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ORIGINAL RESEARCH

The cost of a combination Anti-Retroviral Therapy (cART) optimization pathway as maintenance therapy in HIV-1 infected patients

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ABSTRACT

BACKGROUND: In order to reduce/prevent combination Anti-Retroviral Therapy (cART)-related toxicity, while maintaining its therapeutic effectiveness over time, the optimization of the antiretroviral therapy could be performed.

AIM: To estimate the economic impact on the Italian National Health Service (NHS) of a cART optimization pathway as maintenance therapy in HIV-1 infected patients over one-year period.

METHODS: Patient data were retrieved from the electronic medical record system in use (year 2015) in a reference HIV Center in Northern Italy. The analysis considered naïve patients and non-naïve patients. To estimate the actual ART expenditure charged to the Center we calculated the cost of cART received during 12 months for each patient. Subsequently, referring to the same patients, a "potential" cART expenditure was estimated. This potential expenditure was estimated taking in consideration the adoption of a specific optimization pathway aimed at maintaining over the time the cART efficacy. Lastly, to assess the sustainability of the optimization pathway, we compared the actual cART expenditure with the potential one. We considered only drug costs (ex-factory prices, included all discounts and VAT) from the perspective of the Italian NHS.

RESULTS: In the 2015, the total expenditure for 564 enrolled HIV-1 patients treated with cART was € 4,042,983. The mean treatment cost per patient was € 7,168. If the Center adopted a specific optimization pathway, the total expenditure would be € 3,914,855 (-€ 128,128).

CONCLUSIONS: From the Italian NHS's perspective, the adoption of a specific cART optimization pathway represents a cost-saving option as maintenance antiretroviral therapy in HIV-1 infected patients.

Keywords

Combination Anti-Retroviral Therapy – cART; HIV-1; Italian National Health System

INTRODUCTION

The *Continuum* of Care in the management of HIV infection (Human Immunodeficiency Virus) describes a patient care pathway that begins with the diagnosis, and then continues with the choice of therapy (engagement in care) and its maintenance (retention in care). The selection of the antiretroviral therapy is the foundation of this pathway. The latest Italian Guidelines recommend the combination of two NRTIs (Nucleoside Reverse Transcriptase Inhibitor) with a INI (INtegrase Inhibitor) or a NNRTI (Non-Nucleoside Reverse Transcriptase Inhibitor), or alternatively in particular conditions a PI (Protease Inhibitor), boosted with ritonavir or cobicistat, as a standard treatment for HIV-infected patients [1]. These combination therapies are defined by the term cART (combination Anti-Retroviral Therapy) [1].

Despite the great progress achieved by the pharmacological research, a therapy capable of eradicating HIV remains a mirage. It is therefore crucial to maintain the effectiveness over time of the antiretroviral treatment adopted, despite the fact that the administration of a cART regimen could, in the medium to long term, result in the reduction in adherence, the onset of toxicity, the aggravation of

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already present comorbidities, an increase in the risk of pharmacological interactions with concomitant therapies due to contingent comorbidities, or the loss of strength/evidence (recommendation) of the regimen administered [1-3].

In order to reduce/prevent cART-related toxicity, while maintaining its therapeutic effectiveness over time, the optimization of the antiretroviral therapy could be performed, as indicated in the Italian Guidelines [1]. Three optimization options can be assumed. The first involves the reduction in the number of antiretroviral regimens administered; in this case there would be a switch from a three-drug (triple) to a two-drug (double) therapy. The second option is not aimed at changing the current therapy, but to reduce the number of daily doses/administrations and/or daily tablets. The third option, finally, involves the replacement of the current regimen with other regimens consisting of the same number of drugs or more. For each of the three options, the modification of the cART therapy should occur under virological suppression (HIV-RNA < 50 copies/ml) [1].

Without addressing here the issue of the clinical implications – since they are widely discussed in the Italian Guidelines, to which it is hereby referred to [1] – the optimization of the cART regimens presents a further issue, concerning economic sustainability. If, as seen from past experience [4], the switch from a three-drug (triple) to a two-drug (double) therapy can result in a reduction in the expenditure on antiretroviral drugs, the same cannot be said for the other optimization pathways presented. For example, with regard to the potential cardiovascular and/or metabolic toxicity associated with current antiretroviral regimens, the Italian Guidelines suggest instead to preferably adopt regimens based on integrase inhibitors (and not on protease inhibitors), without however saying anything about their economic sustainability [1].

The objective of this analysis is therefore to ascertain whether and how a cART optimization pathway can, as a whole, be sustainable for the Italian National Health Service.

METHODS

Analysis design

An observational, retrospective and non-interventional analysis was conducted. The statistical source consists of all HIV-diagnosed patients (hereinafter referred to as "patients treated", or even more concisely as "patients") of the Infectious Diseases Operating Unit of the Hospital "G.B. Rossi" in Verona (hereinafter referred to as the "Center"), who received an antiretroviral therapy during the period 1st January- 31st December 2015.

The patients (who in the analysis were identified by encrypted – and therefore strictly anonymous – codes) were classified into two groups: i) naïve, i.e. patients who started the antiretroviral treatment during the observation year, and ii) non-naïve, i.e. patients who were already being treated with an antiretroviral regimen.

For each of them – characterized by the main demographic (mean age, gender, etc.) and clinical variables (virological suppression, resistances, HCV, HBV, etc.) – the antiretroviral therapy received during the last 12 months was identified, in order to calculate its actual pharmaceutical cost borne by the Center. Subsequently, with reference to the same patients, an antiretroviral expenditure was estimated; this was defined as "potential", because it was due to the adoption of a specific optimization pathway aimed at improving the maintenance of the antiretroviral therapy effectiveness over time [1]. The comparison between actual and potential spending finally allowed to express a judgment on the sustainability (or not) of the optimization pathway with regard to the cART regimens administered during the year 2015.

Optimization pathway

The optimization pathway suggested here was constructed in accordance with the indications of the Italian Guidelines [1]. Two optimization options were assumed, in chronological order. The first is the switch from a three-drug to a two-drug regimen. Based on the results of a previous experience gained by the Center, the two-drug regimen selected was the combination nevirapine 400 mg/day (NNRTI) and raltegravir 400 mg *bis in die*, BID (INI) [4]. The therapy switch could only be executed for patients who had been in virological suppression (viral load < 50 copies/ml) for at least 12 months, without any prior exposure to an INI, with no NNRTI-associated resistance mutations and with a toxicity (dyslipidemia and/or chronic renal failure) correlated with the therapy received.

Since – in view of the potential cardiovascular and/or metabolic toxicity of the current cART regimens – the Italian Guidelines suggest instead to preferably adopt regimens based on INIs, the second optimization pathway option involves, for the subjects who do not fall under the first option, the substitution of the toxic regimens with others, less toxic [1]. The identification of the potentially toxic regimens was performed by analyzing the cART therapy received by each patient. Then, based on the history of cART received

and the indications suggested by the Italian Guidelines, a number of possible alternative regimens were assumed [1]. In this case too, the therapy switch had to take place in conditions of virological suppression maintained for at least one year. Naïve patients were not included in the optimization pathway because they have not been in virological suppression for at least 12 months since they received the first antiretroviral treatment during the observation year (2015).

Treatment cost

The two expenditures – actual and potential – for the antiretroviral drugs were calculated considering the purchase prices, net of all (mandatory and not) discounts and including VAT, borne by the Hospital Pharmacy of the Center. All costs are referred to the year 2015. In case of switch from a three-drug regimen to that with nevirapine/raltegravir, for the latter a mean annual treatment cost of € 5,566 was considered [4]. In case of replacement of the potentially toxic antiretroviral regimen (cardiovascular and/or metabolic effect), an average annual cost calculated on the basis of the antiretroviral regimens suggested as alternatives was estimated for each patient [1].

Data analysis

Quantitative variables have been described as mean value (± standard deviation), categorical variables as numeric value (percentage). The significance of the differences between the data found/processed was verified by applying the (two-tier) Student's t-test. The analysis was supported by Microsoft® Excel® for Windows® (Microsoft Corporation,

Characteristics	Naïve	Non naïve	Total
Patients, n.	34	530	564
Mean age, years (± SD)	41.9 (± 9.8)	49.0 (± 9.7)	48.5 (± 9.9)
Time to diagnosis, years (± SD)	5.2 (± 5.1)	13.7 (± 8.1)	13.2 (± 8.2)
Previous treatments failed, n. (± SD)	0.0 (± 0.0)	0.6 (± 1.2)	0.6 (± 1.2)
Virological suppression[1], n. (%)			
• For more than 1 year	0 (0.0)	405 (76.4)	405 (71.8)
• For less than 1 year	1 (2.9)	16 (3.0)	17 (3.0)
• No	33 (97.1)	109 (20.6)	142 (25.2)
CD4, n. (± SD)	394.1 (± 179.0)	625.2 (± 283.3)	611.2 (± 283.4)
%CD4, n. (± SD)	20.3% (± 9.4%)	28.9% (± 9.5%)	28.4% (± 9.7%)
Resistances, n. (%)			
• No	24 (70.6)	168 (31.7)	192 (34.0)
• Resistance/partial resistance	4 (11.8)	127 (24.0)	131 (23.2)
• Test not performed/unavailable	6 (17.6)	235 (44.3)	241 (42.7)
HLA B5701, n. (%)			
• Positive	1 (2.9)	8 (1.5)	9 (1.6)
• Negative	20 (58.8)	344 (64.9)	364 (64.5)
• Test not performed/unavailable	13 (38.2)	178 (33.6)	191 (33.9)
Smoker, n. (%)	13 (38.2)	151 (28.5)	164 (29.1)
Systolic pressure, mmHg (± SD)	126.0 (± 10.1)	128.9 (± 11.5)	128.8 (± 11.5)
Diastolic pressure, mmHg (± SD)	80.7 (± 5.1)	82.5 (± 7.4)	82.4 (± 7.3)
HCV, n. (%)	3 (8.8)	134 (25.3)	137 (24.3)
HBV, n. (%)	0 (0.0)	18 (3.4)	18 (3.2)
Dyslipidemia, n. (%)	6 (17.6)	189 (35.7)	195 (34.6)
Total cholesterol, mg/dl (± SD)	176.0 (± 42.3)	188.8 (± 41.4)	188.0 (± 41.5)
HDL cholesterol, mg/dl (± SD)	47.0 (± 14.6)	51.8 (± 17.4)	51.5 (± 17.3)
Chronic renal failure, n. (%)	1 (2.9)	20 (3.8)	21 (3.7)
Densitometry, n. (%)			
• No	34 (100.0)	465 (87.7)	499 (88.5)
• Osteopenia	0 (0.0)	50 (9.4)	50 (8.9)
• Osteoporosis	0 (0.0)	15 (2.8)	15 (2.7)
Previous CVD event, n. (%)	0 (0.0)	23 (4.3)	23 (4.1)
Dyslipidemia or osteoporosis drugs, n. (%)	1 (2.9)	192 (36.2)	193 (34.2)
Hypertension drugs, n. (%)	1 (2.9)	96 (18.1)	97 (17.2)

Table I. *Main demographic and clinical characteristics of the patients enrolled*
[1] HIV-RNA < 50 copies/ml

Seattle, WA, USA) and SPSS® 13.0 for Windows® (SPSS Inc., Chicago, IL, USA).

RESULTS

Characteristics of the sample

Overall, during the year 2015, 564 HIV-diagnosed patients under treatment with cART regimens were referred to the Center. Of these, 6% (n. = 34) started antiretroviral therapy in 2015 (naïve patients). Table I shows the main demographic and clinical characteristics of the patients enrolled. The mean age was 48.5 (± 9.9) years, with an average duration of HIV infection at diagnosis of 13.2 (± 8.2) years. 71.8% (n. = 405) of patients had been in virological suppression for at least 12 months.

cART regimens

76.4% (n. = 431) of patients received a regimen consisting of at least three antiretrovi-

ART regimens	Patients								
	Naïve			Non-naïve			Total		
	n.	%	Mean cost (€)	n.	%	Mean cost (€)	n.	%	Mean cost (€)
2 NRTI + 1 PI[1]	5	14.7	4,811	181	34.2	9,195	186	33.0	9,077
2 NRTI + 1 NNRTI[1]	16	47.1	3,092	149	28.1	6,397	165	29.3	6,076
3 NRTI[1]	2	5.9	1,518	42	7.9	6,478	44	7.8	6,252
2 NRTI + 1 INI[1]	-	-	-	35	6.6	10,119	35	6.2	10,119
1 NRTI + 1 PI	1	2.9	2,107	34	6.4	5,773	35	6.2	5,668
1 PI	-	-	-	27	5.1	4,455	27	4.8	4,455
1 NNRTI + 1 INI	-	-	-	13	2.5	4,657	13	2.3	4,657
1 INI + 1 PI	-	-	-	13	2.5	10,571	13	2.3	10,571
1 NRTI + 1 INI	-	-	-	11	2.1	6,388	13	2.3	3,960
2 NRTI	-	-	-	10	1.9	3,768	11	2.0	6,388
1 NRTI + 1 NNRTI	-	-	-	9	1.7	2,146	10	1.8	3,768
1 INI	10	29.4	2,960	3	0.6	7,295	9	1.6	2,146
1 NRTI + 1 INI + 1 PI	-	-	-	1	0.2	11,911	1	0.2	11,911
1 NNRTI	-	-	-	1	0.2	432	1	0.2	432
1 CCR5 + 1 PI	-	-	-	1	0.2	15,134	1	0.2	15,134
Total	**34**	**100**	**3,184**	**530**	**100**	**7,424**	**564**	**100**	**7,424**

Table II. *cART regimens administered*
[1] Highly Active Anti-Retroviral Therapy (HAART) regimens

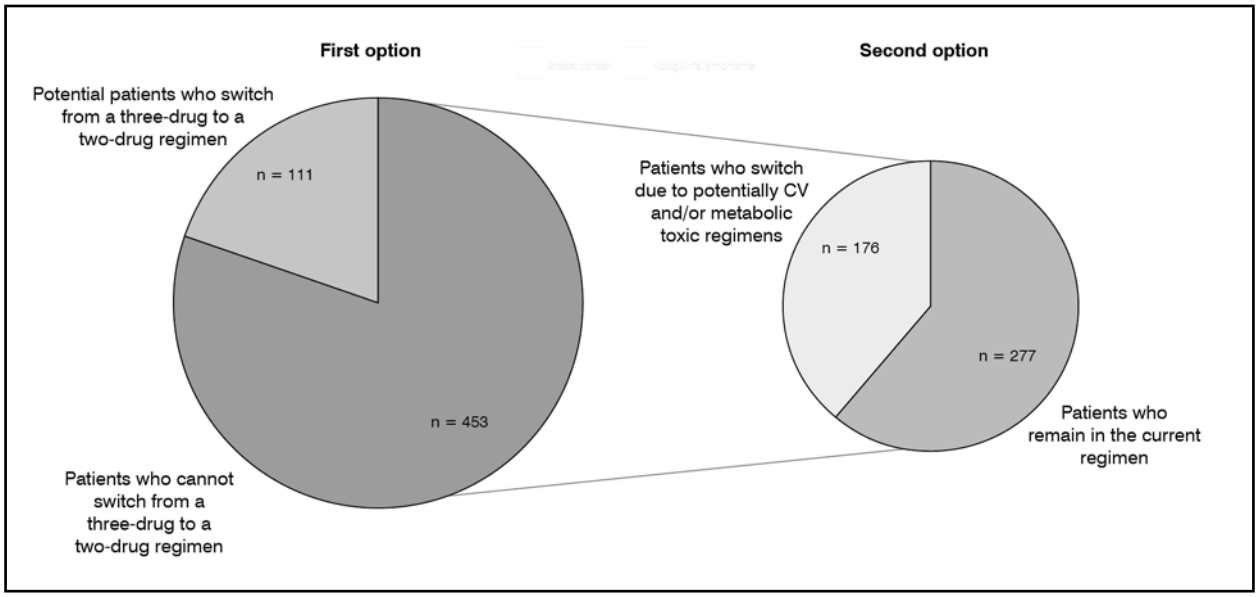

Figure 1. *Optimization pathway*

ral drugs (naïve: 67.6%, non-naïve: 77.0%) (Table II). The most frequently used regimens were 2 NRTIs + 1 PI (n. = 186; 33.0%; € 9,077) and 2 NRTIs + 1 NNRTI (n. = 165; 29.3%; € 6,076). 46.6% of the regimens administered contained a PI, while 15.2% contained an INI. The average duration of treatment during the year for naïve patients was 5.4 (± 3.2) months, whereas for non-naïve patients it was 12 months (all non-naïve patients were in continuous treatment for the 12 months of observation).

Optimization pathway

Following the chronological sequence of the potential therapy switches assumed within the cART optimization pathway, in 111 patients it would have been possible to switch from a three-drug regimen to nevirapine/raltegravir (Figure 1). Of these, 53 were in treatment with 2 NRTIs + 1 PI, 51 with 2 NRTIs + 1 NNRTI and 7 received 3 NRTIs. All 111 patients had been in virological suppression for at least 12 months, without any NNRTI- or INI-associated resistance mutations. Each of them also presented a toxicity due to dyslipidemia (95.5%, n. = 106) and/or chronic renal failure (7.2%, n. = 8).

Of the remaining 453 patients, 176 were the subjects for whom it would have been desirable to replace the adopted regimen (Table III), characterized by a potential cardiovascular and/or metabolic toxicity, with one of those indicated in the Italian Guidelines (Table IV). On average, about 4 alternative regimens for each patient were provided for.

Agents	ART Regimens	Patients		
		n.	%	Mean cost (€)
Atazanavir Maraviroc Ritonavir	1 CCR5 + 1 PI	1	0.6	15,134
Raltegravir Lopinavir/Ritonavir	1 INI + 1 PI	1	0.6	3,706
Raltegravir Darunavir Ritonavir	1 INI + 1 PI	7	4.0	11,224
Darunavir Ritonavir	1 INI + 1 PI	2	1.1	12,203
Tenofovir Raltegravir Atazanavir Ritonavir	1 NRTI + 1 INI + 1 PI	1	0.6	11,911
Lamivudine Lopinavir/Ritonavir	1 NRTI + 1 PI	1	0.6	2,290
Lamivudine Darunavir Ritonavir	1 NRTI + 1 PI	1	0.6	3,782
Lamivudine Atazanavir Ritonavir	1 NRTI + 1 PI	11	6.3	6,209
Lamivudine Fosamprenavir Ritonavir	1 NRTI + 1 PI	3	1.7	5,272
Lopinavir/Ritonavir	1 PI	5	2.8	3,862
Darunavir Raltegravir Ritonavir	1 PI	4	2.3	4,801
Fosamprenavir Ritonavir	1 PI	3	1.7	4,054
Zidovudine/Lamivudine	2 NRTI	2	1.1	211
Abacavir/Lamivudine Raltegravir	2 NRTI + 1 INI	13	7.4	9,723
Abacavir/Lamivudine Nevirapine	2 NRTI + 1 NNRTI	20	11.4	5,688
Abacavir/Lamivudine Efavirenz	2 NRTI + 1 NNRTI	10	5.7	5,537
Zidovudine/Lamivudine Fosamprenavir Ritonavir	2 NRTI + 1 PI	2	1.1	4,118
Abacavir/Lamivudine Lopinavir/Ritonavir	2 NRTI + 1 PI	2	1.1	8,831
Abacavir/Lamivudine Darunavir Ritonavir	2 NRTI + 1 PI	5	2.8	8,869
Abacavir/Lamivudine Atazanavir	2 NRTI + 1 PI	25	14.2	10,416
Abacavir/Lamivudine Atazanavir Ritonavir	2 NRTI + 1 PI	8	4.5	8,225
Abacavir/Lamivudine Fosamprenavir	2 NRTI + 1 PI	3	1.7	9,950
Abacavir/Lamivudine Fosamprenavir Ritonavir	2 NRTI + 1 PI	5	2.8	8,447
Tenofovir/Emtricitabine Lopinavir/Ritonavir	2 NRTI + 1 PI	5	2.8	9,558
Tenofovir/Emtricitabine Darunavir Ritonavir	2 NRTI + 1 PI	3	1.7	8,826
Tenofovir/Emtricitabine Atazanavir Ritonavir	2 NRTI + 1 PI	10	5.7	8,968
Tenofovir/Emtricitabine Fosamprenavir Ritonavir	2 NRTI + 1 PI	2	1.1	9,174
Zidovudine/Lamivudine Tenofovir	3 NRTI	2	1.1	3,535
Abacavir/Lamivudine Rilpivirine	3 NRTI	9	5.1	7,001
Abacavir/Lamivudine Tenofovir	3 NRTI	1	0.6	7,864
Zidovudine/Lamivudine/Abacavir	3 NRTI	9	5.1	6,019
Total		**176**	**100**	**7,690**

Table III. *Regimens characterized by a potential cardiovascular and/or metabolic toxicity [1]*

Agents	ART Regimens	Patients		
		n.	%	Mean cost (€)
Dolutegravir Rilpivirine	1NNRTI + INI	68	9.8	8,712
Rilpivirine Darunavir Ritonavir	1NNRTI + PI/r	36	5.2	7,243
Lamivudine Dolutegravir	1NRTI + INI	67	9.7	6,086
Lamivudine Atazanavir Ritonavir	1NRTI + PI/r	42	6.1	4,440
Tenofovir/emtricitabine	2NRTI	2	0.3	5,267
Tenofovir/emtricitabine Raltegravir	2NRTI + INI	68	9.8	10,534
Tenofovir/emtricitabine Dolutegravir	2NRTI + INI	55	7.9	11,209
Tenofovir/emtricitabine Rilpivirine	2NRTI + NNRTI	63	9.1	8,036
Tenofovir/emtricitabine Nevirapine	2NRTI + NNRTI	62	8.9	5,550
Tenofovir/emtricitabine Efavirenz	2NRTI + NNRTI	10	1.4	5,699
Tenofovir/emtricitabine Nevirapine	2NRTI + NNRTI	9	1.3	7,411
Tenofovir/emtricitabine Atazanavir	2NRTI + PI	77	11.1	11,306
Tenofovir/emtricitabine Fosamprenavir	2NRTI + PI	3	0.4	10,678
Tenofovir/emtricitabine Darunavir Ritonavir	2NRTI + PI/r	15	2.2	9,740
Tenofovir/emtricitabine Atazanavir Ritonavir	2NRTI + PI/r	31	4.5	9,563
Raltegravir Darunavir	INI + PI	13	1.9	11,903
Raltegravir Darunavir Ritonavir	INI + PI/r	27	3.9	12,203
Lamivudine Darunavir Ritonavir	NRTI + PI/r	25	3.6	4,618
Darunavir Ritonavir	PI/r	8	1.2	4,474
Atazanavir Ritonavir	PI/r	12	1.7	4,296
Total		**693**	**100.0**	**8,365**

Table IV. *Alternative regimens in case of switch due to cardiovascular and/or metabolic toxicity [1]*

Current pharmaceutical expenditure

In 2015, the actual pharmaceutical expenditure borne by the Center and generated by the 564 patients receiving antiretroviral drugs was € 4,042,983, of which € 108,271 for naïve patients and € 3,934,712 for non-naïve patients (Table V). The mean pharmacological treatment cost was € 7,168 ± € 2,605 (naïve patient: € 3,184 ± 2,003; non-naïve patient € 7,424 ± 2,426). The pharmaceutical expenditure generated by the 111 patients receiving a triple therapy who could be treated with the nevirapine/raltegravir regimen was € 860,295, with a mean cost of € 7,750 ± 1,827 (Table V). The 2 NRTIs + 1 PI combination resulted in the highest average cost (€ 9,139 ± 1,405), followed by 3 NRTIs (€ 7,030, ± 1,268) and 2 NRTIs + 1 NNRTI (€ 6,406, ± 1,066). Cost differences between the 2 NRTIs + 1 PI and the other two regimens were statistically significant ($p < 0.001$), while that between 3 NRTIs and 2 NRTIs + 1 NNRTI was not ($p = 0.25$). If costs at the individual patient level are analyzed, in 13 cases only (11.7%) the use of a three-drug regimen resulted in an annual cost (range: € 2,328-€ 5,408) lower than that of the nevirapine/raltegravir regimen (€ 5,566).

However, the drug expenditure for the 176 patients for whom it would have been desirable to replace the current regimen at risk of toxicity, with one of those set out in the Italian Guidelines amounted to € 1,353,474, with an average cost of € 7,690 ± 2,634) (Table V). Approximately 70% of these regimens consisted of 2 NRTIs + 1 PI (n. = 70; € 9,297 ± 1,392), 2 NRTIs + 1 NNRTI (n. = 30; € 5,638 ± 864) and 3 NRTIs (n. = 21; € 6,291 ± 1,151).

Finally, the other patients maintaining their current antiretroviral regimen without any change determined a cost of € 1,720,943, with an average cost of € 7,082 ± 2,473 (Table V).

Potential pharmaceutical expenditure

Besides reporting the actual expenditure data for the antiretroviral drugs for the year 2015, Table V indicates the estimate for the same expenditure in light of the proposed optimization path (potential scenario). The expenditure associated with naïve patients (patients who received the first treatment during 2015) remains exactly the same as that calculated for the actual scenario, since – by definition – naïve patients, not having been in virological suppression for at least 12 months, cannot fall within the selection criteria adopted by the optimization path. Therefore, the financial impact would occur only on non-naïve patients. The potential switch from a three-

Patients	n.	Treatment cost with cART (€)				Delta
		Actual scenario		Potential scenario		
		Total expenditure	Average cost	Total expenditure	Average cost	
Naïve	34	108,271	3,184	108,271	3,184	0
Non-naïve	530	3,934,712	7,424	3,806,584	7,182	- 128,128
• switch from a three-drug to a two-drug regimen	111	860,295	7,750	617,826	5,566	- 242,469
• switch due to CV and/or metabolic toxicity	176	1,353,474	7,690	1,467,815	8,340	114,341
• maintenance actual regimen	243	1,720,943	7,082	1,720,943	7,082	0
Total	**564**	**4,042,983**	**7,168**	**3,914,855**	**6,941**	**- 128,128**

Table V. *Pharmaceutical expenditure charged to the Center: actual vs potential scenario*

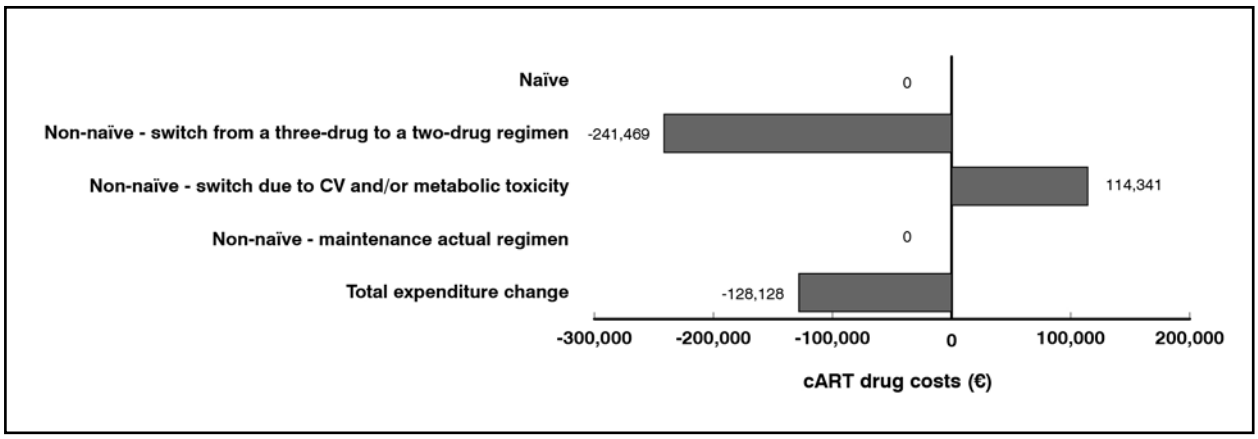

Figure 2. *Financial impact of the optimization pathway (potential vs current scenario)*

drug to a two-drug regimen (nevirapine/raltegravir) would result, for the 111 patients treated, in a reduction in the cost borne by the Hospital Pharmacy of the Center of € 242,469. Conversely, the replacement of the regimens at risk of (cardiovascular and/or metabolic) toxicity with one of those indicated in the Italian Guidelines would cause, for the 176 patients treated, a potential increase in the cost borne by the Hospital Pharmacy of the Center of € 114,341. The average annual cost associated with these alternative regimens was € 8,340 ± 2,000.

Overall, the adoption of the optimization pathway would result in a reduction in cART drug costs of € 128,128 (-3.2%) (Table V and Figure 2).

DISCUSSION

The added value of this retrospective observational analysis – compared to the one previously conducted, again with reference to the Infectious Diseases Operating Unit of the Hospital "G.B. Rossi" in Verona [4] – consists in the fact that it assessed not only the financial impact of the switch from a three-drug to a two-drug regimen, but also the sustainability, on the part of the Center, of an antiretroviral therapy management pathway which, in the face of the potential cardiovascular and/or metabolic toxicities associated with current antiretroviral regimens, suggested instead, according to the indications of the Italian Guidelines [1], to preferably adopt regimens based on integrase inhibitors.

In line with the previous analysis referred to the year 2014 [4], the first optimization pathway option – namely the switch from a three-drug to a two-drug regimen – would allow to reduce the Center-borne antiretroviral expenditure by around € 242,000. This amount would allow the Center itself to cope with the increase in spending (around € 114,000) associated with the second option of the optimization pathways – i.e. the replacement of potentially toxic regimens – as well as maintaining a "comfort zone" (about € 128,000) with which to cope with any therapy switches that might become necessary.

The clinical rationale that makes it possible to switch from a three-drug regimen to the nevirapine/raltegravir combination relies on the results of two recent clinical trials [5,6].

Both were conducted with the aim of evaluating the efficacy of a dual therapy consisting of 1 NNRTI + 1 INI in place of HAART regimens as maintenance treatment of HIV-infected patients in virological suppression. During the period September 2009-January 2012, all patients referred to the centers of Besançon and Nantes with HIV infection, with a viral load < 50 copies/ml for more than six months and without prior exposure to INIs were switched from a three-drug regimen to the combination nevirapine (400 mg/day) and raltegravir (400 mg BID) [5]. The 36 enrolled patients, followed for a maximum of three years, maintained a viral load < 50 copies/ml, without the occurrence of grade 3 or 4 adverse events [5]. The subsequent Italian study replicated and validated *de facto* the previous French analysis [6]. After a 32-month median time, 89.6% of the 77 patients enrolled in the nevirapine/raltegravir regimen were in virological suppression, while 6.5% experienced a virologic failure and 3.9% discontinued the treatment due to adverse events (skin rash or hepatic toxicity) [6]. The results of these experiences show that, in a well-defined case record of patients, the switch to a nevirapine/raltegravir therapy allows the long-term maintenance of an adequate virological suppression.

As indicated in the methods, the identification of the toxic regimens was performed by examining at the individual patient level the regimen administered during the observation year. Table III details the regimens characterized by a risk of cardiovascular and/or metabolic toxicity for the 176 subjects for whom it would have been possible to switch the therapy with a regimen characterized by a reduced risk of toxicity. 71.6% of these regimens (126 out of 176) contain abacavir or lopinavir, the exposure to which is a predictor of cardiovascular risk [7]. The alternative regimens, listed in Table IV and identified according to the indications of the Italian Guidelines, have always been identified at the individual patient level. In 49.4% of cases (87 out of 176), only one alternative method was identified; in the remaining cases, the choice was assumed between multiple treatments with different treatment costs. In 28.4% of cases, the choice could fall on more than seven alternatives. For this reason, the economic impact associated with the switch to a low cardiovascular and/or metabolic toxicity regimen may be subject to variations. Had we considered, instead of the average cost, the minimum cost of the alternatives indicated for each patient (€ 6,888), the "comfort zone" would have increased to € 383,652 compared to the base case; whereas, had we considered the maximum cost of the alternatives indicated for each patient (€ 9,688), the optimization pathway would have resulted in an increase in the cost of the antiretroviral drugs borne by the Center of € 109,201. However, in the absence of the financial effect resulting from the switch from a three-drug to a two-drug regimen (-€ 242,469), this increase in expenditure for the Center would have been higher (€ 351,671).

Local cost containment HIV strategies has been investigated considering different approaches (i.e., generic drugs, switch from a three-drug to a two-drug regimen or monotherapies) and costs (cART, hospitalization, outpatient activities, adverse events' management). For this reason it is difficult to compare the present results with those of already published studies. The analysis, conducted by Angeletti et al. [8], shows how the most cost containing strategy would be the use of generic drugs, followed by simplification to monotherapy. A second analysis investigated the budget impact of ART simplification to less drug regimens over a 3-year horizon (costs referred to 2013) [9]. The Authors considered 4 simplification scenarios: i) de-intensifying only PI-based triple therapies over 1 year period ii) de-intensifying only PI-based triple therapies over a 3-year period, iii) de-intensifying PI-based triple therapies and NRTIs + efavirenz over 1 year period and iv) de-intensifying PI-based triple therapies and NRTIs + efavirenz over a 3-year period. Over a 3-year period, ART cost decreased between € 23.1 million and € 44.3 million considering different scenarios. A third analysis was conducted to evaluating the impact of treatment simplification of atazanavir (ATV) + ritonavir (r) + lamivudine (3TC) in virologically suppressed patients receiving ATV + r + 2 nucleoside reverse transcriptase inhibitors (NRTIs) [10]. The perspective of the Italian National Health Service (NHS) was considered. The antiretroviral treatment simplification strategy considered would lead to lower costs for the Italian NHS in a 5-year time horizon between € -28.7 million and € -16.0 million.

Although the comparison sought to provide a realistic scenario of the economic impact following the adoption of a specific optimization pathway for the cART regimens administered for the treatment of HIV patients with the aim of maintaining the therapeutic effectiveness also over the long term, the results presented here must be interpreted in light of some observations.

First of all, the hypothesis of being able to administer the alternative regimens suggested by the optimization path to the same pa-

tients treated in 2015 with cART drugs. This assumption is the basis of this analysis, since it was not possible to create a real control group treated with the alternative regimens hypothesized by the optimization pathway. In light of this necessary compromise, in addition to the effectiveness data reported in the literature [5,6] and by the Italian Guidelines [1], further criteria supporting the switch to an alternative antiretroviral regimen were sought. For example, in the switch towards a two-drug regimen, since this would reduce the risk of long-term toxicity [11-15], it was established that patients – besides being in virological suppression – had also to report a toxicity associated with the HAART therapy.
A second critical aspect may be represented by the average cost considered in order to enhance the nevirapine/raltegravir regimen, or the alternative ones (cardiovascular and/or metabolic toxicity). Such average cost, in fact, does not derive from real-world consumption data, as was the case with the regimens actually administered by the Center, but is based on the purchase cost of the molecules, borne by the Center's pharmacy, and the relevant dosages indicated in the literature, assuming that the duration of treatment is one year. In actual fact, however, this choice may have overestimated or underestimated the results found here, since – by adopting such administration regimens – a total compliance with the administered treatment was assumed, thus excluding the presence of cases of over- or under-consumption, contemplated instead for the actual spending.
The present analysis collected information only on the cART costs; other cost items were not considered (eg. hospitalizations, specialist visits, etc.), which however are potentially interesting for those wishing to examine in detail the knowledge of the resources required by HIV.
At last, a final limitation could be the representativeness of these results on a national scale, since they are referred to a single center located in Northern Italy. The verification of a possible variability of the data found here could be carried out only in the presence of similar analyses, conducted in other Italian geographic areas.

CONCLUSIONS

This observational analysis was carried out with the objective of estimating the financial impact of an optimization pathway of the antiretroviral therapy, aimed at maintaining its effectiveness over time. In light of the results presented, albeit with some limitations, it would seem possible to state that the optimization pathway proposed here is a valid therapeutic option in the maintenance treatment of suppressed HIV-1 patients, since it can make sustainable the costs of the cART therapy currently charged to the Italian NHS, while ensuring the maintenance over time of adequate levels of effectiveness and safety.

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Conflict of interest

The authors have no conflict of interest concerning the topics of this article.

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