International Journal of Antimicrobial Agents xxx (xxxx) xxx

Contents lists available at ScienceDirect

International Journal of Antimicrobial Agents

journal homepage: www.elsevier.com/locate/ijantimicag

# Switching from tenofovir disoproxil fumarate to tenofovir alafenamide or dual therapy-based regimens in HIV-infected individuals with viral load ≤50 copies/mL: does estimated glomerular filtration rate matter?

A. Vergori[a,*], R. Gagliardini[a], N. Gianotti[b], A. Gori[c], M. Lichtner[d], A. Saracino[e], A. De Vito[f], A. Cascio[g], A. Di Biagio[h], A. d'Arminio Monforte[i], A. Antinori[a], A. Cozzi-Lepri[l], on behalf of the ICONA Foundation Study Network[1]

[a] HIV/AIDS Unit, National Institute for Infectious Diseases 'L. Spallanzani', Institute of Hospitalization and Scientific Care (IRCCS), Via Portuense 292, 00149 Rome, Italy
[b] Infectious Diseases Department, San Raffaele Scientific Institute, IRCCS, Milan, Italy
[c] Infectious Diseases Unit, IRCCS Ca' Granda Ospedale Maggiore Policlinico Foundation, Centre for Multidisciplinary Research in Health Science (MACH), University of Milan, Milan, Italy
[d] Department of Public Health and Infectious Diseases, Sapienza University of Rome, Polo Pontino, Latina, Italy
[e] Clinic of Infectious Diseases, Department of Medical Biosciences and Human Oncology, University of Bari Aldo Moro, Bari, Italy
[f] Unit of Infectious Diseases, Department of Medical, Surgical and Experimental Sciences, University of Sassari, Sassari, Italy
[g] Infectious and Tropical Diseases Unit, Department of Health Promotion Sciences Maternal and Infantile Care, Internal Medicine and Medical Specialties (PROMISE), University of Palermo, Palermo, Italy
[h] Infectious Diseases Clinic, Department of Health Sciences, University of Genoa, Hospital San Martino, IRCCS, Genoa, Italy
[i] Institute of Infectious and Tropical Diseases, Department of Health Sciences, Santi Paolo e Carlo Hospital, University of Milan, Milan, Italy
[l] Centre for Clinical Research, Epidemiology, Modelling and Evaluation (CREME), Institute for Global Health, UCL, London, UK

ARTICLE INFO

*Article history:*
Received 26 February 2020
Accepted 29 August 2020

*Keywords:*
HIV
Tenofovir alafenamide
Tenofovir disoproxil fumarate
Antiretroviral therapy
eGFR
Dual therapy

ABSTRACT

Our aim was to evaluate the association between recent eGFR values and risk of switching from TDF to TAF or dual therapy (DT) in real life. HIV-positive patients achieving HIV-RNA ≤50 copies/mL for the first time after starting a TDF-based regimen were included. Kaplan–Meier (KM) curves and Cox regression models were used to estimate the time from TDF to switch to TAF or DT. 1486 participants were included: median (IQR) age 36 (30–42) years; baseline CKD-EPI eGFR 99.92 (86.47–111.4) mL/min/1.73m$^2$. We observed a consistently higher proportion of people with HIV-RNA ≤50 copies/mL who switched from TDF to TAF rather than to DT. By competing risk analysis, at 2 years from baseline, the probability of switching was 3.5% (95% CI 2.6–4.7%) to DT and 46.7% (42.8–48.5%) to TAF. A significantly higher probability of switching to TAF was found for patients receiving INSTI at baseline versus NNRTIs and PI/b [KM, 65.6% (61.7–69.4%) vs. 4.0% (1.8–6.1%) and 59.9% (52.7–67.2%), respectively; $P < 0.0001$]. eGFR <60 mL/min/1.73m$^2$ both as time-fixed covariate at baseline or as current value was associated with a higher risk of switching to DT [aHR 6.68 (2.69–16.60) and 8.18 (3.54–18.90); $P < 0.001$] but not to TAF-based cART [aHR 0.94 (0.39–2.31), $P = 0.897$; and 1.19 (0.60–2.38), $P = 0.617$]. Counter to our original hypothesis, current eGFR is used by clinicians to guide switches to DT but does not appear to be a key determinant for switching to TAF.



## 1. Introduction

With currently available combination antiretroviral therapy (cART), people living with human immunodeficiency virus (HIV) an achieve and maintain lifetime HIV viral suppression. Current guidelines continue to recommend the use of a three-drug combination regimen when switching patients with suppressed viral loads who

* Corresponding author. Tel.: +39 065 517 0420, +39 065 517 0546.
*E-mail address:* alessandra.vergori@inmi.it (A. Vergori).
[1] Members of the ICONA Foundation Study Network are listed in the Acknowledgments section.

https://doi.org/10.1016/j.ijantimicag.2020.106154

have never experienced virological failure and with no evidence of drug resistance [1–3], although there is growing evidence that some dual therapy (DT) regimens also optimally maintain virological suppression [4–8]. In the context of people currently receiving antiretroviral drugs associated with mild renal impairment, such as tenofovir disoproxil fumarate (TDF), one of the goals of switching strategies is to decrease short- or long-term toxicity, which could progress to nephrotoxicity due to long exposure to TDF [1–3]. Switching from TDF-containing regimens has increased considerably in recent years owing to the availability of alternative nucleoside reverse transcriptase inhibitor (NRTI) backbones, such as tenofovir alafenamide/emtricitabine (TAF/FTC), as well as the use of partially or totally NRTI-sparing DT combinations. As a matter of fact, advances in treatment and the availability of new molecules and co-formulations opened the possibility of switching patients to regimens containing drugs with more favourable toxicity profiles without experiencing a reduction in efficacy [1–3]. For example, randomised clinical trials (RCTs) have demonstrated that switching from TDF to TAF is associated with no change in viral suppression coupled with an improvement in proteinuria and renal biomarkers [9–15] as well as a reduction in the risk of tenofovir discontinuation to 0–3% [16–19] compared with that reported in clinical cohorts (7.4% by 2 years), particularly when co-administered with boosted protease inhibitors (PI/b). A previous analysis, performed in the ICONA Foundation Cohort, showed an increase of TDF discontinuation after 2015 by 14.3% [95% confidence interval (CI) 13.8–14.9%] among ART-naïve patients starting their first regimen with a TDF-based backbone; in this analysis, recent years and anchor drugs [PI/b and integrase strand transfer inhibitor (INSTI)] and, to a lesser extent, estimated glomerular filtration rate (eGFR) decline, were key factors associated with the probability of stopping TDF [20]; eGFR, especially <60 mL/min, appears to be a predictor for receiving TAF, as reported in other studies [21,22]. Nevertheless, robust estimates of the observed real-life rate of switching from TDF-based regimens in the distinct target population of people living with HIV with HIV-RNA ≤50 copies/mL in recent years are lacking; in addition, the role of eGFR as a potential determinant of these switches, specifically in relation to switches to TAF and DT regimens, after controlling for potential sources of confounding, remains poorly studied.

## 2. Materials and methods

### 2.1. Study population

This analysis includes data for HIV-infected individuals enrolled and prospectively followed up in the ICONA (Italian Cohort of Antiretroviral-Naïve Patients) Foundation Cohort. Briefly, ICONA is an Italian multicentre prospective observational cohort study set up in 1997, including HIV-1-infected subjects, naïve from ART at the time of enrolment, seen for care in Italy. To date, the cohort consists of more than 16 000 patients prospectively followed in 51 centres for infectious diseases across the country. Demographic, viro-immunological and clinical data as well as information on antiretroviral regimens are collected and recorded using an electronic database. Creatinine is measured on plasma samples collected as part of routine clinical visits on average twice per year for each participant. Details of the cohort have been described previously elsewhere [23]. Reasons for discontinuing drugs according to the treating physician are also reported on a standardised case report form (the main reason chosen from a pre-specified grid of options for stopping individual drug is reported). In the present analysis, we included patients who had achieved a stable viral load ≤50 copies/mL for the first time after starting a TDF-based triple cART (baseline) from 1 January 2016 (based on the availability of TAF/FTC regimen) to December 2019 and for whom this baseline date was after 1 January 2016. Patients testing positive for hepatitis B surface antigen and/or with an eGFR ≤30 mL/min/1.73m$^2$ [estimated by the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) formula] at baseline were excluded because use of DT and TAF, respectively, are not recommended in these patients. Two primary endpoints were used in the analysis: (i) time from baseline to a switch from TDF to a TAF-based regimen; and (ii) time from baseline to a switch from TDF to a TDF-sparing DT regimen. The main reasons for discontinuation of each antiretroviral as reported by the treating clinicians are available in the ICONA database. These reasons were ignored when defining each of the above endpoints. The ICONA Foundation study was approved by the Ethics Committee (institutional review board) of each participating institution. All of the individuals enrolled provided written informed consent at the time of enrolment. All procedures of the study were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

### 2.2. Objectives

The primary objective was two-fold: first, to provide an accurate estimate of the 2-year rate of switching from TDF to TAF-based cART or DT after baseline; and second, to study the association between baseline and current levels of eGFR and the probability of switching from TDF to DT or to TAF-based regimens. A secondary objective was to evaluate the association between the class of anchor drug used with TDF at entry in the study and risk of these same switching outcomes.

### 2.3. Statistical analysis

Patients' characteristics at baseline stratified by anchor drug class received were described and compared using statistical tests: non-parametric tests to compare medians of continuous variable and $\chi^2$ test to compare proportions for categorical variables. Standard survival analyses of time to switch by means of unweighted Kaplan–Meier (KM) curves were performed, separately for the two endpoints. A competing risk KM analysis was also conducted to jointly model the two endpoints. The main exposure of interest was baseline and current eGFR and we aimed to establish whether there was an association between eGFR and the probability of switching after controlling for confounding factors. In the analysis with endpoint the time to switch to TAF-based regimens, in a sensitivity analysis, an alternative endpoint definition was used by which switches to TAF/FTC + elvitegravir/cobicistat (EVG/c) were not counted as events as they could be triggered by reasons not strictly related to renal toxicity. In the main analysis, the association of current eGFR was evaluated using a marginal model controlling for time-varying confounding by inverse probability of weighting (see footnote to Table 3 for the list of variables included in the numerator and denominator of the weights). In a separate analysis, standard unadjusted and adjusted Cox regression analysis was used to estimate the effect of baseline covariates on the risk of switching for both endpoints. The focus in these analyses was on three key exposure factors: baseline eGFR; extent of co-morbidities (diabetes, hypertension, dyslipidaemia); and antiretroviral class of the third drug used in the TDF-based regimen [INSTI, non-nucleoside reverse transcriptase inhibitor (NNRTI) and PI/b]. The assumption here was that the three exposures of interest shared the same set of baseline potential confounders (i.e. calendar year of baseline, number of previous virological failures and nationality). Co-morbidities were defined as: (i) diabetes (glucose >126 mg/dL); (ii) hypertension (reported information and/or use of blood pressure-lowering drugs); and (iii) dyslipidaemia (fasting total cholesterol >200 mg/dL, LDL >100 mg/dL, HDL <40 mg/dL for females or <50 mg/dL for males, and triglycerides >150 mg/dL). All

**Table 1**
Baseline characteristics of study population ($N = 1486$ patients), overall and grouped by anchor drug

| Characteristic | Anchor drug in TDF-regimen | | | | Total ($N = 1486$) |
|---|---|---|---|---|---|
| | NNRTIs ($N = 425$) | PI/b ($N = 253$) | INSTI ($N = 808$) | *P*-value* | |
| Sex | | | | 0.609 | |
| Female [*n* (%)] | 87 (20.5) | 59 (23.3) | 166 (20.5) | | 312 (21.0) |
| Age (years) | | | | 0.017 | |
| Median (IQR) | 36 (30–42) | 38 (34–40) | 36 (28–44) | | 36 (30–42) |
| Mode of HIV transmission [*n* (%)] | | | | 0.110 | |
| IDU | 31 (7.3) | 18 (7.1) | 42 (5.2) | | 91 (6.1) |
| Homosexual contact | 217 (51) | 111 (43.9) | 391 (48.4) | | 719 (48.4) |
| Heterosexual contact | 144 (33.9) | 109 (43.1) | 301 (37.2) | | 554 (37.3) |
| Other/unknown | 33 (7.8) | 15 (5.9) | 74 (9.2) | | 122 (8.2) |
| Nationality [*n* (%)] | | | | 0.001 | |
| Non-Italian | 154 (36.2) | 104 (41.1) | 262 (32.4) | | 520 (35.0) |
| AIDS diagnosis [*n* (%)] | | | | <0.001 | |
| Yes | 11 (2.6) | 41 (16.2) | 133 (16.5) | | 185 (12.4) |
| HCV-Ab [*n* (%)] | | | | 0.014 | |
| Negative | 341 (80.2) | 200 (79.1) | 606 (75.0) | | 1147 (77.2) |
| Positive | 30 (7.1) | 18 (7.1) | 43 (5.3) | | 91 (6.1) |
| Not tested | 54 (12.7) | 35 (13.8) | 159 (19.7) | | 248 (16.7) |
| Calendar year of baseline | | | | 0.342 | |
| Median (IQR) | 2016 (2016–2017) | 2016 (2016–2017) | 2016 (2016–2017) | | 2016 (2016–2017) |
| $CD4^+$ T-cell count (cells/mm$^3$) | | | | <0.001 | |
| Median (IQR) | 629 (474–848) | 409 (245–590) | 483 (265–692) | | 520 (314–740) |
| $CD4^+$ T-cell nadir (cells/mm$^3$) | | | | <0.001 | |
| Median (IQR) | 468 (344–624) | 233 (110–409) | 311 (121–510) | | 359 (173–537) |
| $CD8^+$ T-cell count (cells/mm$^3$) | | | | 0.548 | |
| Median (IQR) | 917 (673–1313) | 912 (648–1262) | 920 (650–1268) | | 918 (656–1286) |
| Viral load ($log_{10}$ copies/mL) | | | | 0.256 | |
| Median (IQR) | 1.56 (0.00–1.59) | 1.53 (1.28–1.60) | 1.56 (0.00–1.60) | <0.001 | 1.56 (0.00–1.60) |
| Time from HIV diagnosis to date of starting cART (months) | | | | <0.001 | |
| Median (IQR) | 10 (5–41) | 8 (5–15) | 5 (3–11) | | 7 (4–17) |
| Diabetes [*n* (%)] | | | | <0.001 | |
| Yes | 2 (0.5) | 2 (0.8) | 30 (3.7) | | 34 (2.3) |
| Total cholesterol (mg/dL) | | | | <0.001 | |
| Median (IQR) | 163 (140–189) | 176 (152–205) | 166 (141–192) | | 166 (142–193) |
| HDL cholesterol (mg/dL) | | | | 0.712 | |
| Median (IQR) | 43 (35–51) | 41 (35–50) | 42 (34–50) | | 42 (35–51) |
| LDL cholesterol (mg/dL) | | | | | |
| Median (IQR) | 109 (89–133) | 111 (88–131) | 108 (86–131) | 0.673 | 109 (88–132) |
| Triglycerides | | | | | |
| Median (IQR) | 116 (85–162) | 136 (98–203) | 122 (91–176) | <0.001 | 123 (89–178) |
| Use of statins [*n* (%)] | | | | 0.011 | |
| Yes | 6 (1.4) | 4 (1.6) | 33 (4.1) | | 43 (2.9) |
| Use of blood pressure-lowering drugs [*n* (%)] | | | | 0.083 | |
| Yes | 18 (4.2) | 8 (3.2) | 51 (6.3) | | 77 (5.2) |
| eGFR (CKD-EPI formula) (mL/min/1.73m$^2$) | | | | <0.001 | |
| Median (IQR) | 102.7 (89.57–111.4) | 103.5 (89.25–114.3) | 97.26 (84.53–110.6) | | 99.92 (86.47–111.4) |
| eGFR <60 mL/min/1.73m$^2$ [*n* (%)] | 2 (0.5) | 6 (2.4) | 20 (2.5) | 0.04 | |
| Blood glucose (mg/dL) | | | | 0.174 | |
| Median (IQR) | 86 (80–93) | 88 (80–96) | 86 (79–93) | | 86 (80–94) |
| Follow-up (months) | | | | <0.001 | |
| Median (IQR) | 25 (16–35) | 13 (6–21) | 13 (6–20) | | 16 (8–26) |

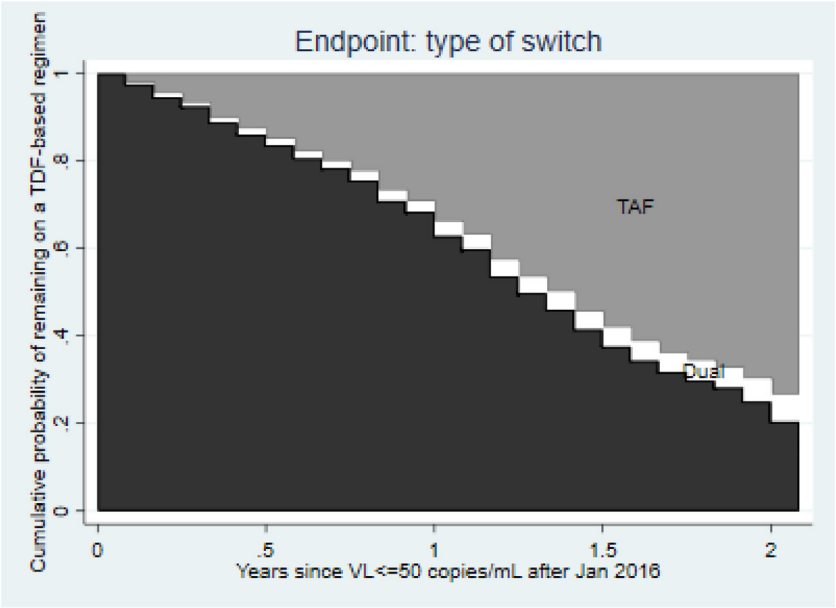
TDF, tenofovir disoproxil fumarate; NNRTI, non-nucleoside reverse transcriptase inhibitor; PI/b, boosted protease inhibitor; INSTI, integrase strand transfer inhibitor; IQR, interquartile range; HIV, human immunodeficiency virus; IDU, intravenous drug user; AIDS, acquired immune deficiency syndrome; HCV-Ab, hepatitis C virus antibody; cART, combination antiretroviral therapy; HDL, high-density lipoprotein; LDL, low-density lipoprotein; eGFR, estimated glomerular filtration rate; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration.
* $\chi^2$ or Kruskal–Wallis test, as appropriate.

statistical analyses were performed using SAS Statistical Software v.9.4 (SAS Institute Inc., Carey, NC, USA). All *P*-values presented are two-sided, and a *P*-value of <0.05 indicated conventional statistical significance.

## 3. Results

### 3.1. Patient characteristics

A total of 1486 HIV-positive patients were included in the analysis and followed for a median of 16 months [interquartile range (IQR) 8–26 months]. At baseline, 253 patients (17.0%) were on regimens combined with PI/b and 808 patients (54.4%) with INSTI, and the remaining 425 (28.6%) with NNRTIs; FTC was the most frequently used NRTI (99.7%), whilst the most commonly used anchor drugs were rilpivirine (RPV) (27%), EVG/c (26%), dolutegravir (DTG) (20%) and darunavir/ritonavir-boosted (DRV/r) (13%). The main characteristics of the study population at baseline, overall and according to anchor drug included in the TDF regimen received at baseline, are shown in Table 1. Briefly, 21.0% were female, 35.0% of non-Italian origin, with a median (IQR) age of 36 (30–42) years, $CD4^+$ T-cell count of 520 (314–740) cells/mm$^3$, HIV-RNA $log_{10}$ 1.56 (0.00–1.60) copies/mL, CKD-EPI eGFR 99.9 (86.4–111.4) mL/min/1.73m$^2$, 85.7% acquired HIV through unprotected sex [men who have sex with men (48.4%) and heterosexual (37.36%)] and 12.4% had been diagnosed with acquired immune deficiency syndrome (AIDS) before baseline. As expected, a higher proportion of patients with AIDS diagnosis before baseline was receiving at baseline a TDF-based combination regimen including an INSTI (16%) or PI/b (17%) vs. NNRTI (3%) ($P < 0.001$) and the CD4 nadir was




| | 2-year KM estimate (95% CI) |
|---|---|
| **DT** | 3.5% (95% CI 2.6-4.7) |
| **TAF-based regimen** | 46.7% (95% CI 42.8-48.5) |

**Abbreviations:** DT, dual therapy, TAF, tenofovir alafenamide

**Fig. 1.** Kaplan–Meier (KM) plot of time to therapy switch (competing risk analysis). VL, viral load; TDF, tenofovir disoproxil fumarate; TAF, tenofovir alafenamide; DT, dual therapy; CI, confidence interval.

also significantly lower in these two drug groups [233 (110–409) cells/mm$^3$ for PI/b and 311 (121–510) cells/mm$^3$ for INSTI, respectively] compared with the NNRTI group [468 (344–624) cells/mm$^3$] ($P < 0.001$). Participants who at baseline were receiving a TDF-based regimen combined with an INSTI showed on average a significantly lower baseline eGFR [97.26 (84.53–110.6) mL/min/1.73$^2$] versus PI/b [103.5 (89.25–114.3) mL/min/1.73$^2$] and NNRTIs [102.7 (89.57–111.4) mL/min/1.73$^2$] ($P < 0.001$). A total of 881 patients (59.3%) had at least one co-morbidity such as diabetes, dyslipidaemia and hypertension, 383 (25.8%) had two or more co-morbidities and 205 (13.8%) patients had no co-morbidities at baseline. There was no evidence for an unequal distribution of the extent of prior co-morbidities by anchor drug (data not shown; $P = 0.99$). The proportion of individuals with an eGFR <60 mL/min at baseline was low ($n = 28$; 1.9%), however for a number of participants their eGFR dropped to <60 mL/min over follow-up reaching a total of 75 (5.2%) with a value below this threshold.

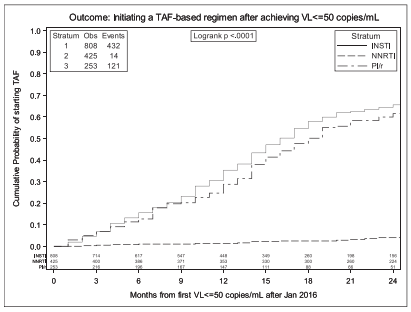
### *3.2. Probability of switching to a TAF-based regimen or to dual therapy*

In the joint competing risk approach to analysis, by 2 years from baseline, the probability of switch to DT was 3.5% (95% CI 2.6–4.7%) and to TAF-based cART was 46.7% (95% CI 42.8–48.5%) (Fig. 1). A significantly higher probability of switching to TAF-based regimen was found for those receiving INSTI at baseline [KM estimates: 65.6% (95% CI 61.7–69.4%) by 2 years, log-rank $P < 0.0001$ compared with PI/b (59.9%, 95% CI 52.7–67.2%) and NNRTI 4.0% (95% CI 1.8–6.1%)] (Fig. 2a), not confirmed in the alternative analysis, after excluding people using EVG/c, in which the highest probability of switch was found for PI/b ($P < 0.0001$) (Fig. 2b). Regarding switch to DT, a higher probability of switch for PI/b [7.9% (95% CI 3.7–12.1%), $P < 0.001$] compared with switches from TDF-regimens including an INSTI (5.6%; 95% CI 3.0–8.2%) or NNRTI (1.1%; 95% CI 0.0–2.1%) was found (Fig. 2c). We also calculated the probability of switching both to TAF-based and to DT regimens according to number of pre-existing co-morbidities (0, 1, ≥2) and no significant association was found (data not shown). After TDF discontinuation, 99% of patients receiving at baseline an INSTI-based regimen switched to TAF triple therapy combined with an INSTI, 82% switched from a PI/b-containing regimen to TAF/FTC/PI/b and only 3/14 (21.4%) patients on a NNRTI-based regimen changed their backbone with TAF/FTC continuing to take the same anchor drug class. Similarly, 71.0% (22/31) of patients who had switched to a DTG-based DT were previously receiving an INSTI regimen, 12.9% (4/31) were taking a PI/b and 16.1% (5/31) were on a NNRTI-based regimen. Overall, 52% patients switched to DTG + lamivudine (3TC) and 9% to DTG + RPV DT, whereas 13% switched to PI/b + 3TC. A detailed description of the composition of the regimen started after TDF discontinuation according to the initial anchor drug class is shown in Supplementary Tables S1 and S2.

### *3.3. Hazard of switching associated with baseline exposure factors: baseline eGFR, type of anchor drug used at baseline and extent of co-morbidities*

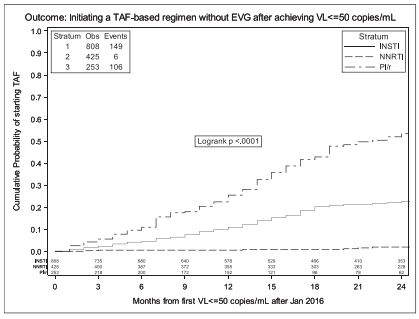
In a multivariable Cox regression analysis with time-fixed covariates at baseline, a more recent calendar year of baseline [adjusted hazard ratio (aHR) = 1.51 per 1 year (95% CI 1.31–1.74) and compared with NNRTIs, receiving at baseline TDF with PI/b

a)



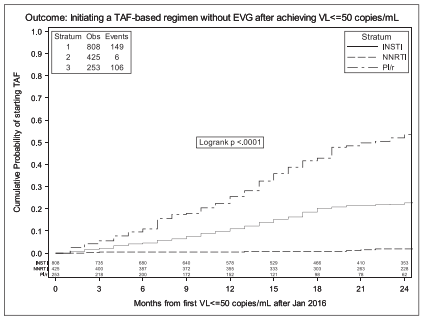

| Kaplan-Meier estimates of probability of switching to TAF-based cART | | |
|---|---|---|
| | No. switches by 24 months | 2-year percent (95% CI) |
| NNRTI | 13 | 4.0 (1.8, 6.1) |
| PI/b | 115 | 59.9 (52.7, 67.2) |
| INSTI | 424 | 65.6 (61.7, 69.4) |
| Total | 385 | 30.2 (27.7, 32.8) |

b)




| Kaplan-Meier estimates of probability of switching to TAF-based cART after excluding TAF/F/EVG/c | | |
|---|---|---|
| | No. switches by 24 months | 2-year percent (95% CI) |
| NNRTI | 6 | 1.9 (0.4, 3.4) |
| PI/b | 100 | 51.9 (44.6, 59.3) |
| INSTI | 145 | 22.6 (19.3, 25.9) |
| Total | 166 | 13.0 (11.2, 14.9) |

c)




| Kaplan-Meier estimates of probability of switching to DT | | |
|---|---|---|
| | No. switches by 24 months | 2-year percent (95% CI) |
| NNRTI | 4 | 1.1 (0.0, 2.1) |
| PI/b | 14 | 7.9 (3.7, 12.1) |
| INSTI | 22 | 5.6 (3.0, 8.2) |
| Total | 35 | 3.2 (2.1, 4.2) |

**Fig. 2.** Probability of switching to (a) tenofovir alafenamide (TAF)-based therapy, (b) TAF-based therapy after excluding people using elvitegravir/cobicistat (EVG/c) and (c) dual therapy (DT) according to anchor drug of the tenofovir disoproxil fumarate (TDF)-based regimen. VL, viral load; INSTI, integrase strand transfer inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; PI/b, boosted protease inhibitor; CI, confidence interval.

HR = 24.57 (95% CI 14.05–42.96) and with INSTI HR = 27.97 (95% CI 16.35–47.84); $P < 0.001$] were independently associated with a higher probability of switching to a TAF-based regimen (Table 2A). In the sensitivity analysis of the time to switch to TAF-based cART, when switches to EVG/c-based regimens were not counted as events, the risk of switching to a TAF-based regimen remained significantly higher for PI/b and INSTI [HR = 36.62 vs. NNRTI (95% CI 15.96–84.02) and HR = 12.90 vs. NNRTI (5.66–29.37), respectively; for both $P < 0.001$] (Table 2B). For the switching to DT endpoint, receiving TDF in combination with a PI/b-based regimen at baseline and a lower baseline eGFR (0–59 mL/min/1.73m$^2$) were independently associated with a higher probability of both studied endpoints [HR = 6.16 (95% CI 2.35–16.11), $P < 0.001$ for the time to switch to DT cART; and HR = 10.68 (95% CI 3.84–29.72), $P = 0.001$ for the time to switch to DT, respectively] (Table 2C).

### 3.4. Association between eGFR and the probability of switching

In the unadjusted analysis of the time to switch to TAF-based cART (the alternative endpoint in which switches to EVG/c-based regimens were not counted as events), an eGFR < 60 mL/min/1.73m$^2$ was not associated with the probability of switching to a TAF-based regimen ($P = 0.4819$) (Fig. 3a). In contrast, when evaluating the switch to DT, still in the unadjusted analysis, a higher probability of switch was found in people with an eGFR <60 mL/min/1.73m$^2$ (30.2%, 95% CI 11.1–49.4; $P < 0.001$) (Fig. 3b). In the adjusted analyses, an eGFR <60 mL/min/1.73m$^2$, both as time-fixed at baseline [aHR from fitting a standard Cox regression model with fixed covariates 6.68 (95% CI 2.69–16.60); $P < 0.001$] or as current value [aHR from fitting a weighted marginal Cox regression model 8.18 (95% CI 3.54–18.90); $P < 0.001$] was associated with a higher probability of switch to DT but not to TAF-based cART (Table 3).

## 4. Discussion

In our cohort of HIV-positive patients who were receiving a TDF-based cART regimen with a viral load ≤50 copies/mL after January 2016 (baseline), the probability of switching from TDF was ~47% to a TAF-based regimen and 4% to DT by 2 years from baseline. Our estimate of the rate of TAF modification is included in the range of those found in similar analyses of data from other European cohorts of patients switching from a TDF-containing regimen: 56% in the Swiss cohort and 34% by 2 years in a cohort in Germany. In both analyses, the main reason for switching was prevention of renal/bone toxicity [21,24]. Higher rates of switch to TAF were found in a retrospective analysis of four treatment centres in the USA showing 86% of patients receiving TAF by 1 year because of renal dysfunction [22]. The higher observed rate of switching to TAF compared with DT could be due to the fact that the amount of evidence coming from randomised studies in recent years is much larger for switches to TAF-based triple regimen compared with switches to DT, which is still considered as a novel potentially risky strategy. Switch to DT more specifically tends to occur to overcome cART toxicity, reducing the potential for drug–drug interactions and costs, by means of concomitant use of raltegravir [25,26], 3TC [4–6] or RPV [27] with PI/b or, in recent years, combining 3TC [8,28–30], PI/b [31] or RPV [7] with DTG. Despite data from RCTs [32–34] demonstrating a more favourable impact of TAF on renal safety, a key result of this analysis was that the switches to TAF-based regimens did not appear to be driven by current eGFR <60 mL/min/1.73m$^2$. In contrast, a current low eGFR level appears to significantly increase the odds of switching to DT. In other words, these results suggest that, in clinical practice, upon the observation of a current value of eGFR below a level indicating renal toxicity, a switch to TDF-sparing DT is pos-

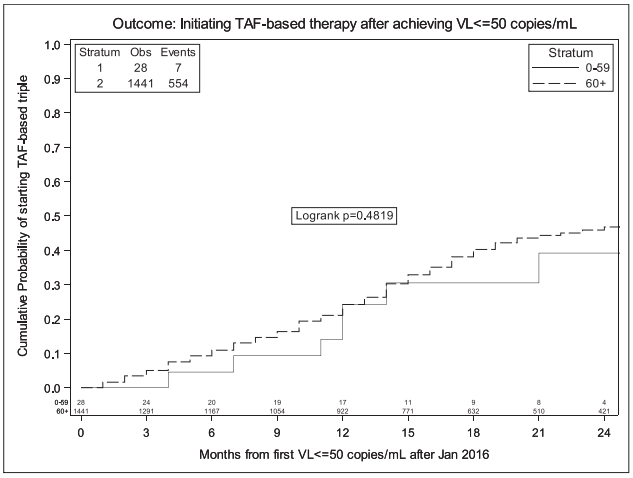
**Table 2**
Relative hazard ratios (HRs) of (A) tenofovir alafenamide (TAF) initiation, (B) TAF initiation with exclusion of elvitegravir/cobicistat (EVG/c) and (C) dual therapy initiation from fitting a Cox regression model

| | Unadjusted HR (95% CI) | *P*-value | Adjusted* HR (95% CI) | *P*-value |
|---|---|---|---|---|
| (A) TAF initiation | | | | |
| Baseline eGFR (mL/min/1.73m$^2$) | | | | |
| ≥60 | 1.00 | | 1.00 | |
| 0–59 | 0.77 (0.36–1.62) | 0.484 | 0.55 (0.26–1.17) | 0.119 |
| No. of co-morbidities[a] | | | | |
| 0 | 1.00 | | 1.00 | |
| 1 | 1.06 (0.82–1.37) | 0.648 | 1.14 (0.87–1.48) | 0.348 |
| ≥2 | 0.97 (0.73–1.29) | 0.844 | 1.11 (0.82–1.50) | 0.512 |
| Calendar year of viral load ≤50 copies/mL | | | | |
| Per more recent | 1.32 (1.16–1.52) | <0.001 | 1.51 (1.31–1.74) | <0.001 |
| Nationality | | | | |
| Italian | 1.00 | | 1.00 | |
| Foreign | 0.95 (0.79–1.14) | 0.600 | 0.89 (0.73–1.09) | 0.270 |
| No. of previous virological failures | | | | |
| Per extra drug | 1.01 (0.76–1.35) | 0.921 | 0.93 (0.70–1.23) | 0.603 |
| Anchor drug | | | | |
| NNRTI | 1.00 | | 1.00 | |
| INSTI | 25.21 (14.79–42.97) | <0.001 | 27.97 (16.35–47.84) | <0.001 |
| PI/b | 22.06 (12.67–38.41) | <0.001 | 24.57 (14.05–42.96) | <0.001 |
| (B) TAF initiation with exclusion of EVG/c | | | | |
| Baseline eGFR (mL/min/1.73m$^2$) | | | | |
| ≥60 | 1.00 | | 1.00 | |
| 0–59 | 1.40 (0.58–3.41) | 0.457 | 1.07 (0.43–2.65) | 0.882 |
| No. of co-morbidities[a] | | | | |
| 0 | 1.00 | | 1.00 | |
| 1 | 0.86 (0.60–1.23) | 0.411 | 0.93 (0.64–1.35) | 0.712 |
| ≥2 | 0.85 (0.57–1.26) | 0.417 | 0.80 (0.53–1.22) | 0.307 |
| Calendar year of viral load ≤50 copies/mL | | | | |
| Per more recent | 1.46 (1.20–1.78) | <0.001 | 1.49 (1.21–1.83) | <0.001 |
| Nationality | | | | |
| Italian | 1.00 | | 1.00 | |
| Foreign | 0.96 (0.74–1.26) | 0.777 | 0.84 (0.63–1.14) | 0.268 |
| No. of previous virological failures | | | | |
| Per extra drug | 1.12 (0.79–1.58) | 0.519 | 0.93 (0.65–1.33) | 0.689 |
| Anchor drug | | | | |
| NNRTI | 1.00 | | 1.00 | |
| INSTI | 14.93 (6.60–33.81) | <0.001 | 12.90 (5.66–29.37) | <0.001 |
| PI/b | 41.37 (18.15–94.29) | <0.001 | 36.62 (15.96–84.02) | <0.001 |
| (C) Dual therapy initiation | | | | |
| Baseline eGFR (mL/min/1.73m$^2$) | | | | |
| ≥60 | 1.00 | | 1.00 | |
| 0–59 | 8.44 (3.65–19.49) | <0.001 | 10.68 (3.84–29.72) | 0.006 |
| No. of co-morbidities[a] | | | | |
| 0 | 1.00 | | 1.00 | |
| 1 | 1.26 (0.48–3.31) | 0.639 | 1.17 (0.39–3.46) | 0.781 |
| ≥2 | 1.45 (0.52–4.05) | 0.479 | 0.91 (0.28–3.00) | 0.879 |
| Calendar year of viral load ≤50 copies/mL | | | | |
| Per more recent | 1.00 (0.59–1.71) | 0.989 | 0.98 (0.54–1.78) | 0.947 |
| Nationality | | | | |
| Italian | 1.00 | | 1.00 | |
| Foreign | 0.54 (0.26–1.13) | 0.104 | 0.57 (0.25–1.31) | 0.184 |
| No. of previous virological failures | | | | |
| Per extra drug | 1.60 (1.07–2.39) | 0.021 | 1.74 (1.09–2.77) | 0.020 |
| Anchor drug | | | | |
| NNRTI | 1.00 | | 1.00 | |
| INSTI | 2.64 (1.12–6.22) | 0.026 | 2.07 (0.84–5.10) | 0.114 |
| PI/b | 6.27 (2.53–15.54) | <0.001 | 6.16 (2.35–16.11) | <0.001 |

CI, confidence interval; eGFR, estimated glomerular filtration rate; NNRTI, non-nucleoside reverse transcriptase inhibitor; INSTI, integrase strand transfer inhibitor; PI/b, boosted protease inhibitor.
* For the variables listed in this table.
[a] Diabetes, dyslipidaemia and hypertension.

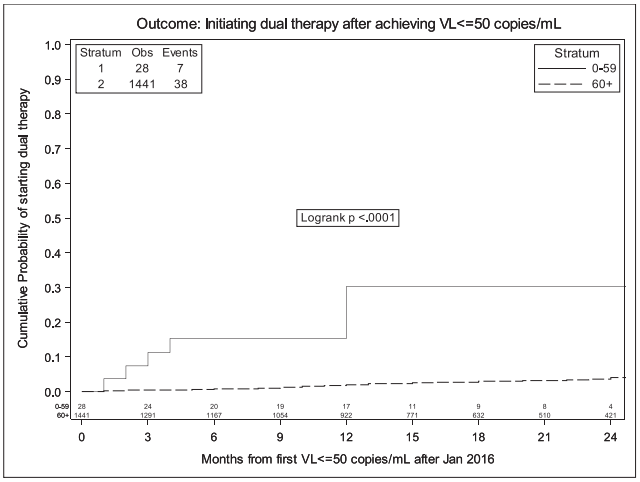
sibly preferred to a switch to TAF-based cART. Whether clinicians might use eGFR in combination with other laboratory parameters (e.g. proteinuria or other abnormalities of urine biomarkers) for their decision to switch remains to be established, as unfortunately these additional markers are not collected in our database. From fitting a multivariable standard Cox regression analysis, we also found that people receiving TDF/FTC combined with INSTI at baseline were at increased probability of switching to TAF. The association was particularly strong in the analysis counting the switches to TAF/FTC/EVG/c as events, whilst no association was found with the probability of switching to DT. The most likely explanation for the results is the availability of TAF/FTC/EVG/c since 2016; indeed, starting from this year, the switch to TAF/FTC/EVG/c became popular in clinical practice as it was shown in RCTs to be beneficial to TDF/FTC/EVG/c users, without additional disadvantage in terms of virological suppression, tolerability or difference in cost [9,12–14]. In contrast, a switch from TDF/FTC/RPV to TAF/FTC/EVG/c could be discouraged because it would imply also a change of the anchor

a)




| Kaplan-Meier estimates of probability of switching to TAF-based cART after excluding TAF/F/EVG/c | | |
|---|---|---|
| | **No. switches by 24 months** | **2-year percent (95% CI)** |
| 60+ | 534 | 45.9 (43.0, 48.8) |
| 0-59 | 7 | 39.2 (15.1, 63.3) |
| Total | 541 | 45.8 (42.9, 48.7) |

b)




| Kaplan-Meier estimates of probability of switching to TAF-based cART after excluding TAF/F/EVG/c | | |
|---|---|---|
| | **No. switches by 24 months** | **2-year percent (95% CI)** |
| 60+ | 25 | 2.3 (1.4, 3.2) |
| 0-59 | 7 | 30.2 (11.1, 49.4) |
| Total | 34 | 3.1 (2.1, 4.1) |

**Fig. 3.** Kaplan–Meier plot of time to (a) tenofovir alafenamide (TAF) initiation [elvitegravir/cobicistat (EVG/c) not counted as an event] and (b) dual therapy initiation by baseline estimated glomerular filtration rate (eGFR). VL, viral load; CI, confidence interval.

**Table 3**
Relative hazard ratios (HRs) of (a) TAF-based therapy and (b) dual therapy (DT) initiation from fitting a Cox regression model–association with time-dependent eGFR after excluding people switching to EVG/c

| | HR (95% CI) Unadjusted | Adjusted[1] | Adjusted[2] |
|---|---|---|---|
| (a) HR of switching to TAF-based regimen from fitting a Cox regression analysis (TAF/FTC/EVG/c not counted as an event) | | | |
| eGFR (mL/min/1.73m$^2$) | | | |
| Baseline value | | | |
| ≥60 | 1.00 | 1.00 | |
| 0–59 | 1.24 (0.51–3.00) $P = 0.640$ | 0.94 (0.39–2.31) $P = 0.897$ | |
| Most recent value | | | |
| ≥60 | 1.00 | 1.00 | 1.00 |
| 0–59 | 1.52 (0.78–2.93) $P = 0.217$ | 1.17 (0.59–2.34) $P = 0.657$ | 1.19 (0.60–2.38) $P = 0.617$ |
| (b) HR of switching to dual therapy regimens from fitting a Cox regression analysis | | | |
| eGFR (mL/min/1.73m$^2$) | | | |
| Baseline value | | | |
| ≥60 | 1.00 | 1.00 | |
| 0–59 | 9.03 (3.89–20.98) $P < 0.001$ | 6.68 (2.69–16.60) $P < 0.001$ | |
| Most recent value | | | |
| ≥60 | 1.00 | 1.00 | 1.00 |
| 0–59 | 9.18 (4.49–18.77) $P < 0.001$ | 8.41 (3.74–18.88) $P < 0.001$ | 8.18 (3.54, 18.90) $P < 0.001$ |

TAF, tenofovir alafenamide; eGFR, estimated glomerular filtration rate; EVG/c, elvitegravir/cobicistat; CI, confidence interval; FTC, emtricitabine; cART, combination antiretroviral therapy; TDF, tenofovir disoproxil fumarate.
** (1) Adjusted for age, calendar year of cART initiation, number of concomitant co-morbidities, number of drugs failed prior to baseline, baseline CD4$^+$ T-cell count, type of anchor drug of TDF-based regimen and current CD4$^+$ T-cell count fitted as time dependent. (2) Adjusted for age, calendar year of cART initiation, number of concomitant co-morbidities, number of drugs failed prior to baseline, baseline CD4$^+$ T-cell count, type of anchor drug of TDF-based regimen and current CD4$^+$ T-cell count using inverse probability of weighting.

drug class. In addition, because of the results of the GS-US-366-1216 study [13], clinicians might have been reluctant to change to a TAF/RPV-based regimen for fear of worsening of the patient's lipid profile. Similarly, in the Swiss cohort analysis, 30% of patients at risk of TDF toxicity and who did not switch to TAF during the observation period were on a NNRTI-based regimen and it appeared to be an important reason for remaining on a TDF backbone [24]. All of these hypotheses are conceivable, although speculative. This cART modification appeared to be dictated by convenience and not strictly related to renal toxicity. For this reason, we also performed an alternative analysis in which switches to EVG/c-based cART were not counted as events. Indeed, in this analysis, the association with the anchor drug used at baseline (the effect of INSTI) was largely attenuated. Of note, this same tendency was not seen for other single-tablet regimens such as TAF/FTC/RPV (for the reasons we speculated above) or TAF/FTC/DRV/r, which had been only recently approved at the time of the analysis.

In contrast, the use of PI/b regimen in combination with a TDF-based regimen at baseline was associated with a higher risk of switching from TDF to both a TAF-based and a DT regimen. The fact that concomitant use of TDF with a PI/b leads to a higher risk of TDF discontinuation than that seen with other anchor drugs has been previously shown and it is probably due to the worse renal damage associated with the use of PI/b-based regimens [19,35–37]. These results are likely to be affected by the epochal context, in which the data from RCTs on newer and safer strategies of switch from TDF to TAF were certainly greater than the amount of data available for DT (particularly for DTG + 3TC). Indeed, we have to consider that DT is becoming more frequent only in recent calendar years, following the results from RCTs on DTG-based DTs both in naive and experienced patients [28–30,37].

Our analysis has a number of limitations that need to be mentioned. First, the analysis was conducted in an observational setting so unmeasured and residual confounding bias is likely to be an issue. Also, evaluation of the association between current eGFR and the risk of switching relies on the fact that the underlying model is correctly specified (e.g. all measured common causes of a modification in eGFR and probability of switching have been correctly accounted for and we did not inappropriately control for mediators or colliders). Also, the median age of our participants was 36 years so the magnitude of the estimated effect cannot be directly applied to the average prevalent patient living with HIV who is typically older. Last but not least, the issue of trying to evaluate whether a modification of eGFR might cause treatment switches is intrinsically problematic. Some argue that it is not a 'well-defined intervention' because eGFR can be modified in a number of different ways and the key condition for the identifiability of causal effects from observational data does not hold [38]. Renal function was evaluated solely by eGFR because other markers of renal impairment, such as urine dipstick analysis, phosphataemia or glycosuria, were not available for analysis. eGFR was calculated from creatinine, which is not as accurate as using cystatin C [39]. Similarly, therapy switches could also be triggered by bone health data, which are also not collected in our database. Furthermore, it would have been important to relate the risk of switching to the actual TDF concentration levels, but unfortunately values of therapeutic drug monitoring for antivirals are also not collected in the ICONA database.

In conclusion, our analysis shows that a consistent proportion of people with a viral load $\leq$50 copies/mL in recent years have been switched from TDF to alternative strategies. The switch to a TAF-based cART was much more common with a rate of 46.7% vs. 3.5% by 2 years of people switching to DT. Both the eGFR observed at entry in this study and the most recently observed value appears to trigger switches to DT but not those to TAF-based cART regimens.

**Acknowledgments**

Members of the ICONA Foundation Study Group are as follows: Board of Directors: A. d'Arminio Monforte (President), A. Antinori (Vice-President), M. Andreoni, A. Castagna, F. Castelli, R. Cauda, G. Di Perri, M. Galli, R. Iardino, G. Ippolito, A. Lazzarin, G.C. Marchetti, G. Rezza, F. von Schloesser and P. Viale; Scientific Secretary: A. d'Arminio Monforte, A. Antinori, A. Castagna, F. Ceccherini-Silberstein, A. Cozzi-Lepri, E. Girardi, A. Gori, S. Lo Caputo, F. Maggiolo, C. Mussini, M. Puoti and C.F. Perno; Steering Committee: A. Antinori, F. Bai, A. Bandera, S. Bonora, M. Borderi, A. Calcagno, M.R. Capobianchi, A. Castagna, F. Ceccherini-Silberstein, S. Cicalini, A. Cingolani, P. Cinque, A. Cozzi-Lepri, A. d'Arminio Monforte, A. Di Biagio, R. Gagliardini, E. Girardi, N. Gianotti, A. Gori, G. Guaraldi, G. Lapadula, M. Lichtner, A. Lai, S. Lo Caputo, G. Madeddu, F. Maggiolo, G. Marchetti, E. Merlini, C. Mussini, S. Nozza, C.F. Perno, S. Piconi, C. Pinnetti, M. Puoti, E. Quiros Roldan, R. Rossotti, S. Rusconi, M.M. Santoro, A. Saracino, L. Sarmati, V. Spagnuolo, V. Svicher and L. Taramasso; Statistical and Monitoring Team: A. Cozzi-Lepri, I. Fanti, L. Galli, P. Lorenzini, A. Rodano', M. Macchia and A. Tavelli; Community Advisory Board: A. Bove, A. Camposeragna, M. Errico, M. Manfredini, A. Perziano and V. Calvino; Biological Bank INMI: F. Carletti, S. Carrara, A. Di Caro, S. Graziano, F. Petroni, G. Prota and S. Truffa; Participating Physicians and Centres: A. Giacometti, A. Costantini, V. Barocci (Ancona); G. Angarano, L. Monno, E. Milano (Bari); F. Maggiolo, C. Suardi (Bergamo); P. Viale, V. Donati, G. Verucchi (Bologna); F. Castelnuovo, C. Minardi, E. Quiros Roldan (Brescia); B. Menzaghi, C. Abeli (Busto Arsizio); L. Chessa, F. Pes (Cagliari); B. Cacopardo, B. Celesia (Catania); J. Vecchiet, K. Falasca (Chieti); A. Pan, S. Lorenzotti (Cremona); L. Sighinolfi, D. Segala (Ferrara); P. Blanc, F. Vichi (Firenze); G. Cassola, M. Bassetti, A. Alessandrini, N. Bobbio, G. Mazzarello (Genova); M. Lichtner, L. Fondaco (Latina); P. Bonfanti, C. Molteni (Lecco); A. Chiodera, P. Milini (Macerata); G. Nunnari, G. Pellicanò (Messina); A. d'Arminio Monforte, M. Galli, A. Lazzarin, G. Rizzardini, M. Puoti, A. Castagna, E.S. Cannizzo, M.C. Moioli, R. Piolini, D. Bernacchia, A. Poli, C. Tincati, (Milano); C. Mussini, C. Puzzolante (Modena); C. Migliorino, G. Lapadula (Monza); V. Sangiovanni, G. Borgia, V. Esposito, G. Di Flumeri, I. Gentile, V. Rizzo (Napoli); A.M. Cattelan, S. Marinello (Padova); A. Cascio, C. Colomba (Palermo); D. Francisci, E. Schiaroli (Perugia); G. Parruti, F. Sozio (Pescara); C. Lazzaretti, R. Corsini (Reggio Emilia); M. Andreoni, A. Antinori, R. Cauda, A. Cristaudo, V. Vullo, R. Acinapura, S. Lamonica, M. Capozzi, A. Mondi, A. Cingolani, M. Rivano Capparuccia, G. Iaiani, A. Latini, G. Onnelli, M.M. Plazzi, G. De Girolamo, A. Vergori (Roma); M. Cecchetto, F. Viviani (Rovigo); G. Madeddu, A. De Vito (Sassari); B. Rossetti, F. Montagnani (Siena); A. Franco, R. Fontana Del Vecchio (Siracusa); C. Di Giuli (Terni); P. Caramello, G. Di Perri, S. Bonora, G.C. Orofino, M. Sciandra (Torino); C. Tascini, A. Londero (Udine); V. Manfrin, G. Battagin (Vicenza); G. Starnini, A. Ialungo (Viterbo).

**Funding:** The ICONA Foundation is supported by unrestricted grants from Gilead Sciences, Janssen, MSD and ViiV Healthcare. The funders had no role in study design, data collection, analysis, decision to publish or preparation of the manuscript.

**Competing interests:** The authors have no competing interests that might be perceived to influence the results and/or discussion reported in this paper. However, AV has received research institutional grants from Gilead Sciences, travel grants from Gilead Sciences and Janssen-Cilag, and speaker's honoraria from Janssen-Cilag; RG has received travel grants from Gilead Sciences, Janssen and ViiV, grants for speakers' honoraria/educational activities from ViiV Healthcare and MSD, grants for advisory board from ViiV Healthcare, and research institutional grants from Gilead Sciences; NG has been an advisor for Gilead Sciences, AbbVie and Janssen-Cilag and has received speakers' honoraria from Gilead Sciences, ViiV Healthcare, Bristol-Myers Squibb and Merck Sharp

and Dohme; AG has served as a paid consultant to Gilead Sciences, Janssen-Cilag, Merck, ViiV Healthcare, Pfizer and Angelini and has received research institutional grants from Gilead Sciences, Janssen-Cilag, ViiV Healthcare, Cilag, Merck, ViiV Healthcare and Pfizer; ADB has served as a paid consultant to Gilead Sciences, Janssen-Cilag, Merck and ViiV Healthcare and has received research institutional grants from Gilead Sciences and ViiV Healthcare; AdAM and/or her institution has received grants for research, honoraria for lectures or for advisory boards and invitation to conferences by AbbVie, Gilead, Janssen, ViiV, MSD and Angelini; AA has served as a paid consultant to Gilead Sciences, Janssen-Cilag, Merck and ViiV Healthcare and has received research institutional grants from Gilead Sciences, Janssen-Cilag and ViiV Healthcare. All other authors declare no competing interests.

**Ethical approval:** The ICONA Foundation study was approved by the Ethics Committee (institutional review board) of each participating institution. All of the individuals enrolled provided written informed consent at the time of the enrolment. All procedures of the study were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

## Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijantimicag.2020.106154.

## References

[1] AIDSinfo. Guidelines for the use of antiretroviral agents in adults and adolescents with HIV. US Department of Health and Human Services; 2018. https://aidsinfo.nih.gov/guidelines/html/1/adult-and-adolescent-arv-guidelines/31/adverse-effects-of-arv [accessed 11 September 2020].
[2] European AIDS Clinical Society (EACS). EACS guidelines, Version n.10.0. EACS; 2019. http://www.eacsociety.org/files/2019_guidelines-10.0-english.pdf [accessed 11 September 2020].
[3] Società Italiana Malattie Infettive e Tropicali (SIMIT). Utilizzo dei farmaci antiretrovirali e gestione diagnostico-clinica delle persone con infezione da HIV-1; 8 edizione, 2017 [Use of antiretroviral drugs and diagnostic-clinical management of people with HIV-1 infection; 8 edition, 2017]. http://www.salute.gov.it/imgs/C_17_pubblicazioni_2696_allegato.pdf [accessed 11 September 2020].
[4] Perez-Molina JA, Rubio R, Rivero A, Pasquau J, Suárez-Lozano I, Riera M, et al. GESIDA 7011 Study Group. Dual treatment with atazanavir–ritonavir plus lamivudine versus triple treatment with atazanavir–ritonavir plus two nucleos(t)ides in virologically stable patients with HIV-1 (SALT): 48 week results from a randomised, open-label, non-inferiority trial. Lancet Infect Dis 2015;15:775–84. doi:10.1016/S1473-3099(15)00097-3.
[5] Fabbiani M, Gagliardini R, Ciccarelli N, et al. ATLAS-M Study Group. Atazanavir/ritonavir with lamivudine as maintenance therapy in virologically suppressed HIV-infected patients: 96 week outcomes of a randomized trial. J Antimicrob Chemother 2018;73:1955–64. doi:10.1093/jac/dky123.
[6] Pulido F, Ribera E, Lagarde M, et al. DUAL-GESIDA-8014-RIS-EST45 Study Group. Dual therapy with darunavir and ritonavir plus lamivudine vs triple therapy with darunavir and ritonavir plus tenofovir disoproxil fumarate and emtricitabine or abacavir and lamivudine for maintenance of human immunodeficiency virus type 1 viral suppression: randomized, open-label, noninferiority DUAL-GESIDA 8014-RIS-EST45 Trial. Clin Infect Dis 2017;65:2112–18. doi:10.1093/cid/cix734.
[7] Llibre JM, Hung CC, Brinson C, et al. Efficacy, safety, and tolerability of dolutegravir–rilpivirine for the maintenance of virological suppression in adults with HIV-1: phase 3, randomised, non-inferiority SWORD-1 and SWORD-2 studies. Lancet 2018;391:839–49. doi:10.1016/S0140-6736(17)33095-7.
[8] van Wyk J, Ajana F, Bisshop F, et al. Efficacy and safety of switching to dolutegravir/lamivudine fixed-dose two-drug regimen versus continuing a tenofovir alafenamide-based three- or four-drug regimen for maintenance of virologic suppression in adults with HIV-1: phase 3, randomized, non-inferiority TANGO Study. Clin Infect Dis 2020 Jan 6 [Epub ahead of print]. doi:10.1093/cid/ciz1243.
[9] Raffi F, Orkin C, Clarke A, et al. Brief report: Long-term (96-week) efficacy and safety after switching from tenofovir disoproxil fumarate to tenofovir alafenamide in HIV-infected, virologically suppressed adults. J Acquir Immune Defic Syndr 2017;75:226–31. doi:10.1097/QAI.0000000000001344.
[10] Orkin C, Molina JM, Negredo E, et al. EMERALD Study Group. Efficacy and safety of switching from boosted protease inhibitors plus emtricitabine and tenofovir disoproxil fumarate regimens to single-tablet darunavir, cobicistat, emtricitabine, and tenofovir alafenamide at 48 weeks in adults with virologically suppressed HIV-1 (EMERALD): a phase 3, randomised, non-inferiority trial. Lancet HIV 2018;5 e23–34. doi:10.1016/S2352-3018(17)30179-0.
[11] Molina JM, Ward D, Brar I, et al. Switching to fixed-dose bictegravir, emtricitabine, and tenofovir alafenamide from dolutegravir plus abacavir and lamivudine in virologically suppressed adults with HIV-1: 48 week results of a randomised, double-blind, multicentre, active-controlled, phase 3, non-inferiority trial. Lancet HIV 2018;5:e357–65. doi:10.1016/S2352-3018(18)30092-4.
[12] DeJesus E, Haas B, Segal-Maurer S, et al. Superior efficacy and improved renal and bone safety after switching from a tenofovir disoproxil fumarate- to a tenofovir alafenamide-based regimen through 96 weeks of treatment. AIDS Res Hum Retroviruses 2018;34:337–42. doi:10.1089/AID.2017.0203.
[13] Orkin C, DeJesus E, Ramgopal M, et al. Switching from tenofovir disoproxil fumarate to tenofovir alafenamide coformulated with rilpivirine and emtricitabine in virally suppressed adults with HIV-1 infection: a randomised, double-blind, multicentre, phase 3b, non-inferiority study. Lancet HIV 2017;4 e195–204. doi:10.1016/S2352-3018(17)30031-0.
[14] Post FA, Tebas P, Clarke A, et al. Brief report: Switching to tenofovir alafenamide, coformulated with elvitegravir, cobicistat, and emtricitabine, in HIV-infected adults with renal impairment: 96-week results from a single-arm, multicenter, open-label phase 3 study. J Acquir Immune Defic Syndr 2017;74:180–4. doi:10.1097/QAI.0000000000001186.
[15] Winston A, Post FA, DeJesus E, et al. Tenofovir alafenamide plus emtricitabine versus abacavir plus lamivudine for treatment of virologically suppressed HIV-1-infected adults: a randomised, double-blind, active-controlled, non-inferiority phase 3 trial. Lancet HIV 2018;5 e162–71. doi:10.1016/S2352-3018(18)30010-9.
[16] Daar ES, Tierney C, Fischl MA, et al. Atazanavir plus ritonavir or efavirenz as part of a 3-drug regimen for initial treatment of HIV-1. Ann Intern Med 2011;154:445–56. doi:10.7326/0003-4819-154-7-201104050-00316.
[17] Molina JM, Andrade-Villanueva J, Echevarria J, et al. Once-daily atazanavir/ritonavir compared with twice-daily lopinavir/ritonavir, each in combination with tenofovir and emtricitabine, for management of antiretroviral-naive HIV-1-infected patients: 96-week efficacy and safety results of the CASTLE study. J Acquir Immune Defic Syndr 2010;53:323–32. doi:10.1097/QAI.0b013e3181c990bf.
[18] Smith KY, Patel P, Fine D, et al. Randomized, double-blind, placebo matched, multicenter trial of abacavir/lamivudine or tenofovir/emtricitabine with lopinavir/ritonavir for initial HIV treatment. AIDS 2009;23:1547–56. doi:10.1097/QAD.0b013e32832cbcc2.
[19] Costarelli S, Cozzi-Lepri A, Lapadula G, et al. Long-term durability of tenofovir-based antiretroviral therapy in relation to the co-administration of other drug classes in routine clinical practice. PLoS One 2016;11 e0160761. doi:10.1371/journal.pone.0160761.
[20] Vergori A, Lorenzini P, Cozzi Lepri A, Maggiolo F, Lapadula G, De Luca A, et al. on behalf of ICONA Foundation Study Group. Incidence and determinants of antiretroviral switching away from TDF-based backbone in recent years in the Icona Foundation Cohort. In: HIV Glasgow 2018, 28–31 October 2018, Glasgow, UK [abstract P100]. J Int AIDS Soc 2018;21(Suppl 8):e25187.
[21] Bickel M, Wyen C, Spinner C, Baumgarten A. Switch from tenofovir disoproxil fumarate (TDF)- to tenofovir alafenamide (TAF)-based regimens in clinical practice—real-world data of the German PROPHET cohort study. In: HIV Glasgow 2018, 28–31 October 2018, Glasgow, UK [abstract P112]. J Int AIDS Soc 2018;21(Suppl 8):e25187.
[22] Elion R, Eron J, Santiago S, Sax P. Clinical observations of antiretroviral (ART) switching in HIV-suppressed patients after availability of TAF. In: HIV Glasgow 2018, 28–31 October 2018, Glasgow, UK [abstract P114]. J Int AIDS Soc 2018;21(Suppl 8):e25187.
[23] D'Arminio MA, Lepri AC, Rezza G, et al. Insights into the reasons for discontinuation of the first highly active antiretroviral therapy (HAART) regimen in a cohort of antiretroviral naïve patients. I.CO.N.A. Study Group. Italian Cohort of Antiretroviral-Naıve Patients. AIDS 2000;14:499–507.
[24] Surial B, Cavassini M, Calmy A, et al. Rates and predictors of switching to tenofovir alafenamide-containing ART in a nationwide cohort. BMC Infect Dis 2019;19:834. doi:10.1186/s12879-019-4454-9.
[25] Nishijima T, Gatanaga H, Shimbo T, et al. Switching tenofovir/emtricitabine plus lopinavir/r to raltegravir plus darunavir/r in patients with suppressed viral load did not result in improvement of renal function but could sustain viral suppression: a randomized multicenter trial. PLoS One 2013;8:e7363.
[26] Cohen C, Green J, Olivet H, et al. A randomized pilot study of tenofovir/emtricitabine (TDF/FTC) + boosted atazanavir (ATV/r) vs. raltegravir (RAL-BID) + ATV/r vs. RAL BID + ATV BID. J Int AIDS Soc 2012;15(Suppl 4):18279.
[27] Maggiolo F, Di Filippo E, Valenti D, et al. NRTI sparing therapy in virologically controlled HIV-1 infected subjects: results of a controlled randomized trial (Probe). J Acquir Immune Defic Syndr 2016;72:46–51.
[28] Maggiolo F, Gulminetti R, Pagnucco L, et al. Lamivudine/dolutegravir dual therapy in HIV-infected, virologically suppressed patients. BMC Infect Dis 2017;17:215. doi:10.1186/s12879-017-2311-2.
[29] Joly V, Burdet C, Landman R, et al. LAMIDOL Study Group. Dolutegravir and lamivudine maintenance therapy in HIV-1 virologically suppressed patients: results of the ANRS 167 trial (LAMIDOL). J Antimicrob Chemother 2019;74:739–45. doi:10.1093/jac/dky467.
[30] Taiwo BO, Marconi VC, Berzins B, et al. Dolutegravir plus lamivudine maintains human immunodeficiency virus-1 suppression through Week 48 in a pilot randomized trial. Clin Infect Dis 2018;66:1794–7. doi:10.1093/cid/cix1131.

[31] Capetti AF, Cossu MV, Orofino G, et al. A dual regimen of ritonavir/darunavir plus dolutegravir for rescue or simplification of rescue therapy: 48 weeks' observational data. BMC Infect Dis 2017;17:658. doi:10.1186/s12879-017-2755-4.
[32] Clotet B, Feinberg J, van Lunzen J, et al. INGI14915 Study Team. Once-daily dolutegravir versus darunavir plus ritonavir in antiretroviral-naive adults with HIV-1 infection (FLAMINGO): 48 week results from the randomised open-label phase 3b study. Lancet 2014;383:2222–31.
[33] Gupta SK, Post FA, Arribas JR, et al. Renal safety of tenofovir alafenamide vs. tenofovir disoproxil fumarate: a pooled analysis of 26 clinical trials. AIDS 2019;33:1455–65. doi:10.1097/QAD.0000000000002223.
[34] Novick TK, Choi MJ, Rosenberg AZ, et al. Tenofovir alafenamide nephrotoxicity in an HIV-positive patient: a case report. Medicine (Baltimore) 2017;96:e8046.
[35] Mocroft A, Kirko Reiss P, et al. Estimated glomerular filtration rate, chronic kidney disease and antiretroviral drug use in HIV-positive patients. AIDS 2010;24:1667–78. doi:10.1097/QAD.0b013e328339fe53.
[36] Goicoechea M, Liu S, Best B, et al. Greater tenofovir-associated renal function decline with protease inhibitor-based versus nonnucleoside reverse-transcriptase inhibitor-based therapy. J Infect Dis 2008;197:102–8. doi:10.1086/524061.
[37] Cahn P, Madero JS, Arribas JR, et al. Dolutegravir plus lamivudine versus dolutegravir plus tenofovir disoproxil fumarate and emtricitabine in antiretroviral-naive adults with HIV-1 infection (GEMINI-1 and GEMINI-2): Week 48 results from two multicentre, double-blind, randomised, non-inferiority, phase 3 trials. Lancet 2019;393:143–55 Erratum in: Lancet 2019;393:132. doi: 10.1016/S0140-6736(18)33041-1. doi:10.1016/S0140-6736(18)32462-0.
[38] Hernán MA. Does water kill? A call for less casual causal inferences. Ann Epidemiol 2016;26:674–80. doi:10.1016/j.annepidem.2016.08.016.
[39] Lucas GM, Cozzi-Lepri A, Wyatt CM, Post FA, Bormann AM, Crum-Cianflone NF, et al. INSIGHT SMART Study Group. Glomerular filtration rate estimated using creatinine, cystatin C or both markers and the risk of clinical events in HIV-infected individuals. HIV Med 2014;15:116–23. doi:10.1111/hiv.12087.