Cost analysis of initial highly active antiretroviral therapy regimens for managing human immunodeficiency virus-infected patients according to clinical practice in a hospital setting

Objective: In the study reported here, single-tablet regimen (STR) versus (vs) multi-tablet regimen (MTR) strategies were evaluated through a cost analysis in a large cohort of patients starting their first highly active antiretroviral therapy (HAART). Adult human immunodeficiency virus (HIV) 1-naïve patients, followed at the San Raffaele Hospital, Milan, Italy, starting their first-line regimen from June 2008 to April 2012 were included in the analysis.

Methods: The most frequently used first-line HAART regimens (>10%) were grouped into two classes: 1) STR of tenofovir disoproxil fumarate (TDF) + emtricitabine (FTC) + efavirenz (EFV) and 2) MTR including TDF + FTC + EFV, TDF + FTC + atazanavir/ritonavir (ATV/r), TDF + FTC + darunavir/ritonavir (DRV/r), and TDF + FTC + lopinavir/ritonavir (LPV/r). Data were analyzed from the point of view of the Lombardy Regional Health Service. HAART, hospitalizations, visits, medical examinations, and other concomitant non-HAART drug costs were evaluated and price variations included. Descriptive statistics were calculated for baseline demographic, clinical, and laboratory characteristics; associations between categorical variables and type of antiretroviral strategy (STR vs MTR) were examined using chi-square or Fisher’s exact tests. At multivariate analysis, the generalized linear model was used to identify the predictive factors of the overall costs of the first-line HAART regimens.

Results: A total of 474 naïve patients (90% male, mean age 42.2 years, mean baseline HIV-RNA 4.50 log10 copies/mL, and cluster of differentiation 4 [CD4+] count of 310 cells/µL, with a mean follow-up of 28 months) were included. Patients starting an STR treatment were less frequently antibody-hepatitis C virus positive (4% vs 11%, P=0.040), and had higher mean CD4+ values (351 vs 297 cells/µL, P=0.004) than MTR patients. The mean annual cost per patient in the STR group was €9,213.00 (range: €6,574.71–€33,570.00) and €14,277.00 (range: €5,908.89–€82,310.30) among MTR patients. At multivariate analysis, after adjustment for age, sex, antibody-hepatitis C virus status, HIV risk factors, baseline CD4+, and HIV-RNA, the cost analysis was significantly lower among patients starting an STR treatment than those starting an MTR (adjusted mean: €12,096.00 vs €16,106.00, P=0.0001).

Conclusion: STR was associated with a lower annual cost per patient than MTR, thus can be considered a cost-saving strategy in the treatment of HIV patients. This analysis is an important tool for policy makers and health care professionals to make short- and long-term cost projections and thus assess the impact of these on available budgets.

Keywords: HIV, HAART, single tablet regimen, pharmacoeconomics, multi-tablet regimen
Introduction
Therapeutic successes against human immunodeficiency virus (HIV) are largely due to the results obtained by scientific research work, which has identified drugs with powerful antiviral activity. Since the mid-1990s, highly active antiretroviral therapy (HAART) has modified the clinical course of HIV infection, reducing the rate of disease progression, the incidence of opportunistic infections, and mortality. This prolonged survival has changed HIV infection into a chronic disease. As a consequence, combination antiretroviral therapy has resulted in longer survival and a better quality of life (QoL) for many HIV-infected patients. The most common drug regimen (HAART therapy) administered to patients entering treatment consists of two nucleoside reverse transcriptase inhibitors combined with either a non-nucleoside reverse transcriptase inhibitor, or a “boosted” protease inhibitor.

The recent development of single-tablet regimen (STRs) has been an important development in the optimization of antiretroviral regimens. Such optimization has the potential to improve long-term adherence, virologic efficacy, clinical outcomes, and QoL. In the past, several studies have shown treatment simplification strategies could enhance patients’ adherence to HAART. Although it has been postulated that this type of intervention works by improving the patients’ QoL, some studies have specifically addressed the relationship between QoL and adherence. For this reason, it seems important to verify how starting an STR, which determines a simultaneous improvement of the patients’ adherence and QoL, may translate into a potential economic value with a reduced number of HAART tablets in a large cohort of patients starting their first HAART. In a context of limited health care resources, pharmacoeconomic considerations are crucial to help policy makers make the most appropriate decisions on resource allocation.

Patients and methods
We evaluated STR versus (vs) multi-tablet regimen (MTR) strategies through a cost analysis in a large cohort of patients starting their first HAART. Adult HIV-1 naïve patients, followed at the San Raffaele Hospital, Milan, Italy, starting their first-line regimen from June 2008 to April 2012 were included in the analysis. The population included and evaluated in the analysis consisted of subjects having similar and superimposable sociodemographic characteristics at the time of enrollment (June 2008). The patients’ characteristics that determined their selection in the group of pooled data were divided into the following macro-groups: demographics, risk factors for HIV, baseline cluster of differentiation 4 (CD4+) count, baseline HIV-RNA, hepatitis C virus (HCV) coinfection, and disease treatment regimen. The most frequently used first-line HAART regimens (10%) were grouped into two classes: 1) STR with tenofovir disoproxil fumarate (TDF) + emtricitabine (FTC) + efavirenz (EFV) and 2) MTR including TDF + FTC + EFV, TDF + FTC + atazanavir/ritonavir (ATV/r), TDF + FTC + darunavir/ritonavir (DRV/r), or TDF + FTC + lopinavir/ritonavir (LPV/r). Taking account of summary of product characteristics of Atripla® (STR; Gilead Sciences, Foster City, CA, USA, and Merck and Co., Inc., Whitehouse Station, NJ, USA), patients can move from an MTR to an STR within 3 months; in this case, patients were included in the STR group. Patients were excluded in case of missing clinical data (subjects not referring to the center for more than 12 months) or cost information (patients not resident in Lombardy) and treatment regimens to less than 10% of the total first-line HAART regimens at enrollment. All data were anonymously processed and analyzed.

Resource consumption and costs
The analysis of only the comparative costs of alternative treatments is common to all forms of economic evaluation; in such situations, the studies performed may be called “cost analyses.” In this study, cost data were analyzed from the point of view of the Lombardy Regional Health Service (RHS) and HAART, hospitalizations, visits, examinations, and other concomitant non-HAART drugs costs were evaluated, price variations included. The consumption of resources for the patients considered in the analysis was linked to the administration of antiretroviral regimens and other direct health care costs, such as hospitalizations, medical examinations, visits, and laboratory tests. The RHS provides reimbursement for outpatient activities (medical examinations, laboratory and diagnostic procedures), hospital admissions, HAART, and non-HAART drugs to each regional health care structure. The collected data were therefore real costs incurred by the RHS – that is, bills paid to the (both public and private) providers of services delivered to each patient. Data on non-HAART drugs included all drugs prescribed to a patient and collected at any provider within the Lombardy Region, such as hospitals and pharmacies. These data were collected for the study period and anonymously linked to the patients’ clinical and personal data through a univocal code. All collected economic data referred to the year in which they were incurred. Costs were then discounted at the 2012 level, based on the Italian inflation rate of average consumer prices. The cost analyses considered the evolution of both
total costs and of each cost category between 2008 and 2012. All clinical data were then analyzed to identify patient characteristics that may be related to the costs in each year, taking into account the CD4+ cell count (≤200, 201–350, 351–500, and >500 cells/µL).

**Statistical analysis**

Descriptive statistics were calculated for baseline demographic, clinical, and laboratory characteristics: means and standard deviations or range were calculated for continuous measures, and frequency (%) for categorical measures. Associations between categorical variables and type of antiretroviral strategy (STR vs MTR) were examined using chi-square or Fisher’s exact tests. The Wilcoxon rank-sum test was applied to detect differences among subjects who started an STR or MTR with respect to distributions of continuous variables. At multivariate analysis, the generalized linear model was used to identify the predictive factors of the overall cost of the first-line HAART regimens; the included covariates were: age, sex, antibody (Ab)-HCV status, HIV risk factors, baseline CD4+, and HIV-RNA. All the recorded variables were entered into the multivariate model. All tests were two-sided and P-values <0.05 were considered statistically significant. Statistical analyses were performed using SPSS Statistics (v 19.0; IBM Corp, Armonk, NY, USA) and NCSS (v 8.0; NCSS, East Kaysville, UT, USA).

**Results**

Table 1 shows the main baseline characteristics. Included in the study was data for 474 naïve patients (90% male, mean age 42.2 years, mean baseline HIV-RNA 4.50 log10 copies/mL, CD4+ count of 310 cells/µL, with a mean follow-up of 28 months). Patients starting an STR treatment were less frequently anti-HCV Ab (antibodies anti-HCV) positive (4% vs 11%, P=0.040), and had higher mean CD4+ values (351 vs 297 cells/µL, P=0.004) than MTR patients. Figure 1A and B show immunological and virological trends after the start of the antiretroviral therapy and independently from switch. After 12 and 24 months since the start of HAART, 93% and 94% of STR patients and 89% and 91% of MTR patients, respectively, had an HIV-RNA <50 copies/mL. Similar CD4+ recovery in both STR and MTR patients was also observed.

The mean annual cost per patient was €9,213.00 (range: €6,574.71–€33,570.00) among STR patients and €14,277.00 (range: €5,908.89–€82,310.30) among MTR patients. Thus, STR was found to be less costly per patient than MTR (Figure 2).

Multivariate analysis (Table 2) revealed the mean cost to be significantly lower among patients starting an STR treatment than among those starting an MTR regimen (adjusted mean: €12,096.00 vs €16,106.00, P=0.0001). It is interesting to notice that the year cost for patients was inversely correlated with CD4+ levels (cells/µL): decreasing immunological values, were associated with increasing mean annual cost.
Figure 1 Results: immunological (A) and virological (B) trends during follow-up according to single- or multi-tablet antiretroviral regimens.

Abbreviations: CD4, cluster of differentiation 4; MTR, multi-tablet regimen; STR, single-tablet regimen.

Discussion

The availability of HAART has modified the natural progression of HIV infection, resulting in an increased survival of sero-positive subjects.16 Adding new single-tablet antiretroviral regimens to conventional therapies can be useful to physicians in choosing the best possible therapy in the treatment of HIV.

However, since STR is not the only available therapeutic option, we deemed it necessary to carry out a pharmacoeconomic comparison with other antiretroviral regimens, taking into account treatments endorsed – though with different degrees of recommendation – by Italian guidelines. Various comparison models for the cost and effectiveness of different therapeutic regimens have recently been reported in the literature, with particular reference to the Italian situation.17-20 These research studies were developed with the use of decision models to highlight any differences in terms of cost per quality-adjusted life years (QALYs) among the different therapeutic regimens. In contrast, in our research we tried to identify the real cost of HIV patients in a hospital setting, based on the costs actually borne by the Italian National Health Service. The results obtained show that STR is the less costly treatment strategy in comparison with the other therapeutic regimens based on MTR. The mean annual cost per patient emerging from our research is basically consistent with a recent analysis of real treatment costs of HIV patients.21,22 These two studies, carried out on the administrative database of the Lombardy Region reimbursements for
the years 2007–2009, show a mean annual cost per patient of €11,734.00 (lower 95% confidence limit [CL]: €11,057.00; upper 95% CL: €12,412.00). In our research, we estimated the mean annual cost per patient as €9,213.00 for the STR group and €14,277.00 for the MTR group. The multivariate probabilistic sensitivity analysis of the main variables confirmed the base case validity. In particular, it is important to highlight that the worsening of the patients’ condition (CD4 drop) corresponds to an increase in the mean annual cost for all patients.19,21,22

In our study, the CD4 levels in the STR group were constantly higher than in the MTR group. It is important to remember that it is possible to correlate the expressed results in terms of CD4, as in other studies,17–19 to utility scores calculated on the EQ-5D53 (www.euroqol.org), as follows: for CD4 values >500 cells/µL, the utility score was 0.9460; for CD4 values 351–500 cells/µL, the utility score was 0.9330; and for CD4+ values ≤200 cells/µL, the utility score was 0.8300.23 As reported by many published papers,17–19 the association of CD4 levels with QoL values imply the complete superiority of the STR strategy (ie, less costly and more effective), which involves lower costs and more preference elements due to the patients’ QoL. A recent publication demonstrated that all these elements could contribute to determine a maximum potential “premium price” of 29% to be assigned to an STR for HIV-infected patients.24

The results of this study need to be interpreted considering some limitations. First, the adoption of a 48-month time interval for the STR vs MTR comparison may not have been sufficient to highlight the long-term effects and complications of HAART. A second limitation is that the statistical analysis did not include some additional predictive factors, such as renal function and baseline resistance; with few exceptions, all the therapies were prescribed based on resistance test, clinical history, and safety issues of the patients. Third, the

Table 2 Multivariate analysis (generalized linear model): factors associated with the overall cost (costs include antiretroviral regimens and hospitalizations and non-antiretroviral treatments)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Patients who did not switch during follow-up: persistence ≥100% (N=309)</th>
<th>Patients who switched during follow-up: persistence &lt;100% (N=165)</th>
<th>All patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Adjusted* mean cost (SE), euros</td>
<td>P-value</td>
<td>Adjusted* mean cost (SE), euros</td>
</tr>
<tr>
<td>CD4+, cells/µL</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>≤200</td>
<td>15,600 (1,377)</td>
<td>0.0034</td>
<td>20,260 (3,196)</td>
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<tr>
<td>201–350</td>
<td>11,594 (1,231)</td>
<td></td>
<td>15,665 (3,357)</td>
</tr>
<tr>
<td>351–500</td>
<td>12,365 (1,365)</td>
<td></td>
<td>12,564 (3,196)</td>
</tr>
<tr>
<td>&gt;500</td>
<td>13,059 (1,708)</td>
<td></td>
<td>14,607 (2,367)</td>
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<tr>
<td>First-line regimen</td>
<td></td>
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<tr>
<td>STR</td>
<td>11,161 (1,353)</td>
<td>&lt;0.0001</td>
<td>13,973 (3,851)</td>
</tr>
<tr>
<td>MTR</td>
<td>15,148 (1,186)</td>
<td></td>
<td>17,575 (2,455)</td>
</tr>
</tbody>
</table>

Note: *Adjusted for age, sex, anti-HCV Ab, HIV risk factor, baseline HIV-RNA.
Abbreviations: CD4, cluster of differentiation 4; MTR, multi-tablet regimen; SE, standard error; STR, single-tablet regimen; anti-HCV Ab, antibodies anti-HCV.
The appropriate prescription of drugs is of critical importance to reach therapeutic objectives and to optimize the use of resources in modern health systems.

**Conclusion**

In our study, STR was associated with a lower annual cost per patient than MTR, thus can be considered a cost-saving strategy in the treatment of HIV patients. This analysis is an important tool for policy makers and health care professionals to make short- and long-term cost projections and thus assess the impact of these on available budgets.

**Disclosure**

This research was supported by Gilead Sciences Srl, Milan, Italy. The authors are employees of independent research organizations and maintained independent scientific control over the study, including data analysis and interpretation of final results.

**References**


