Cost-effectiveness analysis of dolutegravir plus backbone compared with raltegravir plus backbone, darunavir+ritonavir plus backbone and efavirenz/tenofovir/emtricitabine in treatment naïve and experienced HIV-positive patients

Umberto Restelli[1,2]
Giuliano Rizzardini[3,4]
Andrea Antinori[5]
Adriano Lazzarin[6]
Marzia Bonfanti[1]
Paolo Bonfanti[7]
Davide Croce[1,2]

[1]Centre for Research on Health Economics, Social and Health Care Management, LIUC – Università Cattaneo, Castellanza, Varese, Italy; [2]School of Public Health, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa; [3]First and Second Divisions of Infectious Diseases, "Luigi Sacco" Hospital, Milan, Italy; [4]School of Clinical Medicine, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa; [5]National Institute for Infectious Diseases "L Spallanzani", Rome, [6]Department of Infectious Diseases, San Raffaele Scientific Institute, [7]Department of Infectious and Tropical Diseases, A Manzoni Hospital, Lecco, Italy

Correspondence: Umberto Restelli
Centre for Research on Health Economics, Social and Health Care Management, LIUC – Università Cattaneo, Corso Matteotti 22, 21053 Castellanza, Varese, Italy
Tel +39 0331 572346
Fax +39 0331 572513
Email urestelli@gmail.com

Background: In January 2014, the European Medicines Agency issued a marketing authorization for dolutegravir (DTG), a second-generation integrase strand transfer inhibitor for HIV treatment. The study aimed at determining the incremental cost-effectiveness ratio (ICER) of the use of DTG+backbone compared with raltegravir (RAL)+backbone, darunavir (DRV)+ritonavir(r)+backbone and efavirenz/tenofovir/emtricitabine (EFV/TDF/FTC) in HIV-positive treatment-naïve patients and compared with RAL+backbone in treatment-experienced patients, from the Italian National Health Service's point of view.

Materials and methods: A published Monte Carlo Individual Simulation Model (ARAMIS-DTG model) was used to perform the analysis. Patients pass through mutually exclusive health states (defined in terms of diagnosis of HIV with or without opportunistic infections [OIs] and cardiovascular disease [CVD]) and successive lines of therapy. The model considers costs (2014) and quality of life per monthly cycle in a lifetime horizon. Costs and quality-adjusted life years (QALYs) are dependent on OI, CVD, AIDS events, adverse events and antiretroviral therapies.

Results: In treatment-naïve patients, DTG dominates RAL; compared with DRV/r, the ICER obtained is of 38,586 €/QALY (6,170 €/QALY in patients with high viral load) and over EFV/TDF/FTC, DTG generates an ICER of 33,664 €/QALY. In treatment-experienced patients, DTG compared to RAL leads to an ICER of 12,074 €/QALY.

Conclusion: The use of DTG+backbone may be cost effective in treatment-naïve and treatment-experienced patients compared with RAL+backbone and in treatment-naïve patients compared with DRV/r+backbone and EFV/TDF/FTC considering a threshold of 40,000 €/QALY.

Keywords: antiretroviral therapy, costs, economic evaluation, cost-utility analysis

Background

In the last decade, several new antiretroviral drugs for the treatment of HIV have been approved by drug regulatory agencies in Europe, US, Canada and Australia (ie, darunavir [DRV], raltegravir [RAL], elvitegravir, rilpivirine, maraviroc). Most of these marketing authorizations are based on non-inferiority Phase III studies that demonstrated the new drug to be non-inferior compared with the comparators taken into consideration.

Antiretroviral therapy (ART) usually consists of a backbone composed of two nucleoside reverse transcriptase inhibitors (NRTIs) and of a third agent, either a

non-nucleoside reverse transcriptase inhibitor (NNRTI), a protease inhibitor (PI), a CCR5 receptor antagonist or an integrase strand transfer inhibitor (INSTI). The first-line treatment recommended by the Italian Guidelines On The Use Of Antiretroviral Drugs is a backbone plus an INSTI or a backbone plus an NNRTI or, in particular conditions, a backbone plus a PI.[1]

The most recent data available on the Italian National Health Service (NHS) expenditure for ARTs show a total of 672.7 million €, of which 336.9 million € for drug combinations, 161.8 million € for PIs (alone or in one pill combination), 52.4 million € for NRTIs, 33.3 million € for NNRTIs and 88.3 million € for other antiretroviral drugs.[2]

In January 2014, the European Medicines Agency issued a marketing authorization for dolutegravir (DTG), a second-generation INSTI for the treatment of HIV on the European market.[3]

DTG is the only antiretroviral drug recommended with both abacavir/lamivudine (ABC/3TC) and tenofovir disoproxil fumarate/emtricitabine (TDF/FTC) backbones by the Department of Health and Human Services' Panel Guidelines.[4] It proved to be superior for viral suppression in treatment-naïve patients to DRV plus ritonavir (DRV+r) at 48 and 96 weeks[5,6] and to efavirenz/TDF/FTC (EFV/TDF/FTC).[7] Compared to RAL, it proved to be non-inferior in treatment-naïve patients at 48 and 96 weeks[8,9] and to be superior in treatment-experienced patients at 48 weeks.[10]

Within the aforementioned studies, the analyses conducted considering as target population a high viral load patients subgroup (HIV RNA >100,000 copies/mL), provided only assuming DRV+r and RAL+backbone as comparators, showed an increased difference in terms of effectiveness due to the use of DTG+backbone vs the comparator compared with the total population.[5,6,8,9]

In Italy, HIV clinical pathways at a regional level introduced the concept of cost-effectiveness as a parameter to be taken into consideration when selecting ART to be administered.[11–13] Therefore, the investigation of the value for money of ARTs is increasingly needed within the Italian context.

Starting from the efficacy results presented earlier, the study aimed at determining the incremental cost-effectiveness ratio (ICER) of the use of DTG+backbone compared with RAL+backbone, DRV+r+backbone and EFV/TDF/FTC in HIV-positive treatment-naïve patients and compared with RAL+backbone in treatment-experienced patients, adopting the point of view of the Italian National Health Service.

Further analyses were conducted considering a subgroup of patients with high viral load (HIV RNA >100,000 copies/mL) at baseline, where such subgroup was considered in clinical trials (vs DRV+r and RAL in treatment-naïve patients).

Materials and methods
Model structure

The analysis was performed using a Monte Carlo Individual Simulation Model, the ARAMIS-DTG model (an updated version of the ARAMIS model used to evaluate the cost-effectiveness of maraviroc+optimized background therapy [OBT] vs OBT).[14]

This microsimulation model allows patients to pass through successive lines of therapy considering costs and quality of life per monthly cycle in a lifetime horizon. Patients pass through mutually exclusive health states, defined in terms of diagnosis of HIV with or without opportunistic infections (OI) and cardiovascular disease (CVD).

Each patient within the model is assigned to one of 12 mutually exclusive health states: without OIs or with one of five possible OIs combined with the possibility of being affected by CVD. Patients can transition between any of the HIV health states into the CVD health state (if so, they remain within this state until death) and can experience acute OIs. Patients remain in a given health state for at least one cycle (1 month) and are at risk of changes in $CD4^+$ cell count, consequences of the disease (OIs, AIDS-related morbidity), CVD, adverse events (AEs) and treatment failure due to viral rebound.

Figure 1 shows the model structure in terms of transitions among health states.

For the first 48 weeks in which a patient is assigned to a therapy, the model considers the 48 weeks probability to remain virologically controlled (as reported in Table 1). After this period, the probability of a viral rebound becomes monthly, being estimated by dividing the difference in viral load suppression at 48 and 96 weeks[5–10,15] by the viral load suppression at 48 weeks. After 96 weeks, the monthly probability of a viral rebound is derived from the study by Rockstroh et al.[16]

Patients enter the model with a $CD4^+$ level as observed in the cohort considered for each ART and experience a cell recovery based on the mean $CD4^+$ cell count increase (with a cap of 1,500 cells/μL) of the treatment in use for 24 months, after which the pace of $CD4^+$ cells' recovery becomes non-treatment-related. Patients failing ART maintain the $CD4^+$ level, since they are switched to the subsequent ART regimen defined within the algorithm implemented. Twelve months
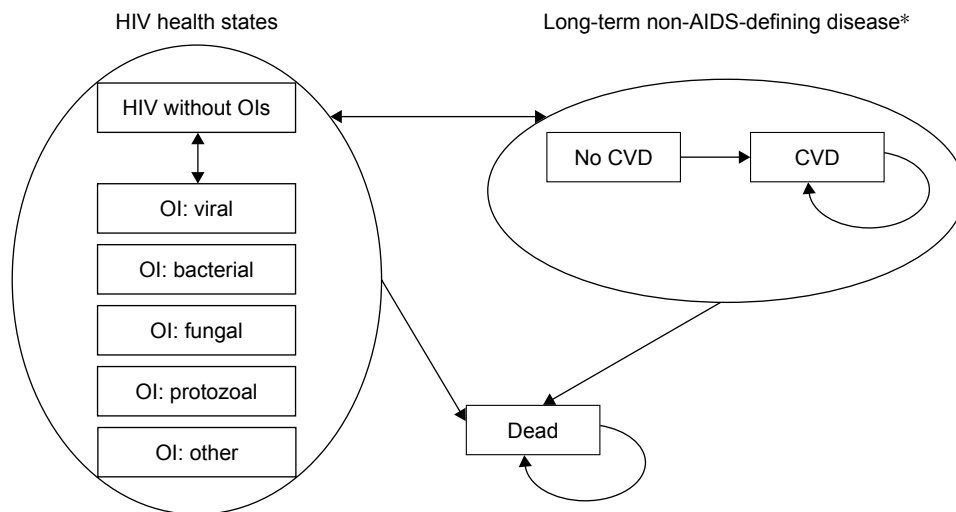
Figure 1 Model structure – health states transitions.
Note: *Long-term non-AIDS-defining diseases refer to CVD.
Abbreviations: CVD, cardiovascular disease; OI, opportunistic infection.

after failing the last ART, a decline of CD4+ cell count is observed, as explained later ("Clinical parameters" section).

CD4+ cell count, along with the time since ART started, affects the monthly probability to experience OIs (viral, bacterial, protozoal, fungal, and others), and they were calculated from the study by D'Arminio et al.[17] Monthly CVD risk is estimated considering the coronary heart disease's Framingham score plus equation for stroke. The parameters tracked in the model and used to estimate the score are the total cholesterol, the high-density lipoprotein cholesterol and age of patients. All other parameters derived from clinical trials remain constant. AIDS diagnosis is defined by CD4+ cell count equal to or lower than 200 cells/μL.

AEs' monthly probability rate is influenced by the ART in use derived from the incidence of AEs emerged from the clinical trials considered.[5,7,8,10] The costs and quality-adjusted life years (QALYs) are dependent on OI, CVD, AIDS, AEs and ART (the latter influencing only costs), as explained in the respective paragraphs. The occurrence of specific events is recorded for each patient from entry into the model until death, using tracker variables.

Both outcomes (QALYs) and costs were discounted at an annual rate of 3%.[18]

Figure 2 illustrates the inter-relationship between the different components of the model.

Death may occur due to acute OI, HIV-related disease (including OI), CVD and background mortality (Italian-specific life tables).

Each cost utility analysis has been conducted with a lifetime horizon.

Table 1 Base case analyses effectiveness values (percentage of patients with HIV RNA of <50 copies/mL at week 48)

Analysis	Treatment	Effectiveness at week 48 (patients with HIV RNA <50 copies/mL)	Source
DTG vs RAL – naïve patients	DTG+backbone	87.8%	Raffi et al[8]
	RAL+backbone	85.4%	
DTG vs DRV+r – naïve patients	DTG+backbone	89.7%	Clotet et al[5]
	DRV+r+backbone	82.6%	
DTG vs EFV – naïve patients	DTG+backbone	88.2%	Walmsley et al[7]
	EFV/TDF/FTC	80.8%	
DTG vs RAL – experienced patients	DTG+backbone	70.9%	Cahn et al[10]
	RAL+backbone	63.7%	
DTG vs RAL – naïve with high viral load	DTG+backbone	82.5%	Raffi et al[8]
	RAL+backbone	75.0%	
DTG vs DRV+r – naïve with high viral load	DTG+backbone	93.4%	Clotet et al[5]
	DRV+r+backbone	70.5%	

Abbreviations: DTG, dolutegravir; RAL, raltegravir; DRV, darunavir; r, ritonavir; EFV, efavirenz; TDF/FTC, tenofovir/emtricitabine.
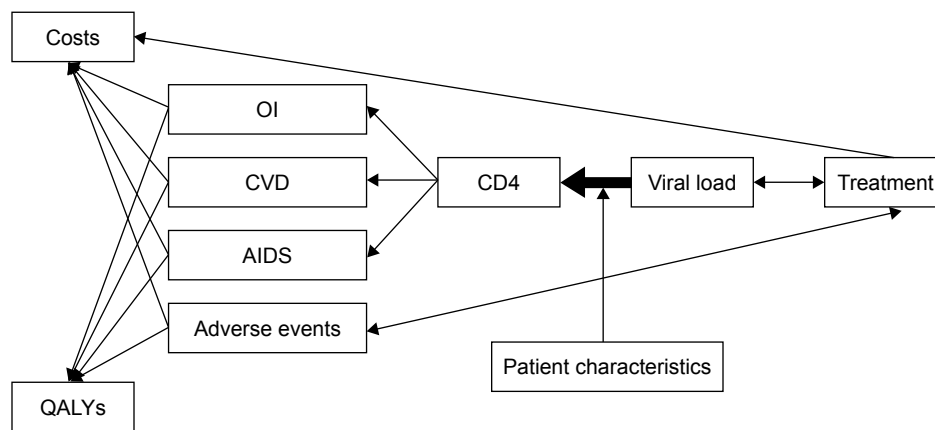
Figure 2 Inter-relationships between the different components of the model.
Abbreviations: OI, opportunistic infection; CVD, cardiovascular disease; QALYs, quality-adjusted life years.

Intervention and comparator

The comparators considered in the analysis are RAL+ backbone, the main competitor within the same drug class as DTG (INSTI); DRV+r+backbone, which, along with atazanavir+r, is the PI recommended by international HIV guidelines in first-line therapies;[1,4] and EFV/TDF/FTC, which represented the gold standard therapy for years, before the development of protease inhibitors, and is among the cheapest ART options on the market.

Population

Each cost utility analysis was conducted considering a theoretical cohort of 1 million patients.

The cohort characteristics in terms of age, gender, CD4+ cell count, viral load at baseline, hepatitis B and C infection and Framingham score are based on the clinical trials mentioned earlier,[5–10] as well as the effectiveness values of the therapies considered.

For naïve patients, the aforementioned studies considered a population with median age between 34 and 37 years, of which males were between 83% and 86%. In Italy, newly diagnosed patients, as reported in the most recent publication by the Italian National Health Institute,[19] were 77.4% males with a median age of 39 years for males and 36 years for females. Caucasians represent between 68% and 86% of the cohorts of the studies considered. In Italy, the proportion of Caucasians is estimated to be >80% based on published data[19] and experts' opinion. Median baseline HIV-1 RNA copies/mL and median CD4 cells/µL were between 4.48 $\log_{10}$ and 4.68 $\log_{10}$ and between 338 and 400 cells/µL, respectively, in clinical trials. Unpublished data of the Italian Cohort of Antiretroviral Naïve patients show higher HIV-1 RNA, while CD4 cells copies' levels are in line with

the aforementioned data. This seems coherent considering that clinical trials' cohorts are selected, presenting lower viral load compared to the general HIV-positive population. Finally, a higher hepatitis B virus (HBV) and hepatitis C virus (HCV) proportion of co-infected patients are observed in Italy, which is due to the higher prevalence of hepatitis virus in Italy, compared with central and north European countries and with United States and Canada.

Model input
Treatment algorithm

Following an algorithm defined by opinion leaders for each arm of the model, based on Italian HIV/AIDS guidelines,[20] patients are assigned to a first-line antiretroviral therapy (ART), DTG+backbone or one of the comparators considered, and to subsequent ARTs (the treatment algorithm is reported as Supplementary materials). The treatment algorithm was defined by four directors of hospital Infectious Diseases departments, among which the Medical Director of the Italian National Institute for Infectious Diseases; the Director of Infectious Diseases Division, the Scientific Director for Clinical Research of a clinical research university hospital and the Director of Infectious Diseases Department of a clinical research university hospital. Consensus was reached through discussions within advisory boards. The choice of subsequent lines of treatment depends on the reason of the switch: tolerability failure with no resistance, virologic failure with no resistance or virologic failure with resistance.

Clinical parameters

The therapy in use influences the viral load of each patient, as observed in the clinical trials reported earlier,[5–10] affecting the

decline of CD4^{+} cell count[21] (also influenced by the patient's characteristics). The effectiveness value of each therapy (percentage of patients with HIV RNA of <50 copies/mL at week 48) is reported in Table 1.

Mortality ratios for CVD, HIV and background mortality are taken from the Italian Statistics National Institute database,[22] and a standardized mortality ratio is considered based on CD4^{+} cell count, as in the study by Lewden et al.[23]

Utility

The utility values related to CD4^{+} cell count, CVD, acute and post-acute OIs and the AEs considered within the model are presented in Table 2. Changes in the quality of life are associated with the following parameters: six CD4^{+}

Table 2 Utility values and utility decrements considered in the analysis

Parameters	Utility value/utility decrement	Source
CD4, cells/μL		
>500	0.798	Kauf et al[29]
350–500	0.784	
200–350	0.778	
100–200	0.750	
50–100	0.742	
0–50	0.742	
CVD	0.560	Simpson et al[30]
Acute OIs utility		
Bacterial (MAC)	0.561	Paltiel et al[31]
Fungal (PCP)	0.652	
Protozol	0.561	
Viral (CMV)	0.652	
Other	0.561	
Post acute OIs utility		
Bacterial (MAC)	0.735	Schackman et al[32]
Fungal (PCP)	0.743	
Protozol	0.731	
Viral (CMV)	0.760	
Other	0.770	
AEs		
Any AE grade ≥2	−0.012	Kauf et al[29]
Diarrhea	−0.009	
Nausea	−0.008	
Vomiting	−0.005	
Rash/injection site reaction	−0.010	
Nightmares/abnormal dreams	−0.019	
Dizziness	−0.033	
Depression	−0.054	
Insomnia	−0.000	
Other AEs	−0.012	

Abbreviations: CVD, cardiovascular disease; OI, opportunistic infection; MAC, *Mycobacterium avium* complex; PCP, *pneumocystis carinii* pneumonia; CMV, cytomegalovirus; AE, adverse event.

cell count categories (0–50, 50–100, 100–200, 200–350, 350–500 and >500 cells/μL), acute OIs according to five categories (bacterial, protozoal, fungal, viral, other), long-term non-AIDS-defining diseases and acute AEs leading to ART discontinuation.

Once an acute OI is experienced, the related utility is applied and after 3 months post-OI utilities are applied for the remainder of time that the individual is alive. Within the model, the lowest utility is applied for health states considering CD4^{+} cell count, OIs and CVD, while utilities decrement are subtracted from the base utility when patients experience one of the AEs considered.

Costs

The costs considered within the model are direct health costs related to ART, OI prophylaxis, treatment of OIs, routine care (hospitalization, outpatient activity, stratified by CD4^{+} cell count), costs of therapy switch, costs due to acute AEs and cost of death.

The cost of OIs, OIs' prophylaxis, CVD and AEs were calculated on the basis of interviews submitted to directors of Infectious Diseases departments of Italian hospitals, to assess the resources consumption in real clinical practice for the diagnosis and care of the aforementioned events. These costs were approximated considering the reimbursement tariffs used within the Italian NHS for DRG and outpatient activities.

The costs, referred to year 2014, are reported in Table 3.

ART costs were considered based on Lombardy Region diagnostic clinical pathway.[11] INSTI- and PI-based first-line therapies' cost (INSTI+backbone and PI+backbone) were considered to be the sum of third drug's cost (INSTI or PI) and of a weighted mean of the cost of the two most relevant backbones for Italian clinical practice on the basis of experts' opinion (40% cost of ABC/3TC and 60% of emtricitabine/tenofovir).

The price of drugs in Italy is negotiated at a national level by the Italian Medicines Agency (AIFA). The ex-factory price is published in the Official Gazette of the Italian Republic and is then reduced by applying mandatory discounts defined at a national level. Regional prices are then subject to regional tenders; however, limited differences are observed for antiretroviral drugs. The prices used in the analysis, published in the Lombardy Region diagnostic clinical pathway,[11] are comparable (with limited differences of <1 €) with those published within the most recent Italian HIV National Guidelines,[1] excluding the drugs whose price was changed after 2014. The different prices (related to

Table 3 Costs considered in the analysis

Parameters	Value		Source
ABC/3TC (600/300 mg)	398.3 €		Directorate General for Health
Atazanavir 300 mg	333.0 €		of Lombardy Region[11]
DRV 800 mg	347.8 €		
DRV 600 mg (×2)	528.0 €		
DTG (50 mg)	495.2 €		
Etravirine (200 mg) (×2)	396.0 €		
Elvitegravir/cobicistat/emtricitabine/ tenofovir (150/150/200/245 mg)	797.6 €		
Emtricitabine/tenofovir (200+245 mg)	438.9 €		
Emtricitabine/tenofovir/efavirenz (200/245/600 mg)	596.7 €		
Emtricitabine/tenofovir/rilpivirine (200/245/25 mg)	598.6 €		
Lopinavir/ritonavir (200/50 mg) (×4)	357.7 €		
Maraviroc (300 mg)	902.9 €		
Nevirapine (400 mg)	178.5 €		
RAL (400 mg) (×2)	438.9 €		
Rilpivirine (25 mg)	230.7 €		
Ritonavir (100 mg)	25.0 €		
Tenofovir (245 mg)	276.9 €		
Monthly routine care cost			
CD4$^+$ (cells/μL)	No OI history	OI history	
>500	65.0 €	65.0 €	Reprocessed from Rizzardini et al[33]
350–500	166.0 €	166.0 €	
201–350	166.0 €	166.0 €	
101–200	354.0 €	354.0 €	
51–100	354.0 €	354.0 €	
0–50	354.0 €	354.0 €	
OIs			
Bacterial	8,186.0 €		Resource consumption assessed
Fungal	8,186.0 €		through expert opinion – Italian
Protozoal	8,186.0 €		tariff nomenclature[a]
Viral	8,186.0 €		
Other OI	8,186.0 €		
OIs' prophylaxis			
Cytomegalovirus	1,788.0 €		Resource consumption assessed
Mycobacterium avium complex	56.0 €		through expert opinion – Italian
Pneumocystis carinii pneumonia	7.0 €		tariff nomenclature[b]
Cost per care			
Tropism (maraviroc)	156.0 €		Italian tariff nomenclature
Genotype	54.2 €		(codes 91.30.3; 90.81.5; 91.22.3;
CD4	17.1 €		90.81.5; 90.50.4)
Viral load	54.2 €		
HLA-B5701 (ABC/3TC)	18.8 €		
CVD – monthly cost	228.8 €		Resource consumption assessed through expert opinion – Italian tariff nomenclature[c]
AEs			
Diarrhea	20.7 €		Resource consumption assessed
Nausea	26.9 €		through expert opinion – Italian
Vomiting	26.9 €		tariff nomenclature[d]
Rash/injection site reaction	22.7 €		
Nightmares/abnormal dreams	20.7 €		
Dizziness	20.7 €		

(Continued)

Table 3 (*Continued*)

Parameters	Value	Source
Depression	20.7 €	
Insomnia	20.7 €	
Other AEs	24.2 €	
Average cost (discontinuation)	20.7 €	
Death	12,502.0 €	Reprocessed from Rizzardini et al[33] and Raitano[34]

Notes: [a]An hospitalization related to DRG 489 was considered for each opportunistic infection. [b]Valganciclovir for cytomegalovirus; azithromycin for mycobacterium avium complex; sulfamethoxazole and trimethoprim for pneumocystis carinii pneumonia. [c]Weighted mean cost of acute myocardial infarction (40%) and hypokinetic cardiomyopathy (60%). For acute myocardial infarction, we considered the cost of coronary angiography and angioplasty, specialist visits (code 89.7) and drug therapy; for hypokinetic cardiomyopathy, we considered the costs of specialist visits (code 89.7), blood tests (codes 90.11.4; 90.13.3; 90.16.3; 90.37.4; 90.40.4; 90.44.1) and drug therapy. [d]One specialist visit (code 89.7) plus drugs, as emerged by interviews with clinicians, based on real clinical practice, and blood tests for "Other AEs" (code 90.62.2).
Abbreviations: ABC/3TC, abacavir/lamivudine; DRV, darunavir; DTG, dolutegravir; RAL, raltegravir; OI, opportunistic infection; CVD, cardiovascular disease; AE, adverse event.

only three drugs) are, however, at the same level of clinical pathways and publications concerning other regions, as the clinical pathway of Veneto[24,25] and that of Calabria,[26] with differences of <0.5 €. Therefore, the prices used in the analysis are considered by the authors as representative at a national level.

Sensitivity analysis

Univariate sensitivity analyses were performed to address the uncertainty of the main parameters of the model. The range of each parameter considered is presented in Table 4. A probabilistic sensitivity analysis was not performed due to its estimated running time being, as reported by Pialoux et al,[27] ~417 days per each comparator.

Based on experts' opinion, we tested the effects of a decrease of 10% of DTG cost (an increase of the drug cost was considered highly unlikely), of a change of ±10% of the cost of subsequent therapies and salvage therapies (due to the possible decrease of therapies' costs and increase due to

Table 4 Ranges and values of the parameters modified within the sensitivity analysis

Parameters	Range/value
DTG therapy cost	−10%
Cost of subsequent therapies	±10%
Cost of salvage therapies	±10%
Discount rates	0%
DTG effectiveness	−2.5%
Alternative utility values[35]	
CD4^{+} cell count: >500 cells/μL	0.946
CD4^{+} cell count: 350–500 cells/μL	0.933
CD4^{+} cell count: 200–350 cells/μL	0.931
CD4^{+} cell count: 100–200 cells/μL	0.853
CD4^{+} cell count: 50–100 cells/μL	0.853
CD4^{+} cell count: 0–50 cells/μL	0.781

Abbreviation: DTG, dolutegravir.

new available drugs), of not considering any discount rate both for costs and QALYs, of a decrease of 2.5% of DTG effectiveness and of the use of alternative utility values associated with each CD4^{+} cell count level.

Results
Base case results
The results of the analyses conducted are reported in Table 5.

DTG dominates RAL in treatment-naïve patients, leading to lower costs for the Italian National Health Service and being more effective, resulting in a higher number of QALYs per patient. The same result is observed in treatment-naïve patients with high viral load.

Compared with DRV+r, DTG leads to an increase of costs and an increase of QALYs, with an ICER of 38,586 €/QALY in treatment-naïve patients and of 6,170 €/QALY in treatment-naïve patients with high viral load. The same scenario is observed in the comparison of DTG+backbone vs EFV/TDF/FTC, with an ICER of 33,664 €/QALY.

Considering treatment-experienced patients, the use of DTG compared with RAL leads to an increase of costs and to an increase of QALYs with an ICER of 12,074 €/QALY.

Sensitivity analysis results
The results of sensitivity analysis are presented in Table 6.

In treatment-naïve patients, the sensitivity analysis results confirmed the dominance of DTG-based therapies compared with RAL-based therapies; confirmed DTG-based therapies to be cost effective compared with DRV+r-based therapies and with EFV/TDF/FTC considering a 40,000 €/QALY threshold, excluding the analyses in which the effectiveness of DTG is lowered by 2.5%, the cost of subsequent therapies is lowered by 10% and the cost of salvage therapies is raised by 10%; confirmed the dominance of DTG-based therapies compared with RAL-based therapies in high viral

Table 5 Results of the analysis performed

Patients	Therapy	Mean lifetime cost (€)	Incremental cost (€)	Mean QALYs	Incremental QALYs	ICER (€/QALY)
Naïve	RAL+backbone	317,054	–	15.310	–	DTG dominates RAL
	DTG+backbone	314,713	–2,341	15.418	+0.108	
	DRV+r+backbone	310,103	–	15.383	–	38,586
	DTG+backbone	318,426	+8,323	15.599	+0.216	
	EFV/TDF/FTC	305,315	–	15.252	–	33,664
	DTG+backbone	316,211	+10,897	15.575	+0.324	
Naïve with high viral load	RAL+backbone	314,191	–	14.744	–	DTG dominates RAL
	DTG+backbone	308,483	–5,708	15.018	+0.274	
	DRV+r+backbone	306,016	–	14.841	–	6,170
	DTG+backbone	309,031	+3,015	15.303	+0.489	
Experienced	RAL+backbone	360,951	–	10.324	–	12,074
	DTG+backbone	366,186	+5,235	10.757	+0.434	

Abbreviations: QALYs, quality-adjusted life years; ICER, incremental cost-effectiveness ratio; RAL, raltegravir; DTG, dolutegravir; DRV, darunavir; r, ritonavir; EFV, efavirenz; TDF/FTC, tenofovir/emtricitabine.

load patients and showed ICERs <12,500 €/QALY for DTG-based therapies vs DRV-based therapies in patients with high viral load.

In treatment-experienced patients, the sensitivity analysis confirmed DTG-based therapies to be cost-effective compared with RAL-based therapies considering a threshold of 40,000 €/QALY in all scenarios.

Discussion

The results of the analysis performed show how the use of DTG+backbone may be cost effective in treatment-naïve patients compared with RAL+backbone (being dominant, leading to lower costs and to a higher number of QALYs), DRV/r+backbone and EFV/TDF/FTC, considering the threshold of 40,000 €/QALY identified by the Italian Health Economics Association.[18]

DTG-based therapies showed a better cost-effectiveness profile compared with RAL+backbone and DRV/r+backbone in treatment-naïve patients subgroup with high viral load.

In 2015, Despiégel et al[14] published an article presenting the results of a cost-effectiveness analysis in which, using the ARAMIS-DTG model, they compared the use of DTG in treatment-naïve patients with EFV, RAL, DRV+r, rilpivirine, elvitegravir/cobicistat, atazanavir+r and lopinavir/r and in treatment-experienced patients with RAL. DTG resulted to be dominant (leading to a decrease of costs for the Canadian NHS and to an increase of QALYs) in all the comparisons. These results are consistent with our analysis considering RAL as a comparator in treatment-naïve patients. When DRV+r and EFV/TDF/FTC are assumed as comparators in treatment-naïve patients and RAL is assumed as comparator in treatment-experienced patients, the Italian results showed increased QALYs and costs due to the use of DTG, while in the analysis performed in Canada, DTG led to higher QALYs and lower costs.

In Europe, a similar analysis was conducted in France by Pialoux et al.[27] The authors performed a cost-effectiveness analysis, through the use of the ARAMIS-DTG model,

Table 6 Results of the sensitivity analysis

Scenario	Naïve			Experienced	Naïve with high viral load	
	DTG vs RAL	DTG vs DRV+r	DTG vs EFV	DTG vs RAL	DTG vs RAL	DTG vs DRV+r
Base	Dominant	38,586 €/QALY	33,664 €/QALY	12,074 €/QALY	Dominant	6,170 €/QALY
DTG cost –10%	Dominant	14,972 €/QALY	17,535 €/QALY	5,128 €/QALY	Dominant	Dominant
Subsequent therapies cost –10%	Dominant	43,094 €/QALY	43,573 €/QALY	12,254 €/QALY	Dominant	12,455 €/QALY
Subsequent therapies cost +10%	Dominant	33,762 €/QALY	23,611 €/QALY	12,128 €/QALY	Dominant	259 €/QALY
Salvage therapies cost –10%	Dominant	34,586 €/QALY	23,013 €/QALY	16,636 €/QALY	Dominant	3,144 €/QALY
Salvage therapies cost +10%	Dominant	42,270 €/QALY	44,171 €/QALY	7,746 €/QALY	Dominant	9,570 €/QALY
DTG effectiveness –2.5%	Dominant	48,965 €/QALY	40,629 €/QALY	13,638 €/QALY	Dominant	8,177 €/QALY
Alternative utility values	Dominant	32,459 €/QALY	28,725 €/QALY	10,028 €/QALY	Dominant	5,382 €/QALY
0% discount rate	Dominant	28,770 €/QALY	22,242 €/QALY	20,781 €/QALY	Dominant	11,328 €/QALY

Abbreviations: DTG, dolutegravir; RAL, raltegravir; DRV, darunavir; r, ritonavir; EFV, efavirenz; QALYs, quality-adjusted life years.

comparing the use of DTG vs RAL in treatment-experienced and INSTI-naïve adults with at least two-class resistance. DTG led to an increase of QALYs (+0.35) and of costs (+7,266 €), with a cost per QALY of 21,048 €, leading the authors to consider DTG cost effective compared to RAL in the target population. The results obtained by Pialoux et al are consistent with those obtained in the analysis presented.

A further study concerning the health economics evaluation of DTG is that of Peng et al,[28] in which DTG+ABC/3TC was compared with EFV/TDF/FTC as first-line treatment of HIV-1 patients in the United States. The study shows a lifetime better result for DTG in terms of QALY gained (+0.12 per person) and higher costs (+58,188 US$ per person), with an ICER of 482,717 US$/QALY. Even if the analysis shows a higher effectiveness and higher costs for DTG+backbone compared with EFV/TDF/FTC as in the study performed in Italy, it is difficult to compare the results of analyses performed in two health systems with different characteristics as those of Italy (universalistic public system) and of the United States (market-based health insurance system).

The analysis performed is the first to assess the cost-effectiveness of DTG vs its main comparators within the Italian context. The main limitation of our analysis is related to the generalizability of the results, being based on Italian costs and on Italian HIV/AIDS guidelines. The prices of HIV drugs are subject to continuous modifications due to pharmaceutical companies' market strategies; therefore, the analysis should be updated whenever changes in drugs prices are observed. To estimate the cost of OIs' management, OIs' prophylaxis, CVD, AEs and laboratory tests, we considered the reimbursement tariffs of the Italian NHS. This is consistent with the point of view assumed but might underestimate the costs for the Italian NHS. In fact, if the cost to perform a health care service for a public provider is higher than the tariff with which it is reimbursed by the NHS, at the end of the fiscal year, the NHS might have to provide further economic resources to the aforementioned provider. Moreover, concerning the clinical effectiveness of the therapies considered, the analysis presented is based on efficacy data coming from published trials, while future analyses should focus on effectiveness data collected within the Italian health service (not available at present) to ensure the reliability of the results. Furthermore, specific studies on the cost of AEs and complications in Italy in HIV-positive patients' cohorts should be performed to provide reference data for future analyses. Limitations related to the model used for the analysis are related to the absence of a probabilistic sensitivity analysis and to a possible underestimation of CVD incidence, due to the fact that the model estimates this risk through Framingham equation, not considering the increased risk associated with HIV infection.

Conclusion

The use of DTG+backbone may be cost effective in treatment-naïve and treatment-experienced patients compared with RAL+backbone and in treatment-naïve patients compared with DRV/r+backbone and EFV/TDF/FTC considering the threshold of 40,000 €/QALY identified by AIES.

Acknowledgment

Disclosure

UR declares honoraria for conference talks by Janssen-Cilag. GR declares honoraria for conference talks and advisory board participations (Abbvie, BMS, MSD, Gilead, ViiV, Janssen-Cilag). AA declares grants, personal fees and non-financial support from Gilead Sciences, personal fees from Merck, grants and personal fees from Bristol Myers Squibb, personal fees and non-financial support from Abbvie, grants, personal fees and non-financial support from ViiV Healthcare and grants and personal fees from Janssen-Cilag, all outside the submitted work. AL declares honoraria for conference talks and advisory board participations: Abbvie, BMS, MSD, Gilead, ViiV and Jannsen-Cilag. MB declares no conflicts of interest. PB declares honoraria for conference talks and advisory board participations: Abbvie, BMS, MSD, Gilead, ViiV and Jannsen-Cilag. DC declares honoraria for advisory board participations by MSD, Abbvie and Baxter. The authors report no other conflicts of interest in this work.

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