSIONS

- **PI/RAL was not superior but was non-inferior to PI/NRTI at week 144 on all outcomes**
- **All regimens were well tolerated**
- **Re-introduction of NRTIs in the PI-mono arm led to good re-suppression of viral load**
- **PI (in this case LPV/r) + 2 NRTI remains the optimal strategy for rollout programmes**

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