

**Background:** Two once-daily, dual-nucleoside, fixed-dose-combination (FDC) tablets are used for adult HIV-1 infection: tenofovir/emtricitabine 300mg (TDF-FTC) and abacavir/lamivudine 300mg (ABC-3TC). While FDC is more effective and safe in HIV-1 treatment.

**Methods:** We conducted a randomized, controlled trial over 96 weeks. Participants were randomized to receive either TDF-FTC or ABC-3TC. The primary endpoint was the proportion of participants who achieved HIV RNA <50 copies/mL plasma at week 96. Secondary endpoints included time to virological failure, defined by repeat viral load >400 copies/mL plasma by intention-to-treat, discontinuation of either treatment, or death. We also assessed serious non-AIDS events, metabolic parameters and body composition (bone mineral density, BMD). We used exact statistics for differences in proportions, T-tests to compare means and Cox regression for hazard ratios for ABC-3TC/FTC HR (95% CI).

**Results:** 360 participants were randomized from January to August 2006. Key baseline characteristics of the 307 treated participants: mean age 40 years, 50% male, mean CD4 count 512 cells/mm<sup>3</sup>, mean HIV RNA >50 copies/mL plasma 19.7 copies/mL, mean CD4 count <350 cells/mm<sup>3</sup> 17%, mean CD4 count <200 cells/mm<sup>3</sup> 7%, mean CD4 count <150 cells/mm<sup>3</sup> 3%, mean CD4 count <100 cells/mm<sup>3</sup> 1%. We used exact statistics for differences in proportions, T-tests to compare means and Cox regression for hazard ratios for ABC-3TC/FTC HR (95% CI).



# SIMPLIFICATION WITH FIXED-DOSE TENOFOVIR-EMTRICITABINE OR ABACAVIR-LAMIVUDINE IN ADULTS WITH SUPPRESSED HIV REPLICATION (THE STEAL STUDY): A RANDOMIZED, OPEN-LABEL, 96-WEEK, NON-INFERIORITY TRIAL



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## Introduction

- Two once-daily, dual nucleoside analogue, reverse transcriptase inhibitor (NRTI), fixed-dose-combination (FDC) tablets available:
  - \* tenofovir 300mg-emtricitabine 200mg (TDF-FTC)
  - \* abacavir 600mg-lamivudine 300mg (ABC-3TC)
- Which FDC is more effective and safe is uncertain.
- We hypothesized that switching to TDF-FTC would be virologically non-inferior to ABC-3TC over 96 weeks in HIV-infected adults with sustained suppression of HIV replication, but that TDF-FTC and ABC-3TC would have different safety profiles.

## Methods

- Eligible participants randomly allocated 1:1 to continue their current NNRTI and/or PI and switch their NRTIs to either TDF-FTC or ABC-3TC.
- Key eligibility criteria:
  - \* Age ≥ 18 years
  - \* on stable zNRTI + NNRTI or PI ART ≥ 12 weeks
  - \* HIV RNA <50 copies/mL plasma ≥ 12 weeks
  - \* glomerular filtration rate (GFR) ≥ 70mL/min/1.73m<sup>2</sup>
  - \* creatinine clearance ≥ 50 mL/min
  - \* HLA-B\*5701 negative (unless already on ABC)
  - \* no prior hypersensitivity, intolerance or failure to study drugs
  - \* no prior exposure to either study FDC drugs
  - \* not on un-boosted atazanavir
  - \* no previous non-traumatic fracture
- Study visits at 0, 4, 12, 24, 36, 48, 60, 72, 84 and 96 weeks.
- At each visit adverse events, concomitant medications, adherence, weight, biochemistry and HIV viral load were assessed; every 12 weeks blood count, liver function tests and CD4 count performed and blood stored; every 24 weeks quality of life (SF-8) and fasting metabolic measures conducted; every 48 weeks body composition measured by dual-energy x-ray absorptiometry
- Primary endpoint was virological failure, defined by repeat viral load >400 copies/mL by intention-to-treat, missing=failure (ITTM=F) analysis. Secondary endpoints (ITT) included death, AIDS, serious non-AIDS events, metabolic parameters and body composition (bone/soft-tissue; ITT-LOCF).
- Exact statistics were used for differences in proportions, T-tests to compare means and Cox regression for hazard ratios. A sample of 175 participants per group yielded a 90% probability to detect a two-tailed 95% confidence interval of 15% around a 0% difference between treatment arms in virological failure rates.

## Results

Figure 1: Participant Disposition

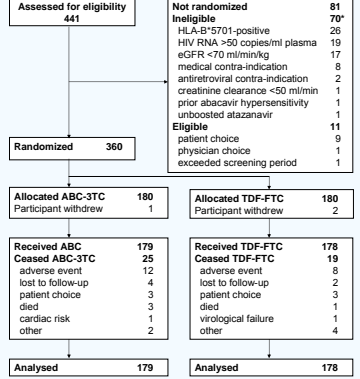


Table 1: Baseline participant characteristics

| Demographics                        | ABC-3TC   | TDF-FTC   |
|-------------------------------------|-----------|-----------|
| Age (years)                         | 46 ± 9    | 44 ± 8    |
| Male (%)                            | 98        | 97        |
| White ethnicity (%)                 | 86        | 86        |
| BMI (kg/m <sup>2</sup> )            | 25 ± 3    | 25 ± 4    |
| <b>HIV History</b>                  |           |           |
| MSM transmission (%)                | 88        | 89        |
| Primary AIDS (%)                    | 17        | 16        |
| HIV duration (years)                | 10 ± 6    | 10 ± 6    |
| CD4+ count (cells/mm <sup>3</sup> ) | 627 ± 306 | 599 ± 257 |
| <b>Non-HIV History</b>              |           |           |
| Hypertension (%)                    | 13        | 11        |
| Ischaemic heart disease (%)         | 4         | 2         |
| Ischaemic stroke (%)                | 1         | 0         |
| Current smoker (%)                  | 40        | 29        |
| Diabetes mellitus (%)               | 5         | 3         |
| Framingham CVD risk (%)             | 8 ± 7     | 7 ± 5     |
| <b>Antiretroviral Therapy</b>       |           |           |
| ABC (%)                             | 20        | 21        |
| TDF (%)                             | 30        | 30        |
| Protease Inhibitor (%)              | 24        | 23        |

Table 2: Virological failures through week 96

| Analysis                        | Treatment | n  | %    | Difference (%) | 95% CI    | P    |
|---------------------------------|-----------|----|------|----------------|-----------|------|
| ITT missing equal failure       | ABC-3TC   | 10 | 5.6  | 1.7            | -2.8, 6.1 | 0.62 |
|                                 | TDF-FTC   | 7  | 3.9  |                |           |      |
| ITT non-completer equal failure | ABC-3TC   | 23 | 12.8 | 3.3            | -3.3, 9.9 | 0.40 |
|                                 | TDF-FTC   | 17 | 9.6  |                |           |      |
| Available data                  | ABC-3TC   | 3  | 1.7  | 0              | -2.7, 2.7 | 1.00 |
|                                 | TDF-FTC   | 3  | 1.7  |                |           |      |
| On-treatment                    | ABC-3TC   | 2  | 1.1  | 0              | -2.2, 2.2 | 1.00 |
|                                 | TDF-FTC   | 2  | 1.1  |                |           |      |

Table 3: Serious non-AIDS events (SNAEs)

|                         | ABC-3TC<br>n | Rate | TDF-FTC<br>n | Rate | Hazard ratio (TDF/ABC) | 95%CI      | P      |
|-------------------------|--------------|------|--------------|------|------------------------|------------|--------|
| Total                   | 14           | 4.4  | 4            | 1.2  | 0.26                   | 0.08, 0.79 | 0.018* |
| Cardiovascular disease  | 8            | 2.2  | 1            | 0.3  | 0.13                   | 0.02, 0.98 | 0.046  |
| Cancer                  | 5            | 2    | 2            | 0.6  | 0.26                   | 0.08, 0.79 | 0.018* |
| Major fracture          | 0            | 0    | 1            | 0.3  | 0.13                   | 0.02, 0.98 | 0.046  |
| Cirrhosis               | 1            | 0    | 0            | 0    |                        |            |        |
| Deaths (all cancer)     | 3            | 1    | 0            | 0    |                        |            |        |
| End-stage renal disease | 0            | 0    | 1            | 0.3  | 0.13                   | 0.02, 0.98 | 0.046  |

\* This association remained significant when adjusted for baseline smoking or time on randomized ART

Table 4: Categorical secondary endpoints

| Endpoint                                                                                               | n  | ABC-3TC<br>Rate/100 pt years<br>(95% CI) | n  | TDF-FTC<br>Rate/100 pt years<br>(95% CI) | Hazard Ratio      | P     |
|--------------------------------------------------------------------------------------------------------|----|------------------------------------------|----|------------------------------------------|-------------------|-------|
| Lipid (new cholesterol >6.5 or increase >2mmol/L; new HDL <0.9 or decrease <0.5mmol/L; or new therapy) | 40 | 13.9 (10.2, 19.0)                        | 19 | 6.1 (3.9, 9.5)                           | 0.4 (0.3, 0.8)    | 0.003 |
| Renal (eGFR <60mL/min/1.73m <sup>2</sup> ; or proteinuria >0.5g/m <sup>2</sup> /d)                     | 5  | 1.6 (0.7, 3.7)                           | 3  | 0.9 (0.3, 2.8)                           | 0.6 (0.1, 2.5)    | 0.48  |
| Glycaemic (new diabetes or diabetic therapy)                                                           | 2  | 0.6 (0.2, 2.5)                           | 2  | 0.6 (0.2, 2.4)                           | 1.0 (0.1, 7.1)    | 1.00  |
| Bone (osteopenia or osteoporosis; fracture; new BMD therapy)                                           | 14 | 4.4 (2.6, 7.4)                           | 27 | 8.5 (5.9, 12.5)                          | -7.3 (-14.0, 0.7) | 0.032 |
| Hepatic (lactate >5mmol/L; ALT >5 x ULN)                                                               | 2  | 0.6 (0.2, 2.5)                           | 2  | 0.6 (0.2, 2.5)                           | 1.0 (0.1, 7.0)    | 0.98  |

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Figure 2: Total HDL cholesterol

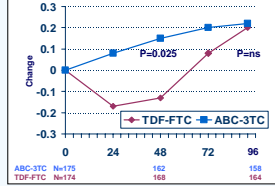


Figure 3: Calendar period at commencement of lipid-lowering therapy

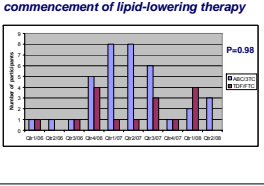
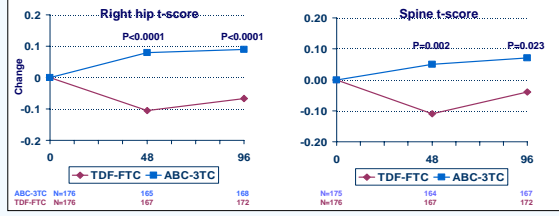


Figure 4: Changes in Bone Mineral Density



## Conclusion

- In this population, TDF-FTC and ABC-3TC had similar virological efficacy.
- However, ABC-3TC was associated with more SNAEs (particularly cardiovascular disease) and lipid endpoints, and TDF-FTC caused more BMD loss.