Antiretroviral Switch Strategies for Lowering Costs of Therapy. 48-Week Cost-efficacy Analysis

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Background

The economic recession has led to a generalized shortage of investment in public health and the antiretroviral treatment (ART) budget in some European countries, with particular seriousness and urgency in Spain. Some ART were proactively switched in selected individuals to generate cost savings. We undertook a complete 48 week cost-efficacy analysis to evaluate this strategy.

Methodology

We defined cost-reduction measures (CRM) as all those switches that aimed to reduce the cost of treatment in patients with virologic suppression (HIV-1 RNA <50 c/mL), without toxicity or any other indication to switch the ART. A list of potential CRM were agreed by the crew of treating physicians in an HIV Unit (Table 1).

Every treatment change strategy was based on strict selection criteria derived from clinical trials or expert opinion, as described elsewhere (1). We registered all treatment changes done during the period of study (May to November 2011). All direct costs were considered: cost of therapy calculated from manufacturer sales price plus 4% VAT, all resource consumption used in the management of toxicity, any treatment change, and therapeutic failure, for which we used the official rates to apply by the hospital.

Table 1 Main types of antiretroviral treatment regimens initiated in switches to a more economical regimen in individuals with suppressed plasma HIV-1 RNA (<50 copies/mL)

Treatment strategy
Tenofovir/emtricitabine → abacavir/lamivudine
Darunavir/ritonavir monotherapy
Lopinavir/ritonavir monotherapy
Nevirapine substituting a more expensive drug
Substitution of raltegravir
Withdrawal of raltegravir*
Darunavir/ritonavir dose reduction**
Generic lamivudine
Atazanavir/ritonavir (300/100 mg) → atazanavir 400 mg
Withdrawal® or substitution of etravirine
Switches to efavirenz/tenofovir/emtricitabine
Reduction of dose or withdrawal of maraviroc*
Withdrawal of inactive NRTI
Switching tipranavir to other drugs
Other

Notes: *In subjects receiving more than three active antiretroviral drugs, generally patients from clinical trials or advanced salvage regimens; **usually from 600 mg/100 mg twice daily to 800 mg/100 mg once daily.
Abbreviation: NRTI, nucleoside reverse transcriptase inhibitor.

A snapshot analysis was done 48 weeks after the treatment switch (Intention-to-reat analysis, S/M=F) to assess the percentage of patients still on the same regimen and with a plasma HIV-1 RNA < 50 copies/mL.

Results

During the study period, 673 switches were made, of which 378 (56.2%) were CRM (16% of all patients treated), leading to overall savings of €87,410/month (Table 2). This represented a 87.46% increase vs the same period in the preceding year. This represented a 87.46% increase vs the same period in the preceding year.

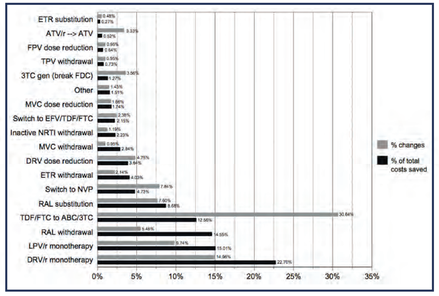
Table 2 Different categories of switches in antiretroviral treatment undertaken in a cohort of 2401 HIV-1-infected patients during the study period

Treatment change goal	Monthly cost (€)	N	Percentage
Cost-saving measures	–87,409.80	378	56.17%
Toxicity	12,022.50	76	11.29%
Treatment-naïve patients initiating ART, patients receiving treatment in the center for the first time, or reinitiation of ART >1 year after withdrawal#	52,995.60	64	9.51%
Inclusion in clinical trials*	–2712.00	47	6.83%
Virological failure	17,657.85	44	6.54%
Others	8100.00	31	4.61%
Postexposure prophylaxis	16,710.00	22	3.27%
Ends a clinical trial*	3826.80	9	1.34%
Toxicity plus adherence or pharmacokinetic issues	1406.70	2	0.30%
Total	30,962.85	673	100.00%

Notes: #Reinitiation <1 year after withdrawal was not included because it was not considered a change in treatment; *only clinical trials in which the sponsor paid for any part of the antiretroviral treatment are included.
Abbreviation: ART, antiretroviral treatment.

Switching TDF/FTC for ABC/3TC was the most common CRM (129, 31.3%), followed by simplification to PI/r monotherapy (102, 26%). The correlation between the number of every CRM and the costs saved was not complete.
The CRMs that generated the greatest savings were switching to PI/r monotherapy (38%), substitution of raltegravir (24%), switching TDF/FTC for ABC/3TC (13%), and switching to nevirapine (5%) (Figure 1).

Figure 1. *Correlation between the number of switches identified as cost-saving measures and the costs saved with them (shown as percentages).*



Abbreviations: ABC/3TC, abacavir/lamivudine; ATV, atazanavir; DRV/r, darunavir/ritonavir; EFV, efavirenz; ETR, etravirine; FDC, fixed-dose combinations; FPV, fosamprenavir; LPV/r, lopinavir/ritonavir; MVC, maraviroc; NRTI, nucleoside reverse transcriptase inhibitor; NVP, nevirapine; RAL, raltegravir; TDF/FTC, tenofovir/emtricitabine; TPV, tipranavir; 3TC gen, generic lamivudine.

The amount of monthly costs saved in € by every measure is shown in Table 3. The total monthly savings generated by the CRM; was 87,409.80 €.

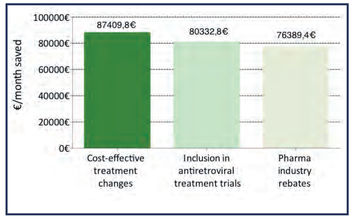
Table 3. *Comparison of the number of cost-reduction measures undertaken (shown as categories) and costs saved with each one*

Category of antiretroviral cost-reduction measure	N changes	Percentage of changes	€/month saved	Percentage of costs saved
Darunavir/ritonavir monotherapy	63	14.96%	19,845.15	22.70%
Lopinavir/ritonavir monotherapy	41	9.74%	13,132.00	15.01%
Withdrawal of raltegravir	23	5.46%	12,718.50	14.55%
TDF/FTC to ABC/3TC	129	30.64%	10,977.15	12.56%
Substitution of raltegravir	32	7.60%	7582.95	8.68%
Switch to nevirapine	33	7.84%	4135.50	4.73%
Withdrawal of etravirine	9	2.14%	3518.40	4.03%
Reduction of dose of darunavir	20	4.75%	3355.50	3.84%
Withdrawal of maraviroc	4	0.95%	2486.70	2.84%
Withdrawal of inactive NRTI	5	1.19%	1947.90	2.23%
Switch to EFV/TDF/FTC	10	2.38%	1878.00	2.15%
Reduction of dose of maraviroc	7	1.66%	1518.15	1.74%
Other	6	1.43%	1324.20	1.51%
Lamivudine generic (break FDC)	15	3.56%	1111.20	1.27%
Withdrawal of tipranavir	4	0.95%	639.90	0.73%
Reduction of dose of fosamprenavir	4	0.95%	559.80	0.64%
ATV/ritonavir to unboosted ATV	14	3.33%	451.80	0.52%
Substitution of etravirine	2	0.47%	237.00	0.27%
Total	421	100.00%	87,409.80	100.00%

Abbreviations: ABC/3TC, abacavir/lamivudine; ATV, atazanavir; EFV/TDF/FTC, efavirenz/emtricitabine/ tenofovir; FDC, fixed-dose combinations; NRTI, nucleoside reverse transcriptase inhibitors; TDF/FTC, tenofovir/emtricitabine.

We compared the savings generated by CRM with the total savings generated in clinical trials during the same period (when the promoter payed the treatments given in the trials), and with the total savings generated through any discount arrangements in the purchase costs of antiretroviral drugs (Figure 2).

Figure 2. *Final savings achieved during the study period with the three main cost-saving strategies: CRM, inclusion in antiretroviral treatment trials (with antiretroviral medication totally or partially paid for by the sponsor of the clinical trial), and discount arrangements (shown as € per month saved).*



After 48 weeks, 318/378 (84.1%) patients remained on the same treatment with plasma HIV-1 RNA <50 copies/mL, while 60 (15.9%) had changed it.

Only in 30 patients (7.9%) the change was related with the switch undertaken: side effects (22, 5.8%) and virological failure (8, 2.1%) (Table 4). The most common side effects were low-grade gastrointestinal toxicity (diarrhea and abdominal discomfort) related to abacavir (2.4%), lopinavir (1.3%), and darunavir (0.5%), followed by rash by nevirapine (1,1%), and central nervous system toxicity by efavirenz (0.5%) (Table 5). Changes unrelated to the switch included adverse events (20, 5.3%), pharmacokinetic interactions (7, 1.9%), treatment withdrawal (2, 0.5%) and simplification (1, 0.26%). All toxicities were grade 1-2.

Remaining on the same ARV regimen	318 (84.1%)
Changed the regimen	60 (15.9%)
Adverse events	
- Related with the new regimen	22 (5.8%)
- Not related with the new regimen	20 (5.3%)
Virological failure *	8 (2.1%)
PK interactions ¶	7 (1.9%)
Treatment withdrawal	2 (0.5%)
Treatment simplification	1 (0.3%)

Table 4. *Outcomes at 48 weeks in subjects receiving a CRM.*

** Defined as two consecutive plasma HIV-1 RNA >50 c/mL.*
¶ PK Interactions: 1 tuberculosis (rifampin), 3 hepatitis C virus antivirals, 3 corticosteroids (PI/rs).

Table 5. *Toxicities related with the new CRM regimen at 48 weeks.*

Drug	Toxicity (any grade, related with the CCM)	Grade	N (%)
Overall			22(5.8%)
Abacavir	GI (diarrhea, abdominal discomfort, asthenia, myalgias)	1-2	9 (2.4%)
Lopinavir/r	Diarrhea	1-2	5 (1.3%)
Nevirapine	Rash	1	4 (1.1%)
Darunavir/r	Diarrhea	1	2 (0.5%)
Efavirenz	CNS Neuropsychiatric	2	2 (0.5%)

Among 8 virologic failures, 4 had been switched to PI/r monotherapy, 3 to triple PI/r, and 1 unboosted ATV. The switch was related to the virological failure in only 1 subject.

Figure 6. *Virologic failures at 48 weeks in subjects receiving a CRM: 8/378 (2.1%). 4 subjects received a PI/r mono, 3 a triple PI/r-based regimen, and 1 a triple unboosted ATV.*

Prior GRT	GRT at failure	HIV-1 RNA at 48 weeks
Wild-type: 5 Not done: 3	Wild-type: 2, Not evaluable: 1, not done: 2 Not evaluable: 1, Not done: 1 Resistance in RT and PRO *: 1	4: < 50 c/mL; 1: 340 c/mL 2: <50 c/mL; 1: 281 c/mL

** RT: M184V L210W T215Y. PR : L10I, K20R, V32I, M36I, M46I, I54V, Q58E, A71L, V82A, I84V, L90M. Treated with ATV/r + ABC/3TC.*

During 48 weeks of follow-up, the new treatment changes generated a cost of €40,124, extra visits 2,553 €, and supplemental tests 2,971 €, therefore generating a final net saving of €922,855 (out of the 87,409.80 €/month saved in pure drug costs).

Conclusions

Proactively switching the ART in properly selected patients with sustained virological suppression generated significant cost savings at 48 weeks, and proved to be a cost-effective strategy. These findings might have implications for decision makers in designing safe strategies that maintain HIV-1 suppression at lower costs.
This treatment optimization can presumably be done only once. Once applied, no further CRM can probably be done further unless new treatments are approved (generics).

References

JM Llibre, G Cardona, JR Santos, et al. ClinicoEconomics and Outcomes Research 2013:5 215–221