Treatment initiation or switch to BIC/FTC/TAF – real-world safety and efficacy data from two HIV centers in Romania

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Abstract

Introduction **Development of highly active antiretroviral therapy marked an important step forward in the management of people living with HIV and fixed dose combinations are now available to be used as modern antiretroviral regimens. The single-tablet regimen bictegravir/emtricitabine/tenofovir alafenamide (BIC/FTC/TAF) was recently approved in Europe and included in international guidelines and recommendations. It became available in Romania in early 2021. We present the real-world results from a retrospective analysis of patients initiating BIC/FTC/TAF in two HIV centers in Romania.**

Methods **This retrospective analysis included patients treated with BIC/FTC/TAF (first-line or switch) in two HIV centers in Romania, one in Bucharest and one in Iaşi. We collected data on baseline patient characteristics, reasons for initiation of BIC/FTC/TAF and preliminary clinical and laboratory efficacy, safety and tolerability data. All assessments had been performed according to local practice. Statistical analyses were mostly descriptive and association analysis was performed to assess changes in laboratory parameters from baseline to data cut-off (October 2021).**

Results **In total, 122 patients were initiated on BIC/FTC/TAF in routine clinical practice from February to October 2021 in the two HIV centers, either as first-line or switch. The majority of patients were male (71%). The median age at baseline was 35.0 years (IQR 32.0-50.8 years). Overall, 91 patients (75%) were treatment-experienced and the most frequent reason for switch was treatment simplification (79%). The mean ± standard deviation follow-up duration on treatment with BIC/FTC/TAF was 101.6 ± 64.2 days until the cut-off date for this analysis. We found no significant changes in lipid values, blood glucose or liver enzymes, coupled with a significant decrease in viral load (p=0.001). A low number of adverse events occurred during the treatment period (n=4): two cases of fatigue and two gastrointestinal reactions. No patient discontinued BIC/FTC/TAF and the overall tolerability was good.**

Conclusions **The insights of the first report on BIC/FTC/TAF use in routine clinical practice in Romania provide an overview of effectiveness and safety to local clinicians treating this patient population.**

Keywords **PLWH, BIC/FTC/TAF, real-world, Romania.**

Introduction

The development of highly active antiretroviral therapy (HAART) marked an important step forward in the management of people living with HIV (PLWH). Initial treatment regimens incurred a high pill burden, both in antiretroviral (ARV)-naïve and experienced patients, thus increasing the risk of therapeutic fatigue, non-adherence and consequent lack of efficacy.[1] An important improvement in the

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quality of life of PLWH was noticed after the introduction into clinical practice of single-tablet regimens with fixed dose combinations (FDCs).[2]

One of the most recent classes of ARVs, integrase inhibitors (INSTIs), have shown strong efficacy data and good safety and tolerability, supplemented with high barrier to resistance,[3-8] thus leading to the inclusion in European, North American and World Health Organization (WHO) guidelines as top treatment choices in PLWH.[9-11] Accumulated evidence support INSTIs as first-line and switch options,[9,12] allowing a versatile individualization of treatment. Currently, five INSTI-based FDCs (three single-tablet three-drug regimens (BIC/FTC/TAF, DTG/3TC/ABC and EVG/c/FTC/TAF) and two two-drug regimens (DTG/3TC and DTG/RPV) are used in Europe, including Romania.[9]

BIC/FTC/TAF was approved in Europe in 2018[13] and became available in Romania at the beginning of 2021, being indicated for the treatment of adults infected with HIV-1 without history of resistance to integrase inhibitors, emtricitabine or tenofovir.[14] Clinical trials and meta-analyses showed high efficacy.[6-8,15-18] Moreover, switch studies revealed a lower rate of drug-drug interactions and a favorable safety profile compared to other active regimens.[16] Coupled with the comfort in administration, these attributes place this combination high among the current treatment choices, considering the need to re-think HIV management as that for a lifelong, chronic infection.[19] Real-world evidence data need to be generated to ensure the results from clinical trials may be generalized in broader populations and to assess to which extent

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they can be replicated in daily clinical practice.

After 40 years of HIV and over 20 years of experience with ARV therapy (ART),[20,21] infectious disease specialists in Romania see an advancement in the role of ART, from *lifesaver* to *quality-of-life keeper* for PLWH. In this context, selection of the most appropriate treatment option takes into consideration long-term goals such as efficacy and tolerability, as well as the ease of administration which comes with a lower pill burden.

The current retrospective analysis aimed to describe the baseline characteristics of PLWH being switched to or initiated on BIC/FTC/TAF in two clinical centers in Romania, and to analyze the real-life efficacy and tolerability data.

Methods

This retrospective analysis included all patients with HIV infection who were initiated on BIC/FTC/TAF (either as first-line therapy or as switch from a previous regimen) between February and October 2021 in two tertiary infectious disease clinics in Romania (the National Institute for Infectious Diseases "Prof. Dr. Matei Balş" (Center 1) in Bucharest and the Clinical Hospital of Infectious Diseases in Iaşi (Center 2).

The analysis was approved by the Bioethics Committee of the National Institute for Infectious Diseases "Prof. Dr. Matei Balş" in Bucharest and the Clinical Infectious Diseases Hospital "Sf Parascheva" in Iaşi, with a waiver for informed consent due to the retrospective nature of the analysis, based on data collected in routine clinical practice. All clinical procedures were performed according to the local practice, no additional tests or examinations were requested for this analysis. Data were collected by the consultation of medical patient charts.

This retrospective analysis was not designed to confirm or reject any pre-defined hypothesis. Statistical analyses were of explorative and descriptive nature. Descriptive statistics included mean ± standard deviation (SD) for parametric variables and median (interquartile range – IQR) for non-parametric variables, as well as frequency and percentages for categorical variables. All statistical analyses were performed for the full analysis set, which included all patients with data available at the time of the analysis.

Changes in laboratory parameters from baseline to data cut-off were assessed with the Wilcoxon signed-rank test for continuous non-parametrical data and the paired two-sample *t*-test for continuous parametrical data.

All statistical analyses were performed using *R* programming language version 3.6.2 (https://www-rproject.org/). Missing data were not replaced.

Results

This analysis included a total of 122 patients started on BIC/FTC/TAF in routine clinical practice from February to October 2021, of which 89 in Center 1 and 33 in Center 2. Their baseline demographic and clinical characteristics are presented in Table 1. The majority of patients (73.8%) were less than 50 years of age (Figure 1), 43 (35%) of them belonging to the Romanian pediatric HIV cohort. Information about comorbidities were available for 92 patients. The most common associated diseases were ischemic cardiac disease (15%), hypertension (12%), dyslipidemia (14%) and co-infection with HBV (11%) (Figure 2).

A total of 30 patients (25%) were treatment-naïve, and among them 20 were classified as late presenters based on a CD4 cell count below 350 cells/mm^3 at the time of HIV diagnosis. Treatment-naïve patients had a median age of 35 years old (IQR 25-41 years), and associated the following comorbidities in decreasing order of their frequency: neurologic conditions (n=3), HBV coinfection (n=2), arterial hypertension (n=2), Kaposi sarcoma (n=2), other lymphomas (n=1), ischemic heart disease (n=1), diabetes mellitus (n=1). Treatment-naïve patients were initiated on BIC/FTC/TAF at a median CD4 cell count of 199 (IQR 117-339) cells/mm^3 and a median HIV viral load of 533000 (IQR 134000-890000) copies/mL, and displayed rapid immunological and virological response, with an increase to a median CD4 cell count of 320 (IQR 224-431) cells/mm^3 and a decrease in HIV viral load to a median of 156 (98-308) copies/mL over the course of follow-up in this analysis, with 25 of the patients achieving a viral load below 1000

copies/mL at their first on-treatment evaluation. Treatment initiation was generally well tolerated, with only 2 patients reporting an adverse event, i.e., fatigue, which was self-limited in all cases.

In total, 91 patients (75%) were treatment-experienced, with a median of 6 (IQR 3-11) previous ARV regimens and a median pill burden of 3 (IQR 1-4 and a range of 1 to 7) pills/day prior to the switch. Among treatment-experienced patients, 48 (52.7%) had detectable HIV-RNA and 20 (22.0%) had HIV viral loads >1000 copies/mL at the time of the switch, while after the switch 8 patients had detectable HIV-RNA and only 2 patients still had an HIV viral load >1000 copies/mL (data available for 12 patients). Patients who underwent a switch to BIC/FTC/TAF had had various different ART regimens, most frequently 2 nucleos(t)ide reverse transcriptase inhibitors (NRTIs) + INSTI (46.2%) (Table 2). Simplification of treatment was the most frequent reason for switch (79%), followed by immunological/virological failure (25%), and the presence of comorbid diseases (21%) (Figure 3). Change of treatment due to tolerability issues was recorded as the reason for switch in 8.8% of the patients. For an equal proportion (48.5%) of patients undergoing a switch to BIC/FTC/TAF, the physician reported one or two reasons for this change. Treatment switch was generally well tolerated, with 2 patients reporting an adverse event, i.e., self-limited diarrhea (n=1) and nausea (n=1).

After initiation of BIC/FTC/TAF (first-line or switch), the mean ± SD follow-up duration until data cut-off for this analysis was 101.6 ± 64.2 days for the entire study group. We identified no statistically significant changes in liver function, renal function, lipid values, blood glucose, other biochemical parameters during follow-up compared to baseline values (Figure 4 and Table 3). HIV viral load assessment was repeated during the available follow-up period in 21 of the 74 patients with detectable viral load at baseline, and a statistically significant decrease was noticed (difference between median values of 7.2 $\log_{10}$ copies/mL), with a large effect size (r=0.57, V=23, p=0.001) (Figure 5).

During the duration of the available follow-up, we identified no events of special interest such as liver-related or kidney-related adverse events, significant increases in serum lipid or glucose parameters, immune reconstitution inflammatory syndrome (IRIS), autoimmune reactions, or osteonecrosis. We noted a low occurrence rate of adverse events labelled as frequent in the summary of product characteristics, such as: headache (0%), diarrhea (1.1%), nausea (1.1%), dizziness (0%), fatigue (2.2%), depression (0%), abnormal dreams (0%). None of the patients discontinued BIC/FTC/TAF and the overall tolerability was good.

Discussion

With the current access to highly active antiretroviral therapy, the majority of PLWH may achieve and maintain virological suppression and immune control. Timely diagnosis and ART initiation, coupled with the efficacy and safety of modern ART regimens, have led to improvement of life expectancy and an overall shift of treatment objectives from simple virological suppression to virological suppression with improved quality of life. PLWH now live longer and develop age-related comorbidities, with specific therapeutic and monitoring needs. However, late presenters still represent an important share of newly-diagnosed cases (two-thirds of the treatment-naïve patients in our analysis), and may pose important therapeutic management issues. Optimization of treatment algorithms in this patient population is possible provided that novel ARV combinations are available, with good efficacy and safety profiles and good tolerability.

This is the first analysis of data for PLWH receiving BIC/FTC/TAF in real world settings in two large HIV centers in Romania, following the recent introduction of this FDC into clinical practice in Romania. Most of the patients treated with this FDC were ARV-experienced (75%), and less than half of them were fully virologically suppressed at baseline while almost one quarter (22%) had high pre-switch HIV viral loads suggestive of virological failure. Simplification of the treatment regimen was the top reason mentioned by clinicians initiating the switch, but virological or immunological failure was also an important contributing reason in 25% of cases.

Table 1. Baseline patient characteristics (prior to initiation of BIC/FTC/TAF)

Variable	N	Baseline value
Male, n (%)	122	87 (71)
Age, years, median (IQR)	122	35.0 (32.0-50.8)
Caucasian, n (%)	122	122 (100)
Comorbidities		
None, n (%)	92	45 (49)
1-2, n (%)	92	34 (37)
≥3, n (%)	92	13 (14)
BMI, kg/m^2, mean ± SD	70	25.5 ± 4.4
Random blood glucose, mg/dL, mean ± SD	122	104.2 ± 26.3
Total cholesterol, mg/dL, mean ± SD	119	192.2 ± 54.1
LDL-cholesterol, mg/dL, mean ± SD	106	118.6 ± 48.2
HDL-cholesterol, mg/dL, mean ± SD	109	43.4 ± 17.7
Triglycerides, mg/dL, mean ± SD	119	172.0 ± 119.1
Creatinine clearance (Cockcroft-Gault), mL/min, mean ± SD	75	114.9 ± 31.3
eGFR (MDRD), mL/min/1.73 m^2, mean ± SD	121	93.1 ± 26.7
Urea, mg/dL, mean ± SD	122	34.5 ± 11.0
Alanine aminotransferase, U/L, mean ± SD	122	35.6 ± 33.1
Alkaline phosphatase, U/L, mean ± SD	101	99.2 ± 80.1
Gamma-glutamyl transferase, U/L, mean ± SD	119	57.3 ± 177.4
Current CD4 count, cells/mm^3, median (IQR)	121	435 (196-644)
Nadir CD4, cells/mm^3, median (IQR)	122	215 (100-367)
Undetectable HIV-1 RNA, n (%)	115	41 (36)
>1000 copies/mL HIV-1 RNA, n (%)	115	43 (37)
≤1000 copies/mL HIV-1 RNA, n (%)	115	31 (27)
HIV-1 RNA, $\log_{10}$ copies/mL, median (IQR) in patients with detectable viremia	74	9.7 (4.4-12.4)

BIC/FTC/TAF – bictegravir/emtricitabine/tenofovir alafenamide; **eGFR** – estimated glomerular filtration rate; **HDL** – high-density lipoprotein; **HIV-1 RNA** – human immunodeficiency virus-1 ribonucleic acid; **LDL** – low-density lipoprotein; **MDRD** – modification of diet in renal disease; **SD** – standard deviation.

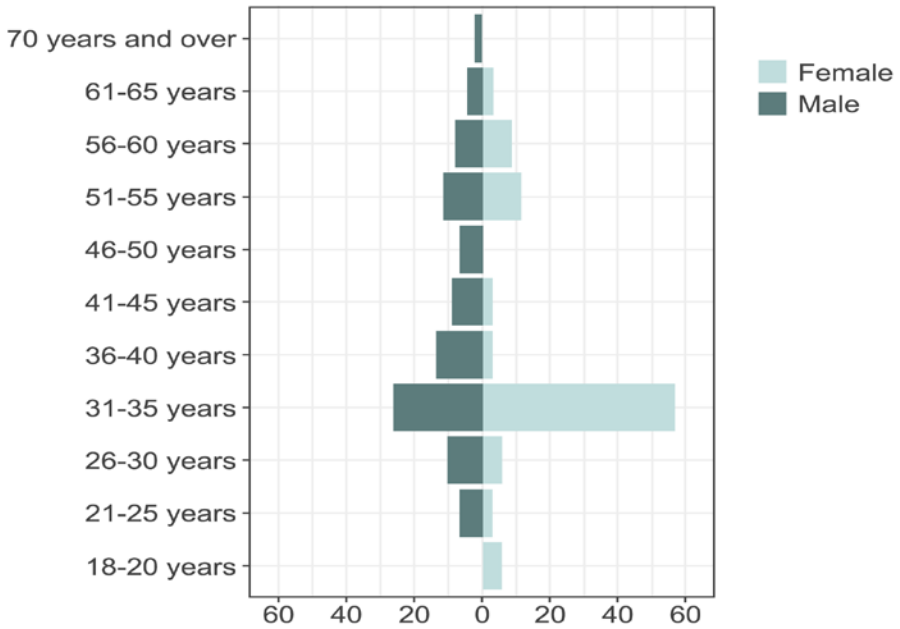
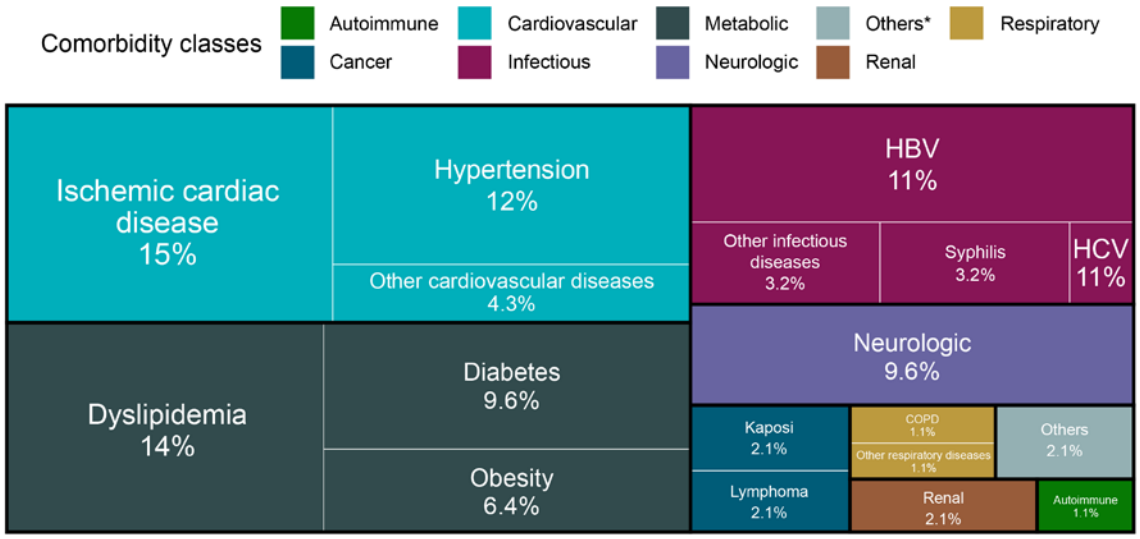


Figure 1. Age pyramid in the overall cohort (n=122)



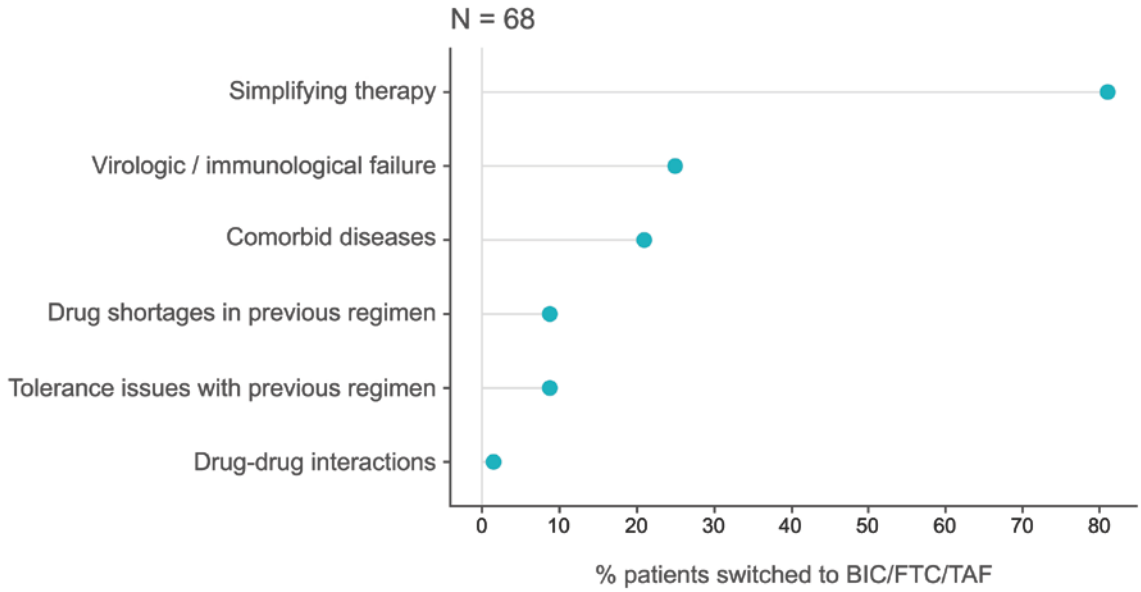
*Others include psychiatry and urological diseases.
COPD – chronic obstructive pulmonary disease; **HBV** – hepatitis B virus; **HCV** – hepatitis C virus.

Figure 2. Distribution of comorbidities by disease group

Table 2. Distribution of ARV regimens prior to the switch to BIC/FTC/TAF

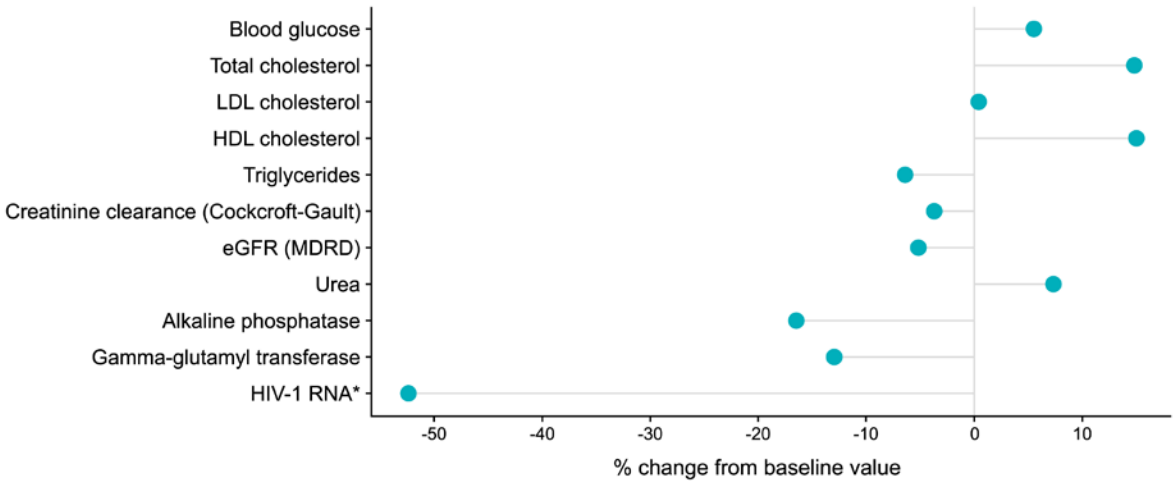
ARV regimen	N (%)
2NRTIs + INSTI	42 (46.2%)
2NRTIs + PI/c or PI/r	26 (28.6%)
2NRTIs + PI/c or PI/r + INSTI	6 (6.6%)
2NRTIs + NNRTI	2 (2.2%)
NRTI + PI/r + INSTI	2 (2.2%)
NNRTI + PI/r	2 (2.2%)
NNRTI + PI/r + INSTI	2 (2.2%)
Other	7 (7.7%)

Missing: n=2; % are calculated from the total number of treatment-experienced patients, n=91.
Other included: CCR5 inhibitor + INSTI, CCR5 inhibitor + NRTI + PI/r, 2NRTIs + NNRTI + INSTI, NNRTI + INSTI, PI/r + 3 NRTIs.
CCR5 – C-C chemokine receptor type 5; **BIC/FTC/TAF** – bictegravir/emtricitabine/tenofovir alafenamide; **INSTI** – integrase strand transfer inhibitor; **NRTI** – nucleos(t)ide reverse transcriptase inhibitor; **NNRTI** – non-nucleoside reverse transcriptase inhibitor; **PI** – protease inhibitor; **/c** – pharmacologically boosted with cobicistat; **/r** – pharmacologically boosted with ritonavir.



It was possible to provide more than one answer.
BIC/FTC/TAF - bictegravir/emtricitabine/tenofovir alafenamide.

Figure 3. Reasons for switching to BIC/FTC/TAF



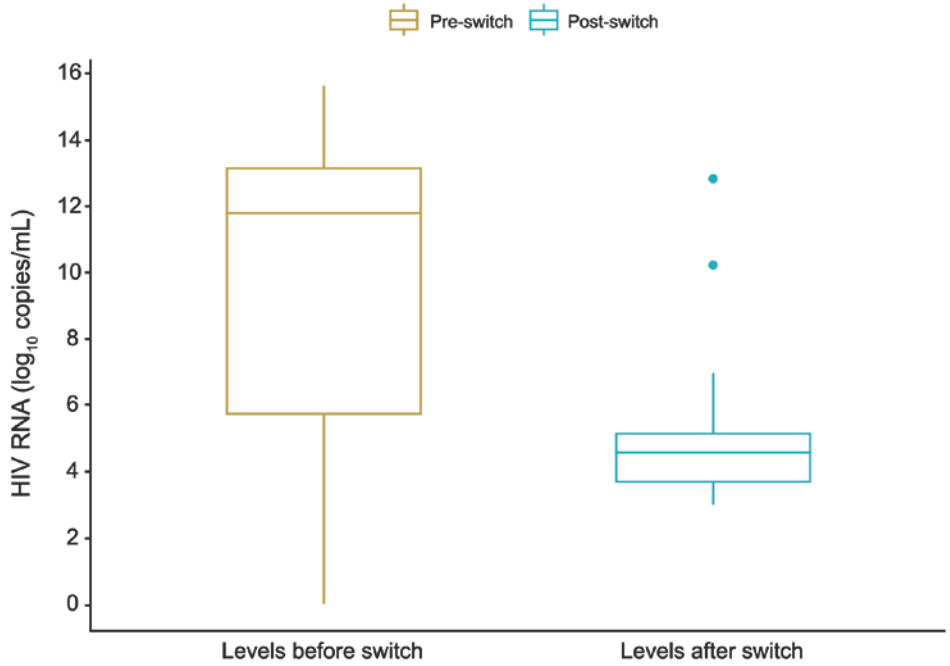
*In a separate Wilcoxon signed-rank test that included 21 patients with complete data in both pre- and post- setting, the change from baseline was statistically significant (V=23, p=0.001) with Δ median value (% from baseline median value) = 7.2 $\log_{10}$ copies/mL (61%) and a large effect size, r=0.57.
BIC/FTC/TAF – bictegravir/emtricitabine/tenofovir alafenamide; **eGFR** – estimated glomerular filtration rate; **HDL** – high-density lipoprotein; **HIV-1 RNA** – human immunodeficiency virus-1 ribonucleic acid; **LDL** – low-density lipoprotein; **MDRD** – modification of diet in renal disease.

Figure 4. Difference between pre- and post- BIC/FTC/TAF initiation, expressed as percentage of baseline median value

Table 3. Changes in laboratory values from baseline (prior to BIC/FTC/TAF initiation) to last follow-up prior to data cut-off

Parameter	Baseline		Current		Change (Δ median)	Statistical analysis		Effect size
	N	Median	N	Median		Statistic test	P value	
Random blood glucose, mg/dL	122	99.0	26	104.5	5.5	167.5*	0.904	Small (r=0.08)
Total cholesterol, mg/dL	119	192.0	22	220.5	28.5	1.39(20)**	0.180	Small (Cohen's d=0.30)
LDL-cholesterol, mg/dL	106	120.5	19	121.0	0.5	-0.12(17)**	0.906	Small (Cohen's d=0.03)
HDL-cholesterol, mg/dL	109	40.0	17	46.0	6.0	103*	0.218	Small (r=0.17)
Triglycerides, mg/dL	119	141.0	21	132.0	-9.0	86*	0.490	Small (r=0.05)
Creatinine clearance (Cockcroft-Gault), mL/min	75	113.1	18	109.0	-4.2	0.77(16)**	0.451	Small (Cohen's d=0.19)
eGFR (MDRD), mL/min/1.73 m^2	121	89.1	27	84.5	-4.6	-0.6(25)**	0.552	Small (Cohen's d=0.12)
Urea, mg/dL	122	34.0	28	36.5	2.5	229.5*	0.073	Small (r=0.09)
Alkaline phosphatase, U/L	101	73.0	13	61.0	-12.0	34*	0.442	Small (r=0.12)
Gamma-glutamyl transferase, U/L	119	27.0	24	23.5	-3.5	101*	0.626	Small (r=0.01)
HIV-1 RNA, log_{10} copies/mL	21	5.1	21	1.99	-3.1	23*	0.001	Large (r=0.57)

*Wilcoxon signed rank test statistic: V-statistic; **Paired t-test statistic: t-statistic(df)
eGFR – estimated glomerular filtration rate; **HDL** – high-density lipoprotein; **LDL** – low-density lipoprotein; **MDRD** – modification of diet in renal disease.



BIC/FTC/TAF – bictegravir/emtricitabine/tenofovir alafenamide; **HIV-1 RNA** – human immunodeficiency virus-1 ribonucleic acid.

Figure 5. Changes in viral load (log_{10} copies/mL) from initiation of BIC/FTC/TAF to data cut-off in patients with data recorded pre- and post-switch

Our results reinforce the effectiveness of BIC/FTC/TAF in our cohort of PLWH in general and particularly in the subgroup of PLWH who had highly replicating HIV infection at baseline. A large share of the patients from our analysis (35%) belonged to the Romanian pediatric HIV cohort. These patients are, by definition, multi-experienced to ART, as they have lived with HIV infection since early childhood,[22] and have experienced multiple episodes of therapeutic success and failure, as well as multiple challenges in terms of adherence to older ART with a high pill burden.[19]

In this real word data analysis, we found a low frequency of adverse events in patients receiving BIC/FTC/TAF, and specifically no cases of adverse events of special interest, as defined in the summary of product characteristics. These data are consistent with results from clinical trials and the BICStar observational cohort reporting high suppression rates in patients treated with BIC/FTC/TAF FDC.[23]

Although the sample size for this analysis was relatively low, and the duration of follow-up was not uniform, the results may already inform clinicians on the expected real-world outcomes. As in other therapeutic areas, the COVID-19 pandemic had reduced to a certain extent the number of medical visits and the frequency of viro-immunological monitoring was consequently impacted. Limitations are inherently related to the retrospective nature of the analysis, the inability to measure relevant laboratory parameters at standardized time points and in all patients initiating BIC/FTC/TAF, and the fact that the data come from two infectious disease clinics in Romania which might have different protocols in place for periodic monitoring and for assessing the occurrence of adverse events. We also acknowledge that the number of reported adverse events is low, a difference that probably stems from the patient's or the clinician's interpretation of whether or not a reported sign or symptom should be classified as an adverse event, interpretation which is not present in clinical trials, where any untoward medical occurrence is recorded and reported. The current analysis is further limited by the fact that data on resistance testing were not routinely collected for treatment-experienced patients who had high viral loads suggestive of virological failure at the time of the switch and that we do not have information on the baseline rate of INSTI resistance.

The treatment landscape in Romania is complex and sometimes challenging for infectious disease specialists. This report on one of the most recent single tablet regimens introduced in clinical practice provides the first highlights of its efficiency and tolerability in a local patient population and supports BIC/FTC/TAF as a valid treatment option in PLWH with different ART history, comorbidity burden, or viral suppression levels.

Conclusions

This retrospective analysis supports the effectiveness and safety of treatment with BIC/FTC/TAF in PLWH irrespective of their disease continuum and can inform clinical practice regarding real-world expected outcomes of treatment with BIC/FTC/TAF.

Authors' contributions statement: All authors had equal contributions. All authors read and approved the final version of the manuscript.

Conflicts of interest: All authors – none to declare.

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