TITLE

Metabolic profiles of individuals treated for HIV-1 infection on second-line antiretroviral therapy after switch from failing standard first-line ART in a randomised, controlled trial.

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RUNNING HEAD

Metabolic outcomes in the SECOND-LINE study

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Abstract

Background: To investigate metabolic changes associated with second-line antiretroviral therapy (ART) following virological failure of first-line ART.

Methods: SECOND-LINE was an open-label randomized controlled trial. Participants were randomized 1:1 to receive ritonavir-boosted lopinavir (LPV/r) with 2-3 nucleoside/nucleotide reverse transcriptase inhibitors (N(t)RTI-group) or raltegravir (RAL-group) Two hundred and ten participants had a dual energy X-ray absorptiometry (DXA)-scan at baseline, week 48 and 96. We categorized participants according to second-line ART backbone: 1. thymidine analogue (ta-NRTI)+lamivudine/emtricitabine (3[F]TC) [ta-NRTI group]; 2. tenofovir (TDF)+3[F]TC [TDF group]; 3. TDF+ta-NRTI+/-3[F]TC [TDF+ta-NRTI group]; 4. RAL. Changes in fasted total cholesterol, LDL-cholesterol, HDL-c, TC/HDL-cholesterol ratio, triglycerides and glucose from baseline to week 96 were examined. We explored the association between metabolic and DXA-assessed soft-tissue changes. Linear regression methods were used.

Results: We analyzed 454 participants. Participants in RAL group had greater TC increases TC (adjusted mean difference (aMD)=0.65, 95%CI 0.33, 0.96), LDL-c (aMD=0.38, 95%CI 0.15, 0.61) and glucose (aMD = 0.47, 95%CI -0.01, 0.92) compared to TDF group, and had greater increases in TC (aMD=0.65, 95%CI 0.28, 1.03), HDL-c (aMD=0.12, 95%CI 0.02, 0.23) and LDL-c (aMD=0.41, 95%CI 0.13, 0.69;) compared to TDF+ta-NRTI group. TC/HDL ratio and triglycerides increased in all groups without

significant differences between groups. A 1kg increase in trunk fat mass was associated with an increase in TC.

Conclusions: We observed metabolic changes of limited clinical significance in the relatively young population enrolled in this study. However, the metabolic changes observed may have greater clinical significance in older people living with HIV or those with concomitant cardiovascular risks.

Background

Antiretroviral therapy (ART) has been associated with unfavourable changes in lipid parameters that increase cardiovascular risk. Some data also suggests an association between ART, particularly some protease inhibitors (PI), and impaired glucose tolerance (1, 2). Confusing the interpretation is the fact that lipid changes may not be a direct consequence of ART but rather signify a return to health induced by successful ART and associated weight gain, with increase in body fat driving metabolic changes as found in the general population. This is supported by studies indicating that weight increase is correlated with increased CD4 count (3). A recent dual energy X-ray absorptiometry (DXA) -scan substudy of ACTG 5257 showed that darunavir/ritonavir (DRV/r), atazanavir/ritonavir (ATV/r) and raltegravir (RAL) (all combined with tenofovir [TDF]/ emtricitabine[FTC]) were associated with the same degree of visceral fat accumulation(4). The SECOND-LINE DXA substudy showed that participants on lopinavir/ritonavir (r/LPV)+RAL and those on r/LPV+ nucleoside/nucleotide reverse transcriptase inhibitors (N(t)RTIs) experienced similar increases in limb fat and total body and trunk fat mass over 48 weeks(5)**.**

Dyslipidemia has been reported to occur with use of thymidine analogue-NRTIs (ta-NRTI) (zidovudine [AZT] and stavudine [d4T]). Other N(t)RTIs, including TDF, have shown milder effects on metabolic parameters in comparison to ta-NRTIs. (6-10) TDF has also been associated with less metabolic disturbance compared to abacavir/lamivudine (ABC/3TC)(11-13). The ACTG5206 study (10) suggested that TDF has an independent effect on improving lipid profiles. Non high density lipoprotein

cholesterol (HDL-c), low density lipoprotein cholesterol (LDL-c) and total cholesterol (TC) decreased with addition of TDF to a stable ART regimen and a 'rebound' effect occurred when TDF was withdrawn. The lipid-lowering effect of TDF has been further supported by a recent RCT that found that addition of TDF/FTC to stable DRV/r or r/LPV regimens was associated with decreases in TC, LDL-c and HDL-c. (6)

The integrase inhibitor class has been associated with more favourable lipid profiles compared to older ART classes. Switching from non-nucleoside reverse-transcriptase inhibitors (NNRTI) or PI- based therapy to RAL-based therapies has been associated with improvements in lipid profiles(14-16). There have been similar findings in studies involving treatment-naïve patients, comparing RAL with efavirenz (EFV) and PI regimens. Other integrase inhibitors including dolutegravir (DTG) and elvitegravir (EVG) have also demonstrated milder effects on lipid profiles when compared to drugs of other classes (17-19). However, an RCT comparing EVG/cobicistat/FTC/TDF to ATV/r + FTC/TDF found that EVG-based therapy was associated with greater increase in TC, but less increase in TG when compared to the ATV/r arm. (20)

PIs have been consistently associated with lipid changes, in both monotherapy and switch studies (15, 16, 21, 22). The dyslipidemic effect of PIs is heavily influenced by the use of ritonavir as a booster, with regimens requiring higher dosage of ritonavir associated with greater dyslipidemia (23-25). Whilst NNRTIs have been less associated with lipid changes compared to other ART classes, studies have indicated that EFV has negative effects on lipid levels, whilst other NNRTIs including nevirapine

(NVP), etravine (ETV), rilpivirine (RPV) have been associated with beneficial increases in HDL-c and reductions in TC/HDL-c ratios (26-31).

Insulin resistance associated with HIV may result from increased visceral adipose tissue, an indirect effect of long-term ART. (2). Changes in glucose, insulin and homeostatic model assessment insulin resistance (HOMA-IR) have been associated with changes in body mass index (BMI), lean body mass, limb and trunk fat (32). However the extent to which increased visceral adipose tissue is an ART-incited pathology rather than a 'return-to-health' is debated. The recent results of the DXA-scan ACTG5257 substudy suggests that increased visceral adiposity is simply weight gain upon return-to-health as seen in the general population (4). [ADD email suggestion]

There is limited data investigating the metabolic changes associated with switches to boosted-PI containing second-line ART, following virological failure of World Health Organization (WHO)-recommended first-line ART. For first-line regimens, the new WHO recommendations (33) recommend EFV+TDF+ lamivudine or emtricitabine (3[F]TC) or Dolutegravir (DTG) + TDF/3[F]TC if EFV is found to be intolerable. For second-line regimens, WHO recommends boosted PI (LPV/r or ATV/r or DRV/r) + 2N(t)RTIs or boosted PI + RAL as an alternative.

Hypothesis

We hypothesized that second-line PI-containing ART regimens combined with ta-NRTIs would be associated with less favourable lipid profiles than regimens

containing TDF. We also hypothesised that the addition of TDF to taNRTI may have off-set some of the adverse lipid changes associated with taNRTI- regimens.

Methods

Main Study Design

SECOND-LINE was a 96-week open-label RCT including 541 HIV-1 infected adults at 37 sites located in 15 countries, who had evidence of virological failure (defined as plasma HIV viral load>500 copies per mL on two consecutive [≥7 days apart] occasions). Participants were randomized (1:1) to receive LPV/r with either 2-3N(t)RTI or RAL. N(t)RTI backbone selection was conducted by local investigators and was guided through pre-randomisation genotypic ART or by a simple algorithm (34). A subset of 210 patients in 8 sites from 5 countries (Argentina, India, Malaysia, Thailand, South Africa) underwent DXA scans to assess body composition changes at weeks 0 and 96 (5).

Study participants and categorization

For this post-hoc analysis participants were categorised in two ways (Figure 1):

1. Participants were categorized purely on the basis of their second-line ART group (on-study groups)

2. Participants were further categorized by both their first-line ART and their second-line ART regimens (switch groups) (Figure 1).

For the TDF + ta-NRTI on-study group, we combined participants who did (n=40/63 [63%]) and did not (n=23/63 [37%]) receive 3[F]TC. This was done similarly for switch groups containing second-line TDF + ta-NRTI +/- 3[F]TC + r/LPV (22/30 [67%] switching from taNRTI to taNRTI + TDF did not receive 3[F]TC; 1/10 [10%] switching

from TDF to taNRTI + TDF did not receive 3[F]TC). Sensitivity analysis conducted to compare the metabolic outcomes between the two groups indicated no clinically or statistically significant differences between the groups.

Participants who were on non-WHO recommended regimens, including non-3[F]TC and abacavir- and didanosine- containing regimens were excluded, as were those who switched regimens following initial second-line randomization. Groups with a database cell size ≤11 were included in analysis but were excluded from our report as small numbers would preclude meaningful and reliable results.

Data collection:

Fasting serum lipids and glucose were measured (in mmol/L) during protocol-specified visits at weeks 0, 4, 12, 24 and 48, 72 and 96. Homeostatic model assessment (HOMA) was calculated via electronic case report form. For the DXA-substudy population, DXA-scans were conducted at baseline, week 48 and week 96 on Lunar or Hologic scanners according to a standard protocol provided to all sites. (5)

Statistical Analysis

The primary study objective was to determine and compare the changes in TC/HDL-c ratio from baseline to week 96 by on-study groups. Secondary study objectives include descriptions of TC, HDL-c, LDL-c, triglyceride, glucose and HOMA changes from baseline to week 96 by on-study groups and switch groups.

Exploratory objectives included an assessment of the correlations between the changes in metabolic markers (TC/HDL-c, TC, HDL-c, LDL-c, triglyceride, glucose and HOMA) and changes in body composition (total fat mass, total lean mass, trunk fat mass, trunk lean mass, limb fat mass, limb lean mass, weight (all reported in kg), body mass index (BMI) (kg/m^2),and waist/hip ratio) from baseline to week 96 in the subset of participants enrolled in the SECOND-LINE DXA-scan substudy.

Analyses included all randomized participants who received at least one dose of study medication. Missing data was excluded from analysis. At baseline, there were 4 participants (0.9%) with missing data for TC/HDL-c ratio, TC, HDL-c, triglyceride and glucose, 12 (2.6%) missing values for LDL-c and 5 (1.1%) missing values for HOMA. At week 96, there were 39 (8.6%) participants with missing data for TC/HDL-c ratio, TC, HDL-c, triglyceride, glucose and HOMA and 50 (11%) missing values for LDL-c.

The primary endpoint of the SECOND-LINE study was the proportion of participants with a plasma HIV-1 RNA of less than 200 copies per ml at week 48 and has previously been reported (34). Sample size calculations were based on the primary endpoint.

Linear regression methods were used to compare adjusted mean changes from baseline to week 96 in metabolic parameters between on-study group and switch group. Due to the non-randomised selection of the N(t)RTI regimens in the LPV/r + 2-3 N(t)RTI arm, all analyses were adjusted a priori for measured confounders. These 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, (log) viral load, duration of first-line ART, alcohol consumption, estimated glomerular filtration rate (eGFR), hepatitis C antibody and use of lipid-lowering drugs. For the exploratory DXA component of our study, backwards-stepwise linear regression was used to assess the correlation between body composition change and metabolic change from baseline to week 96. Any body composition correlate with $p<0.1$ in univariate analysis was included in the multivariate model.

Results

Of the 541 participants who formed the analysis population for the primary study, 454 meet the criteria for analysis in this sub-study (Figure 1). Reason for exclusion included use of non-3[F]TC regimen in second-line, didanosine- or ABC-containing second-line regimen, second-line regimen switch at follow-up and use of a non-TDF- or taNRTI- containing first-line regimen (see figure 1).

On-study group

Compared to the overall study population, there were a greater proportion of women in the TDF+taNRTI group (60.3%) (Table 1). Compared to the overall population, there was a greater proportion of Africans (81.1% v 39.2%) in the taNRTI group, as well as lower median (IQR) baseline LDL-c (1.7 (1.4-2.2) vs 2.5 (1.9, 3.0)), duration of infection (2.7 years (2.0-5.1) vs 6.1 (3.7-8.7)), duration of pre-randomisation cART (2.2 (1.5-4.3) vs 3.5 (2.0-5.7), baseline CD4 (64 (41-200) vs 199 (101-296)) and baseline CD8 counts (536 (310-844) vs 800 (533.5-1095). Other variables were generally well balanced.

TC/HDL ratio increased in all on-study groups, however there were no statistically significant differences between the groups (Figure 2). Similarly, triglyceride increased in all on-study groups, with no statistically significant differences between groups. Compared to participants receiving TDF+taNRTI, participants receiving second-line RAL experienced greater increases in TC (adjusted mean difference between groups

(aMD)=0.65, 95%CI [0.28, 1.03], p<0.001), LDL-c (aMD=0.41, 95%CI [0.13, 0.69], p=0.004) and HDL (aMD=0.12, 95%CI [0.02, 0.23], p=0.024). Participants receiving RAL also saw a greater increase in TC (aMD=0.65, 95%CI [0.33, 0.96], p<0.001), LDL-c (aMD=0.38, 95%CI [0.15, 0.61], p=0.001) and HOMA (aMD=1.37, 95%CI[0.01, 2.73] p=0.05) when compared to those receiving TDF, and a greater increase in glucose compared to those receiving TDF (aMD=0.47, 95%CI[-0.01, 0.92], p=0.05) and taNRTIs (aMD=0.89, 95%CI [0.09, 1.70], p=0.03). Participants receiving taNRTI experienced greater increases in HDL when compared to those receiving TDF (aMD= 0.22, 95%CI [0.05, 0.39], p=0.012) and those receiving TDF+taNRTI (aMD=0.27, 95%CI [0.01, 0.44], p=0.003).

Switch group

Compared to the overall study population, there was a greater proportion of males in the taNRTI to TDF group (66% vs 54%) and a greater proportion of females in the taNRTI to taNRTI+TDF group (62% vs 46%) (Table 2). There were a greater proportion of Africans in the TDF to taNRTI group (85%) compared to the overall population (39%). A greater proportion of the taNRTI to taNRTI+TDF group were overweight or obese (BMI>25) (50%), compared to the overall population (36%). For participants in the TDF to taNRTI group, there were lower median (IQR) baseline levels of LDL-c (median, IQR) (1.7 (1.3-2.1) vs 2.5 (1.9-3.0)), duration of HIV infection (3.1 years (2.0-5.1) vs 6.1 (3.7-8.7)), duration of cART (2.2 (1.5-4.3) vs 3.5 (2.0-5.7)), baseline CD4 (62 (35-176) vs 199 (101-296)) and baseline CD8 counts (495 (300-778) vs 800 (533.5-1095)), when compared to the overall population. Other variables were well balanced.

TC/HDL levels increased in all switch groups, however there were no significant differences between groups (Figure 3). Similarly, triglyceride increased in all switch groups, with no statistically significant differences between switch groups.

Participants in the TDF to RAL switch group experienced greater increases in HDL (aMD=0.14, 95%CI [-0.01, 0.28], p=0.004) and TC (aMD=0.73, 95%CI [0.25, 1.21], p=0.003) when compared to those switching from taNRTI to TDF. Participants switching from TDF to RAL also experienced greater increases in HDL(aMD=0.22, 95%CI [0.06, 0.37], p=0.006), TC (aMD=0.92, 95%CI [0.37, 1.47], p<0.01) and LDL-c (aMD=0.48, 95%CI [0.07, 0.89], p=0.02) when compared to those switching from taNRTI to TDF+taNRTI, and greater increase in HOMA (aMD=1.99, 95%CI [0.07, 3.90], p=0.04) when compared to those switching from taNRTI to RAL.

Participants switching from taNRTI to RAL experienced greater increase in HDL (aMD=0.15, 95%CI [0.04, 0.27], p=0.009), TC (aMD=0.80, 95%CI [0.39, 1.21], p<0.001), LDL-c(aMD=0.55, [95%CI 0.24, 0.85], p<0.001) and HOMA (aMD=1.88, 95%CI [0.10, 3.67], p=0.038) when compared to those switching from taNRTI to TDF+taNRTI. However, those switching from TDF to taNRTI experienced greater increase in HDL **(**aMD=0.19, [95%CI 0.02, 0.36], p=0.03) compared to taNRTI to RAL. Participants switched from taNRTI to RAL also saw greater increase in TC (aMD=0.61, 95%CI [0.28, 0.94], p<0.001)), LDL-c (aMD=0.38, 95%CI [0.13, 0.62] p=0.003), glucose (aMD=0.56, 95%CI [0.08, 1.04], p=0.02) and HOMA (aMD=1.78, 95%CI [0.35, 3.2], p=0.015) when compared to those switched from taNRTI to TDF.

Participants switched from TDF to taNRTI experienced greater increases in HDL-c when compared to those switched from taNRTI to TDF+taNRTI (aMD=0.35, 95%CI[0.15, 0.54], p<0.001) and taNRTI to TDF (aMD=0.27, 95%CI [0.09, 0.45], p=0.003).

Exploratory Component Results

The exploratory component of this study included the 210 patients enrolled in the DXA sub-study of the Second-Line study. (5) This population had a greater proportion of females (52%) compared to the primary study (46%). Multivariate analysis found no statistically significant correlations between body composition changes and baseline to week 96 changes in TC/HDL-c ratio, HDL-c, triglyceride, glucose and HOMA. 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) and an increase in LDL-c (aMC=0.08 mmol/L, 95%CI [0.03, 0.14], p=0.002). In univariate analysis, a one-kilogram increase in trunk fat mass from baseline to week 48 was not found to be significantly associated with changes in HDL-c (aMC= -0.01, 95%CI [-0.038, 0.012], p=0.3) or triglyceride levels (aMC=0.03, 95%CI [-0.06, 0.11], p=0.6).

Discussion

In this study, 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 glucose changes. These findings were consistent with those of the parent study which found the RAL group experienced increases in TC, HDL-c and LDL-c when compared to r/LPV + 2-3 N(t)RTI (34). Additionally, switches to second-line r/LPV + RAL regardless of first-line ART composition was associated with greater increases in all cholesterol fractions compared to switches to second-line N(t)RTI regimens.

Contrary to our hypothesis, TDF-containing second-line ART regimens did not demonstrate a more favourable metabolic profile when compared to taNRTI-containing regimens. The taNRTI group experienced greater beneficial HDL-c increases compared to the TDF and TDF+taNRTI groups, but there were no statistically significant differences in the TC/HDL-c ratio between the groups. As the population studied were individuals who had failed first-line ART, the regaining of virological control could be associated with an increase in HDL-c.

A continuing challenge of investigating the metabolic effects in combination ART is the difficulty of distinguishing between the effects of individual drugs. Whilst our study found RAL to be associated with greater metabolic changes, prior studies have found that integrase inhibitors have minimal effects on metabolic profiles compared with N(t)RTIs and PIs (17, 19, 35). However, these studies have been conducted in

ART-naïve participants or switch studies with virological suppression and therefore the results are not directly comparable to those in our study of viremic participants. It is likely that the unfavourable metabolic profile associated with the N(t)RTI-sparing arm reflects the unopposed dyslipidemic effects of r/LPV rather than a specific contribution of RAL per se (22, 36, 37).

The metabolic changes seen in this study could possibly be an effect of switching from NNRTI-based regimens to PI-based regimens. Ritonavir-boosted lopinavir has well known effects on serum lipid levels. There is limited data from studies comparing NNRTI-based to PI-based therapy and most switch studies examine the metabolic effects of switching from a PI-based therapy to PI-sparing therapy. The 2-LADY (38) and EARNEST (39) studies have explored efficacy and safety of second-line antiretroviral regimens. However they have not reported metabolic changes. As WHO recommends a switch from first-line NNRTI-based regimens to second-line PI-based regimens with sequencing of the N(t)RTIs, our study provides valuable information regarding the expected metabolic effects of this common regimen switch (33).

We have previously examined 10-year cardiovascular disease risk (CVD) in the SECOND-LINE DXA-subset population and found little change in CVD risk from baseline to week 48 despite increases in TC, LDL-c, triglyceride and TC/HDL-c ratio (5). The relatively young population and low prevalence of other known CVD risk factors such as smoking, hypertension and Type II Diabetes Mellitus indicate the ART-related lipid changes experienced during this study are unlikely to have great

clinical significance in this population. However, the described metabolic changes may have greater clinical impact later in this population and in older populations with greater prevalence of CVD risk factors and comorbidities.

This study consisted of a relatively large and ethnically diverse population, with a high proportion of women. Sampling conducted in multiple sites across a variety of low- to middle- income countries allows our findings to be applicable to a broad population of people living with HIV worldwide.

This study was limited by the fact that the selection of N(t)RTI regimen in the 2-3 N(t)RTI + LPV/r was non-randomised. We adjusted for this by considering relevant confounders that may have influenced clinician choice. However, there may be other unknown confounders for which we are unable to adjust. The study took advantage of an opportunity presented by the conduct of a randomised controlled trial designed to assess the efficacy of an N(t)RTI-sparing ART as second-line therapy as opposed to a standard WHO-recommended N(t)RTI-containing therapy. As a consequence the study was not powered to detect specific metabolic differences between arms and therefore Type II errors may have been made. Other limitations include small data cells in some instances that were excluded due to unreliability. Additionally, some participants in the parent SECOND-LINE study were excluded due to non-WHO-recommended drugs (e.g. abacavir, didanosine) as it was believed they would not add valuable information for the purpose of this study.

Conclusion

Our study explored the metabolic changes associated with WHO –recommended first-line to second-line N(t)RTI-containing or –sparing antiretroviral therapy switch. Contrary to our hypothesis, TDF-containing second-line regimens were not found to demonstrate more favourable lipid changes compared to taNRTI regimens. Management of serious non-AIDs events including dyslipidemia and consequently cardiovascular disease have become a crucial component of HIV management. Thus identifying and understanding the ART-induced metabolic changes is important. Our findings overall were expected and are in concordance with the findings of the parent SECOND-LINE study. Further research is required to examine the effects of switching from first-line to second-line WHO –recommended ART regimens, particularly as a substantial increase in the need for second-line drugs is predicted during the next few years (40).

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Author Contributions

This study was conceived by Amanda H. Yao, Cecilia L. Moore, Mark A. Boyd and David A. Cooper.

All authors contributed to the statistical analysis plan.

Amanda H. Yao and Cecilia L. Moore carried out statistical analysis.

Amanda H. Yao wrote the first draft of the report with supervision from Cecilia L. Moore and Mark A. Boyd.

All authors contributed to the final revision of the report submitted for peer-review.

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Tables

Table 1 – Baseline characteristics by on-study 2nd-line ART group

Variable	All	TDF	taNRTI (AZT/d4T)	TDF + taNRTI	RAL
Number of patients (n)	454	107	37	63	247
Demographic					
Sex					
Male (n, %)	245 (54%)	71 (66.4%)	18 (48.7%)	25 (39.7%)	131 (53.0%)
Female (n, %)	209 (46%)	36 (33.6%)	19 (50%)	38 (60.3%)	116 (46.0%)
Age	38.6 (32.5-44.4)	38.9 (32.9-45.7)	34.7 (32.4-40.8)	38.0 (34.6-42.8)	38.8 (32.3-44.5)
Ethnicity					
Caucasian (n, %)	33 (7.3%)	2 (1.9%)	0 (0%)	10 (15.9%)	21 (8.5%)
Asian (n, %)	189 (41.6%)	62 (57.9%)	5 (13.5%)	16 (25.4%)	106 (42.9%)
Hispanic (n, %)	54 (11.9%)	9 (8.4%)	2 (5.4%)	10 (15.9%)	33 (13.4%)
African (n, %)	178 (39.2%)	34 (31.8%)	30 (81.1%)	27 (42.9%)	87 (35.2%)
Clinical					
Weight (kg)	63 (55.5-73)	61.4 (55.0-70.7)	61.0 (55.5-68)	64.6 (56.8-81.5)	63.3 (55-71.6)
BMI (kg/m^2)	23.2 (20.6-26.5)	23.1 (19.6-25.6)	22.5 (20.3-25.9)	24.5 (21.3-28.2)	23.4 (20.7-26.3)
BP (mmHg)					
Systolic	117 (108-126)	120 (108-132)	110 (100-118)	120 (111-123)	115 (107-125)
Diastolic	74 (70-80)	78 (70-85)	70 (67-80)	75 (70-82)	73 (70-80)
Waist/Hip Ratio	0.89 (0.84-0.95)	0.89 (0.84-0.94)	0.91 (0.85-0.95)	0.87 (0.83-0.95)	0.90 (0.84-0.95)
Metabolic markers (fasting)					
Total Cholesterol (mmol/L)	4.4 (3.8-5.1)	4.5 (3.9-5.2)	4.5 (3.5-5.1)	4.3 (3.5-5.0)	4.4 (3.8-5.1)
Triglycerides (mmol/L)	1.3 (0.9-1.9)	1.3 (0.9-2.0)	1.4 (1.0-1.9)	1.2 (0.9-1.8)	1.3 (0.9-1.9)
HDL-C (mmol/L)	1.1 (0.9-1.4)	1.1 (0.9-1.3)	1.2 (1.0-1.5)	1.1 (0.9-1.5)	1.1 (0.9-1.4)
LDL-C (mmol/L)	2.5 (1.9-3.0)	2.6 (2.2-3.2)	1.7 (1.4-2.2)	2.4 (1.9-3.1)	2.5 (1.9-3.0)
TC/HDL Ratio	3.9 (3.2-4.8)	4.2 (3.5-5)	3.8 (3.2-4.3)	3.4 (2.9-4.2)	3.9 (3.2-4.9)
Glucose (mmol/L)	4.8 (4.4-5.2)	4.8 (4.4-5.2)	4.7 (4.5-5.3)	4.8 (4.3-5.1)	4.8 (4.4-5.3)
Insulin (mU/L)	7.9 (5.0-14.0)	7.0 (4.0-14.0)	7.2 (4.50-13.00)	7.5 (5.4-12.3)	8 (5-14.1)
HOMA-IR	1.6 (1.0-3.1)	1.6 (0.9-3.2)	1.6 (0.9-2.9)	1.5 (1.1-2.8)	1.7 (1.0-3.2)
HIV and cART history					
Duration of infection (years)	6.1 (3.7-8.7)	6.5 (4.5-8.8)	2.7 (2.0-5.1)	7.0 (4.2-9.9)	6.2 (3.7-8.9)
HIV disease stage					

Category A	172 (37.9%)	43(40.2%)	10 (27.0%)	31 (49.2%)	88 (35.6%)
Category B	70 (15.4%)	11 (10.3%)	9 (24.3%)	8 (12.7%)	42 (17.0%)
Category C	212 (46.7%)	53 (49.5%)	18 (48.7%)	24 (38.1%)	117 (47.4%)
CD4 Count (cells/µL)	199 (101-296)	207 (108-293)	64 (41-200)	223 (135-315)	202 (109-311)
CD8 Count (cells/µL)	800 (533.5-1095)	849 (567-1135)	536 (310-844)	721 (478-948)	812 (569-1126)
Log 10 HIV RNA level (copies/mL)	4.2 (3.6-4.8)	4.4 (3.8-5.0)	4.5 (3.9-5.0)	4.0 (3.5-4.4)	4.2 (3.6-4.8)
cART duration pre-randomisation (years)	3.5 (2.0-5.7)	3.4 (2.1-5.4)	2.2 (1.5-4.3)	3.8 (2.1-6.0)	3.7 (2.2-5.8)
Other relevant risk factors/medical history					
Alcohol consumption					
2 drinks a day or less	442 (97.4%)	106 (99.1%)	36 (97.3%)	58 (92.1%)	242 (98.0%)
More than 2 drinks a day	12 (2.6%)	1 (0.9%)	1 (2.7%)	5 (7.9%)	5 (2.0%)
Smoking					
Currently (n, %)	70 (15.4%)	19 (17.8%)	3 (8.1%)	12 (19.1%)	36 (14.6%)
Recent (n, %)	19 (4.2%)	5 (4.7%)	0	0	14 (5.7%)
Past (n, %)	75 (16.5%)	15 (14.0%)	10 (27.0%)	10 (15.9%)	40 (16.2%)
Never (n, %)	290 (63.9%)	68 (63.6%)	24 (64.9%)	41 (65.1%)	157 (63.6%)
Use of lipid-lowering drugs					
No (n, %)	382 (84.1%)	89 (83.2%)	36 (97.3%)	59 (93.7%)	198 (80.2%)
Yes (n,%)	72 (15.9%)	18 (16.8%)	1 (2.7%)	4 (6.4%)	49 (19.8%)

Table 2 - Baseline characteristics by 1L to 2L treatment switch group

Variable	All	taNRTI (AZT/d4T) To TDF	taNRTI to taNRTI + TDF	taNRTI to RAL	TDF To taNRTI	TDF To RAL
Number of patients (n)	454	100 (22.0%)	52 (11.5%)	200 (44.1%)	33 (7.3%)	47 (10.4%)
Demographics						
Sex						
Male	245 (54%)	66 (66%)	20 (38.5%)	107 (53.5%)	17 (51.5%)	24 (51.1%)
Female	209 (46%)	34 (34%)	32 (61.5%)	93 (46.5%)	16 (48.5%)	23 (48.9%)
Age	38.6 (32.5-44.4)	39.6 (33.2-45.8)	38.0 (34.6-43.2)	39.0 (32.2-44.5)	35.0 (33.1-40.8)	37.8 (32.3-44.5)
Ethnicity						
Caucasian	33 (7.3%)	2 (2.0%)	8 (15.4%)	20 (10.0%)	0 (0%)	1 (2.1%)
Asian	189 (41.6%)	57 (57.0%)	14 (26.9%)	83 (41.5%)	5 (15.2%)	23 (48.9%)
Hispanic	54 (11.9%)	9 (9.0%)	10 (19.2%)	30 (15.0%)	0 (0%)	3 (6.4%)
African	178 (39.2%)	32 (32.0%)	20 (38.5%)	67 (33.5%)	28 (84.9%)	20 (42.6%)
Clinical						
Weight (kg)	63 (55.5-73)	61.7 (54.5-70.4)	64.8 (56.8-79.5)	64.6 (55.7-74.1)	60.4 (55-67)	60 (54-65.4)
BMI (kg/m^2)	23.2 (20.6-26.5)	22.9 (19.6-25.5)	25.1 (21.1-28.3)	23.4 (21.0-27.4)	21.1 (20.3-25.2)	22.9 (19.7-24.4)
BP (mmHg)						
Systolic	117 (108-126)	119.5 (107-132)	120 (112-123)	117.5 (109-127)	110 (100-118)	110 (100-115)
Diastolic	74 (70-80)	78 (70-85.5)	75 (70-81).5	75 (70-80)	70 (70-80)	70 (70-80)
Waist/Hip Ratio	0.89 (0.84-0.95)	0.89 (0.84-0.94)	0.90 (0.83-0.96)	0.89 (0.84-0.95)	0.91 (0.85-0.95)	0.90 (0.84-0.97)
Metabolic markers (fasting)						
Total Cholesterol (mmol/L)	4.4 (3.8-5.1)	4.5 (3.9-5.2)	4.3 (3.7-5.3)	4.3 (3.8-5.2)	4.5 (3.7-5.1)	4.5 (3.9-4.9)
Triglycerides (mmol/L)	1.3 (0.9-1.9)	1.4 (0.9-2.0)	1.2 (0.9-1.9)	1.3 (0.9-2.0)	1.4 (1.0-1.9)	1.4 (0.9-1.9)
HDL-C (mmol/L)	1.1 (0.9-1.4)	1.1 (0.9-1.4)	1.2 (1.0-1.6)	1.1 (0.9-1.4)	1.2 (1.0-1.5)	1.1 (0.9-1.3)
LDL-C (mmol/L)	2.5 (1.9-3.0)	2.7 (2.2-3.2)	2.4 (1.9-3.2)	2.5 (2.0-3.0)	1.7 (1.3-2.1)	2.4 (1.6-2.8)
TC/HDL Ratio	3.9 (3.2-4.8)	4.2 (3.5-5.0)	3.4 (2.8-4.1)	3.9 (3.1-4.9)	3.8 (3.2-4.3)	4 (3.4-4.7)
Glucose (mmol/L)	4.8 (4.4-5.2)	4.8 (4.4-5.2)	4.7 (4.3-5.1)	4.8 (4.4-5.3)	4.9 (4.5-5.4)	4.9 (4.7-5.4)
Insulin (mU/L)	7.9 (5.0-14.0)	7.0 (4.7-14.0)	7.9 (5.8-13.0)	8.0 (5.0-14.5)	6.1 (3.5-12.5)	7.5 (4.0-12)

HOMA-IR	1.6 (1.0-3.1)	1.6 (0.9-3.1)	1.6 (1.1-3.0)	1.7 (1.0-3.3)	1.4 (0.8-2.8)	1.6 (0.9-3.0)
HIV & cART History						
Duration of infection (years)	6.1 (3.7-8.7)	6.6 (4.6-8.9)	7.0 (4.4-9.4)	6.5 (4.0-9.8)	3.1 (2.0-5.1)	4.6 (2.8-7.4)
HIV disease stage						
Category A	172 (37.9%)	42 (42%)	29 (55.8%)	74 (37%)	8 (24.2%)	14 (29.8%)
Category B	70 (15.4%)	10 (10%)	7 (13.5%)	31 (15.5%)	9 (27.3%)	11 (23.4%)
Category C	212 (46.7%)	48 (48%)	16 (30.8%)	95 (47.5%)	16 (48.5%)	22 (46.8%)
CD4 Count (cells/µL)	199 (101-296)	207 (115-291)	253 (177-324)	218 (119-323)	62 (35-176)	144 (56-243)
CD8 Count (cells/µL)	800 (533.5-1095)	853.5 (600-1138)	773 (566-971)	820 (593-1141)	495 (300-778)	723 (463-1092)
Log 10 HIV RNA level (copies/mL)	4.2 (3.6-4.8)	4.4 (3.7-5.0)	3.9 (3.3-4.3)	4.2 (3.5-4.7)	4.5 (3.9-5.1)	4.4 (3.7-5.3)
cART duration pre-randomisation	3.5 (2.0-5.7)	3.4 (2.1-5.3)	4.0 (2.2-6.0)	3.9 (2.5-5.9)	2.2 (1.5-4.3)	3.3 (1.3-5.0)
Other Relevant Risk Factors/Medical History						
Alcohol consumption (per day)						
≤ 2 drinks	442 (97.4%)	99 (99%)	50 (96.2%)	195 (97.5%)	32 (97%)	47 (100%)
>2 drinks	12 (2.6%)	1 (1%)	2 (3.9%)	5 (2.5%)	1 (3%)	0 (0%)
Smoking						
Currently	70 (15.4%)	19 (19%)	10 (19.2%)	32 (16.0%)	3 (9.1%)	4 (8.5%)
Recent	19 (4.2%)	5 (5%)	0 (0%)	12 (6.0%)	0 (0%)	2 (4.3%)
Past	75 (16.5%)	14 (14%)	8 (15.4%)	33 (16.5%)	10 (30.3%)	7 (14.9%)
Never	290 (63.9%)	62 (62%)	384 (65.4%)	123 (61.5%)	20 (60.6%)	34 (72.3%)
Lipid lowering drugs						
No	382 (84.1%)	83 (83%)	48 (92.3%)	159 (79.5%)	32 (97.0%)	39 (83%)
Yes	72 (15.9%)	17 (17%)	4 (7.7%)	41 (20.5%)	1 (3.0%)	8 (17%)

Figure 1: Participant disposition

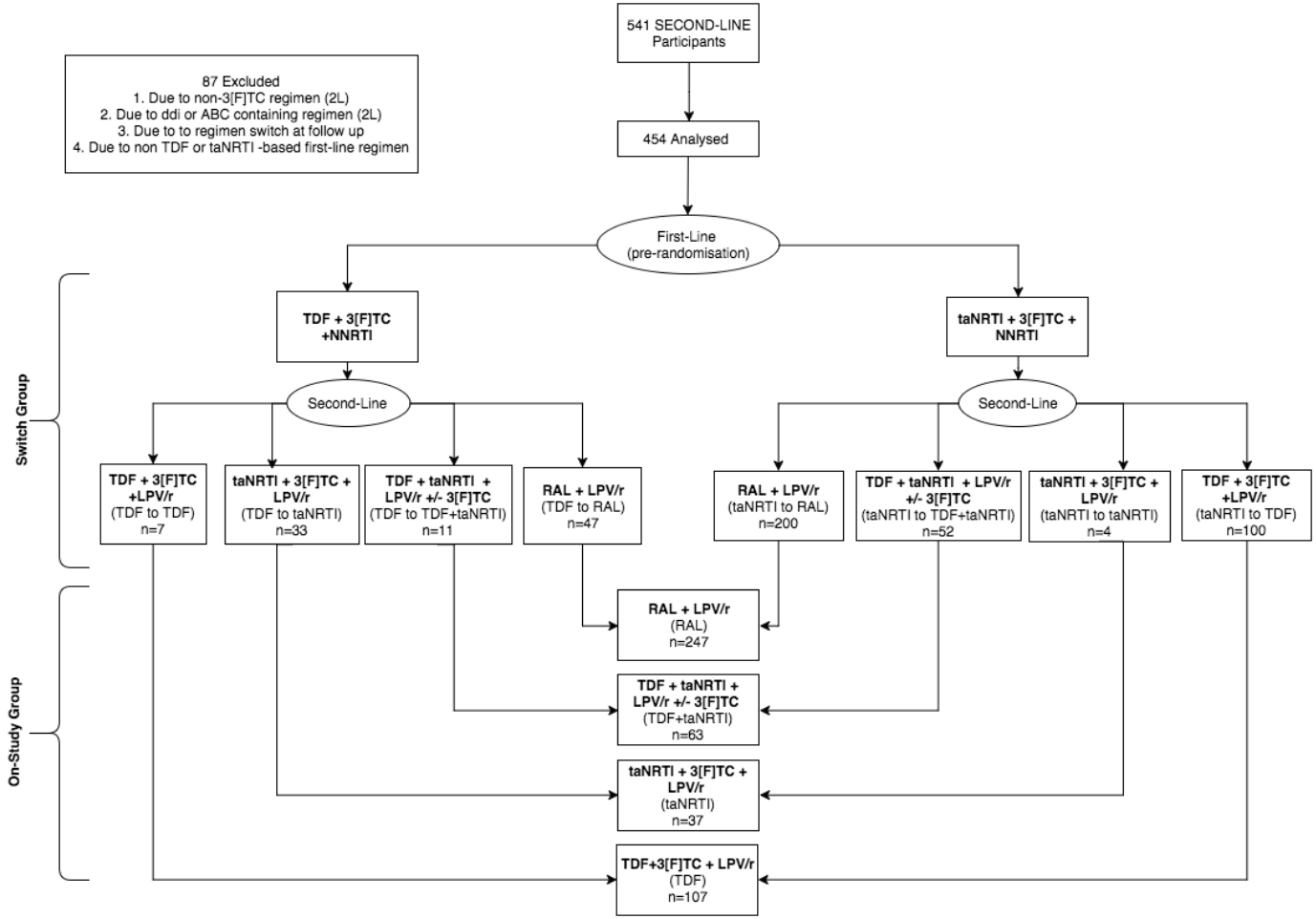

Figure 2: Adjusted mean metabolic change, by on-study 2nd line ART Group

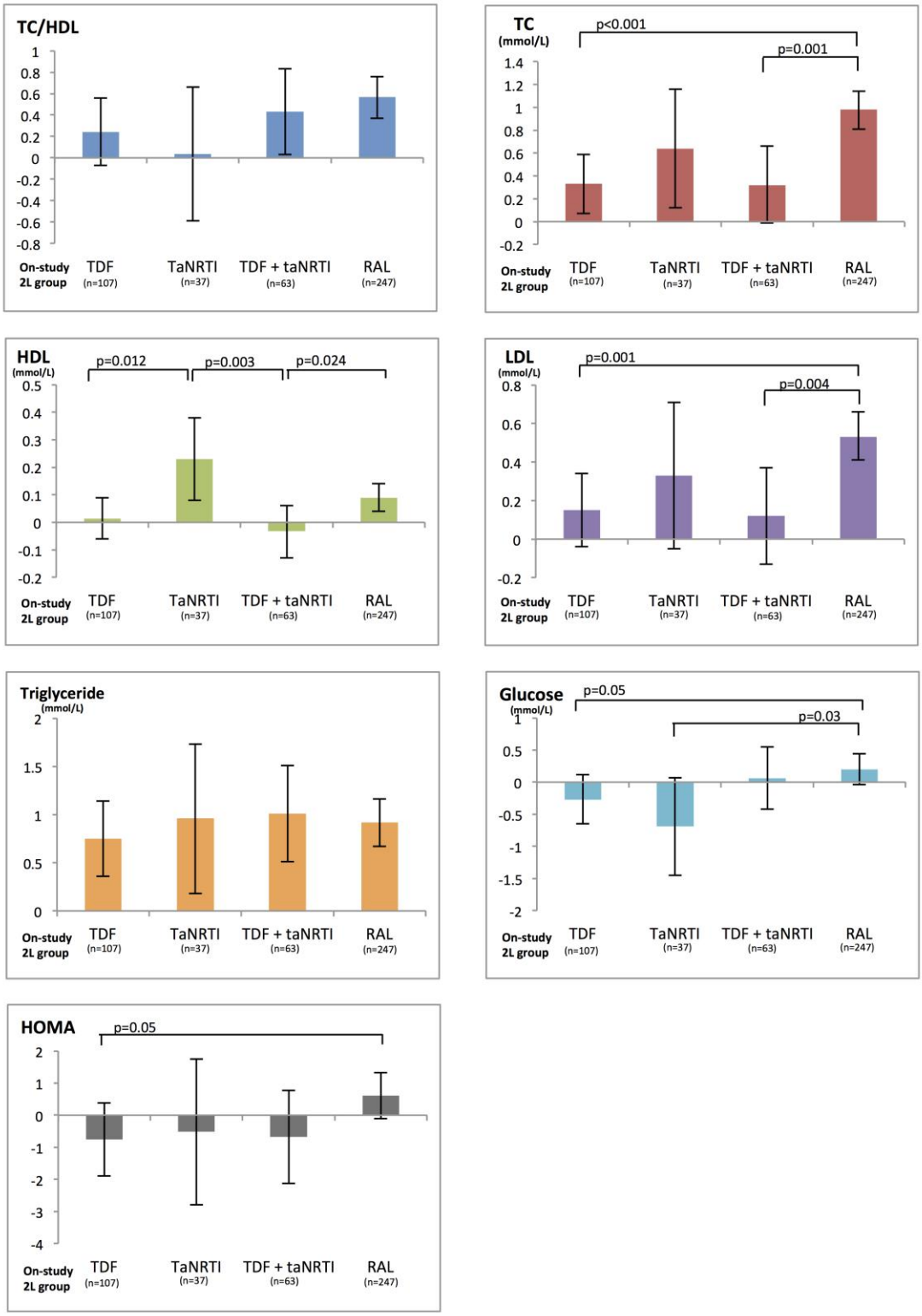

Figure 3 : Adjusted mean metabolic change, by 1st-line to 2nd-line switch group