New Microbiologica, **37**, 247-261, 2014

Health technology assessment in the HIV setting: the case of monotherapy

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SUMMARY

Despite the success of multiple-drug therapy regimens, the idea of treating human immunodeficiency virus (HIV) infection with fewer drugs is captivating due to issues of convenience, long-term toxicities and costs. This study investigated the impact on a local health budget of the introduction of a protease inhibitor (PI)-based antiretroviral monotherapy. An analysis of 23,721 administrative records of HIV-infected patients and a health technology assessment (HTA) were performed to assess cost-effectiveness, budget, organizational, ethics, and equity impact.
Data showed that monotherapy had a annual cost of € 7,076 (patient with undetectable viral load) and € 7,860 (patient with detectable viral load), and that its implementation would realise economic savings of between 12 and 24 million euro (between 4.80% and 9.72% of the 2010 total regional budget expenditure for HIV management) in the first year, with cumulated savings of between 48 and 145 million euro over the following five years. Organizational, ethical and equity impact did not indicate any significant differences.
The study suggests that for specific categories of patients monotherapy may be an alternative to existing therapies. Its implementation would not result in higher operating costs, and would lead to a reduction in total expenditure.

KEY WORDS: Health technology assessment, PI-based monotherapy, Standard therapies, Budget impact analysis.

Received December 20, 2013 *Accepted* May 23, 2014

INTRODUCTION

Over the last decade, highly active antiretroviral therapies (HAART) have radically improved the prognosis of human immunodeficiency virus (HIV) disease (The Antiretroviral Therapy Cohort Collaboration, 2008). In terms of direct results many life years have been saved, highlighting the significant improvements made in treating HIV (Walensky 2006). However, the resulting epidemiological transition of HIV infection, from a fatal condition to a chronic disease, is now having a significant impact on decision-making processes that ensure the appropriateness of a therapy and that monitor the rising costs of antiretroviral therapy (ARV).
The "gold standard" treatment for HIV infection to date has been a multiple-drug combination regimen that typically includes two nucleoside analogue reverse transcriptase inhibitors (NRTI), plus either one protease inhibitor (PI) or one non-nucleoside reverse transcriptase inhibitor (NNRTI) (Thompson 2012). These drugs need to be used over the lifespan of a patient. This treatment strategy has been well documented and is still used, but these complex therapeutic regimens may give rise to problems of long-term adherence and toxic effects

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(Chesney 2008; Volberding & Deeks, 2008). In addition, the cost of multiple-drug therapy is expensive, thus leading to an increase in the mean total cost of providing health care to HIV patients (Rizzardini 2011).

The latest published International (2012), European (2011), and Italian (2012) guidelines recommend the administration of HAART therapies to HIV+ patients who have a CD4 cell counts equal to or lower than 500/ml (European AIDS Clinical Society, 2011; Department of Health and Human Services, 2012; Ministero della Salute, 2012). Potentially, this could lead to problems related to the economic impact of the burden of HIV infection on national health budgets.

One solution to reduce the need of funneling resources and investment into these specific treatments might be to propose different therapeutic strategies for other categories of patients.

Despite the success of multiple-drug therapy regimens, the idea of treating HIV infection with fewer drugs is captivating due to issues of convenience, long-term toxicities, and costs. PI-based regimens have shown high rates of virological efficacy as monotherapy (Cameron 2008; Arribas 2009; Arribas 2010), although they may be better for induction-maintenance or simplification strategies (Nunes 2009; Waters 2013).

An interesting hypothesis (Waters 2013) suggests using only PIs in second-line treatments for potency and as a high genetic barrier in patients with previous failure of NRTIs. This therapeutic option could optimise second-line therapies in resource-limited settings, thus minimizing the number of agents required for second-line treatments with a resulting general gain in terms of toxicity, tolerability, adherence and costs (Waters 2013).

Although attempts dating from the late 1990s to decrease the number of drugs required to maintain HIV viral suppression have been unsuccessful (Havlir 1998; Reijers 1998), the use of boosted protease inhibitor (PI) single-drug monotherapy is now proving an effective new strategy to treat patients infected with HIV (Gathe 2004; Arribas 2005; Pulido 2008; Cameron 2008; Delfraissy 2008), decreasing the number of drugs used to treat HIV infection, thus reducing the cost of treatment (Escobar 2006) and hopefully minimizing the long-term toxicities of HAART (Cameron 2008). Recently published articles and reports suggest that PI-based monotherapy may be an effective therapeutic option for treatment of HIV infection (Ruane 2004; Campo 2005; Goelz 2006; Pierone 2006; Molto 2007; Arribas 2008).

The efficacy and safety of PI-based monotherapy has been well documented and has shown promising results in controlled randomized clinical trials (RCTs), while economic studies in the U.K. and Spain have demonstrated advantages (Gazzard 2011; Arribas 2011). In addition, information is available concerning the economic impact of PI-based monotherapy in routine clinical practice, as well as information related to the total expenditure from the payer's (that is, the regional or national health service) point of view.

In Italy, the Italian National Institute of Health has investigated the epidemiological topic of HIV infection in several of its Regions. New cases of infection, since the beginning of the epidemic in 1985, have been estimated to be 59,629, with 3,461 new diagnoses of infection reported in 2011.

Lombardy Region, which had 23,721 HIV-positive patients receiving treatment in 2010 (data taken from the Integrated Patients' Database - Banca Dati Assistito - of Lombardy Region, 2010), has the highest distribution of new cases of HIV infection in Italy (21.81% in 2011) (Istituto Superiore di Sanità, 2012). This has made a strong impact on the regional health care budget.

Further information concerning the economic impact of the disease is, however, limited due to there being few publications on health care costs for HIV-infected patients in Italy (Rizzardini 2011; Rizzardini 2012).

In a healthcare service characterized by a scarcity of resources, the opportunity to identify areas for cost rationalization would 'free up' of resources, thus increasing the number of clinical alternatives and ensuring a wider therapeutic service.

In this context, health technology assessment (HTA), a multidisciplinary approach of clinical governance (Scally & Donaldson, 1998), could perform a key role to evaluate HIV technologies

(Canadian Agency for Drugs and Technologies in Health, 2006). To date, the HTA technique has never been applied to this specific pathology.
As a result of all these considerations, a HTA of the introduction of a PI-based monotherapy in Lombardy Region was performed, considering the significance of the Region for the whole Italian context and, in particular, for the size of HIV infection. The results of this would allow policy-makers at a regional level to assess the cost-efficacy, budget impact and organizational impact (Canadian Agency for Drugs and Technologies in Health, 2006) of therapeutic alternatives, and would, therefore, support the decision-making process in real life practice.
The present study aimed to investigate the hypothetical and potential impact following the introduction of a PI-based monotherapy as an additional, alternative, antiretroviral therapy for the treatment of HIV-positive stable patients.
The objective of this HTA analysis was not to consider monotherapy as a substitute for standard multiple-drug therapies (a mandatory switching therapy), but as an additional, optional alternative in specific categories of HIV therapies (one more option, available for the clinicians, on the market), thus providing a wider choice from which to select the most appropriate pathway for the treatment of patients.

MATERIALS AND METHODS

Perspective
The perspective assumed for this analysis was that of the payer, namely, the Lombardy Region Healthcare Service (RHS).

Patients and eligibility criteria
In order to evaluate the impact of the new technology introduction, the starting cohort was the administrative records of Lombardy Region people living with HIV. From the records of 23,721 HIV-positive patients inserted in the Integrated Patient's Database of Lombardy Region (2010), the first step of analysis required the evaluation of how many of these patients met the inclusion criteria for monotherapy, considering the latest Italian Guidelines (Ministero della Salute, 2012).
The eligibility criteria were the following: age >18 years, HIV+, receiving a PI-based treatment for at least 6 months, HIV-RNA <50 copies/ml for at least 6 months, lymphocytes CD4+ >350/µl.
The exclusion criteria were: nadir lymphoid cells CD4+ <100/µl, previous PI failures (HIV-RNA > 50 copies/ml in 2 consecutive determinations, within a "2-week" time frame, while being treated with a PI), HIV mutations associated with resistance to PIs, pregnancy or breastfeeding, HBsAg+ (Ministero della Salute, 2012).

Cost data
Cost data for each therapeutic regimen were evaluated considering the costs of HAART drugs, outpatient activities, hospitalizations, and non-HAART drugs (this cost category includes all other drugs and medications prescribed to the patient not to treat HIV infection, but for other health issues and comorbidities).
All costs were extrapolated from the Integrated Patients' Database (Banca Dati Assistito) of Lombardy Region, a database containing all the health care services provided for each patient by a provider - public and/or private - participating in the RHS. Cost data were based on the same clinical records taken from Rizzardini (2011), capitalised to 2011, considering the Italian inflation rate of average consumer prices (ISTAT).
The costs refer to a cohort of HIV-infected patients who had been receiving treatment up to the end of 2010 within a Lombardy Region Hospital Authority who met the inclusion criteria mentioned above, and who were receiving treatments at the first Infectious Disease Department (a centre of excellence for the care of HIV patients) at "Luigi Sacco" Hospital, Milan. Patients were excluded if clinical data (those not referring to the centre for more than 12 months) or cost information (of patients not resident in Lombardy) were missing (Rizzardini 2011; Rizzardini 2012). The HAART drugs cost for multiple-drug regimens represents the real consumption of resources referring to the above-mentioned cohort, and related data were measured. The actual consumption of resources

for multiple-drug regimens was proposed both for patients under virological control and for those not virologically suppressed. The average drug cost for the monotherapy arm depends on the real distribution of possible HAART regimens in the cohort analyzed, and is related to the real resources absorption in PI-based standard regimens, considering patients meeting the inclusion criteria for monotherapy and the reduction in HAART costs, and switching to a new treatment scheme. From a cohort of 3,220 to 6,468 patients meeting the inclusion criteria of switching to a single agent therapy, considering typology and distribution of PI-based triple therapies in this cohort, the average cost of the monotherapy arm in the present study was calculated with respect to the hypothesis of simplification of these treatment schemes into the therapeutic alternative.
Economic data were obtained following approval of the present study by the Medical Superintendent of the Hospital Authority's Health Department.

Efficacy data
A literature review was performed to collect efficacy data concerning therapeutic failure of monotherapy, as real life data for Italy and, in particular, Lombardy Region, are not currently available. The information obtained demonstrated that the clinical and efficacy differences between multiple-drug therapy and monotherapy were not statistically significant. The effectiveness primary endpoint was the percentage of patients with undetectable viral load (HIV RNA <50 copies/ml after 48 weeks). Studies identified in the literature review (Arribas 2005; Meynard 2010; Cahn 2011; Mathis 2011) reported the following efficacy data: 95% (maximum efficacy for both therapies), 81% minimum efficacy of monotherapy, and 88% minimum for the multiple-drug one (Arribas 2005; Meynard 2010; Cahn 2011; Mathis 2011).

Design
In order to study the correlation between the real costs incurred by the payer for the treatment of HIV-infected patients, a HTA was performed on the cost-efficacy, budget, organizational impact, and generalizability/reproducibility of the introduction of a new additional therapeutic regimen at a RHS level.

Cost-efficacy analysis
The cost-efficacy value (CEV) of standard multiple-drug therapies and monotherapy was calculated by correlating the cost data described with the efficacy data obtained from the abovementioned literature review.

Budget impact analysis
A model for the regional/institutional budget impact analysis was developed to analyse both short (one year) and long term (five years) periods. In order to explain and clarify the economic model, it is necessary to understand the hypothesis underlying the budget impact analysis. The starting point was to evaluate how many patients may be potentially involved in simplification to a monotherapy regimen, following the inclusion criteria of Italian guidelines (Ministry of Health 2012), considering the total number of patients treated for HIV infection in Lombardy Region. By analyzing data contained in the Integrated Patient's Database and in a large clinical database already published (Rizzardini 2011; Rizzardini 2012), the probabilities of patient enrolment in the innovative regimen was found, thus establishing the minimum or maximum number of HIV-infected patients that could switch in a different setting of care. In order to find the number of potential patients to enrol in Lombardy Region, the percentage of stable patients (not naïve) on first-line treatment, with no previous experience of failure of PI-based regimens was studied. 64.69% of the patients were found to meet these criteria: in the regional sample, a total of 15,345 subjects could be taken into consideration. Of those 15,345 patients, with no previous experience of failure, only 50% were on a PI-based regimen. As required by the latest Italian and international guidelines (Antinori 2012; Arribas 2013), only patients under virological control were considered for the monotherapy regimen. Among these 7,673 patients using PI-based therapeutic strategies, 41.97% (Rizzardini 2011; Rizzardini 2012) were found to be under virological control (defined as HIV RNA <50 copies/ml, verified in their last two clinical controls) in both semesters of 2010 (this scenario was called

"conservative" as it presents stringent inclusion criteria to monotherapy required by the Italian and International guidelines (European AIDS Clinical Society, 2011; Department of Health and Human Services, 2012; Ministry of Health 2012), while 84.31% for at least one semester of the same year (called a "realistic" scenario, defined as the most probable impact considering the levels of virological control observed in the database already cited, from the papers by Rizzardini 2011, and Rizzardini 2012). From the cohort of 3,220 to 6,468 patients, this was the basis of patients who were eligible for the 1-year model at a regional level. It should be noted, however, that the model was based on realistic/conservative hypotheses and represented the least optimistic picture (worst case analysis).

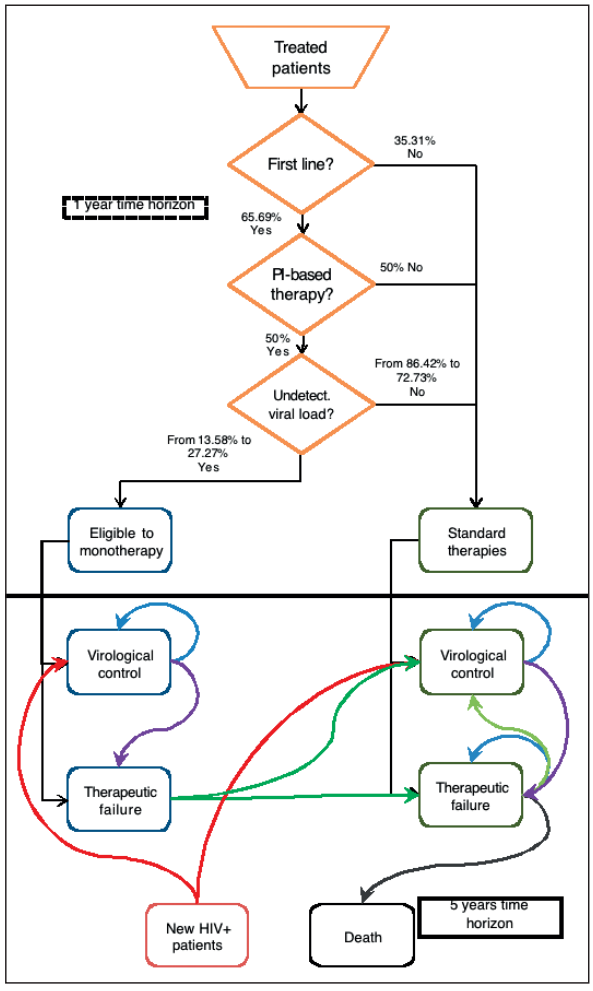

FIGURE 1 - *Algorithm for the assessment of budget impact of short and long time horizon (source: authors reprocessing of the study data).*

As regards the 5-year model, in each yearly cycle new HIV-infected patients increased the regional cohort studied (5% of the whole sample), while 1% of the population was considered to have resulted in death. The patients involved present the probability of remaining in the multiple drug standard therapy arm or in the monotherapy one, for every year/cycle, of 95% maximum value or 88%/81% minimum value, as the efficacy data demonstrated (Arribas 2005; Meynard 2010; Cahn 2011; Mathis 2011). The probabilities associated with transitions of HIV-infected patients were 100% minus 95% or 81% efficacy (Arribas 2005; Meynard 2010; Cahn 2011; Mathis 2011), to move to the monotherapy stage for failure, or a probability equal to the innovative treatment efficacy, to remain at the same stage in the next cycle/year (Meynard 2010; Cahn 2011; Mathis 2011).

Four scenarios were considered:

1) patients under virological control for at least one semester with maximum efficacy of monotherapy;
2) patients under virological control for at least one semester with minimum efficacy of monotherapy;
3) patients under virological control for at least two semesters with maximum efficacy of innovative treatment;
4) patients under virological control for at least two semesters with minimum efficacy of innovative treatment.

Organizational impact

The organizational impact was assessed for both short and long-term horizons, as well as for the main dependent variables that could influence the organizational context of regional and national Hospital Authorities at the introduction of innovative monotherapy treatment.

A survey was conducted through the administration of a questionnaire (to Directors of Infectious and Tropical Disease Divisions in Lombardy Region), with both open and closed questions, the latter based on perception using a Likert scale with 7 levels (Quinn Patton 2002). The Delphi methodology (Quinn Patton 2002) was used for completing the questionnaire, where the areas investigated were the follow-

ing: training of clinicians and nurses involved in the administration of a new treatment, impact on the processes of drug delivery, errors risk, the Hospital Authority's purchasing processes, treatment protocols, and patient management.

Ethics and equity impact

In order to complete the HTA analysis, the ethics and equity impact of monotherapy introduction is a dimension that also needed evaluation (Canadian Agency for Drugs and Technologies in Health 2006). The administration of a "patient's needs and perceptions" questionnaire directly to the HIV-infected patients was not possible, because the alternative treatment analysed in this study is not currently in use in Italian clinical practice. It was decided, therefore, to investigate these dimensions taking into consideration the clinicians' point of view, with a pilot qualitative study concerning the equity dimensions of interest for the HIV patients, and potential elements of future investigation. To achieve this objective a questionnaire was designed, one to be administrated by Infectious and Tropical Disease Divisions clinicians, based on closed questions and using a Likert-type scale, with 7 levels (Quinn Patton 2002) from 0 to 6; where 0 indicates the worst negative impact and 6 indicates the best positive impact.

RESULTS

The annual cost of HIV-infected patients' management, treated with a standard multiple-drug therapy and with both undetectable and detectable viral load, was higher than that for monotherapy. In particular, the cost per patient for a standard multiple-drug therapy was € 10,427 (undetectable viral load) and € 11,211 (detectable viral load), with an average value equal to € 10,505. Patients selected to be treated with monotherapy had a annual cost of € 7,076 (undetectable viral load) and € 7,860 (detectable viral load), with an average value equal to €

TABLE 1 - *Costs results, efficacy data, cost-efficacy value and ICER (source: personal reprocessing of Lombardy Region Integrated Patient's Database and study data).*

Costs	*Standard therapies Patient in virological control (€/year)*	*Standard therapies Patient not virologically suppressed (€/year)*	*Mono therapy Patient in virological control (€/year)*	*Mono therapy Patient not virologically suppressed (€/year)*	*Efficacy*	*Max Virological control*	*Min Virological control*
HAART drugs	7,655	7,655	4,304	4,304	Monotherapy efficacy	95%	81%
Outpatient activities	1,487	1,756	1,487	1,756	Standard therapies efficacy	95%	88%
Hospital admissions	752	1,355	752	1,355			
Non-HAART drugs	533	445	533	445			
Total	10,427	11,211	7,076	7,860			
Cost-efficacy	Costs (€/year)	Min Efficacy	Δ Costs (€)	Δ Efficacy	Cost-efficacy Value	ICER	
Standard therapies	10,505	88%	10,505	88%	11,938	-	
Monotherapy	7,123	81%	-3,382	-7%	8,794	48,319	

7,123. The economic impact of HAART costs on the total annual expenditure had a greater incidence for standard multiple-drug therapy patients, equal to 73% for patients with undetectable viral load, and 68% for patients with detectable viral load. For monotherapy, the same impact was equal to 61% for patients with undetectable viral load and 68% for patients with detectable viral load.
Considering the maximum efficacy value, equal to 95% for both treatment categories, the use of monotherapy presents lower costs compared with standard multiple-drug therapies (an average value of € 7,123 € 10,505). From a health-economics point of view, this results' projection did not require the CEV calculation and further investigation because, in the case of the same efficacy, the option with lower resources absorption is the preferable one (Drummond 2005).
Taking into consideration the minimum efficacy values, the CEV was lower for monotherapy than for standard multiple-drug therapies (€ 8,794 € 11,938). In this case, however, the efficacy value of monotherapy was lower than that of standard multiple-drug therapies, thus requiring a stratification of patients with the purpose of investigating the existence of preferred categories for the administration of monotherapy for long-term toxicities and resources savings.
The incremental cost-efficacy ratio (ICER) did not provide additional information since, in this specific case, it was impossible to calculate and use the utility parameter. There was no threshold value with which to make a comparison (Drummond 2005).

Budget impact analysis
An analysis was conducted using the minimum and maximum efficacy values for both monotherapy and standard multiple-drug therapies for patients under virological control, both for a 6-month period and a 12-month period. Different economic scenarios were created and compared with the total regional budget expen-

TABLE 2 - *Short period Budget Impact Analysis*
(source: personal reprocessing of Lombardy Region Integrated Patient's Database and study data).

				Max standard therapies efficacy 95%		*Min standard therapies efficacy 88%*	
	Patients eligible for monotherapy	*Patients eligible for standard therapies*	*Total budget Lombardy Region 2011* €	*Budget Impact on Lombardy Region* €	*Impact on total regional budget %*	*Budget impact on Lombardy Region* €	*Impact on total regional budget %*
Max monotherapy efficacy 95%	6,468 (virological control for 6 months)	23,721 patients	251,000,000	226,593,133	9.72	227,539,956	9.35
	3,220 (virological control for 12 months)			237,477,849	5.39	238,602,933	4.94
Min monotherapy efficacy 81%	6,468 (virological control for 6 months)			227,303,105	9.44	228,249,928	9.06
	3,220 (virological control for 12 months)			237,831,298	5.25	238,956,382	4.80

diture. Of the 251 million euro spent in 2011 by Lombardy Region for the management of HIV+ patients, the implementation of a new, additional, alternative therapy selected for specific categories of subjects, such as monotherapy, would lead to savings in the first year of introduction of between 12.04 and 24.41 million euro (equal to 4.80% and 9.72% of the total HIV budget, as shown in Tab. 2).

For the 5-year time horizon following the introduction of monotherapy, using the long-term budget impact model combined with the number of eligible patients (virological control for 6 or 12 months) and with the treatment efficacy minimum and maximum values, four scenarios were created (namely, "a", "b", "c" and "d").

Figure 2 considers the entire cohort of Lombardy Region HIV-positive patients, the criteria of eligibility for monotherapy, the level of efficacy, economic savings in k/euros and years of implementation, with four different scenarios depending on:

a) 27.27% eligible patients for monotherapy, monotherapy with maximum value of efficacy;
b) 27.27% eligible patients for monotherapy, monotherapy with minimum value of efficacy;
c) 13.58% eligible patients for monotherapy, monotherapy with maximum value of efficacy;
d) 13.58% eligible patients for monotherapy, monotherapy with minimum value of efficacy.

It is important to emphasize that in all cases the analysis showed significant savings. In particular, if the maximum parameters of efficacy (scenario "a" and "c") were considered, a steady increase in the advantage of using monother-

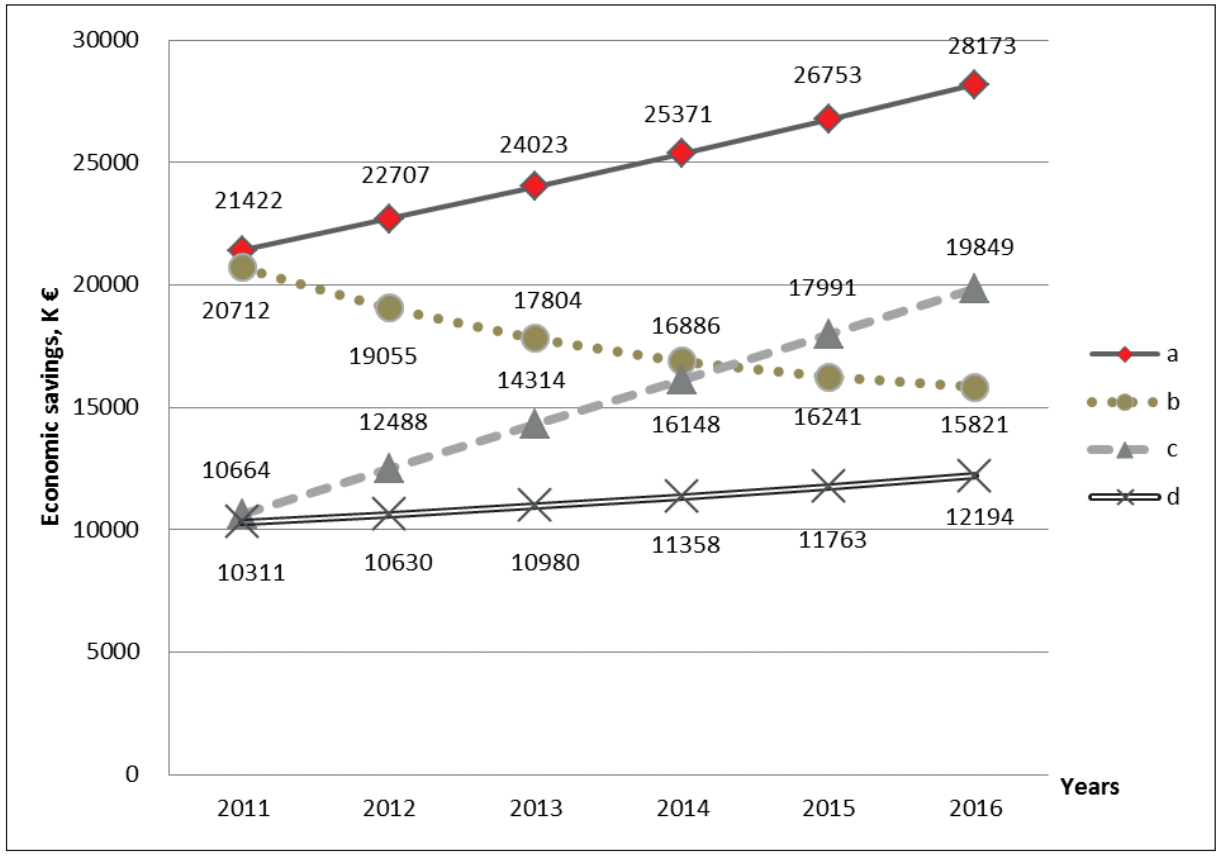

FIGURE 2 - *Long term period Budget Impact Analysis, considering economic savings and years (source: personal reprocessing of Lombardy Region Integrated Patient's Database and study data).*

apy was estimated compared with a scenario in which it was not used: in the 5-year horizon after implementation of a new additional therapeutic alternative, there was a constant increase in cost savings for the RHS. The same trend emerged from the "d" scenario in which the minimum value of efficacy and the conservative option of patients under virological control for 12 months were considered.

Instead, the economic advantage of using monotherapy decreased over time with a tendency to settle on values of around 15 million euro in the "b" scenario.

The same data could be assessed for a projection of the cumulated savings in a time period from year "0" to year "5" following implementation of the new technology (for a total of 6 years).

The savings over this period were within a range of 47.6 million euro ("d" scenario) to 144.8 mil-

TABLE 3 - *Short and Long-term organisational impact of monotherapy vs. standard therapies (source: personal reprocessing of study questionnaire).*

	Monotherapy Short Term										*Mono Short Term*	*Monotherapy Long Term*										*Mono Long Term*	*Standard Therapies*										*Standard Therapies*
	Subject surveyed										*Mean*	*Subject surveyed*										*Mean*	*Subject surveyed*										*Mean*
Variables	1	2	3	4	5	6	7	8	9	10	Mean	1	2	3	4	5	6	7	8	9	10	Mean	1	2	3	4	5	6	7	8	9	10	Mean
Impact on drug administration processes	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
Impact on hospital purchasing processes	3	3	4	2	3	3	3	3	3	3	3	3	3	4	2	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
Impact on therapeutic patient management protocols	3	3	4	2	3	3	4	2	3	3	3	3	3	4	2	3	3	4	2	3	3	3	3	3	3	3	3	3	3	3	3	3	3
Impact on the likelihood to commit errors	4	2	3	3	4	2	3	3	3	3	3	4	2	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
Training of the personnell who administer drug therapy	3	3	3	2	3	3	4	3	3	3	3	3	3	3	4	3	3	3	3	3	2	3	3	3	3	3	3	3	3	3	3	3	3
Meetings needed to coordinate and inform personnel on the use of the new drug	4	5	4	5	4	4	3	4	3	4	4	4	5	5	5	4	4	3	4	3	3	4	3	3	3	3	3	3	3	3	3	3	3
Training of prescribers	2	2	2	2	2	3	1	2	3	1	2	3	3	3	3	3	4	2	3	4	2	3	3	3	3	3	3	3	3	3	3	3	3
Total mean value											3											3,14											3

lion euro ("a" scenario), with a total amount of 73.4 million euro in the "b" scenario and 89.4 million euro in the "c" scenario.

Organizational impact

Of the 16 Hospital Divisions of Infectious Diseases present in Lombardy Region that were sent the organizational impact and ethics questionnaire, 10 responded positively and provided all the requested data (62.5% responsive rate).

The organizational impact of monotherapy introduction was considered insignificant from the payer's point of view.

However, taking into account each Division, some practices and clinics varied, disclosing a gap, in the short and long term, directly related to the introduction of monotherapy. Despite this, the effect is very low, as reported in Table 3 and Figure 3.

This dimension was investigated with the support of qualitative methods, considering the clinicians' perceptions (10 respondents), using a Likert-type scale, with 7 levels (Quinn Patton 2002) from 0 to 6, where 0 indicates the worst negative impact and 6 the best positive impact. Analysis of Table 3 shows values for the short term of between 2 and 4 (from low negative to low positive impact) and, for the long term, of between 2 and 5 (low negative to medium positive); the overall result being of null impact and of a slight shift respectively.

Monotherapy showed low negative short-term organizational results, that only considered the incremental training required for clinicians and health professionals, not only evaluating the new technology implementation phase, but also considering the whole learning curve of using monotherapy therapeutic strategy. However, in the long run, at the end of the learning curve this element changed

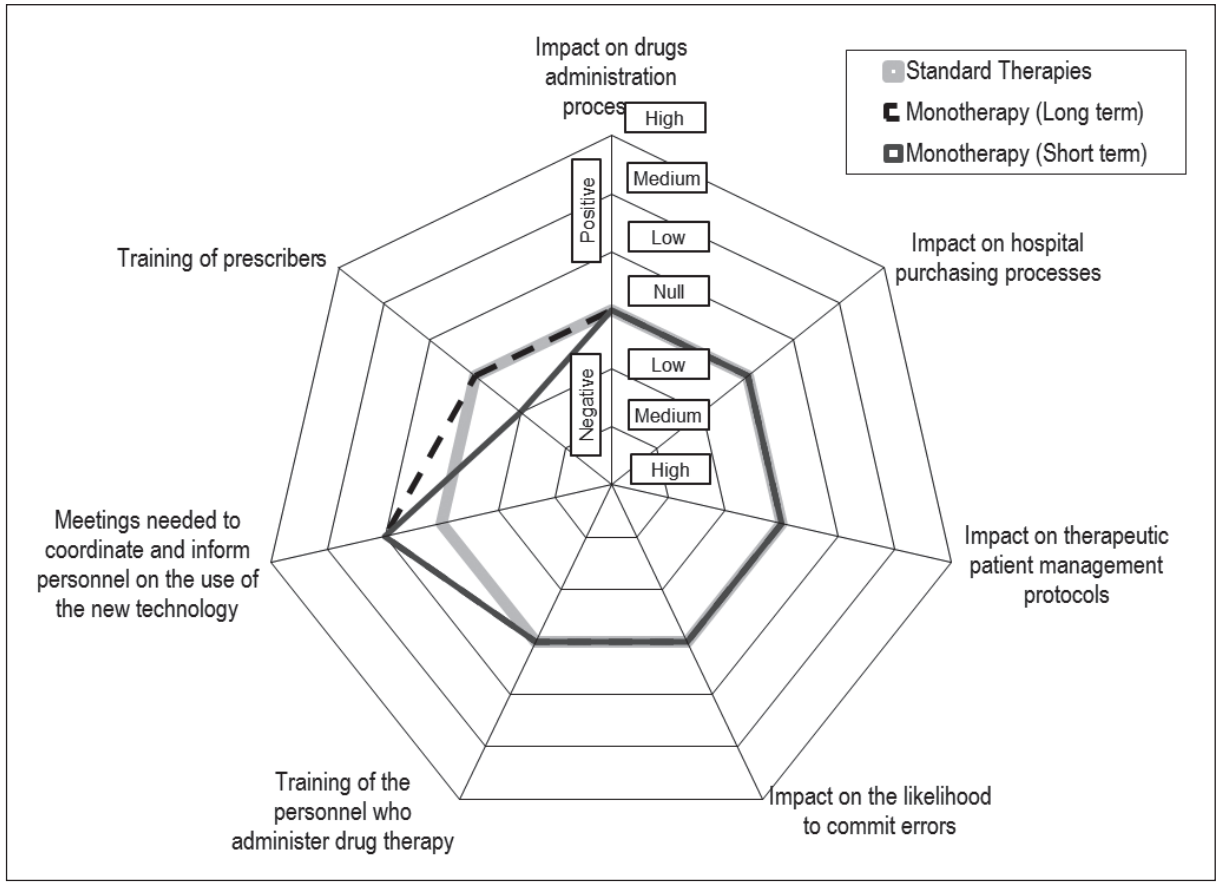

FIGURE 3 - *Short and Long-term organizational impact of monotherapy vs. standard therapies (source: personal reprocessing of study questionnaire).*

TABLE 4 - *Ethic and equity impact of monotherapy vs. standard therapies (source: personal reprocessing of study questionnaire).*

	Monotherapy Short Term										*Mono*	*Standard Therapies*										*Standard Therapies*
Variables	*Subject surveyed*										*Mean*	*Subject surveyed*										*Mean*
Adherence to therapy	5	5	5	5	5	5	5	5	5	5	5	3	3	4	3	2	3	4	3	2	3	3
Long-term toxicities	5	5	5	5	5	5	5	5	5	5	5	3	4	3	3	2	3	3	3	3	3	3
Convenience	3	5	3	5	3	4	5	4	4	4	4	3	3	3	3	4	3	3	2	3	3	3
Severe adverse events	4	2	3	3	4	2	3	3	3	3	3	3	4	3	3	3	2	3	3	3	3	3
Mild and moderate adverse events	3	3	3	2	3	3	4	3	3	3	3	3	3	3	4	3	3	3	2	3	3	3
Treatment's accessibility	3	4	3	2	2	3	3	3	3	4	3	3	3	4	3	2	3	4	3	2	3	3
Total mean value											3,8											3

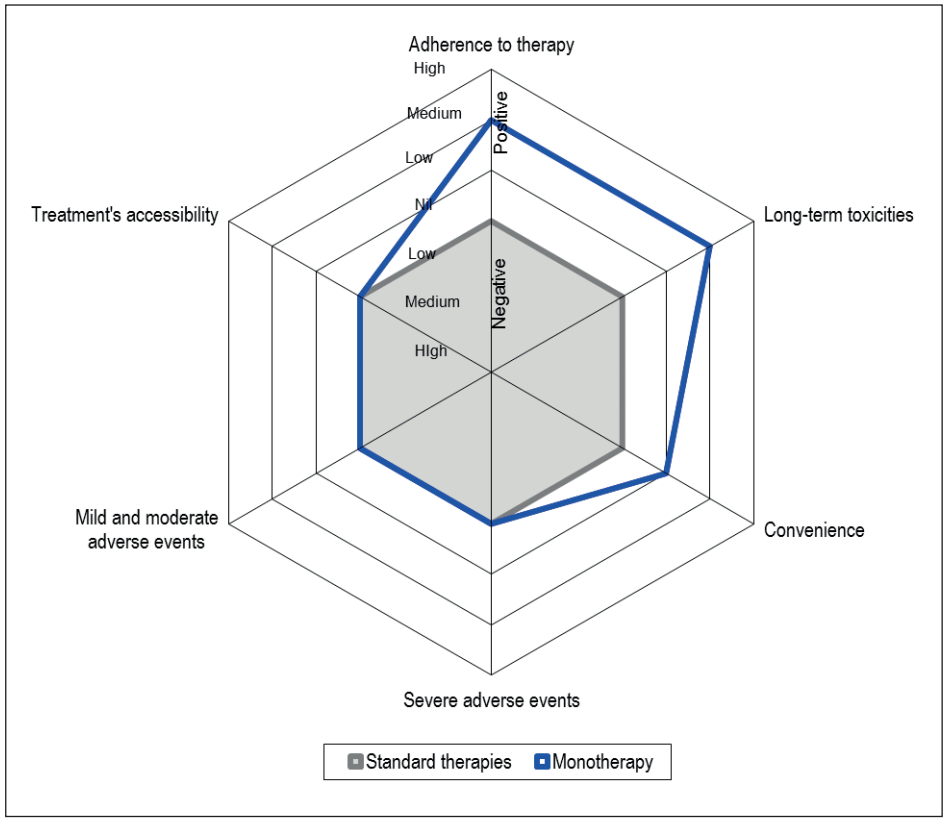

FIGURE 4 - *Ethic and equity impact of monotherapy vs. standard therapies (source: personal reprocessing of study questionnaire).*

and became positive with respect to the new therapy. In the case of a real implementation of an innovative additional therapy, the organisational and internal change efforts paid off, in the long run, thus favoring its choice if compared with existing and standard multiple-drug therapies.

Ethics and equity impact

The latest Italian and international guidelines emphasise the importance of the patients' point of view evaluation, as also required by HTA methodology. Six dimensions, through many questions, were investigated in the qualitative survey in order to understand which of these could have a higher impact in the comparison between the two technologies under investigation.

In this case, the respondents provided values for each variable of between 2 (low negative) and 5 (medium positive) for both technologies being assessed; the overall average result being 3.8 for monotherapy and 3 for standard therapies.

As shown, the innovative and standard therapeutic strategies do not differ in terms of severe or mild and moderate adverse events, and even for accessibility to treatment. Assuming the patient's point of view, aspects of relief are adhesion, convenience, and toxicity over a long period.

Taking a cue from the results of this survey, a direct HIV-positive subjects' participation and opinion is needed, deepening the investigation of these three dimensions in order to understand the real existence of an advantage in the monotherapy arm as would appear from the evidence provided by clinicians.

Generalizability/replicability

Although the sample studied may not be fully representative of the entire population of HIV-positive patients in all the Italian Regions, at a macro level the high replicability of the proposed methodology allows the possibility to use the same framework for further investigation outside of the Lombardy Region context. This could be done by changing the economic and epidemiological data, and adapting them to the Hospital Authority, national or regional scenario of reference.

DISCUSSION

The economic crisis within the European Union that began in 2008 forced Italy to conduct a health spending review, resulting in a higher number of urgent measures being taken. In such a scenario, it is advisable to analyse current activities by assessing the appropriateness of the services offered and by evaluating the cost-efficacy (or cost-effectiveness) of care. The crisis is forcing healthcare providers to recognise and accept similar important concepts of public services management such as the HTA approach, clinical governance (defined as the ability to provide quality services to users in excellent working conditions) (Department of Health 1997), and monitoring and control systems that could become a pivot for a coherent and rational review of work activities.

In this context, the results of the present study show that increasing the alternative approaches to standard therapies (defined as classic HAART) provides a wider choice for prescribing clinicians and, therefore, a wider availability of treatment options for patients.

As already demonstrated in previous studies (Arribas 2011; Gazzard 2011) related to different European countries, this local analysis showed an economic advantage following the introduction of PI-based monotherapy, which has given a positive reflection on the entire regional health budget.

In particular, the introduction, where possible, of a new alternative treatment, namely PI-based monotherapy, if compared with the standard multiple-drug therapy treatments would lead to a reduction of costs for the RHS of between 12.04 and 24.41 million euro, in the first year of its introduction.

The long-term model with a 5-year time horizon took into consideration two main hypotheses, a conservative one, and a more flexible one, that considered respectively 3,220 and 6,468 patients eligible for monotherapy treatment. An analysis of the entire diagnostic-therapeutic pathway of the patients, as well as the minimum and maximum values of therapies efficacy for the five years following the introduction of the new monotherapy strategy showed that there would be an overall reduction in costs ranging from 47.6 million euro to 144.8 million euro.

Other results showed a better cost-efficacy value of monotherapy, not only with the maximum value, but also in the minimum efficacy scenario. However, since the latter hypothesis saw not only a significant reduction of costs, but also a reduction in terms of efficacy for the patient, further investigation is necessary.
The organisational impact did not show substantial differences due to the potential introduction of monotherapy, except for a greater effort in terms of the training of personnel in the short term.
The ethics and equity dimension, taking into consideration the pilot survey that involved clinicians, could be investigated in more depth. This point probably represents a limitation of the present study.
However, if a monotherapy is used in a standardized manner on HIV-positive patients in the future, it will be possible to better evaluate the three principal dimensions of interest for HIV-positive subjects related to convenience, adherence and long-term toxicities.
A final note: the Italian Official Gazzette dated 31st May 2013 (Determina AIFA 2013) published an extended article describing the use of LPV and DRV as monotherapies and their importance not only for economic and monetary reasons, but also for the clinician's responsibility and legal reasons. It argued that clinicians should have an alternative to triple therapies with a regional reimbursement of prescribed drugs, thus being able to choose whether or not to operate "off-label". Furthermore, it stated that this would not result in higher operating costs.

CONCLUSIONS

In this context, the results of the present study suggest the possibility for institutional and regulatory decision-makers at national and regional level to reduce the absorption of scarce resources and at the same time maintain high levels of efficacy and safety for patients' care.
The advantage of the analysis in the present study is that it provides for the first time in the "HIV infection world" a comprehensive technology evaluation framework thanks to the application of HTA methodology.
It should be mentioned that to limit any analysis to economic aspects only would not be correct and/or useful. The inclusion of a survey concerning different dimensions shows how all impacts, under a profile of comprehensive health economic evaluation, improve or suggest good results following the introduction of monotherapy. The present analysis therefore provides evidence to support PI-based monotherapy as an alternative treatment regimen; indeed, it could lead to a reduction in total expenditure for the national or regional healthcare service of reference.

Conflict of interest

There are no potential conflicts of interest for any author concerning the submitted manuscript.

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