

## Background

Lamivudine and emtricitabine are equally recommended by guidelines with tenofovir and efavirenz, nevirapine, or boosted PI as first-line cART for ART naive HIV-1 patients.

The use of generic lamivudine could replace emtricitabine to constrain costs. The evidence for their clinical equivalence with tenofovir and NNRTIs or boosted PIs in ART naive HIV-1 patients is inconclusive.

The aim of this study was to evaluate the virological responses to lamivudine and emtricitabine in combination with tenofovir and efavirenz, nevirapine, or a boosted PI in the ATHENA cohort.

## Methods

Nationwide cohort study between 2002 - 2012 on 6322 ART naive HIV-1 patients without documented baseline resistance.

Clinical endpoints:

1. Virological failure at week 48 and week 240.
2. Time to HIV-RNA <400 c/mL.
3. Time to virological failure after HIV-RNA <400 c/mL.
4. Acquired resistance.

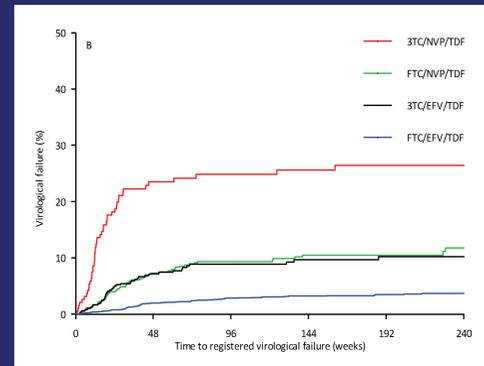
Virological failure was defined as (1) HIV-RNA >400 c/mL at 48±10 weeks, (2) ART switches for failure, (3) death while last HIV-RNA was >400 c/mL. Responses were analyzed by multivariate Cox proportional hazard models.

## Baseline Characteristics

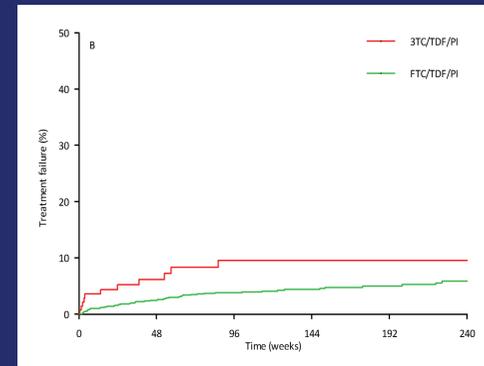
|                                      | Lamivudine/tenofovir (n=870) |        | Emtricitabine/tenofovir (n=5452) |        |
|--------------------------------------|------------------------------|--------|----------------------------------|--------|
|                                      | N                            | (%)    | N                                | (%)    |
| <b>Boosted protease inhibitor</b>    | 142                          | (16.3) | 1440                             | (26.4) |
| <b>Efavirenz</b>                     | 535                          | (61.5) | 3343                             | (61.3) |
| <b>Nevirapine</b>                    | 193                          | (22.2) | 669                              | (12.3) |
| <b>Male sex</b>                      | 673                          | (77.4) | 4760                             | (87.3) |
| <b>Age (median)</b>                  | 39                           |        | 41                               |        |
| <b>cART initiation year (median)</b> | 2005                         |        | 2009                             |        |
| <b>Hepatitis B</b>                   | 90                           | (10.3) | 373                              | (6.8)  |
| <b>Hepatitis C</b>                   | 75                           | (8.6)  | 434                              | (8.0)  |
| <b>HIV-1 Transmission</b>            |                              |        |                                  |        |
| MSM                                  | 415                          | (47.7) | 3696                             | (67.8) |
| Heterosexual                         | 335                          | (38.5) | 986                              | (18.1) |
| Other                                | 120                          | (13.8) | 770                              | (14.1) |
| <b>Region of origin</b>              |                              |        |                                  |        |
| Western Countries                    | 489                          | (56.2) | 3803                             | (69.8) |
| Sub-Saharan Africa                   | 170                          | (19.5) | 551                              | (10.1) |
| Other                                | 211                          | (24.3) | 1098                             | (20.1) |
| <b>HIV-RNA ≥100,000 copies/mL</b>    | 465                          | (53.4) | 2587                             | (47.5) |
| <b>CD4 cells/mm<sup>3</sup></b>      |                              |        |                                  |        |
| <100                                 | 249                          | (28.6) | 842                              | (15.4) |
| 100 - 199                            | 226                          | (26.0) | 860                              | (15.8) |
| 200 - 349                            | 333                          | (38.3) | 2573                             | (47.2) |
| ≥350                                 | 62                           | (7.1)  | 1177                             | (21.6) |

## Results

### Time to virological failure

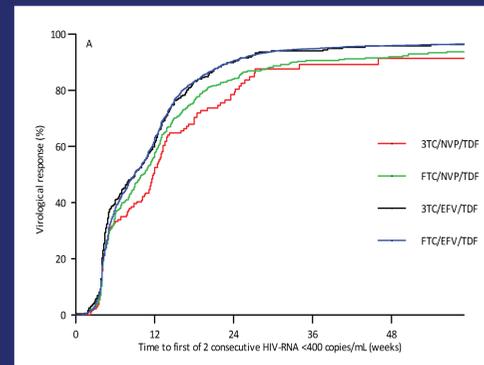


Adjusted HR (95%CI) on virological failure with lamivudine compared to emtricitabine were 2.4 (1.6-3.4) with efavirenz, and 2.0 (1.4-3.0) with nevirapine.

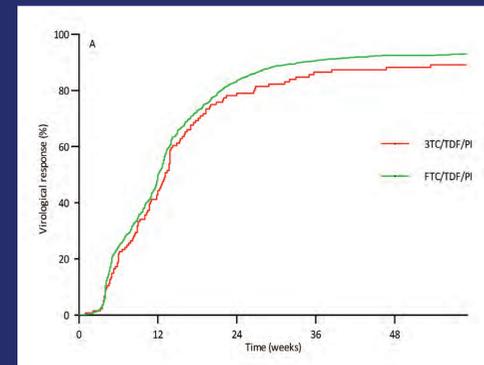


Adjusted HR (95%CI) on virological failure with lamivudine compared to emtricitabine was 1.2 (0.6-2.3) with boosted PIs.

### Time to HIV-RNA <400 c/mL

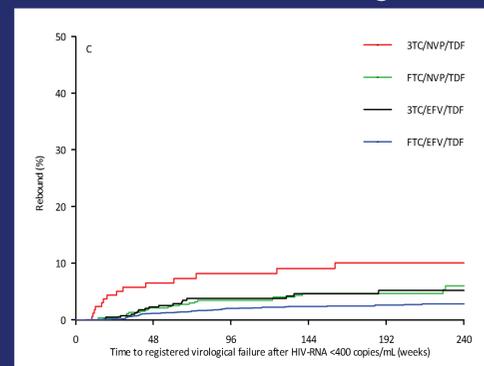


Adjusted HR (95%CI) on HIV-RNA <400 c/mL with lamivudine compared to emtricitabine were 1.0 (0.9-1.2) with efavirenz, and 1.0 (0.8-1.2) with nevirapine.

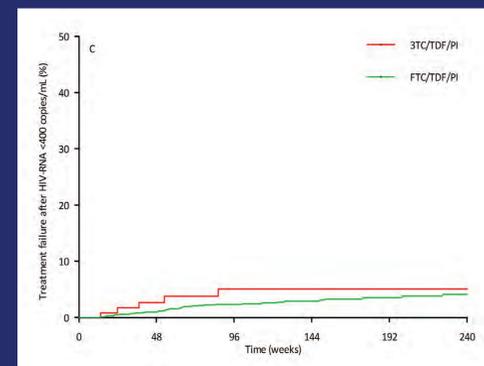


Adjusted HR (95%CI) on HIV-RNA <400 c/mL with lamivudine compared to emtricitabine was 0.9 (0.8-1.2) with boosted PIs.

### Time to virological failure after HIV-RNA <400 c/mL



Adjusted HR (95%CI) on virological failure after HIV-RNA <400 c/mL with lamivudine compared to emtricitabine were 1.6 (0.9-2.8) with efavirenz, and 1.5 (0.8-2.9) with nevirapine.



Adjusted HR (95%CI) on virological failure after HIV-RNA <400 c/mL with lamivudine compared to emtricitabine was 0.9 (0.4-2.5) with boosted PIs.

### Acquired Resistance with NNRTI and boosted PIs

|                            | Efavirenz/Tenofovir |                        | Nevirapine/Tenofovir |                        | Overall             |                        |
|----------------------------|---------------------|------------------------|----------------------|------------------------|---------------------|------------------------|
|                            | Lamivudine (n = 9)  | Emtricitabine (n = 16) | Lamivudine (n = 35)  | Emtricitabine (n = 28) | Lamivudine (n = 44) | Emtricitabine (n = 44) |
|                            | No.                 | (%)                    | No.                  | (%)                    | No.                 | (%)                    |
| <b>NNRTI RAM</b>           |                     |                        |                      |                        |                     |                        |
| K65R                       | 2                   | (22.2)                 | 3                    | (18.8)                 | 13                  | (37.1)                 |
| K70E                       | 0                   | (0)                    | 0                    | (0)                    | 0                   | (0)                    |
| Y115F                      | 0                   | (0)                    | 0                    | (0)                    | 2                   | (7.1)                  |
| M184I/V                    | 4                   | (44.4)                 | 9                    | (56.2)                 | 23                  | (65.7)                 |
| <b>NNRTI RAM</b>           |                     |                        |                      |                        |                     |                        |
| A98G                       | 1                   | (11.1)                 | 1                    | (6.2)                  | 0                   | (0)                    |
| K101E                      | 1                   | (11.1)                 | 1                    | (6.2)                  | 2                   | (5.7)                  |
| K103N                      | 2                   | (22.2)                 | 10                   | (62.5)                 | 6                   | (17.1)                 |
| V106A/M                    | 1                   | (11.1)                 | 1                    | (6.2)                  | 6                   | (17.2)                 |
| Y181C                      | 0                   | (0)                    | 0                    | (0)                    | 20                  | (57.1)                 |
| Y188C/L                    | 2                   | (22.2)                 | 2                    | (12.5)                 | 4                   | (11.4)                 |
| G190A/E/S                  | 3                   | (33.3)                 | 2                    | (12.5)                 | 5                   | (14.3)                 |
| P225H                      | 0                   | (0)                    | 3                    | (18.8)                 | 0                   | (0)                    |
| F227L                      | 0                   | (0)                    | 0                    | (0)                    | 2                   | (5.7)                  |
| K238T                      | 0                   | (0)                    | 1                    | (6.2)                  | 0                   | (0)                    |
| Y318F                      | 0                   | (0)                    | 0                    | (0)                    | 1                   | (2.9)                  |
| <b>Resistance patterns</b> |                     |                        |                      |                        |                     |                        |
| No RAM                     | 2                   | (22.2)                 | 2                    | (12.5)                 | 2                   | (5.7)                  |
| ≥1 NRTI/NNRTI RAM          | 7                   | (77.8)                 | 14                   | (87.5)                 | 33                  | (94.3)                 |
| ≥1 NRTI and ≥1 NNRTI RAM   | 6                   | (66.7)                 | 12                   | (75.0)                 | 31                  | (88.6)                 |

Patients had documented wild-type HIV-1 at baseline and HIV-RNA >1000 c/mL at failure. A total of 49 patients on a boosted PI had virological failure and documented baseline wild-type HIV-1; 3 of these patients had acquired new resistance mutations: V179D/M184VI, K65R/V108I/Y181C/M184V/H221Y, K70Q/M184V.

## Conclusions

With efavirenz or nevirapine, the use of lamivudine instead of emtricitabine in combination with tenofovir for ART naive HIV-1 patients was associated with more virological failure.

With a boosted PI, the use of lamivudine instead of emtricitabine in combination with tenofovir for ART naive HIV-1 patients was not associated with different virological responses.

The evidence for their equal recommendation with tenofovir in NRTI backbones of first-line cART is not based on RCTs that have directly compared lamivudine/tenofovir with emtricitabine/tenofovir. Our results support their equivalence in boosted PI containing cART only.

Our observations warrant a direct randomized blinded comparison of lamivudine with emtricitabine in tenofovir and NNRTI containing cART.