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Cost-Efficacy of Antiretroviral Regimens Recommended in Treatment-Naive HIV-Infected Adults. A Single Center Experience

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Abstract: We aimed to assess the prescription trends of combined antiretroviral therapy (cART) in one infectious diseases department and the cost-efficacy (C/E) of different regimens used in treatment-naïve patients. The C/E was assessed with a software application developed by a group of researchers in Spain. The efficacy was already calculated in the application. The costs included the local cost of antiretrovirals and other direct costs specific to our institution. In the software application, the C/E reference regimen was ABC/3TC/DTG. In total, 181 HIV-infected patients were diagnosed and initiated cART during 2015–2019. The proportion of patients treated with integrase-strand transfer inhibitor (INSTI)-based regimens increased from 2015–2018 (54%) to the end of 2019 (81%). The relative C/E ranged from 0.90 to 1.28 for the evaluated INSTI-based regimens. Among INSTI-based regimens, ABC/3TC/DTG and TAF/FTC/EVG/c are the regimens with similar efficacy and relative C/E.

Keywords: HIV; ART initiation; cost-efficacy; Romania

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1. Introduction

The therapeutic landscape has changed dramatically over the last 30 years, resulting in a significant improvement in the survival and quality of life of people living with HIV (PLWH) [1–3]. The development of better drugs and improvement of overall access to treatment have been accompanied by a consistent increase in HIV-related healthcare costs [3].

In an era where economic evaluation is mandatory for policy decision-makers in the field of HIV management, we have to consider the cost and efficiency of each regimen, in order to attain the highest gains. Even in resource-limited settings, it is vital to maintain high-quality medical care for HIV patients, but limited budgets can greatly influence allocation decisions. In this context, cost-effectiveness analysis could improve resource allocations [4–6]. Publications in the last decade have suggested a growing importance of economic evaluations in the HIV/AIDS field [7–10].

A group of experts from the AIDS Study Group (GESIDA) of the Spanish Society of Infectious Diseases recently developed a software application that can be used to estimate cost-efficacy (C/E) parameters.

In Romania, combined antiretroviral therapy (cART) is fully available and has been initiated in all PLWH, irrespective of CD4 count, immediately after diagnosis. In practice, any cART can be prescribed, based on clinical judgment, indication, and guideline recommendations. Efforts have been made to develop and implement evidence-based protocols for optimal results [11]. However, no local budgetary analysis of HIV-related expenditures is currently available in Romania to guide treatment choices from this perspective.

The objective of our analysis was to assess the prescription trends of cART in our department and the C/E of different regimens used in treatment-naïve patients.

2. Methods

This was a single-center analysis, with a retrospective component (between 2015 and 2019) to analyze the prescription changes of initial cARTs (drug-class level) and a component of cost-efficacy analysis of European AIDS Clinical Society (EACS) recommended regimens at the end of 2019.

The retrospective analysis was based on information collected in the database of the Infectious Diseases Department Adults 4, National Institute for Infectious Diseases "Prof. Dr. Matei Balș" Bucharest, Romania. Descriptive statistics were calculated using the statistical software SPSS v20.

The method used to obtain the cost-efficacy results consisted of applying the software application developed in Spain [available at http://gesida-seimc.org/category/guias-clinicas/antirretroviral-vigentes/, accessed on 4 February 2020] to cART used in clinical practice and local costs, as available in December 2019. The complete description of the design and methodology implemented within the application was presented in the original publication of Perez-Molina et al. [12].

The selected regimens for the analysis were those recommended by the 2018 EACS guidelines and used in clinical practice in our institution; the efficacy data were maintained in the application, as considered by the Spanish group [5]. As in the Spanish model, only direct costs were considered, including the costs of antiretrovirals and of the resources for the management of adverse events, HIV genotypic antiretroviral resistance, and HLAB5701 testing, which are specific to our institution. All costs were expressed in Romanian currency (RON). The time horizon of the model was 48 weeks [12].

The costs were introduced in the application and the C/E for each regimen was calculated as the quotient of the cost of initiating treatment with that regimen (numerator) and efficacy (denominator), representing the probability of achieving a responder (undetectable viral load) by week 48.

In the software application, ABC/3TC/DTG received the value 1 in terms of relative C/E, being evaluated as the treatment regimen with the least cost per responder. A relative C/E lower than 1 should be interpreted as better relative efficacy for the associated cost.

This setting was maintained automatically in our calculation, as a part of the software algorithm; therefore the C/E for the rest of cART included in the analysis was relative to ABC/3TC/DTG.

3. Results

A total of 181 patients diagnosed with HIV receiving initial cART during 2015–2019 were included in the analysis. The median age was 34 years (IQR 27–39) and 79% were male. Overall, 53% were late presenters and 32% had advanced HIV disease. The median CD4 count was 298 cells/mm^3 (IQR 129–488).

In terms of treatment type initiated at diagnosis of HIV infection, the proportion of INSTI-based regimens increased between 2015–2018 (54%) and to the end of 2019 (81%), whereas the proportions of NNRTI-based and PI-based regimens decreased (10% to 5%, and 36% to 14%, respectively).

At the end of 2019, viral suppression <50 copies/mL had been achieved and maintained in 98 patients out of 129 patients (76%) with available viral counts. A total of 27 patients had been diagnosed within the last six months of 2019.

3.1. Costs

The direct costs required by the C/E application are those associated with cART (Table 1) and other resources (Table 2).

Table 1. Cost (RON) for initiation and treatment of up to 48 weeks with each regimen.

Combination ART	Cost (RON)
ABC/3TC/DTG (PR)	40,522
TAF/FTC + DTG (PR)	53,532
TAF/FTC + RAL (PR)	50,131
TAF/FTC + RPV (PR)	34,527
TAF/FTC + DRV/r (PR)	28,829
TAF/FTC + DRV/c (PR)	44,708
TAF/FTC/EVGc (AR)	40,720

ABC, abacavir;/c, cobicistat; DRV, darunavir; DTG, dolutegravir; EVG, elvitegravir; FTC, emtricitabine;/r, ritonavir-boosted; RAL, raltegravir; RPV, rilpivirine, TAF, tenofovir alafenamide; 3TC, lamivudine. PR, preferred regimen; AR, alternative regimen as indicated in EACS Guidelines 2018.

Table 2. Direct cost per patient associated with ART, not including the cost of drugs, as requested by the software application.

Resource	Cost (RON)
Drug-resistance testing	
NRTIs, NNRTIs, PIs	290
INSTIs	290
HLA-B 5701	150
Specialist medical consultations	
First consultation	200
Control	100
Emergency department consultation	200
Day of hospitalization	440
Diagnostic testing	
Ultrasound	120
Complete blood count	13
Liver function (transaminases)	10
Coagulation testing	15
Stool culture	187

INSTI, integrase strand transfer inhibitor.

In the base-case scenario, the cost of initiating cART varied from 29,142 RON for TAF/FTC + DRV/r to 53,122 RON for TAF/FTC+DTG. The cost intervals were similar in the most favorable (29,095 to 53,208 RON) and least favorable (29,193 to 53,040 RON) scenarios. Regimens associated with the highest and lowest values in the base-case setting maintained their ranks in the least and most favorable scenarios (Table 3).

3.2. Cost/Efficacy (C/E)

In the base-case scenario, the relative C/E was less than 1 for TAF/FTC/EVG/c, TAF/FTC + RPV, and TAF/FTC + DRV/r (Table 3 and Figure 1), which was similar to the least favorable scenario.

Table 3. Cost/efficacy parameters and relative efficiency at 48 weeks after ART initiation.

Initial Regimen	Base Case Scenario				Most Favorable Scenario				Least Favorable Scenario			
	Cost (RON) [a]	Efficacy	C/E [b]	Relative C/E [c]	Cost (RON) [a]	Efficacy	C/E [b]	Relative C/E [c]	Cost (RON) [a]	Efficacy	C/E [b]	Relative C/E [c]
ABC/3TC/DTG	40,640	0.89	45,481	1.000	40,605	0.91	44,479	1.000	40,681	0.87	46.534	1.000
TAF/FTC+DTG	53,122	0.91	58,402	1.284	53,208	0.93	57,189	1.286	53,040	0.89	59.677	1.282
TAF/FTC+RAL	49,801	0.86	58,047	1.276	49,830	0.87	57,003	1.282	49,775	0.84	59.134	1.271
TAF/FTC/EVG/c	40,759	0.90	45,190	0.994	40,738	0.91	44,614	1.003	40,784	0.89	45.785	0.984
TAF/FTC+DRV/c	44,666	0.90	49,667	1.092	44,667	0.92	48,487	1.090	44,671	0.88	50.912	1.094
TAF/FTC+DRV/r	29,142	0.82	35,508	0.781	29,095	0.84	34,633	0.779	29,193	0.80	36.430	0.783
TAF/FTC+RPV	34,819	0.84	41,226	0.906	34,759	0.87	39,920	0.898	34,885	0.82	42.621	0.916

[a] Cost in RON of initiating a regimen including all potential consequences of deciding to initiate ART with that regimen (adverse effects and changes to other regimens) that may occur within 48 weeks[7]. [b] Efficiency or cost/efficacy[7]. Cost in RON of achieving one responder (<50 copies of RNA of HIV/mL of plasma by week 48). [c] To calculate the relative C/E, a value of 1 was assigned to ABC/3TC/DTG[7].

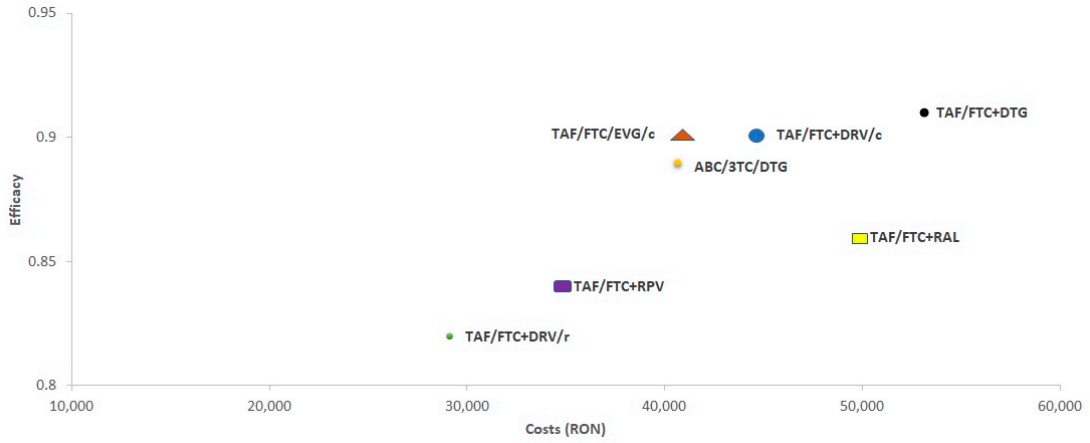

Figure 1. Illustration of efficacy scores by associated costs (RON) for cARTs included in the analysis (base-case scenario).

Figure 1 illustrates efficacy, as derived from the Spanish study and the costs from the payer perspective, namely the Romanian Health Insurance HIV Program. Each point represents the studied regimens, allowing us to identify the regimen with the best ratio of cost/efficacy and rank the regimens.

Considering all the parameters of the C/E calculation, ABC/3TC/DTG, TAF/FTC/EVG/c, and TAF/FTC + DRV/c were the regimens with similar efficacy and C/E values in all three scenarios.

4. Discussion

Among economic evaluation studies, the most common analytical method identified is the cost-effectiveness analysis [4,13]. The research topics in the field of economic evaluation are diverse, due to different settings and methodologies [14], and are mainly related to prevention (pre- and post-exposure prophylaxis, mother-to-child transmission, drug use prevention intervention) [15–18], co-infections (tuberculosis, HPV) [19,20], and HIV-related services (testing and counseling, hospitalizations) [21,22]. In resource-limited settings, C/E studies based on mathematical modeling, assessments of the optimal timing of ART initiation, strategies for initiating ART, and the use of second-line ART have been conducted, exhibiting substantial variations in unit costs and interventions, in order to improve outcomes [23].

A comparison with data from other studies evaluating C/E of different cART is difficult because the end points are variable, mainly focused on reduction of HIV-related mortality and morbidity (e.g., new HIV infections prevented, quality-adjusted life years, incidence of opportunistic infections, CD4 T-cell recovery), and rarely focused on reaching viral suppression [6,24–26]. In addition, estimates of efficacy in other studies were local data-based and not an analysis of overall efficacy as resulted from major randomized clinical trials assessed in the Spanish study [25,27].

INSTI-based regimens are preferred in clinical practice due to their favorable efficacy and tolerability profiles [28]. In our clinical practice, we noticed the increasing use of INSTI-based regimens in patients diagnosed with HIV infection from 2015 to the end of 2019. We further evaluated the estimated cost per responder with seven ART combinations, using the software application developed by the Spanish group [12].

As mentioned in the ECDC HIV treatment and care report, the cost of HIV treatment per patient in 2016 varied widely among countries in the European region. The cost of drugs per patient ranged from 4000 EUR in Latvia and Estonia to approximately 20,000 EUR [29]. In Romania, the cost of treatment is fully reimbursed by the Ministry of Health. The National Program for HIV/AIDS includes the strategy and principles of management to achieve the assigned objectives [30]. The ultimate cost burden is borne by the overall

healthcare system and society, yet clinicians treating HIV patients should also be aware of the economic impact of different ARTs in the context of budget limitations.

Although this was a single center experience, our results represent the first cost-efficacy assessment in Romania, expressed as the amount spent by the healthcare system to achieve one responder with viral suppression of less than 50 copies/mL at 48 weeks of cART recommended for treatment initiation. The cost per responder with TAF/FTC/EVG/c and TAF/FTC + DRV/c was 0.06% lower and 0.92% higher, respectively, as compared to the regimen of reference with similar efficacy. TAF/FTC + DRV/r and TAF/FTC +RPV were the least expensive regimens, but with lowest efficacy of all the cARTs included in the analysis.

Other combinations, ABC/3TC/DTG, TAF/FTC/EVG/c, and TAF/FTC + DRV/c, stood out due to their higher efficacy and small differences in associated costs and should be preferred. The most efficient regimens (best efficacy for the cost) were ABC/3TC/DTG in Spain and TAF/FTC/EVG/c in our setting, although the differences in relative efficiency were small.

A series of limitations of the C/E analysis were identified by the Spanish group [8]: calculation of efficacy based on heterogeneous clinical trial results and intend-to-treat exposed analytical approach, and an assumption of similar efficacy and safety for TDF/FTC and TAF/FTC. Our present study also had some limitations. When applying this algorithm, as performed in our study, to studies other than those on which it was elaborated, the results might be affected by characteristics of local patient assessments. In addition, this was a single-center analysis in which retrospective data were used. Moreover, the costs of interventions might be subject to changes in time and differences among various settings.

Nevertheless, we consider that the results should be viewed as guidance for therapeutic choices in naïve-ART patients. Additionally, when selecting the first treatment regimen, the clinician might need to consider the combined information of efficacy and cost, as derived from our analysis.

5. Conclusions

Effective cART has changed the lives of PLWH. Due to their established efficacy/risk profiles, INSTI-based regimens are currently preferred and recommended internationally. When resources are limited, the strategy evolves toward the optimal use of resources. As part of the healthcare system impacted by HIV-related expenditures, infectious disease specialists should be aware not only of the efficacy and safety information, but also of the costs associated with each therapeutic regimen. Our analysis provides cost-efficacy information for several different cARTs recommended for treatment initiation, based on established efficacy data and local costs. The results could offer insight and guide treatment choices for ART-naïve adult HIV-infected people.

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