Metabolic Profiles After Switch From Failing First-line ART in the SECOND-LINE Study

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Introduction

•Antiretroviral therapy (ART) is associated with unfavourable changes in metabolic parameters that increase cardiovascular (CV) risk.

• Dyslipidaemia has been reported to occur with use of protease inhibitors (PI) and thymidine-analogue nucleoside reverse transcriptase inhibitors (ta-NRTI; zidovudine [AZT]/stavudine[d4T]). Other N(t)RTIs such as tenofovir (TDF), integrase inhibitors (InSTI) and non-nucleoside reverse transcriptase inhibitors (NNRTI) have been associated with more favourable metabolic profiles.

•There is limited data on the metabolic changes associated with switch to a boosted-PI-containing second-line ART following virological failure of WHO-recommended first-line (NNRTI+2N(t)RTI) ART.

•SECOND-LINE was a 96-week open-label RCT including 541 HIV-1 infected adults who were randomized (1:1) to receive LPV/r with either 2-3N(t)RTI or RAL following virological failure of first-line NNRTI+2N(t)RTI.

•A subset of 210 patients underwent DXA-scans at weeks 0 , 48 and 96.

Method

•Participants were categorised in two ways (Figure 1):

- Firstly, according to their second-line ART regimen ('on-study group').
- Secondly, based on their first-line ART (TDF+3[F]TC + NNRTI or taNRTI + 3[F}TC + NNRTI) and their second-line ART regimens ('switch group')

•We analysed associations between on-study groups and switch groups and changes in fasted total cholesterol (TC), LDL cholesterol (LDL-c), HDL-c, TC/HDL-c ratio, triglycerides (TG) and blood-sugar (BSL), from baseline to week 96, adjusting for confounders.[1] Linear regression methods were used.

•We explored the correlations between changes in metabolic markers (TC, LDL-c, HDL-c, TC/HDL-c, TG and BSL) and changes in weight and body fat composition (total fat mass, total lean mass, trunk fat mass, trunk lean mass, limb fat mass, limb lean mass) from baseline to week 96 in the subset of participants enrolled in the SECOND-LINE DXA-scan substudy. Backwards-stepwise linear regression was used.

[1] Confounders were measured at baseline and all subsequent analyses adjusted for them. Confounders included: age, sex, ethnicity, weight, BMI, systolic blood pressure, diastolic blood pressure, waist/hip ratio, smoking, HIV disease stage, duration of HIV infection, CD4, CD8, viral load (log), duration of first-line ART, alcohol consumption, eGFR, hepatitis C antibody and use of lipid-lowering drugs.

Hypothesis

•We hypothesised that regimens containing thymidine analogues (ta-NRTIs; d4T or AZT) would be associated with less favourable lipid profiles than regimens containing TDF.

Results

Figure 1. Adjusted mean metabolic change (mmol/L) by <u>on-study group</u> [1]

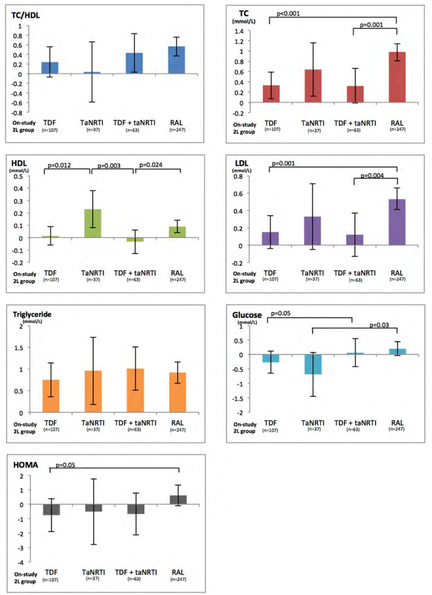


Figure 2. Adjusted mean metabolic change (mmol/L) by <u>switch group</u> [1]

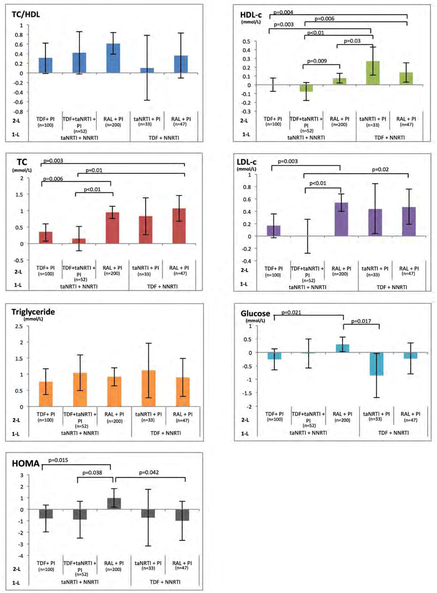
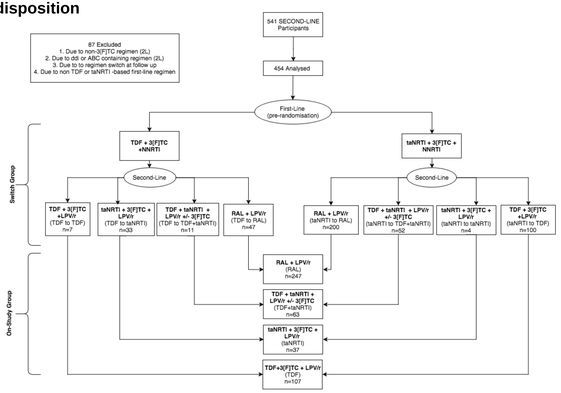


Figure 3. Participant disposition



Exploratory Component: Body composition changes

- Multivariate analysis found a one-kilogram increase in trunk fat mass from baseline to week 96 was associated with an:
  - increase in TC (adjusted mean change (aMC)=0.1mmol/L, 95%CI [0.03, 0.17], p=0.009)
  - increase in LDL-c (aMC=0.08mmol/L, 95%CI [0.03, 0.14], p=0.002)

Conclusion

•TDF-containing regimens did not demonstrate a more favourable metabolic profile when compared to taNRTI-containing regimens.

•Second-line N(t)RTI-sparing ART with RAL+LPV/r was associated with greater increases in all cholesterol fractions, with a stable TC/HDL-c ratio and statistically significant but clinically insignificant BSL changes.

•Described metabolic changes are unlikely to have much clinical significance in this relatively young population with a low prevalence of known CV risk factors, but may have greater clinical impact in older people living with HIV.

• Our findings are consistent with the findings of the parent SECOND-LINE study. Whilst there is comprehensive data regarding metabolic changes in first-line ART, further research is required to examine the effects of switching from first- to second-line ART.

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