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To cite this version:

Lise Cuzin, Pascal Pugliese, Clotilde Allavena, Christine Katlama, Laurent Cotte, et al.. Comparative Effectiveness of First Antiretroviral Regimens in Clinical Practice Using a Causal Approach.. Medicine, Lippincott, Williams & Wilkins, 2015, 94 (39), pp.e1668. 10.1097/MD.0000000000001668. hal-01309275

HAL Id: hal-01309275

https://hal.archives-ouvertes.fr/hal-01309275

Submitted on 8 Jun 2021

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Comparative Effectiveness of First Antiretroviral Regimens in Clinical Practice Using a Causal Approach

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Abstract: The objective of this study was to estimate the cumulative incidences of failure by months 12 (M12) and 24 (M24) for the most prescribed first-line anti-retroviral regimens (ART).

It is retrospective analysis of a prospectively collected database.

All patients who initiated their first ART with the most prescribed regimens between 1st January 2004 and 30th June 2013 in 12 large HIV reference centers in France were included. The outcome was treatment failure—defined by any treatment modification for virological or tolerability reasons—and comparisons between regimens were carried out at M12 and M24. Adjusted and weighted methods via the propensity score (PS) were used to compare the effectiveness of the first antiretroviral regimens. Potential confounders of the treatment-outcome association were used to estimate PS with multinomial logistic regression.

Overall, 3128 and 2690 patients were included in the M12 and M24 analyses, respectively. Patients received 5 different regimens (ABC/3TC with ATV/r or DRV/r, TDF/FTC with ATV/r, or EFV).

Failure was reported in 25% and 42% at M12 and M24, respectively. Patients who received TDF/FTC/EFV had a significantly higher proportion of failure at M12 by comparison with TDF/FTC with DRV/r (reference), but not at M24. Patients in the 3 other groups had a trend toward a higher proportion of failure at M12 although not statistically significant. No difference was found at M24.

Using data from a large prospective cohort, we found that boosted atazanavir and darunavir had comparable effectiveness, whatever the associated NRTIs, whereas efavirenz-based regimens were relatively less performing on the short term.

DOI: 10.1097/MD.0000000000001668

Medicine 94(39):e1668
INTRODUCTION

Currently, recommended first-line antiretroviral regimens (ART) include 2 nucleoside analog reverse transcriptase inhibitors (NRTIs) in association with either a non-nucleoside reverse transcriptase inhibitor (NNRTI), a ritonavir boosted protease inhibitor (PI/r), or an integrate strand-transfer inhibitor (INSTI). Due to the number of different drugs in each class, multiple potential triple combinations can be prescribed. Randomized controlled trials (RCTs), considered as the methodological gold standard, have been designed to compare virological efficacy of some of the potential triple drug regimens. These studies provide the core knowledge for recommendations and guidelines, but they have limits. Selection and volunteer biases may compromise the generalization of their results to the general patient population.

Observational cohort studies offer a complementary research design by providing information on comparative effectiveness of different antiretroviral regimens used in clinical practice. These studies allow comparisons between strategies not evaluated by RCTs, and they are representative of treatment strategies used in routine care settings. Reasons for modifying or interrupting ART may be different in this setting by comparison with RCTs, due to a broader use of ART. It is well known that in observational studies, unlike in RCTs, characteristics of patients between the treatment groups are quite different. The potential for confounding by indication may strongly impact the outcome interpretation and reliability of study findings.

Statistical methods have therefore been introduced to provide a causal approach of the analysis of observational data. Most of these methods are based on the propensity score (PS), which is the probability of receiving a treatment given some observed covariates. The goal of propensity scores is to balance observed covariates between subjects from the treatment groups in order to mimic what happens in a randomized study. In practice propensity scores are unknown and are estimated via regression models. Adjusting and weighting via the PS for observed covariates. Selection for the PS model was an iterative process given subject to one of the treatment groups given the observed covariates.

Using a large prospectively collected observational cohort, we analyzed the effectiveness of the most prescribed first-line regimens. The outcome—treatment failure—was defined as any modification of the regimen because of lack of efficacy or poor tolerability. Crude analyses were compared with analyses adjusted for multiple PS or weighted via marginal structural models and doubly robust estimators.

METHODS

Subjects and Data Collection

The patients were HIV-1-infected adults receiving care in 12 large HIV reference centers from 11 distinct geographical regions in France. These centers maintain prospective cohorts of all HIV-infected patients who received care and provided written consent. The data collection has been approved by the French national commission on informatics and liberty (CNIL). The database collects demographic, clinical, antiretroviral history, viral load, and CD4 T cell counts data at regular 3 to 6 months intervals during routine clinical assessment. For the purpose of this study, we selected all patients who initiated their first ART between 1st January 2004 and 30th June 2013. We then restricted the population to patients receiving a regimen, which has been used by at least 200 patients and which was still recommended as the first regimen in the most recent years (thus regimens including lopinavir were excluded).

Key confounders of the treatment-outcome association included continuous and categorical variables that were assessed at or before the initiation of ART. Continuous variables were age, baseline viral load (log_{10} copies/ml), baseline CD4 T cell counts (cells/mm$^3$), and duration of known HIV infection (time in months from HIV diagnosis to ART initiation). Categorical variables were hepatitis B or C co-infection (yes/no), AIDS at ART initiation (yes/no), prior history of depression (yes/no), having a glomerular filtration rate estimated by the abbreviated Modification of Diet and Renal Disease (eGFR) $<$90 ml/min per 1.73 m$^2$ (yes/no), a combination of sex and route of transmission (men who have sex with men [MSM], other men and women) and year of ART initiation (2004–2008, 2009–2010, or 2011–2013).

The outcome was treatment failure, defined by any modification of the first regimen due to the lack of efficacy or to poor tolerability. This outcome was investigated by month 12 (M12) and month 24 (M24). All other reasons for regimen modification, such as treatment simplification, pregnancy (planned or current), clinical trial participation, or planned antiretroviral interruptions were not considered as treatment failures and were considered as censored. For patients treated with tenofovir/entecavir and tenofovir/efavirenz, simplification to the single-pill formulation was not considered as a treatment modification. When the reason for ART modification was not clear, we searched for the last viral load value before modification. If this last viral load was $>$2.6 log_{10} copies/ml, failure was considered as the reason for the ART modification. Otherwise, the observation was censored.

Two dataset were used for each of the M12 and M24 analyses. Patients who did not experience the outcome and who had a follow-up $<$12 months were excluded from the M12 analysis. Similarly patients who did not experience the outcome and who had a follow-up shorter than 24 months were excluded from the M24 analysis.

STATISTICAL METHODS

Unadjusted analysis and adjusted/weighted analyses based on the propensity score (PS) were used to compare the effectiveness of the first ART regimens at M12 and M24. Adjusted method used multiple PSs estimated by multivariable logistic regression. Each PS is the conditional probability of assigning a given subject to one of the treatment groups given the observed covariates. Selection for the PS model was an iterative process similar to that suggested previously. Marginal structural models were also used in a weighting strategy. We used stabilized weights based on the product of Inverse Probability of Treatment Weighted (IPTW) and Inverse Probability of Censoring Weighted (IPCW). The double robust (DR) estimator combines 2 approaches to estimate the causal effect of a treatment on an outcome. The first is based on an outcome-model and the second is a model for the propensity score. DR produces a consistent estimate of the treatment effect if either of the 2 models has been correctly specified. Generalized doubly robust estimator for multiple treatments has been proposed recently. We use the bootstrap method to estimate confidence intervals and P values of doubly robust estimators as recommended.

Two sensitivity analyses were performed. A first sensitivity analysis excluded censored patients (patients who...
modified their initial ART regimen due to another reason than lack of efficacy or tolerability). A second analysis included only patients having an estimated PS or stabilized weight between the 1st and 99th percentile. All analyses were done with SAS (version 9.3; SAS Institute Inc, Cary, NC).

RESULTS

On the basis of our inclusion criteria, we selected 3628 patients who initiated ART with 5 different regimens. The 5 regimens were the following: atazanavir/ritonavir (ATV/r) with abacavir/lamivudine (ABC/3TC) (N = 250); ATV/r with tenofovir/emtricitabine (TDF/FTC) (N = 958); TDF/FTC with efavirenz (EFV) (N = 721); darunavir/ritonavir (DRV/r) with ABC/3TC (N = 340); and DRV/r with TDF/FTC (N = 1259). Among the 3628 patients, 500 patients were excluded from the M12 analysis because of a follow-up of <12 months. Thus, the M12 analysis was based on 3128 patients. Similarly, the M24 analysis was based on 2690 patients.

Baseline characteristics of the 3128 patients included in the M12 analysis are summarized in Table 1, showing to what extent the treatment groups initially differed. The use of TDF/FTC with DRV/r was more likely among subjects with high baseline viral load, low baseline CD4⁺ T cell count, in those with AIDS at ART initiation or among those who had been recently diagnosed. Use of ATV/r was more likely in patients who initiated ART at ART initiation or among those who had been recently diagnosed. Table 2 reports adjusted odds ratios (ORs) based on multivariable logistic regression of treatment failure on potential confounders. Several covariates were associated with increased treatment failure: women versus MSM (OR = 1.46; P < 0.01), having an eGFR <90 ml/min per 1.73 m² (OR = 1.26; P = 0.05); presence of AIDS at ART initiation (OR = 1.73; P < 0.01); and higher baseline viral load (OR = 1.16 per log10; P < 0.01). Probability of treatment failure was lower in patients treated early in the 2000 s (OR = 0.57 in 2004–2008 vs 2011–2013; P < 0.01; OR = 0.68 in 2009–2010 vs 2011–2013; P < 0.01).

Patients who received TDF/FTC with DRV/r had the lowest probability of failure whatever the method used; thus we used them as the reference group. Table 3 shows estimates of the probability of treatment failure in the reference group and risk differences for the other treatment groups. A positive difference in probability indicates a higher estimate of treatment failure by comparison with the reference group. The unadjusted analysis showed no significant difference in proportions of failure between the 4 treatment groups by comparison with TDF/FTC with DRV/r. Among the 2789 uncensored patients with a follow-up >12 months, we estimated a 4.5% to 8.8% higher absolute probability of treatment failure at M12 in the 4 treatment groups by comparison with the TDF/FTC with the

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**TABLE 1. Patients Characteristics at The Time of ART Initiation in Each Treatment Group**

|                          | ABC/3TC/ATV/r | TDF/FTC/ATV/r | TDF/FTC/EFV | ABC/3TC/DRV/r | TDF/FTC/DRV/r | Unadjusted | Adjusted |
|--------------------------|--------------|---------------|-------------|---------------|---------------|------------|----------|
| Continuous variables, median (IQR) | N = 319      | N = 895       | N = 647     | N = 239       | N = 1028      |            |          |
| Age (years)              | 40.2 (31–48) | 39.1 (32–47)  | 36.9 (30–44) | 40.6 (32–49)  | 39.7 (32–47)  | 0.002      | 0.06     |
| Baseline viral load (log10 copies/ml) | 4.5 (4.0–5.0) | 4.7 (4.2–5.2) | 4.7 (4.1–5.1) | 4.6 (4.1–5.2) | 5.0 (4.5–5.4) | <0.001     | 0.19     |
| Baseline CD4⁺ T cell count (cells/ml) | 319 (232–393) | 306 (215–406) | 368 (280–469) | 309 (204–414) | 289 (121–421) | <0.001     | 0.02     |
| Time since HIV diagnosis (months) | 52 (10–135)  | 47 (6–157)    | 38 (7–122)  | 28 (5–108)    | 8 (2–96)      | <0.001     | 0.34     |
| Categorical variables, N (%) |              |               |             |               |               |           |          |
| AIDS at initiation of ART, yes | 19 (6)       | 63 (7)        | 33 (5.1)    | 27 (11.3)     | 175 (17)      | <0.001     | 0.24     |
| Hepatitis B or C coinfection, yes | 22 (6.9)     | 137 (15.3)    | 75 (11.6)   | 19 (7.9)      | 129 (12.5)    | 0.007      | 0.21     |
| eGFR < 90 ml/min per 1.73 m² | 84 (26.3)    | 164 (18.3)    | 94 (14.5)   | 67 (28.0)     | 210 (20.4)    | <0.001     | 0.39     |
| Depression, yes           | 31 (9.7)     | 57 (6.4)      | 15 (2.3)    | 12 (5.0)      | 50 (4.9)      | <0.001     | 0.05     |
| Gender and route of transmission, N (%) |              |               |             |               |               |           |          |
| MSM                       | 125 (39.2)   | 415 (46.5)    | 349 (53.9)  | 101 (42.3)    | 511 (49.7)    | <0.001     | 0.09     |
| Other men                 | 101 (31.7)   | 266 (29.7)    | 176 (27.2)  | 79 (33.1)     | 314 (30.5)    | <0.001     | 0.05     |
| Female                    | 93 (29.2)    | 214 (23.9)    | 122 (18.9)  | 59 (24.7)     | 203 (19.7)    | <0.001     | 0.21     |
| Year at initiation of ART |              |               |             |               |               |           |          |
| 2004–2008                 | 120 (37.6)   | 318 (35.5)    | 27 (4.2)    | 10 (4.2)      | 25 (2.4)      | <0.001     | 0.21     |
| 2009–2010                 | 99 (31.0)    | 353 (39.4)    | 300 (46.6)  | 77 (32.2)     | 383 (37.3)    | <0.001     | 0.21     |
| 2011–2013                 | 100 (31.3)   | 224 (25.0)    | 320 (49.5)  | 152 (63.6)    | 620 (60.3)    | <0.001     | 0.21     |

3TC = lamivudine, ABC = abacavir, AIDS = acquired immune deficiency syndrome, ART = antiviral therapy, ATV/r = ritonavir boosted atazanavir, DRV/r = ritonavir boosted darunavir, EFV = efavirenz, eGFR = glomerular filtration rate estimated by the abbreviated modification of diet and renal disease, FTC = emtricitabine, HIV = Human immunodeficiency virus, IQR = 25% interquartile, MSM = men who have sex with men, TDF = tenofovir.
TABLE 2. Adjusted Odd-Ratios Based on Multivariable Logistic Regression of Treatment Failure by M12 on Potential Confounders

| Potential Confounder                        | Adjusted OR | 95% CI       | P-Value |
|--------------------------------------------|-------------|--------------|---------|
| Age (per 10 years)                         | 1.05        | 0.96 to 1.15 | 0.25    |
| Baseline viral load (per 1log_{10}copies/ml)| 1.16        | 1.04 to 1.30 | <0.01   |
| Baseline CD4+ T cell count (per 100 cells/ml)| 1.03        | 0.98 to 1.09 | 0.22    |
| Time since HIV diagnosis (per year)        | 0.99        | 0.97 to 1.01 | 0.40    |
| AIDS at initiation of ART                  | 1.73        | 1.26 to 2.37 | <0.01   |
| Hepatitis B or C co-infection              | 1.06        | 0.78 to 1.44 | 0.73    |
| eGFR < 90 ml/min per 1.73 m²               | 1.26        | 0.99 to 1.58 | 0.05    |
| Depression                                 | 0.92        | 0.60 to 1.42 | 0.71    |
| Other male versus MSM                      | 0.86        | 0.68 to 1.09 | 0.22    |
| Female versus MSM                          | 1.46        | 1.15 to 1.86 | <0.01   |
| Treated in 2004–2008 versus 2011–2013      | 0.57        | 0.42 to 0.78 | <0.01   |
| Treated in 2009–2010 versus 2011–2013      | 0.68        | 0.56 to 0.84 | <0.01   |

AIDS = acquired immune deficiency syndrome, CI = confidence interval, eGFR = glomerular filtration rate estimated by the abbreviated modification of diet and renal disease, HIV = Human immunodeficiency virus, MSM = men who have sex with men, OR = odds ratio.

DRV/r group. These estimates were higher than the unadjusted associations. In particular, patients receiving TDF/FTC with EFV had a significantly higher probability of failure than patients receiving TDF/FTC with DRV/r. Patients receiving ABC/3TC with ATV/r, TDF/FTC with ATV/r, or ABC/3TC with DRV/r had a trend toward a higher probability of failure with P values ~0.08–0.10.

**Treatment Failure at M24**

Among the 2690 subjects of the M24 analysis, 536 (19.9%) patients were censored. Among the 2154 remaining patients 893 (41.5%) presented with treatment failure before M24. Most of the predictors of M12 treatment failure (Table 2) were also predictive of failure at M24 (Table 4), except for an eGFR <90 ml/min per 1.73 m². In addition, higher baseline CD4+ T cell count (OR = 1.07 per 100 cells/ml; P = 0.03) was significantly associated with an increased probability of treatment failure at M24.

Probabilities of treatment failure varied from 41% to 46% in the TDF/FTC with DRV/r group (Table 5). In the unadjusted analysis, patients receiving an ATV/r-containing regimen had a lower absolute probability of failure compared with the reference group (~8% for ABC/3TC with ATV/r; P = 0.008; ~3.8% for TDF/FTC with ATV/r; P = 0.38). The use of appropriate statistical methods showed a quite different picture with a higher probability, although not statistically significant, of failure in patients receiving an ATV/r-containing regimen. Marginal structural models and double robust estimators showed no statistical difference in probability of treatment failure of the 4 treatment groups by comparison with the reference group.

All sensitivity analyses described in the method section provided similar results for both M12 and M24 analyses (data not shown).

**DISCUSSION**

We here provide a comparison of the effectiveness of the 5 most prescribed first-line ART regimens for HIV-infected patients in France between 2004 and 2013. The 2 most frequently used regimens were TDF/FTC with either EFV or DRV/r.

**TABLE 3.** Estimates of the Probability of Treatment Failure by M12 in the Reference Group and Risk Differences in the Other Groups

| Treatment Group          | Unadjusted Analysis | Adjusted on the Multiple PS | Marginal Structural Models | Doubly Robust |
|--------------------------|---------------------|-----------------------------|---------------------------|--------------|
| Reference TDF/FTC/DRV/r   | Treatment failure 24.6% | Treatment failure 21.4% | Treatment failure 20.8% | Treatment failure 21.5% |
|                          | Difference in proportions of failure, % (95% CI) | Difference in failure probability, % (95% CI) | Difference in failure probability, % (95% CI) | Difference in failure probability, % (95% CI) |
| ABC/3TC/ATV/r            | 0.7 (–5.8 to 7.2)   | 0.83 6.3 (–0.6 to 13.2) | 0.08 7.0 (–2.1 to 16.0) | 0.13 7.4 (–0.02 to 16.2) |
| TDF/FTC/ATV/r            | –0.8 (–5.2 to 3.6)  | 0.71 5.9 (0.9 to 10.9) | 0.02 6.0 (–0.2 to 12.2) | 0.06 4.5 (–0.01 to 10) |
| TDF/FTC/EFV              | 4.2 (–0.8 to 9.3)   | 0.10 7.5 (2.4 to 12.6) | 0.004 8.8 (1.4 to 16.3) | 0.02 8.0 (0.1 to 15.4) |
| ABC/3TC/DRV/r            | 4.9 (–2.2 to 12.0)  | 0.18 6.2 (–0.8 to 13.3) | 0.08 8.1 (–0.8 to 16.9) | 0.07 7.7 (–0.01 to 15.8) |

/rt = ritonavir boost, 3TC = lamivudine, ABC = abacavir, ATV = atazanavir, CI = confidence interval, DRV = darunavir, EFV = efavirenz, FTC = entricitabine, PS = propensity score, TDF = tenofovir.
TABLE 5. Estimates of the Probability of Treatment Failure by M24 in the Reference Group and Risk Differences in the Other Groups

| Reference Treatment group | Treatment failure 45.6% | Adjusted on the Multiple PS | Marginal Structural Models | Doubly Robust |
|---------------------------|-------------------------|-----------------------------|---------------------------|---------------|
| TDF/FTC/DRV/r             | Treatment failure 41.1% | Treatment failure 41.9%     | Treatment failure 44.1%   |               |
| ABC/3TC/ATV/r             | Difference in failure probability, % (95% CI) | P | Difference in failure probability, % (95% CI) | P | Difference in failure probability, % (95% CI) | P |
| ABC/3TC/ATV/r             | –3.8 (–12.2 to 4.6)     | 0.38                        | 8.5 (–0.4 to 17.4)        | 0.06          | 8.3 (–4.8 to 21.5)        | 0.22          | 4.3 (–8.2 to 16.7)        | 0.50          |
| TDF/FTC/ATV/r             | –8.0 (–13.8 to –2.1)    | 0.008                       | 6.3 (–0.6 to 13.2)        | 0.07          | 3.3 (–7.2 to 13.8)        | 0.54          | 1.2 (–12.8 to 10.4)       | 0.85          |
| TDF/FTC/EFV               | 0.6 (–6.0 to 7.1)       | 0.86                        | 5.1 (–1.7 to 11.9)        | 0.14          | 6.7 (–5.0 to 18.5)        | 0.26          | –0.8 (–13.3 to 11.6)      | 0.89          |
| ABC/3TC/DRV/r             | 5.5 (–3.9 to 14.9)      | 0.25                        | 6.5 (–2.9 to 15.9)        | 0.18          | 3.0 (–10.8 to 16.9)       | 0.67          | 3.5 (–8.9 to 15.9)        | 0.58          |

/r = ritonavir boost, 3TC = lamivudine, ABC = abacavir, ATV = atazanavir, CI = confidence interval, DRV = darunavir, EFV = efavirenz, FTC = entricitabine, PS = propensity score, TDF = tenofovir.
to avoid that first-line regimens be chosen by the physicians on the basis of self-conviction, indirect comparisons, or other factors.

By choosing a pragmatic definition of treatment failure, we took into account some reasons for failure that may not be accounted for in RCTs. Most trials used virological failure as primary endpoints, but treatment modifications should also be considered as failures. The large number of planned visits in an RCT, especially during the first year, and strict protocol rules are 2 important differences with observational studies. One can suspect that clinicians modified patients’ regimen more easily and early in clinical practice than in an RCT. The surprisingly high probability of failure rate in the most recent calendar years can be explained by the availability of an increasing number of potent drugs leading to treatment modifications for minor toxicities. Comparative effectiveness of initial antiretroviral therapy regimens based on virological failure between RCTs and observational studies have been made and showed a good agreement.23

The methods we used were designed to limit the indication bias, taking into account the major patients characteristics that drive a physician decision while selecting ART. A key feature of the methods used here is the variable selection for propensity score models or for inverse probability weights.24,25 There is trade-off between reducing confounding bias and increasing bias and variance due to a large selection of variables in the propensity model.25 We followed the current recommendations to construct both propensity scores and stabilized weights.10,25 Similar statistical methods have been used to compare the virological efficacy of boosted double versus boosted single protease inhibitor regimens.26

A limitation of our analyses is that some unmeasured confounders, including baseline viral load and the year of ART initiation, were included in the models used.

In conclusion, using data from a large prospective cohort of patients seeking care in France in the recent years, we found that TDF/FTC with DRV/r had the lowest probability of treatment failure at months 12 and 24. At month 12, patients receiving TDF/FTC with EFV had a significant higher probability of treatment failure whereas no difference was found for the patients receiving boosted atazanavir regimens and ABC/3TC with DRV/r. At month 24, all regimens had a comparable effectiveness. This approach allowed us to address some questions that have not been and will probably not be considered in RCTs, adding important information for physicians and patients that will be making decisions on the choice of the first ART regimen.

ACKNOWLEDGMENTS

All authors contributed significantly to the study. PF and LC designed the study. PF was responsible of the statistical analysis. LC, PP, CA, CK, LC, AC, AC, DR, CC, and FB-S were responsible for the data collection in their centers. PF and LC wrote the first version of the paper, which was amended by all co-authors. All authors approved the final version.

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