Antiretroviral therapy management and rationalisation of available resources

La gestione della terapia antiretrovirale nell'ottica della razionalizzazione delle risorse disponibili

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INTRODUCTION

Antiretroviral therapy (ART) is generally based on the combination of three drugs, two of which are defined as "backbone", belonging to the class of reverse transcriptase inhibitors (NRTIs) and a third belonging to the family of protease inhibitors of HIV (PI) or that of the non-nucleoside reverse transcriptase inhibitors (NNRTIs) or, more recently, to the family of integrase inhibitors (INSTI) [1, 2].
Several studies have compared in terms of effectiveness the two backbone mainstream in ARV regimens: one based on the association tenofovir-emtricitabine (TDF/FTC) and one based on the couple abacavir-lamivudine (ABC/3TC), including both naïve patients, both experienced patients [3-7].
Controlled clinical trials set to compare different antiretroviral regimens, while making useful suggestions about the efficacy and safety of themselves, are susceptible to criticism because they do not accurately reflect the conditions of real life that are routinely addressed in the clinics and in wards. In fact, in reality the specialists are more often inclined to change the ART acting on the backbone or the third drug or, not infrequently, the entire regimen for various reasons, taking into account both the information on the efficacy and tolerability of the drugs, both pharmacoeconomic considerations related to the direct and indirect costs of the overall management of the patients.
This survey, conducted in normal offer care to patients with HIV infection treated in the Infectious Diseases Units of the University Hospitals of two regions (Marche and Abruzzo) in Central Italy, investigated the impact of the modification of the ART (backbone nucleoside/nucleotide only or also the third drug) both on efficacy and safety of the treatment, both on the annual costs of the management of these patients.

PATIENTS AND METHODS

The intent of knowledge underlying the present clinical and pharmacoeconomic investigation was to obtain reliable data on the consequences of a switch between two ART reasonably equally effective if the switch has the prerequisites of a good tolerability in the short and long term. It has there-

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fore been created, using the normal activity outpatient care, a model that can deliver within a set time minimum of 96 weeks of observation useful informations to provide an answer to the question. It was for this purpose conducted a surveillance study on the first 50 patients, all clinically stable, with good viro-immunological response to the ART and without HBV infection, that since June 2012 switched from an ART based on the triple combination of tenofovir (TDF), emtricitabine (FTC) and a protease inhibitor boosted with ritonavir (PI/r) or a non-nucleoside reverse transcriptase inhibitor (NNRTI), to a treatment based on abacavir (ABC), lamivudine (3TC) and PI/r or NNRTI.

Clinical evaluation
All patients were followed with medical examinations and laboratory controls according to the protocol adopted at our clinics for patients clinically stable, with good immune recovery and optimal virologic suppression. In particular:
1) renal function was monitored by creatinine blood level, glomerular filtration rate (GFR) and proteinuria;
2) bone metabolism was evaluated by determining phosphorus and bone alkaline phosphatase blood levels;
3) lipid metabolism by dosage of serum triglycerides, total cholesterol and HDL cholesterol;
4) cardiovascular function was evaluated by routine clinical controls and performing echocardiography examination.

According to the protocol, patients were checked every 4 months (only echocardiography was performed every 12 months).

Pharmacoeconomic evaluation
The survey involved the main pharmacoeconomic aspect of the medical care for HIV-infected subjects: the direct costs of the drugs delivered. To conduct pharmacoeconomic evaluation, the cost of the therapy was calculated over a period of 365 days, while the frequency of visit and tests was kept unchanged even in case of demonstration of equal efficacy and lower toxicity by the new regimen. In fact, only in case of real demonstration of better tolerability and equal efficacy by the new regimen compared to the original scheme, the data obtained would be abducted to support the eventual future deferral of clinic controls and examinations.

Statistical evaluation
Statistical analysis of the results was performed using the *t* test for paired data, where each of the fifty patients were evaluated as control of himself at the end of the observation period. Significance was accepted when the P value was ≤0.05.

RESULTS

To get the programmed number of subjects (50 patients receiving TDF/FTC) it was necessary to consider the switches operated from June 2012 to May 2013. From these subjects were then collected the data for a minimum period of 96 weeks (range 96-132 weeks) until may 2015 (Tab. 1). It is important to note that the number of subjects treated with NNRTI as third drug increased from 10 to 39 as result of the switch. Among these 39 individuals, 2 have maintained nevirapine as third drug, while 8 and 29 subjects switched, respectively, to nevirapine from efavirenz and from PI/r (Tab. 2).

Renal function
The evaluation of serum creatinine showed a modest reduction in the levels of this index, from an average of 1.058 mg/dL at time 0 to 0.996 mg/dL af-

Table 1 - Clinical and demographic characteristic of the patients.

Number of subjects switched to ABC/3TC	50
Age (years- range)	39.9 (22-71)
Gender (M/F)	31/19
HCV coinfection (%)	7 (14)
HBV coinfection (%)	0 (0)
Serum creatinine level at T0 (mean, mg/dL)	1.058
Glomerular filtration rate at T0 (mean, mL/min)	80.4
Serum phosphorus levels at T0 (mean, mg/dL)	3.26
Bone alkaline phosphatase levels at T0 (mean, mg/dL)	23.22
Serum triglycerides levels at T0 (mean, mg/dL)	153.24
Serum total cholesterol levels at T0 (mean, mg/dL)	156.94
Serum HDL cholesterol levels at T0 (mean, mg/dL)	46.20
HIV viral load (copies/ml) at T0	<40
Lymphocytes CD4+ (cells/mmc) at T0	517

Table 2 - Third drug as part of ART in fifty patients receiving TDF/FTC switched to ABC/3TC.

Third drug	*Subjects before the switch*	*Subjects after the switch*
Atazanavir 300 mg/rtv	24	11
Darunavir 800 mg/rtv	4	0
Lopinavir/rtv	12	0
Efavirenz	8	0
Nevirapine	2	39

ter 24 months. Our results show that creatinine levels recovered about 0.112 mg/dL during the first 12 months. During the following months their levels remained substantially stable. The statistical analysis performed by *t* test for paired data showed both significant reduction (P=0.005) in creatinine and significant increase (P=0.008) in glomerular filtration rate (from 80.4 to 85.3 mL/min).
The dosage of proteinuria did not lead to any significant differences: the maximum values found have never exceeded 30 mg/dL.

Bone metabolism
The study of bone metabolism showed significant changes after the switch from TDF/FTC to ABC/3TC. Indeed, the dosage of phosphorus highlighted in this case a modest variation in the levels of this index, increasing from an average of 3.26 mg/dL at time 0 to 3.41 mg/dL after 24 months. Again the statistical analysis performed by Student *t* test for paired data showed significance for this variation (P=0.005).
In a similar manner, bone alkaline phosphatase levels were measured and again by the Student *t* test for paired data it was noted a significant change in the levels after switch from TDF/FTC to ABC/3TC: in fact, the mean bone alkaline phosphatase values decreased from 23.22 mg/dL to 21.72 mg/dL (P<0.001).

Cardiovascular function
During the entire period of observation, there were no statistically significant changes in blood pressure or heart rate. Patients reported no symptoms consistent with cardiovascular events (myocardial infarction, stroke, arrhythmia, heart failure and hypertensive heart disease). The echocardiographic examinations showed no variations between annual controls.

Lipid metabolism
The effects of ARV therapy on lipid metabolism have revealed conflicting aspects: on the one hand the shift to regimens based on ABC/3TC resulted in a significant reduction in the average levels of triglycerides from time 0 to 24 months (from 153.24 mg/dL to 138.74 mg/dL, P<0.031), on the other hand it produced an increase in total cholesterol (TC) and a concomitant significant reduction in HDL cholesterol (HDL-C). These variations, both in TC and HDL-C, were statistically significant (TC from 156.94 mg/dl to 174.50 mg/dl, P <0.001; HDL-C from 46.20 mg/dl to 42.06 mg/dl, P<0.001) in patients who retained unchanged the third drug (11 subjects receiving PI/r and two receiving nevirapine), while they were not found significant in those in which the third drug was replaced with nevirapine.

Viro-immunological study
During the 96 weeks of observation the backbone ABC/3TC has ensured the maintenance of an optimal suppression of HIV viral load (<40 copies/mL). In no case were detected viremic blips or therapeutic failures. On the other hand, there was a modest increase in CD4 + lymphocytes during 48 weeks of monitoring, without statistically significant difference (from 517 cells/mmc at T0 to 528 cells/mmc at 96 weeks).

Table 3 - Cost in Euros of the different TDF/FTC - and ABC/3TC - based regimens.

ARV regimen	*Cost of daily therapy*	*Cost of annual (365 days) therapy*
TDF/FTC + atazanavir/rtv	23.39	8,537.35
TDF/FTC + darunavir 800 mg/rtv	24.63	8,989.95
TDF/FTC + lopinavir/rtv	24.14	8,811.10
TDF/FTC + efavirenz	19.80	7,227.00
TDF/FTC + nevirapine	19.00	6935.00
ABC/3TC + atazanavir/rtv	22.16	8,088.40
ABC/3TC + nevirapina	17.77	6,486.05

Table 4 - Comparison between the real cost of annual therapy after the switch and the hypothetical in the absence of switch.

ART	*€ 365 days*
TDF/FTC-based ART	418,275.40
ABC/3TC-based ART	341,928.35
Difference	76,347.05

Pharmacoeconomic evaluation
For the second purpose of the study, *i.e*. on the pharmacoeconomic analysis, the actual cost of ART after the switch has been compared with what would have been if the switch had not been made.
The typology of the third drug used in the context of the ART before and after the switch has been previously summarized in Table 2, while Table 3 itemizes the costs of the different therapeutic ABC/3TC- and TDF/FTC-based regimens. Moreover, Table 4 detailed the difference in the annual cost, highlighting the savings achieved through the switch: 76,347 euros (average 1527 per patient). Finally, it is noteworthy that there were no costs of hospitalization, since no patient had need to be hospitalized during the observation period.

DISCUSSION

The present study involved two different aspects of the management of the HIV-infected individuals: the safety and efficacy of the therapy and its direct costs.
This study is substantially different from the usual controlled clinical trials. The problem with clinical trials is that they compare different types of people but under conditions which only partially correspond to real life [8]. These trials, while making very useful suggestions on the respective efficacy and tolerability of the investigated drugs, they correspond only partially to the situations that doctors are called to manage in the clinics and wards where are treated patients with HIV infection [9-11].
In fact, in reality, the medical specialist is frequently inclined to change the antiretroviral regimen acting not so much on the backbone, but rather on the third drug and, not infrequently, is induced to change the entire treatment for various reasons, taking into account both the reliability of drugs, both of pharmacoeconomic considerations related to the direct cost of all drugs and the fallout on the indirect costs of the overall management of the patient.
This study, conducted in normal offer care to patients with HIV infection treated in the Infectiuos Diseases Units of the University Hospitals of two regions (Marche and Abruzzo) in Central Italy, investigated the pharmacoeconomic impact of the optimization of the antiretroviral therapy, by modifying the backbone alone or jointly also the third drug. Premise of the pharmacoeconomic survey was that the new antiretroviral regimen would guarantee at least equal efficacy and tolerability of the original scheme based on TDF/FTC. For these reasons, all patients who had operated the switch were followed with the medical and laboratory examinations required in the diagnostic/therapeutic protocol adopted in our clinics for patients medically stable, with good immune recovery and optimal virologic suppression. According to the protocol adopted, patients in these conditions were checked every 4 months.
As expected, based on the most recent studies reported in the literature, statistical analysis, carried out on each subject as control of himself, showed that the switch to ABC/3TC resulted in a significant improvement in the parameters of renal function and bone metabolism [12-15].
Most of these results, especially the reduction in creatinine levels, may be related not only to the substitution of TDF with ABC, but also to the switch from PI/r to nevirapine that involved most of the patients.
Actually, it is known that decreased renal function may be a result of assumption of protease inhibitors [2, 8, 9]. Finally, the viremic suppression persisted and the gradual slow immune recovery continued over 96 weeks.
Ultimately, the study has provided clear results both on the clinical and pharmacoeconomic aspects. In fact, the clinical and laboratory controls showed the maintenance of an optimal viremic suppression after the switch from TDF/FTC to ABC/3TC compared to a better overall tolerability as regards the renal metabolism and the bone. At the same time, the pharmacoeconomic survey showed a substantial direct cost savings after the switch from TDF/FTC to ABC/3TC, laying the groundwork for future possible delay time for any control currently performed to monitor people taking antiretroviral drugs.

Keywords: antiretroviral therapy management, pharmaeconomic.

SUMMARY

The treatment of HIV disease has led to a new division of management costs by shifting most of the necessary resources from inpatient treatment to outpatient management. Among the initiatives aimed at rationalising the resources available, we compared efficacy, tolerability and pharmacoeconomic impact of different regimes of antiretroviral therapy (ART). The survey covered the first 50 patients, clinically stable and with good viro-immunological response, who switched in June 2012 from an ART based on the triple combination of tenofovir (TDF), emtricitabine (FTC) and a protease inhibitor boosted with ritonavir (PI/r) or a non-nucleoside reverse transcriptase inhibitor (NNRTI), to a treatment based on abacavir (ABC), lamivudine (3TC) and a PI/r or NNRTI. Of the 50 patients who operated the switch, 39 replaced a PI with nevirapine (NVP), for which the largest group of patients was treated with ABC + 3TC + NVP. On 31 May 2015, all patients completed the observation period of 96 weeks, with a mean observation period of 132 weeks and clinical-laboratory checks every four months. Laboratory analysis revealed an optimal maintenance of viral suppression and absolute and relative number of CD4 + lymphocytes and improving trend of creatinine, proteinuria, serum phosphate and bone alkaline phosphatase. There was a variable effect on lipids, with a drop in triglycerides associated with a modest increase in total cholesterol. Much of the HIV-positive population reporting to our hospitals (>50%) comprises individuals who have for years been in stable viraemic suppression, making a satisfactory immune recovery while in good overall clinical condition. This type of patient was the target of the present survey. At the end of 96 weeks of observation the new regimes were well tolerated and did not lead to viro-immunological or clinical deterioration. Pharmacoeconomic analysis showed better containment of the overall costs. No patient needed to be hospitalised during the observation period.

RIASSUNTO

La terapia dell'infezione da HIV ha comportato una nuova ripartizione dei costi di gestione spostando una parte preponderante delle risorse necessarie dal trattamento ospedaliero alla gestione ambulatoriale. Nell'ambito delle iniziative indirizzate alla razionalizzazione delle risorse disponibili, è stato impostato un protocollo volto alla valutazione di efficacia, tollerabilità ed impatto farmacoeconomico di differenti regimi di terapia antiretrovirale (ARV).

L'indagine ha riguardato i primi 50 pazienti, clinicamente stabili e con buona risposta viro-immunologica, che da giugno 2012 sono passati da un trattamento ARV basato sulla triplice associazione di tenofovir (TDF), emtricitabina (FTC) e un inibitore delle proteasi boosterato con ritonavir (PI/r) o un inibitore non-nucleosidico della trascriptasi inversa (NNRTI) a un trattamento basato su abacavir (ABC), lamivudina (3TC) e un PI/r o un NNRTI.

Tra i 50 pazienti che hanno operato lo switch*, 39 hanno sostituito un PI con nevirapina (NVP), per cui il gruppo più consistente di pazienti è stato quello trattato con ABC + 3TC + NVP. Al 31 maggio 2015, tutti i pazienti hanno completato il periodo di osservazione di 96 settimane, con un periodo medio di osservazione di 132 settimane e controlli clinico-laboratoristici ogni 4 mesi. Tali controlli hanno evidenziato, nei soggetti che avevano operato lo* switch*, un ottimale mantenimento della soppressione virale e del numero assoluto e relativo dei linfociti CD4+ e* trend *in miglioramento di creatininemia, proteinuria, fosfatemia e fosfatasi alcalina ossea. Variabile l'effetto sui parametri della lipemia, con un discreto calo della trigliceridemia a cui si associava un modico aumento della colesterolemia totale.*

Buona parte della popolazione HIV-positiva afferente ai nostri ambulatori (>50%) è costituita da individui da anni in stabile soppressione viremica, soddisfacente recupero immunologico e buone condizioni cliniche generali. Questa tipologia di pazienti è stata il target *dell'offerta assistenziale descritta. Al termine delle 96 settimane di osservazione i regimi di* switch *risultano ben tollerati e non hanno determinato deterioramento della situazione viro-immunologica e clinica. L'analisi farmacoeconomica ha evidenziato un miglior contenimento dei costi complessivi. Nessun paziente ha avuto necessità di ospedalizzazione durante il periodo di osservazione.*

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