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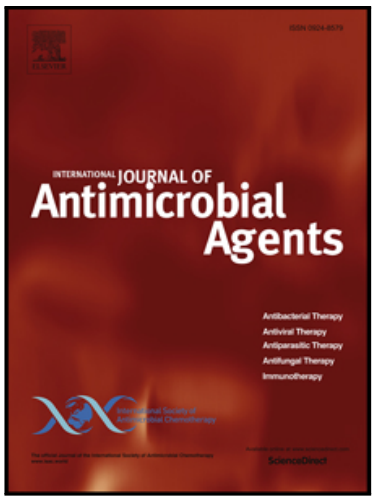

Effectiveness and safety of tenofovir alafenamide fumarate–based therapy compared to tenofovir disoproxil fumarate- and abacavir-based therapy in children and young people living with HIV in Europe

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HIGHLIGHTS

- This is the largest study of children and young people on TAF to date
- Virological suppression on TAF was high and similar to TDF and ABC
- No difference was observed between drugs in the bone/ renal markers collected
- Rates of lipid events on TAF were higher than on TDF, but not ABC
- Rate of treatment discontinuation was lowest among those on TAF

Effectiveness and safety of tenofovir alafenamide fumarate–based therapy compared to tenofovir disoproxil fumarate- and abacavir-based therapy in children and young people living with HIV in Europe

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Word count: 3659/4000 words

Abbreviations

ABC: Abacavir

AE: Adverse event

aIRR: Adjusted incident rate ratio

aHR: Adjusted hazard ratio

aOR: Adjusted odds ratio

aSHR: Adjusted sub-hazard ratio

ALP: Alkaline phosphatase

ALT: Alanine aminotransferase

AST: Aspartate aminotransferase

ART: Antiretroviral therapy

ATZ/r: Atazanavir

BMI: Body mass index

CI: Confidence Interval

CYPLHIV: Children and young people living with HIV

DRV/r: Darunavir

DTG: Dolutegravir

EFV: Efavirenz

EVG: Elvitegravir

EPPICC: European Pregnancy and Paediatric Infections Cohort Collaboration

FTC: Emtricitabine

HDL: serum high-density lipoprotein

HICDEP: HIV Cohorts Data Exchange Protocol

INSTI: Integrase strand transfer inhibitor

IQR: Interquartile range

LDL: serum low-density lipoprotein

LPV/r: Lopinavir

NNRTI: Non-nucleoside reverse transcriptase inhibitor

NRTI: Nucleoside reverse transcriptase inhibitor

PI: Protease inhibitor

PY: Person-years

SAE: Serious adverse event

TAF: Tenofovir alafenamide fumarate

TDF: Tenofovir disoproxil fumarate

VL: Viral load

3TC: Lamivudine

ABSTRACT

Word count: 250 words

Objective

Effectiveness and safety outcomes were compared between those on tenofovir alafenamide fumarate (TAF), tenofovir disoproxil fumarate (TDF) or abacavir (ABC), among children and young people living with HIV (CYPLHIV) aged 6-<25 years.

Results

577 CYPLHIV received TAF, 428 TDF and 426 ABC. 96%/83%/55% were ART-experienced, median age at drug start was 15·8/14·6/12·5 years, and median duration of follow-up was 1·6/2·3/3·0 years, respectively.

Among all ART-experienced CYPLHIV at drug start there was no difference in the proportion virologically suppressed at 48 weeks. However, in those suppressed at drug start, the proportion suppressed at 48 weeks was higher on TDF than TAF (p=0·008). There was no difference in time to suppression (amongst unsuppressed at start) or to viral failure.

Among those on TAF, there were four serious adverse events, of which 1 (renal colic) was considered related to TAF and led to discontinuation. The rate of treatment-emergent grade≥1 laboratory events was highest on TAF (adjusted incidence rate ratio vs. TAF: TDF 0·74(0·56-0·99, p=0·046); ABC 0·69(0·53-0·88), p=0·004). Rates of grade≥1 LDL and total cholesterol events on TAF were comparable on ABC, but higher than TDF, with no difference in bone/renal markers. There was no significant difference in grade≥3 events (p>0·500), although numbers were small.

The risk of discontinuation (for reasons other than optimisation/simplification/unknown reason) was lowest for TAF.

Conclusion

Virological outcomes were similar across drugs. Rates of any grade laboratory events were highest on TAF, driven by higher rates of lipid events. As TAF uptake increases, studies with long-term follow-up are required.

Keywords: HIV; tenofovir alafenamide; treatment; children; young people

1. INTRODUCTION

Tenofovir alafenamide fumarate (TAF) is a prodrug of tenofovir and is closely related to tenofovir disoproxil fumarate (TDF). TDF has been used extensively as a preferred nucleoside reverse transcriptase inhibitor (NRTI) backbone in adults, however it has been associated with adverse bone and renal effects[1]. TAF produces lower plasma concentrations of the active substance tenofovir than TDF, and can therefore be used at a lower dose[2].

TAF is included as an option for first- and/or second-line use in children and young people living with HIV (CYPLHIV) in World Health Organization (WHO), USA and European guidelines[3-5]. It is available

in several fixed-dose combinations with emtricitabine (FTC) and sometimes with an anchor drug. In Europe, most combinations are licensed from 6 or 12 years of age, although in recent years some have been additionally licensed from 2 years of age.

In adults, TAF has been shown to have a better bone and renal safety profile than TDF, with generally no evidence of a difference in effectiveness[6, 7]. However, there is some evidence of a greater increase in adverse lipid parameters on TAF than TDF, possibly due to a lipid lowering effect of TDF[8, 9]. In CYPLHIV, data on TAF are limited. Four single-arm clinical trials, which had a combined sample size of less than 350, provide evidence suggesting good viral suppression and no obvious safety concerns[10-13]. One single-centre study of 74 paediatric patients receiving TAF/FTC/bictegravir in a real-world setting in France reported 38% experienced viral failure, although the majority resuppressed with no change in antiretroviral therapy (ART) [14]. The only comparative paediatric data of TAF to other NRTIs is the recently published CHAPAS-4 trial, which randomised children starting second-line ART in three African countries to TAF (n=458) or standard-of-care NRTIs (abacavir (ABC) or zidovudine). Findings demonstrated superior virological efficacy of TAF and a favourable safety profile. As CYPLHIV in high income settings are now receiving TAF in accordance with guidelines, it is important to understand how safety and effectiveness differs from other NRTIs, including TDF and ABC (another widely used NRTI shown to be safe and effective for CYPLHIV[16, 17]).

This study aimed to describe the uptake of TAF, and to compare the effectiveness and safety of TAF-based therapy with TDF- and ABC-based therapy among CYPLHIV in real-world settings, using data from the European Pregnancy and Paediatric Infections Cohort Collaboration (EPPICC) study.

2. MATERIAL AND METHODS

Twelve observational cohorts from 12 countries across Europe with access to TAF contributed individual-level demographic, clinical, laboratory and treatment-related patient data, which were pseudonymised and pooled electronically using a modified HIV Cohorts Data Exchange Protocol

(HICDEP, www.hicdep.org). All procedures were carried out in accordance with relevant law and institutional guidelines. EPPICC has ethics committee approval from University College London (reference 17493/001) and all cohorts received approval from local and/or national ethics committees. Cohorts sought informed consent or a waiver of consent in line with national guidelines.

CYPLHIV aged <18 years at diagnosis of HIV and ever in paediatric HIV care were considered for inclusion. CYPLHIV were eligible for the TAF analysis group if they ever initiated TAF <25 years of age; those initiating aged <6 years (i.e. off-label at the time of data analysis) were included in the uptake analysis but not the comparative effectiveness and safety analyses. CYPLHIV were eligible for the TDF/ABC analysis groups if they started TDF/ABC for the first time while aged 6-<25 years since 1 January 2013 (to provide a comparison group similar to those on TAF while ensuring sufficient numbers for analysis). CYPLHIV who were eligible for inclusion and had exposure to >1 drug of interest with different start dates were included in each group (those with the same start date were excluded).

Follow-up was from drug start until the earliest of 25th birthday, drop out, death or last visit, with data following transfer to adult care included where available. Date of last follow-up varied by cohort from December 2020 to May 2023. CYPLHIV who stopped TAF/TDF/ABC for >30 days and subsequently restarted were considered to have multiple episodes on drug, and unless otherwise specified, analyses focused on the first episode.

Uptake of TAF was calculated as the number ever on TAF divided by the total number of CYPLHIV in follow-up in a participating cohort since 2016.

The following effectiveness outcomes were compared between those on TAF/TDF/ABC: (i) cross-sectional viral suppression (defined as viral load (VL) <50 copies(c)/mL) at 48 weeks (+/-12 weeks) after drug start among those treatment experienced at drug start (numbers naïve too small) and remaining on drug, overall and by viral suppression at drug start; (ii) time to viral suppression among

those not suppressed (VL≥50c/mL) at drug start; (iii) time to viral failure, defined as failure to suppress <50c/mL within 48 weeks, or ≥2 consecutive VL≥400c/mL following suppression, or 1 VL≥400c/mL followed by change in anchor drug, accounting for the competing risks of death, discontinuation for reasons other than virological failure and loss to follow-up, overall and by viral suppression; (iv) change in CD4 count; and (v) change in CD4% to 48 weeks (+/-12 weeks) among those treatment experienced (numbers naïve too small).

Safety outcomes were: (i) death; (ii) for each drug group, the number of treatment-emergent laboratory events, and the rate of first event grade ≥1 (overall and by laboratory marker) and first event of grade ≥3 (overall only), from drug start until 30 days after discontinuation. Markers considered were: serum high-density lipoprotein (HDL), serum low-density lipoprotein (LDL), total cholesterol, triglycerides, serum calcium, serum creatinine, serum phosphate, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), haemoglobin and fasting plasma glucose. Non-fasting glucose and urine glucose data were collected but not analysed due to small numbers. Events were classified according to the highest grade reached before returning to normal, and were graded according to DAIDS criteria[18], apart from HDL which was graded according to paediatric specific guidelines from the US National Heart, Lung, and Blood Institute, with 'acceptable' considered normal, 'borderline' as grade 1 and 'low' as grade 2[19]. Among those changing from TDF to TAF with a gap of <30 days, rates were compared in the 12 months before/after start of TAF. Other safety outcomes were (iii) among those on TAF only, numbers of serious clinical adverse events (SAE) and any non-serious adverse event (AE) related (definitely, probably, possibly) to TAF, from TAF start until 30 days after TAF discontinuation; and (iv) for each drug group, time to discontinuation of first episode on drug, accounting for competing risks of simplification/optimisation and of unknown reason for discontinuation.

Time-to-event outcomes (time to viral suppression, viral failure and drug discontinuation) were compared between those on TAF and both TDF and ABC using Cox regression (with follow-up censored at the 90th percentile of TAF follow-up), cross-sectional viral suppression using logistic

regression, changes in CD4 count/% using linear regression, and incidence rates of laboratory events using Poisson regression offset for duration of exposure. Competing risks analyses (for time to viral failure and drug discontinuation) used the method of Fine and Gray to estimate sub-distribution hazard ratios (sHR)[20]. All analyses used clustered standard errors to account for patients contributing to multiple drug groups. Estimates were presented unadjusted, and adjusted for the following potential confounders (defined a priori): sex (male, female), country (UK/Ireland, Spain, other), born abroad from country of cohort (yes, no, unknown), age at ART initiation (<5, ≥5 years), and the following characteristics at drug start: age (6-<12, 12-<18, ≥18 years), anchor drug class (integrase strand transfer inhibitor (INSTI), protease inhibitor (PI), non-NRTI (NNRTI), other/mixed), previous AIDS diagnosis (yes, no), viral load/treatment history (ART naïve, ART experienced VL<50c/mL, ART experienced VL≥50c/mL, ART experienced VL unknown), previous ART change for failure (yes, no) and severe immunosuppression-for-age[21] (severe, non-severe, unknown; not used for CD4 analyses). CD4 analyses also adjusted for nadir CD4 prior to and CD4 count/% at drug start. A window of -/+12 weeks was used for CD4 count, CD4% and severe immunosuppression at drug start, and -12/+1 weeks for VL.

Sensitivity analyses compared drugs using complete case analysis and using propensity score analysis to weight adjusted models for differences between groups on the key characteristics above (not used as the primary analysis due to a reduction in effective sample size)[22]. Additionally, sensitivity analyses considered the impact of the COVID-19 pandemic by censoring data 1st January 2020.

All analyses were conducted using Stata 18 (StataCorp, College Station, TX, USA).

3. RESULTS

3.1 Uptake of TAF and patient characteristics

Among 2,979 CYPLHIV in follow-up in a participating cohort since 2016, 580 (19%) ever used TAF, of whom three initiated TAF under 6 years of age and were excluded from subsequent analyses. Of the remaining 577, 309 (54%) had previously used TDF, of whom 266 (86%) had a gap between TDF and

TAF of <30 days (Figure A1). In total, 428 and 426 CYPLHIV met the inclusion criteria for the TDF and ABC groups respectively. Of the 1149 patients included; 882 (77%) contributed to only one drug group, 252 (22%) to two drug groups, and 15 (1%) had eligible time on all three drugs.

Characteristics of those on TAF/TDF/ABC are shown in Table 1. The majority of CYPLHIV had perinatally acquired HIV in all groups (>90%). Those who started ABC aged ≥6 years were older at ART initiation than those on TAF and TDF (median 8·3 years vs. 3·1 and 5·5 on TAF and TDF respectively) and younger at drug start (median 12·5 years vs. 15·8 and 14·6). A higher percentage were treatment naïve at start of ABC (45% vs. 4%/17%) and fewer had previously experienced ART failure (10% vs. 37%/31%). At drug start the most common anchor drug was an INSTI for those on TAF and ABC (58%, 39% respectively), and NNRTI for those on TDF (40%, of whom 71% on efavirenz). The median follow-up time on drug was 1·6 [IQR 0·7, 2·8] years on TAF, 2·3 [1·1, 3·7] on TDF, and 3·0 [1·4, 4·9] on ABC.

3.2 Effectiveness

Of those ART experienced and with available VL data at 48 weeks after drug start, 84% (95% CI 80%, 88%) were virally suppressed <50c/mL on TAF, compared to 84% (79%, 88%) on TDF and 89% (83%, 93%) on ABC (Table 2), with the proportions suppressed higher among those with VL<50c/mL at drug start (Table S1). Overall, in both unadjusted and adjusted analysis, there was no evidence of a difference in the odds of viral suppression at 48 weeks comparing TAF to TDF or ABC (adjusted odds ratio (aOR) vs. TAF: TDF 1·61 (95%CI 0·92, 2·82), p=0·093; ABC 1·24 (0·61, 2·49), p=0·554), however when restricting to those with VL<50c/mL at drug start, those on TDF were more likely to be suppressed at 48 weeks than those on TAF (aOR 4·45 (1·49, 13·29), p=0·008), with no difference between TAF and ABC (Table A1). Among those not suppressed at drug start, there was no evidence of a difference in time to viral suppression<50c/mL (adjusted hazard ratio (HR) vs. TAF: TDF 1·10 (0·82, 1·46), p=0·535; ABC 1·07 (0·78, 1·47) p=0·684) (Table 2, Figure 1a).

By 96 weeks on drug, the cumulative incidence of viral failure was 12% (9%, 15%) among those on TAF, 16% (12%, 20%) on TDF and 12% (9%, 16%) on ABC (Figure 1b). Unadjusted competing risks analysis suggested some evidence of an increased risk of viral failure for those on TDF compared to TAF. Although this was not statistically significant in adjusted analysis overall (Table 2, adjusted sub-HR vs. TAF: TDF 1·13 (0·80, 1·59), p=0·501; ABC 1·27 (0·85, 1·91), p=0·247), the increased risk on ABC vs TAF was significant when restricted to those with VL<50c/mL at drug start (Table A2, adjusted sHR 2·78 (1·18, 6·54), p=0·019).

In terms of immunological response, in adjusted analysis of those ART experienced there was no evidence of a difference in mean change to 48 weeks in CD4 count or CD4% between TAF and ABC (p>0·100). There was weak evidence of a greater increase in CD4% on TDF compared to TAF (mean difference 1·2 (95% CI -0·1, 2·5), p=0·063), but not CD4 count (difference 30 (-22, 82) cells/mm^3, p=0·262) (Table 2).

3.3 Safety

Overall, there was one death, a 20-year-old patient in the ABC group who died of non-Hodgkin's lymphoma, which was considered not ART-related.

Laboratory data after TAF/TDF/ABC start were available for 366 (63%), 241 (56%) and 258 (61%) patients respectively. The number of grade ≥3 events was low; 20 (5%) patients had 23 grade ≥3 events in the TAF group, 13 (5%) had 13 grade ≥3 events in the TDF group and 19 (7%) had 31 grade ≥3 events in the ABC group. The rate of grade ≥3 event of any marker was similar between groups; 2·3 (1·5, 3·6), 2·1 (1·2, 3·6), 2·1 (1·3, 3·3) per 100 person-years (PY) among those on TAF/TDF/ABC respectively (adjusted incidence rate ratio (aIRR) p>0·5 for both comparisons) (Table 3).

When comparing number and rates of grade ≥1 events across all markers, 268 (73%) patients had 880 grade ≥1 events in the TAF group, compared to 183 (76%) with 568 events in the TDF group and 205 (79%) with 769 events in the ABC group. The rate of grade ≥1 event for any marker was 83 (95% CI 71, 97) per 100PY among those on TAF, 69 (58, 83) on TDF, and 58 (49, 69) on ABC (Table 3). In

adjusted analysis, there was evidence that the rate was higher among those on TAF compared to both TDF and ABC (aIRR vs. TAF; TDF 0·74 (0·56, 0·99), p=0·046; ABC 0·69 (0·53, 0·88), p=0·004).

The rates of grade ≥1 LDL and total cholesterol events were statistically significantly higher on TAF compared to TDF in adjusted analysis (p=0·020, p=0·001 respectively), with no significant difference between TAF and ABC, or in rates of HDL or triglycerides events between either TDF/ABC and TAF. In adjusted analysis. there was no evidence of a difference between drugs for serum calcium, creatinine, phosphate, ALP, haemoglobin, or fasting blood glucose. In adjusted analysis there was a higher rate of grade ≥1 ALT on TAF compared to ABC (p=0·009), but no difference between TDF and TAF and no difference in AST.

Among 130 patients who changed from TDF to TAF with a gap of <30 days and had any lab data available in the 12 months before and after TAF start, there was no significant difference in the rate of grade ≥3 events pre/post TAF start (0·5 (0·0, 6·9) vs. 0·8 (0·1, 8·7) (p=0·599), or in the rate of any grade ≥1 events (86 (67, 112) vs. 108 (83, 141), p=0·175) (Table A3).

Among 503 (87%) patients on TAF with clinical adverse event data available, 16 (3%) experienced 59 AEs causally related to TAF (of which 49 (83%) were grade 1 or 2), and four patients discontinued TAF following AEs. Three patients (1%) experienced four SAEs on TAF, of which one was reported as possibly related to TAF (renal colic, regimen changed from dolutegravir(DTG)/FTC/TAF to DTG/ lamivudine/ABC). The relationship to TAF was unknown for three SAEs and did not lead to TAF discontinuation (raised haemoglobin and low serum phosphate related to non-Hodgkin lymphoma, and psychiatric disturbance).

Across all follow-up, 64 (11%), 243 (57%) and 134 (31%) of patients discontinued TAF, TDF and ABC respectively. Among these, reason for discontinuation was unknown for 21 (33%), 38 (16%) and 22 (16%) respectively. Excluding those with unknown reason, the most common reason for discontinuation across all drug groups was simplification/optimisation (11 (17%), 112 (46%) and 40 (30%) respectively). Two (3%), 15 (6%), 19 (14%) patients discontinued for treatment failure, and 9

(14%), 34 (14%), 13 (10%) discontinued for safety, respectively (Table A4). Of those who discontinued TAF, 23/64 (36%) subsequently restarted TAF, of whom 20 were still on TAF at last follow-up.

By 192 weeks since drug start, accounting for the competing risks of both discontinuation for simplification/optimisation and for unknown reason, 8% (95% CI 5%, 11%), 23% (18%, 27%) and 17% (13%, 21%) had discontinued TAF, TDF, ABC respectively (Figure 2), with those on TAF least likely to discontinue in adjusted analysis (adjusted sHR vs TAF: TDF 2·19 (1·39, 3·46), p=0·001; ABC 1·99 (1·21, 3·28), p=0·007, Table A5).

3.4 Sensitivity analyses

Results of sensitivity analyses were generally consistent with those of the main analyses (Tables A5-A8).

4. DISCUSSION

This is the largest study of CYPLHIV on TAF in routine care settings to date, with detailed safety and effectiveness data, and represents the first comparative analysis of TAF, TDF and ABC-based backbones for CYPLHIV. In our primary adjusted analyses, there was no evidence of a difference in viral or immunological outcomes for TAF compared to the other drugs. In terms of safety, there was no difference across the groups in severe or life-threatening (grade ≥3) events. The majority of the laboratory events observed were grade 1 or 2 events and rates of any grade (≥1) treatment-emergent laboratory events were highest on TAF, driven by statistically significantly higher rates of total cholesterol and LDL events compared to TDF, with no difference in bone or renal markers. The rate of drug discontinuation for reasons other than simplification/optimisation/unknown was lowest on TAF.

Our primary results demonstrate no difference in viral or immunological outcomes between those on TAF compared to TDF or ABC, however, when restricting to those virologically suppressed at drug start, those on TAF were less likely to be suppressed at 48 weeks than those on TDF. There was also

some evidence of a decreased risk of viral failure for those on TAF compared to ABC in the subgroup virologically suppressed at drug start. The significance of these findings is unclear, especially given the wide confidence intervals. Adult studies have generally reported similar efficacy for TAF and TDF[7], although one adult meta-analysis found higher rates of viral suppression on TAF/FTC compared to TDF/FTC among those on boosted regimens (p=0·0004), with no difference for unboosted regimens (p=0·4)[6]. The paediatric CHAPAS-4 trial of second-line therapy found that TAF/FTC was more effective than ABC/ZDV[15].

Overall, higher rates of any grade treatment-emergent laboratory events were seen on TAF compared to both TDF and ABC, with most of the events in all groups being mild or moderate grade 1 or 2. Although there was no statistically significant difference between treatments in the rates of grade ≥3 events, the estimates were similar to rates of grade ≥1, but with wider confidence intervals due to small numbers of events. Differences between TAF and TDF were primarily driven by higher rates of lipid events on TAF, however rates were similar between TAF and ABC, suggesting differences may be explained by a lipid-lowering effect of TDF, as reported elsewhere[8, 9]. This aligns with results from CHAPAS-4[15], which reported no difference in lipid parameters between the TAF and ABC/ZDV group. Findings from another analysis of our cohort demonstrated comparable patterns of growth on TAF and ABC, but slower increases in BMI for those on TDF[23]. Comparative analysis of rates of grade ≥3 lipid events was not possible here due to small numbers of events, and the clinical significance and longer-term outcomes of lower grade events is unclear and requires further investigation. Dyslipidaemia and obesity are drivers of cardiovascular disease within the general population, and in adults there is a known increase in risk of cardiovascular events for people with HIV, as a result of factors including ART exposure as well as immune activation and inflammation [24, 25], with available data in children and young people suggesting similar risks[26, 27]. Recommended management of dyslipidaemia in children includes dietary modifications and daily physical activity, with pharmacological therapy considered in those with more severe forms of lipid abnormalities and in those who do not benefit from other changes[28]. The only significant

difference between TAF and ABC was in rates of grade ≥1 ALT events, which were higher on TAF even after adjustment for anchor drug. We observed no difference in the renal and bone parameters available in our study, however we had no data on creatinine clearance or on bone mineral density, for which some small differences were observed in CHAPAS-4. A meta-analysis of 26 studies (including both adults and CYPLHIV) reported no proximal renal tubulopathy among those on TAF, significantly less than among those receiving TDF[29]. Our data suggest TDF was well tolerated, which may in part be related to only a third of TDF patients being on a boosted regimen, which has been shown to increase the risk of renal events in meta-analysis[6]. There were few grade ≥3 laboratory events across all groups, and only 4 SAEs reported whilst taking TAF, with one reported to have a causal association with TAF and leading to discontinuation.

This analysis has several limitations. Firstly, there may be residual confounding we were unable to account for, which may explain some of the difference between groups. Secondly, laboratory data were not available for 40% of patients; in most cases availability of data depended on clinic/cohort rather than individual patient characteristics, and therefore results are unlikely to be biased. Similarly, CD4, VL, and reason for discontinuation data were not available for all. Thirdly, key markers such as eGFR, proteinuria and bone mineral density were not available; testing of some of these markers in routine care is often targeted at where there is clinical suspicion, therefore a prospective study with systematic testing would be required to explore this further. Fourthly, due to the sample size we were unable to consider interactions between NRTIs and anchor drug class. Finally, information on whether drugs were given as a fixed-dose combination or individually was not available.

5. CONCLUSION

In conclusion, in our large HIV European cohort TAF-based therapy had similar effectiveness to TDF- and ABC- based therapy in CYPLHIV. Few patients had severe or life-threatening events, although there were increased rates of grade ≥1 lipid events on TAF-based regimens compared to TDF-based

regimens. As TAF becomes increasingly available, in particular in low- and middle-income countries with large HIV burden and for younger children, there is a need to confirm these findings and assess longer term outcomes, in particular in relation to abnormal lipids.

CONTRIBUTORS

Author contributions:

All members of the Project Team participated in discussions about the study design, choice of statistical analyses, and interpretation of the findings, and were involved in the preparation and review of the final manuscript. Additionally, Elizabeth Chappell, Charlotte Jackson and Hannah Castro drafted the manuscript, and Siobhan Crichton, Elizabeth Chappell, Hannah Castro and Charlotte Jackson performed analysis, had access to and verified the data.

All members of the Writing Group were involved in the collection of data, interpretation of the findings, and the preparation and review of the final manuscript.

DECLARATIONS

Competing Interests: AB reports a previous fixed-term consultancy with Gilead Sciences relating to treatment of COVID-19 in children.

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Ethical Approval: University College London (reference 17493/001)

Sequence Information: Not applicable

DATA SHARING STATEMENT

The EPPICC data are held at MRC CTU at UCL, which encourages optimal use of data by employing a controlled access approach to data sharing, incorporating a transparent and robust system to review requests and provide secure data access consistent with the relevant ethics committee approvals. The rationale for this approach has been published (doi:10.1186/s13063-015-0604-6). Ethics committee approval for use of EPPICC data restrict the ability for EPPICC data to be shared publicly without request. Rather, ethics approval does allow a controlled access approach. All requests for data are considered and can be initiated by contacting mrcctu.datareleaserequest@ucl.ac.uk.

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REFERENCES

[1] Hall AM, Hendry BM, Nitsch D, Connolly JO. Tenofovir-associated kidney toxicity in HIV-infected patients: a review of the evidence. American Journal of Kidney Diseases. 2011;57:773-80.

[2] Ray AS, Fordyce MW, Hitchcock MJM. Tenofovir alafenamide: A novel prodrug of tenofovir for the treatment of Human Immunodeficiency Virus. Antiviral Research. 2016;125:63-70.

[3] Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV. Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection. 2022.

[4] Penta HIV Guidelines Writing Group on behalf of Penta. PENTA HIV first and second line antiretroviral treatment guidelines. 2019.

[5] World Health Organization. Consolidated guidelines on HIV prevention, testing, treatment, service delivery and monitoring: recommendations for a public health approach: World Health Organization; 2021.

[6] Pilkington V, Hughes SL, Pepperrell T, McCann K, Gotham D, Pozniak AL, Hill A. Tenofovir alafenamide vs. tenofovir disoproxil fumarate: an updated meta-analysis of 14 894 patients across 14 trials. AIDS. 2020;34:2259-68.

[7] Tao X, Lu Y, Zhou Y, Zhang L, Chen Y. Efficacy and safety of the regimens containing tenofovir alafenamide versus tenofovir disoproxil fumarate in fixed-dose single-tablet regimens for initial treatment of HIV-1 infection: A meta-analysis of randomized controlled trials. International Journal of Infectious Diseases. 2020;93:108-17.

[8] Lacey A, Savinelli S, Barco EA, Macken A, Cotter AG, Sheehan G, et al. Investigating the effect of antiretroviral switch to tenofovir alafenamide on lipid profiles in people living with HIV. AIDS. 2020;34:1161-70.

[9] Mallon PWG, Brunet L, Fusco JS, Prajapati G, Beyer A, Fusco GP, Wohlfeiler MB. Lipid Changes After Switch From TDF to TAF in the OPERA Cohort: LDL Cholesterol and Triglycerides. Open Forum Infectious Diseases. 2022;9:ofab621.

[10] Gaur AH, Cotton MF, Rodriguez CA, McGrath EJ, Helström E, Liberty A, et al. Fixed-dose combination bictegravir, emtricitabine, and tenofovir alafenamide in adolescents and children with HIV: week 48 results of a single-arm, open-label, multicentre, phase 2/3 trial. The Lancet Child & Adolescent Health. 2021;5:642-51.

[11] Gaur AH, Kizito H, Prasitsueubsai W, Rakhmanina N, Rassool M, Chakraborty R, et al. Safety, efficacy, and pharmacokinetics of a single-tablet regimen containing elvitegravir, cobicistat, emtricitabine, and tenofovir alafenamide in treatment-naive, HIV-infected adolescents: a single-arm, open-label trial. The Lancet HIV. 2016;3:e561-e8.

[12] Natukunda E, Gaur AH, Kosalaraksa P, Batra J, Rakhmanina N, Porter D, et al. Safety, efficacy, and pharmacokinetics of single-tablet elvitegravir, cobicistat, emtricitabine, and tenofovir alafenamide in virologically suppressed, HIV-infected children: a single-arm, open-label trial. The Lancet Child & Adolescent Health. 2017;1:27-34.

[13] O'Rourke J, Townsend CL, Milanzi E, Collins IJ, Castro H, Judd A, et al. Effectiveness and safety of tenofovir alafenamide in children and adolescents living with HIV: a systematic review. Journal of the International AIDS Society. 2023;26:e26037.

[14] Frange P, Veber F, Burgard M, Blanche S, Avettand-Fenoel V. Bictegravir/emtricitabine/tenofovir alafenamide in paediatrics: Real-life experience from a French cohort (2019–2023). HIV Medicine. 2024;25:299-305.

[15] Musiime V, Bwakura-Dangarembizi M, Szubert AJ, Mumbiro V, Mujuru HA, Kityo CM, et al. Second-Line Antiretroviral Therapy for Children Living with HIV in Africa. New England Journal of Medicine. 2025;392:1917-32.

[16] Jesson J, Dahourou DL, Renaud F, Penazzato M, Leroy V. Adverse events associated with abacavir use in HIV-infected children and adolescents: a systematic review and meta-analysis. Lancet HIV. 2016;3:e64-75.

[17] Paediatric European Network for Treatment of AIDS (PENTA). Comparison of dual nucleoside-analogue reverse-transcriptase inhibitor regimens with and without nelfinavir in children with HIV-1 who have not previously been treated: the PENTA 5 randomised trial. Lancet. 2002;359:733-40.

[18] US Department of Health Human Services. National Institute of Allergy and Infectious Diseases, Division of AIDS. Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.1.[July 2017]. 2017.

[19] Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents National Heart Lung and Blood Institute. Expert panel on integrated guidelines for cardiovascular health and risk reduction in children and adolescents: summary report. Pediatrics. 2011;128:S213.

[20] Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. Journal of the American Statistical Association. 1999;94:496-509.

[21] World Health Organization. WHO case definitions of HIV for surveillance and revised clinical staging and immunological classification of HIV-related disease in adults and children. Geneva: World Health Organization; 2007.

[22] Austin PC. An Introduction to Propensity Score Methods for Reducing the Effects of Confounding in Observational Studies. Multivariate Behavioral Research. 2011;46:399-424.

[23] The European Pregnancy Paediatric Infections Cohort Collaboration Study Group. Weight gain on tenofovir alafenamide fumarate-based therapy compared to tenofovir disoproxil fumarate- and abacavir-based therapy in children and young people living with HIV in Europe. HIV Medicine. 2025;26:1418-28.

[24] Grinspoon SK, Fitch KV, Zanni MV, Fichtenbaum CJ, Umbleja T, Aberg JA, et al. Pitavastatin to Prevent Cardiovascular Disease in HIV Infection. New England Journal of Medicine. 2023;389:687-99.

[25] Feinstein MJ. HIV and Cardiovascular Disease: From Insights to Interventions. Top Antivir Med. 2021;29:407-11.

[26] Dirajlal-Fargo S, McComsey GA. Cardiometabolic Complications in Youth With Perinatally Acquired HIV in the Era of Antiretroviral Therapy. Current HIV/AIDS Reports. 2021;18:424-35.

[27] Mallik I, Henderson M, Fidler S, Foster C. Aging of adult lifetime survivors with perinatal HIV. Curr Opin HIV AIDS. 2025;20:379-87.

[28] Fiorentino R, Chiarelli F. Treatment of Dyslipidaemia in Children. Biomedicines. 2021;9:1078.

[29] Gupta SK, Post FA, Arribas JR, Eron JJ, Jr., Wohl DA, Clarke AE, et al. Renal safety of tenofovir alafenamide vs. tenofovir disoproxil fumarate: a pooled analysis of 26 clinical trials. AIDS. 2019;33:1455-65.

Table 1 – Demographics and characteristics at TAF/TDF/ABC start

	TAF (n=577)	TDF (n=428)	ABC (n=426)
	n (%) or median [IQR]		
Demographic and HIV characteristics			
Female sex	332 (58%)	235 (55%)	217 (51%)
Ethnicity (n=1394)			
Black	322 (57%)	241 (58%)	244 (59%)
White	159 (28%)	115 (28%)	107 (26%)
Other	79 (14%)	62 (15%)	65 (16%)
Born abroad			
No	306 (53%)	219 (51%)	171 (40%)
Yes	261 (45%)	203 (47%)	242 (57%)
Unknown	10 (2%)	6 (1%)	13 (3%)
Year of birth ≥2000	422 (73%)	231 (54%)	338 (79%)
Country			
UK & Ireland	237 (41%)	226 (53%)	181 (42%)
Spain	190 (33%)	114 (27%)	123 (29%)
Other	150 (26%)	88 (21%)	122 (29%)
Perinatal HIV acquisition (n=1273)	504 (98%)	366 (92%)	341 (94%)
Age (years) at ART initiation	3·1 [0·6, 8·8]	5·5 [1·5, 11·0]	8·3 [2·7, 12·6]
Age (years) at HIV diagnosis (n=1289)	1·7 [0·3, 5·4]	3·1 [0·6, 7·5]	5·3 [1·2, 9·2]
Characteristics at TAF/TDF/ABC start			
Age (years)	15·8 [12·7, 18·5]	14·6 [12·5, 17·2]	12·5 [9·7, 15·7]
Year	2018 [2017, 2019]	2014 [2013, 2016]	2016 [2014, 2017]
Prior ART exposure and viral load			
Naive	24 (4%)	71 (17%)	192 (45%)
Treatment experienced, VL<50c/mL	305 (53%)	161 (38%)	144 (34%)
Treatment experienced, VL≥50c/mL	145 (25%)	131 (31%)	45 (11%)
Treatment experienced, VL unknown	103 (18%)	65 (15%)	45 (11%)
Prior TDF use among those on TAF	309 (54%)	-	-
Previously experienced ART failure	212 (37%)	131 (31%)	42 (10%)
CD4 count, cells/mm^3 (n=1089)	646 [457, 926]	618 [372, 844]	576 [360, 870]
CD4% (n=968)	34 [27, 41]	30 [22, 37]	28 [19, 37]
Severe immunosuppression			
No	358 (62%)	307 (72%)	294 (69%)

Yes	38 (7%)	43 (10%)	50 (12%)
Unknown	181 (31%)	78 (18%)	82 (19%)
Prior AIDS diagnosis	138 (24%)	98 (23%)	55 (13%)
Anchor drug			
INSTI	335 (58%)	50 (12%)	165 (39%)
DTG	123 (37%)	22 (44%)	149 (90%)
EVG	162 (48%)	14 (28%)	0 (0%)
Other	50 (15%)	14 (28%)	16 (10%)
PI	157 (27%)	152 (36%)	141 (33%)
DRV/r	129 (82%)	95 (62%)	48 (34%)
ATZ/r	26 (17%)	29 (19%)	50 (35%)
LPV/r	1 (1%)	26 (17%)	42 (30%)
Other	1 (1%)	2 (1%)	1 (1%)
NNRTI	47 (8%)	171 (40%)	101 (24%)
EFV	5 (11%)	122 (71%)	63 (62%)
Other	42 (89%)	49 (29%)	38 (38%)
Other/mixed	38 (7%)	55 (13%)	19 (4%)
Other NRTIs at regimen start			
FTC	575 (100%)	327 (76%)	1 (<0·5%)
3TC	0 (0%)	37 (9%)	409 (96%)
Other/multiple	2 (<0·5%)	64 (15%)	16 (4%)
BMI-for-age z-score (n=923)	0·4 [-0·4, 1·4]	0·3 [-0·4, 1·2]	0·3 [-0·7, 1·1]

Abbreviations: ABC: abacavir; ART: antiretroviral therapy; ATZ/r: atazanavir; BMI: body mass index; c/mL: copies/mL; DRV/r: darunavir; DTG: dolutegravir; EFV: efavirenz; EVG: elvitegravir; FTC: emtricitabine; INSTI: integrase inhibitor; IQR: interquartile range; LPV/r: lopinavir; NRTI: nucleoside reverse transcriptase inhibitor; NNRTI: non-nucleoside reverse transcriptase inhibitor; PI: protease inhibitor;; TAF: tenofovir alafenamide; TDF: tenofovir disoproxil fumarate; 3TC: lamivudine; VL: viral load; UK: United Kingdom

Table 2 – Virological and immunological outcomes among those on TAF/TDF/ABC

		Number with data available	Estimate (95% CI)	Unadjusted			Adjusted		
				OR	95% CI	p	OR	95% CI	p
Cross-sectional viral suppression <50c/mL at 48 weeks among treatment experienced	TAF	296	84% (80, 88)	1·00	-	-	1·00	-	-
	TDF	246	84% (79, 88)	0·95	(0·60, 1·51)	0·821	1·61	(0·92, 2·82)	0·093
	ABC	152	89% (83, 93)	1·46	(0·81, 2·63)	0·206	1·24	(0·61, 2·49)	0·554
		Number with data available	**Cumulative incidence by 48 weeks (95% CI)**	**HR**	**95% CI**	**p**	**HR**	**95% CI**	**p**
Time to viral suppression (<50c/mL) among those not suppressed at start (≥50c/mL)	TAF	143	79 (70, 86)	1·00	-	-	1·00	-	-
	TDF	188	81 (75, 87)	1·03	(0·80, 1·33)	0·795	1·10	(0·82, 1·46)	0·535
	ABC	192	86 (80, 90)	1·23	(0·97, 1·57)	0·090	1·07	(0·78, 1·47)	0·684
		Number with data available	**Cumulative incidence by 96 weeks (95% CI)**	**sHR**	**95% CI**	**p**	**sHR**	**95% CI**	**p**
Time to viral failure	TAF	469	12 (9, 15)	1·00	-	-	1·00	-	-
	TDF	352	16 (12, 20)	1·55	(1·15, 2·08)	0·004	1·13	(0·80, 1·59)	0·501
	ABC	345	12 (9, 16)	1·24	(0·89, 1·73)	0·204	1·27	(0·85, 1·91)	0·247
		Number with data available	**Mean change (95% CI)**	**Beta***	**95% CI**	**p**	**Beta***	**95% CI**	**p**
Change in CD4 count (cells/mm^3) to 48 weeks among treatment experienced	TAF	191	-12 (-44, 20)	0	-	-	0	-	-
	TDF	213	39 (1, 76)	51	(-1, 102)	0·052	30	(-22, 82)	0·262
	ABC	122	26 (-27, 80)	38	(-23, 100)	0·221	46	(-11, 103)	0·113
Change in CD4% to 48 weeks among treatment experienced	TAF	173	0·1 (-0·7, 0·9)	0	-	-	0	-	-
	TDF	192	2·0 (1·1, 3·0)	1·9	(0·7, 3·2)	0·003	1·2	(-0·1, 2·5)	0·063
	ABC	94	0·1 (-1·3, 1·5)	0·0	(-1·6, 1·6)	0·992	-0·1	(-1·4, 1·2)	0·834

*Beta represents the mean difference in change in CD4 count/% to 48 weeks between those on TAF and those on TDF/ABC

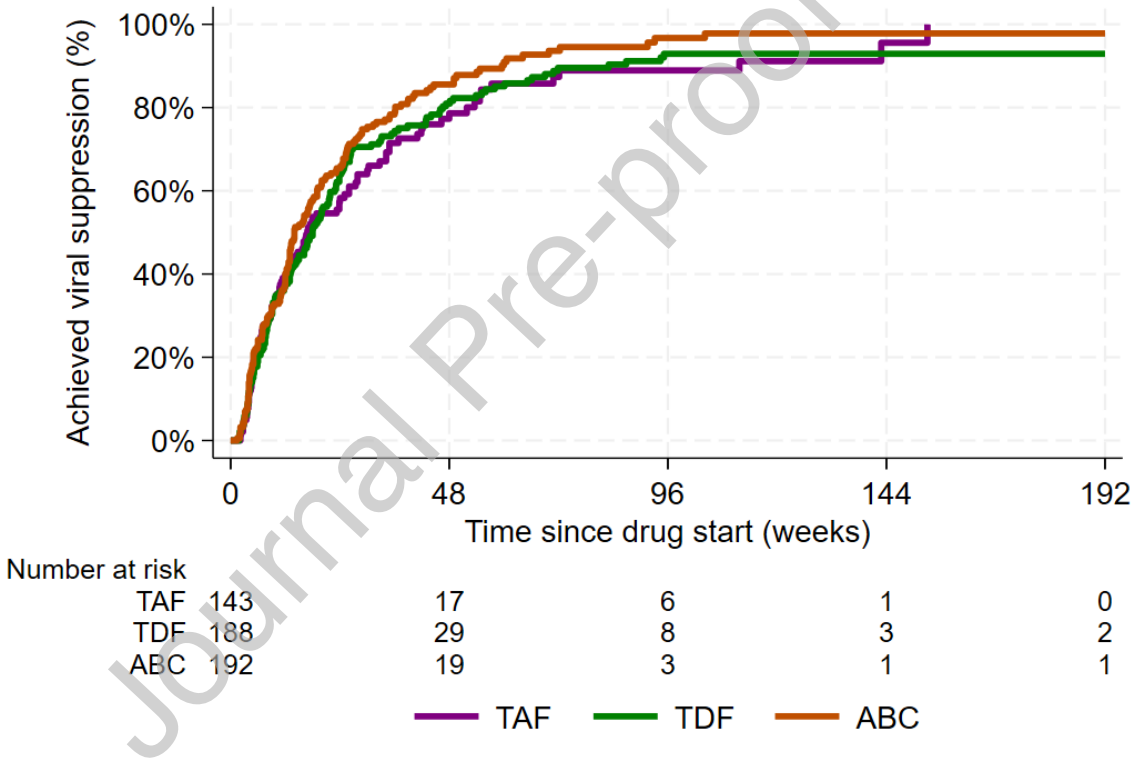
Adjusted estimates adjusted for: sex, country, born abroad from country of cohort, age at ART initiation, and

at drug start: age, anchor drug class, previous AIDS diagnosis, viral load/treatment history, previous ART change for failure and severe immunosuppression-for-age. CD4 analyses also adjusted for nadir CD4 prior to and CD4 count/% at drug start.

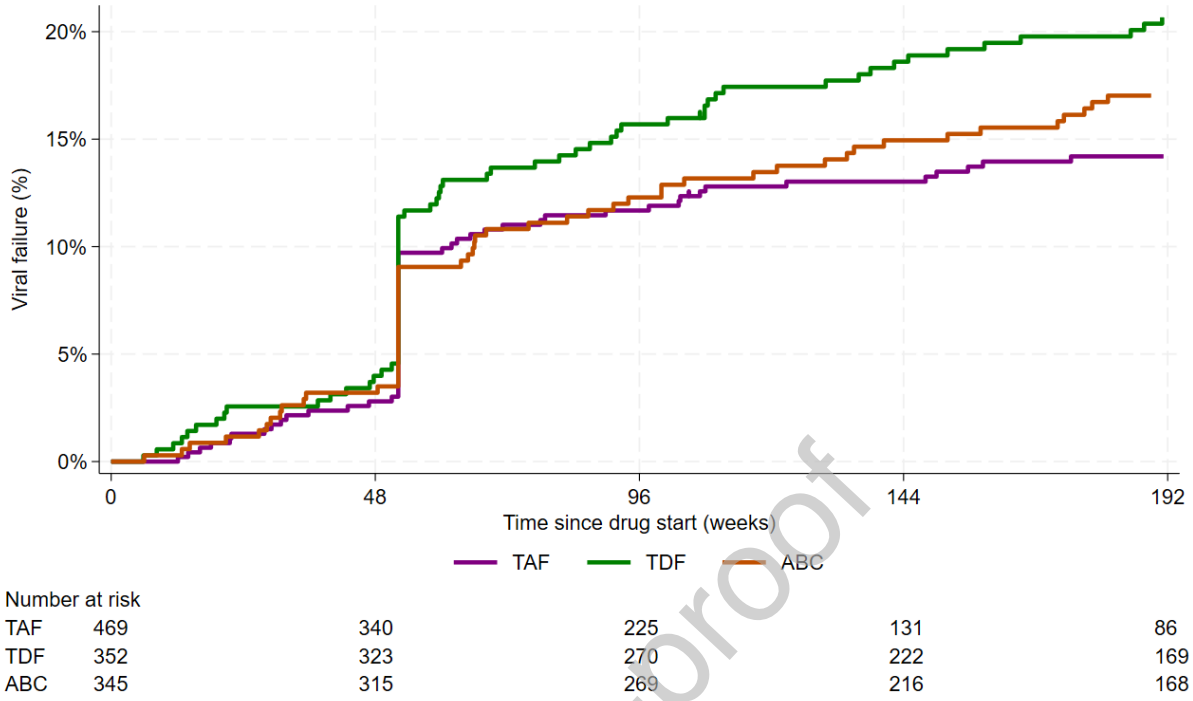
Abbreviations: ABC: abacavir; CI: confidence interval; c/mL: copies/mL; HR: hazard ratio; OR: odds ratio; p: p-value; sHR: sub hazard ratio; TAF: tenofovir alafenamide; TDF: tenofovir disoproxil fumarate

Figure 1 – (a) Time to viral suppression (<50c/mL) among those not suppressed (≥50c/mL) at start of TAF/TDF/ABC, and (b) time to viral failure

(a)



(b)



Number at risk					
TAF	469	340	225	131	86
TDF	352	323	270	222	169
ABC	345	315	269	216	168

Abbreviations: ABC: abacavir; c/mL; copies/mL; TAF: tenofovir alafenamide; TDF: tenofovir disoproxil fumarate

Table 3 – Rates of grade≥1 (overall and by marker) and grade≥3 (overall) treatment emergent laboratory events

	TAF	TDF	TDF vs TAF		ABC	ABC vs TAF	
	Number with an event; rate per 100PY (95% CI) (N=366 with any laboratory data)	Number with an event; rate per 100PY (95% CI) (N=241 with any laboratory data)	Unadjusted IRR (95% CI), p	Adjusted IRR (95% CI), p	Number with an event; rate per 100PY (95% CI) (N=258 with any laboratory data)	Unadjusted IRR (95% CI), p	Adjusted IRR (95% CI), p
Any event of grade ≥1	268; 83 (71, 97)	183; 69 (58, 83)	0·83 (0·66, 1·05), p=0·126	0·74 (0·56, 0·99), p=0·046	205; 58 (49, 69)	0·72 (0·58, 0·90), p=0·003	0·69 (0·53, 0·88), p=0·004
HDL	108; 17 (14, 21)	80; 22 (17, 28)	1·28 (0·95, 1·74), p=0·109	1·29 (0·85, 1·96), p=0·231	82; 13 (11, 17)	0·81 (0·59, 1·10), p=0·179	0·74 (0·50, 1·08), p=0·117
LDL	82; 13 (10, 16)	37; 8 (5, 11)	0·64 (0·43, 0·94), p=0·022	0·55 (0·33, 0·91), p=0·020	69; 11 (9, 14)	0·99 (0·71, 1·39), p=0·973	0·89 (0·59, 1·34), p=0·580
Total cholesterol	117; 20 (16, 24)	71; 14 (11, 17)	0·68 (0·51, 0·92), p=0·013	0·51 (0·35, 0·76), p=0·001	104; 18 (14, 22)	0·96 (0·71, 1·28), p=0·763	0·83 (0·60, 1·16), p=0·274
Triglycerides	86; 12 (10, 16)	64; 12 (9, 15)	0·91 (0·65, 1·27), p=0·576	0·77 (0·50, 1·18), p=0·232	70; 10 (8, 12)	0·86 (0·62, 1·20), p=0·378	0·73 (0·48, 1·12), p=0·155
Serum creatinine	62; 10 (8, 14)	23; 5 (3, 7)	0·43 (0·27, 0·68), p<0·001	0·65 (0·35, 1·18)· p=0·156	44; 7 (5, 9)	0·56 (0·37, 0·85), p=0·006	1·00 (0·61, 1·65), p=0·986
Serum phosphate	37; 8 (6, 11)	25; 9 (6, 13)	1·19 (0·69, 2·04), p=0·541	0·96 (0·46, 2·00), p=0·923	31; 8 (5, 11)	1·04 (0·63, 1·70), p=0·877	0·88 (0·49, 1·55), p=0·651
Serum calcium	12; 2 (1, 4)	9; 3 (1, 5)	0·98 (0·38, 2·52), p=0·963	0·61 (0·20, 1·86), p=0·382	8; 2 (1, 3)	0·80 (0·32, 1·97), p=0·623	0·66 (0·17, 2·56), p=0·548
ALP	11; 2 (1, 3)	15; 4 (2, 6)	2·39 (1·09, 5·24), p=0·030	1·12 (0·44, 2·81), p=0·816	19; 3 (2, 5)	2·02 (1·00, 4·09), p=0·051	0·93 (0·38, 2·23), p=0·865
ALT	45; 7 (5, 9)	29; 6 (4, 8)	0·89 (0·56, 1·41), p=0·607	0·76 (0·41, 1·41), p=0·380	22; 3 (2, 4)	0·47 (0·27, 0·82), p=0·008	0·43 (0·23, 0·81), p=0·009
AST	33; 5 (3, 7)	38; 10 (7, 14)	2·04 (1·27, 3·28), p=0·003	1·58 (0·81, 3·09), p=0·184	31; 5 (3, 7)	0·99 (0·59, 1·64), p=0·966	0·62 (0·33, 1·18), p=0·145
Haemoglobin	30; 4 (2, 5)	31; 5 (4, 8)	1·64 (1·01, 2·67), p=0·047	1·64 (0·75, 3·60), p=0·219	22; 2 (2, 4)	0·82 (0·48, 1·40), p=0·479	0·76 (0·37, 1·55), p=0·450
Fasting blood glucose	9; 5 (3, 10)	10; 11 (5, 21)	2·47 (0·92, 6·59), p=0·072	2·13 (0·48, 9·49), p=0·323	10; 5 (3, 9)	1·01 (0·37, 2·80), p=0·982	0·53 (0·15, 1·87), p=0·321

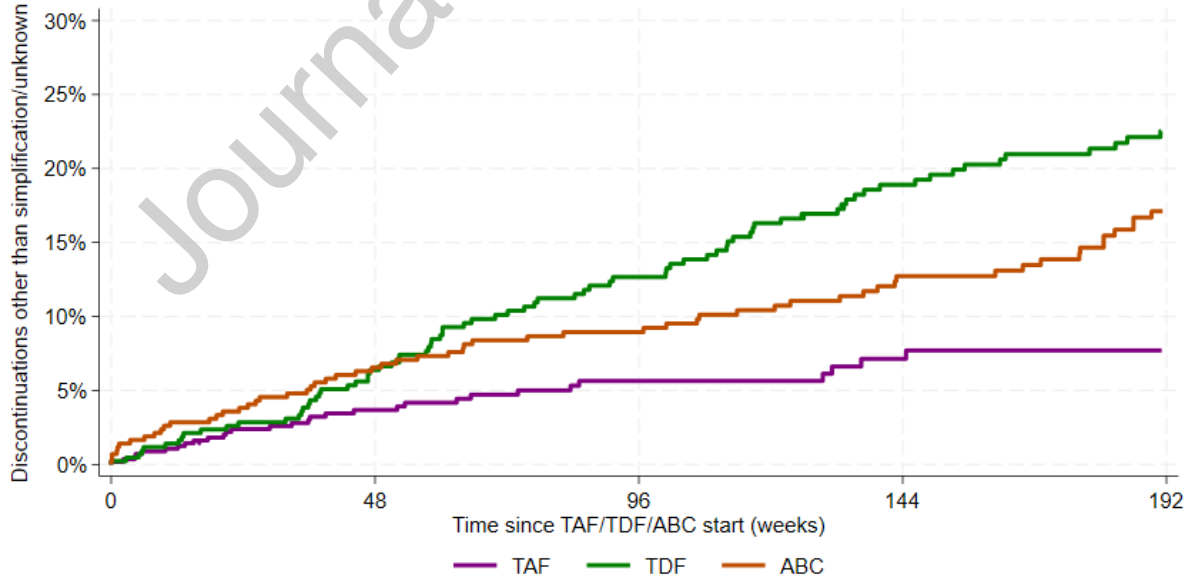
Any event of grade ≥3	20; 2·3 (1·5, 3·6)	13; 2·1 (1·2, 3·6)	0·94 (0·47, 1·87), p=0·863	0·75 (0·31, 1·83), p=0·529	19; 2·1 (1·3, 3·3)	1·04 (0·55, 1·98), p=0·900	0·78 (0·37, 1·65), p=0·509

Abbreviations: ABC: abacavir; ALT: alanine aminotransferase; ALP: alkaline phosphatase; AST: asparate aminotransferase; CI: confidence interval; IRR: incidence rate ratio; HDL: high-density lipoprotein; N: number; LDL: low-density lipoprotein; p: p-value; PY: person-years; TAF: tenofovir alafenamide; TDF: tenofovir disoproxil fumarate.

Adjusted estimates adjusted for: sex, country, born abroad from country of cohort, age at ART initiation, and at drug start: age, anchor drug class, previous AIDS diagnosis, viral load/treatment history, previous ART change for failure and severe immunosuppression-for-age.

Rates of first events grade ≥3 by laboratory marker are not presented as there were insufficient numbers of events to provide meaningful estimates. For TAF/TDF/ABC, the number of CYPLHIV with a grade ≥3 event were: LDL, 3/2/7; total cholesterol, 2/0/3; triglycerides, 1/1/2; serum creatinine, 3/0/2; serum phosphate, 1/0/1; serum calcium, 1/2/3; ALT, 3/2/4; AST, 2/0/4; haemoglobin, 6/6/4; fasting blood glucose, 1/0/0. There were no grade ≥3 events for HDL or ALP.

Figure 2 - Time to discontinuation for reasons other than simplification/optimisation and unknown reason



Number at risk					
TAF	577	408	272	168	104
TDF	428	365	296	233	180
ABC	426	367	314	255	197

Abbreviations: ABC: abacavir; TAF: tenofovir alafenamide; TDF: tenofovir disoproxil fumarate

Graphical Abstract