

## Economic Evaluation of Drug Resistance Genotyping for the Adaptation of Treatment in HIV-Infected Patients in the VIRADAPT Study

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**Background:** Costs of antiretroviral therapy for HIV-infected patients have increased at a time when most countries are attempting to contain health care costs. Part of this increase results from HIV drug resistance associated with virologic failure and a subsequent shift to more complex and costly therapies. Genotypic guided treatment is associated with better virologic outcome. However, it is not yet known whether it will be cost effective.

**Methods:** We present here an economic evaluation based on the results from the VIRADAPT study, a prospective, open-label, randomized trial comparing patients assigned to standard of care ( $n = 43$ ), versus genotypic guided treatment ( $n = 64$ ) for 6 months. Total follow-up for the extended trial was 1 year. Costs were computed from the viewpoint of the health care system. Hospitalization data were retrieved from the VIRADAPT study case report forms, costs were estimated from the cost of the corresponding diagnosis-related groups derived from the French national cost data base: these were actual costs and not charges. Data on the volume of tests prescribed, drugs, and clinic visits were retrieved from the VIRADAPT study database. The unit costs of tests and clinic visits were determined using the French national Social Security reimbursement price; costing of drugs used were based upon purchase price by either retail pharmacies or hospitals. Genotyping using TruGene HIV-1 assay was estimated at \$500 per test from manufacturer's data (all figures in this paper are expressed in U.S. dollars).

**Results:** Total mean (standard deviation) yearly costs per patients were \$20,412 ( $\pm$ \$10,129) in the standard of care group and \$18,484 ( $\pm$ \$9,652) in the genotyping group ( $p = .35$ ). Drug costs represented 55% of total costs. There was a trend toward a decrease in drug costs in the genotyping arm ( $p = .07$ ), the greatest reduction being in the decreased use of protease inhibitors in the genotyping arm. The additional expense of genotyping appeared to be offset by the savings obtained in drug costs.

**Conclusion:** In our study, the cost of drug resistance testing is offset by a reduced use of protease inhibitors and their attendant costs. Although not reaching statistical significance, this trend in the reduction of drug costs and drug use presents a great interest for future trials.

**Key Words:** Drug resistance—Genotyping—Economics.

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Combination therapy has been associated with a sharp decrease in HIV-related mortality and morbidity with its associated costs (1). Furthermore, viral load has been demonstrated to be a good surrogate marker of clinical evolution (2). To lower HIV RNA for as much and as

long as possible, empirical combination of three or even more antiretroviral drugs has become the standard of care. Antiretroviral therapy is the major cost driver in the care of HIV-infected people. The cost of care for HIV-infected patients has become an important issue at a time when most countries belonging to the Organization for Economic Cooperation and Development (OECD) attempt to contain the rise of their health care costs. Drug resistance testing could help to rationalize the therapeutic choice using drugs with a better chance of success, lower costs, and better tolerance when possible. With the availability of resistance testing, the question arises whether better choice of treatments based on genotypic information will result in a lower viral load, fewer hospitalizations, and lower costs. We undertook an economic evaluation to test this hypothesis.

## MATERIALS AND METHODS

This economic evaluation was based on the data collected for patients included in the VIRADAPT study (3). VIRADAPT was a prospective, open, randomized trial comparing patients assigned to standard of care ( $n = 43$ ) versus genotypic-guided treatment. Resistance-associated mutations in protease and reverse transcriptase genes were determined using home-brew (a locally engineered test; first 6 months) and Visible Genetics (Evry, France) OpenGene DNA sequencing system ( $n = 64$ ) in the last 6 months. HIV RNA, viral load, genotypic resistance testing and clinical evolution were assessed every 3 months. If viral load failed to decline at least 0.5 log, therapy could be changed. In the first 6 months after randomization, the study arm received genotype-guided treatment and the control arm received standard of care. After the interim analysis, genotype-guided treatment was offered in both arms due to higher HIV RNA decrease in the study arm. The study methods and clinical results have been previously reported (3,4).

### Hypotheses

The following hypotheses were used for the economic analysis (5,6): costs were computed from the viewpoint of the health care system. All hospital-based costs including those of hospital clinic visits, outpatient treatments, and ambulatory costs were included. Loss-of-work-productivity costs were excluded because no data were collected on the number of days lost from work. The time horizon was the duration of follow-up (i.e., 1 year), the case type was that of the study patients, the reference strategy was standard of care and no genotyping. However, after the interim analysis (at 6 months) patients in the standard of care arm were allowed genotyping. Given that some patients died, were otherwise lost to follow-up, or had already completed the study, only 69% of the patients in the control arm received genotype-guided treatment changes in the second 6-month open label genotyping phase. Therefore, we computed the 12-month cost in the standard of care arm with and without genotyping costs. The other costs were those of resources actually expended for the patients over the entire duration of the trial.

In the absence of results on survival, we did not attempt a cost-

effectiveness analysis, but a comparison of the costs in both groups (cost-minimization analysis). French francs were converted into U.S. dollars using the OECD purchasing power parity index (at the time of writing, 6 French francs = \$1.00 U.S.).

## Cost Computations

### Hospital Costs

We used the cost of the diagnosis-related group (DRG) that corresponded to each individual admission. Data were retrieved from the hospitals' information system and the cost of an admission was derived from the French Ministry of Health national cost database, which provided a national estimate of the cost of each DRG (7). This represented the official cost of an admission in France, which will be used in the future for prospective reimbursement.

### Ambulatory Costs

Ambulatory costs comprised the costs of drugs, tests, and clinic visits (including professional fees). The data on the number of tests prescribed and of clinic visits were drawn from the database used by the investigators of the VIRADAPT study for follow-up on their patients. When necessary and relevant, case report forms and patient charts were retrieved. The total dose of medications prescribed was retrieved from case report forms: these include both HIV medications (nucleoside reverse transcriptase inhibitors, protease inhibitors, non-nucleoside reverse transcriptase inhibitors) and all other drugs prescribed to the patients.

Costing of tests and clinic visits to both hospital-based and private physicians used the French national Social Security reimbursement price. We used the purchase price of drugs from retail pharmacies or the average wholesale price for drugs available only to hospitals.

### Costs of Drug Resistance Genotyping

There was no officially set price for the DRG test. We estimated a cost to the hospital from the U.S. price: this cost comprises the reagents and the amortization of the sequencing machine but does not include the wages of the laboratory technician. The cost per test was estimated to be \$500 and was used to compute test cost in the DRG arm; the additional genotyping cost for the standard of care arm after genotyping was introduced (interim analysis) was \$345 per patient

### Data Analysis

We computed mean costs and standard deviations in each arm of the trial for each line-item and total costs. The costs were compared using two-tailed Student's *t*-test (8).

### Data Retrieval

Data on volume of resources used was retrieved from the patient charts and from the hospital's information system. We obtained for each patient and each admission: diagnosis codes, procedure codes, and length of stay.

For ambulatory care, data on tests and drugs prescribed were obtained from the computerized medical record that was developed spe-

cifically for the follow-up of HIV-infected patients (ADDIS) (9) The software recorded:

- biologic tests
- imaging tests
- nonmedical services (e.g., physical therapy)
- clinic visits (other than those that were part of the protocol)
- drugs (total dose of each drug per patient)

*Protocol-Driven Costs*

Protocol-driven costs were those of the health care resources that would not have been expended if the patients had not been included in a protocol. Because these costs are identical in both arms, they can be kept in the baseline analysis because they will be canceled out in the cost comparisons. However, they introduce an error in the estimation of the total cost of a strategy. We therefore computed an estimate of total cost without protocol-driven costs, by subtracting the costs of clinic visits and tests that would not have taken place for non protocol patients.

*Patients*

From March 1997 until March 1998, 108 consecutive patients (3,4) who did not improve on a course of highly active antiretroviral therapy (HAART) (75% male patients, mean CD4 cells 210/ $\mu$ l, mean HIV RNA  $4.7 \pm 0.6 \log_{10}$  in the study arm and  $4.8 \pm 0.5 \log_{10}$  copies in the control arm), were enrolled in the study. Inclusion criterion was an HIV RNA >10,000 copies/ml, despite treatment with at least 6 months of nucleoside analogues and at least 3 months with a protease inhibitor. Forty-three patients were randomly assigned to the control arm. Sixty-five patients were randomly assigned to the study arm in which treatment changes were based on genotypic resistance assays. Our patients were heavily pretreated. They were exposed to a mean of 3.9 nucleoside analogues for a mean of 3.5 years and to a mean of 1.8 protease inhibitors for a mean of 11.6 months. This level of exposure was similar in both arms. The two arms were also comparable in terms of risk factor, age, gender, and previous treatment. At month 3, the mean drop in HIV RNA was  $1.04 \pm 0.14 \log_{10}$  in the study group versus  $0.46 \pm 0.17 \log_{10}$  in the control group (mean difference 0.58 log; 95% confidence interval [CI] 0.14–1.02;  $p = .01$ ). This difference persisted at month 6 with a drop of  $1.15 \pm 0.15 \log_{10}$  copies/ml, and  $0.67 \pm 0.19 \log_{10}$  copies/ml, in the study and the control arms, respectively. Difference in the drop in viral load combined at 3 months and 6 months was significant ( $p = .015$ ). In the genotyping arm, the reduction in viral load was maintained throughout the 12 months of study with a mean drop in HIV RNA of  $1.15 \log_{10}$ . In control arm, during the second 6 months open label genotyping phase, there was an additional drop to  $0.98 \log_{10}$ .

In the genotype arm, the percentage of patients with an HIV RNA level lower than level of detection remained stable around 30% throughout the 12 months of follow-up. In the control arm, the proportion of patients with an HIV RNA level below the limit of detection rose from 14% at month 6 to 30.5% at month 12.

**RESULTS**

Use of resources was retrieved for a total number of 107 patients, 43 patients in the standard of care group

and 64 in the genotype-guided treatment group. The mean number of hospital admissions was 2 in both groups (standard deviation  $\pm 4$ ). The mean (standard deviation) number of antiretroviral drugs per patient was 2.88 ( $\pm 1.19$ ) in the standard of care arm and 2.6 ( $\pm 1.33$ ) in the arm with DRG. The medians were, respectively, 3.2 and 3.1.

The mean costs of tests, hospitalization, and treatments are presented Table 1. There is no statistically significant difference between arms in either the total cost or the total drug cost.

The major cost driver was medication-related expenses, which represented 55% of total costs. Hospitalizations accounted for 20% of total costs. The total cost for DRG represented 10% of the total cost of the treatment. The two-tailed *t*-test found a nearly significant difference in total drug costs for patients with DRG ( $p = .07$ ).

**DISCUSSION**

Our cost analysis of this open-label, randomized trial comparing the therapy of HIV-infected adults with and without the benefit of DRG found that the additional cost of DRG may be offset by the reduction of drug costs and improvement in therapeutic efficacy. Effectively, viral load reduction and percentage of patients with an HIV RNA level lower than the detection limit were better in

**TABLE 1.** Mean costs of tests, hospitalization, and treatments, with (standard deviation in parentheses), and [Confidence Intervals in braces], for patients included in the VIRADAPT study. Costs are in 1999 U.S. dollars, computed over the duration of a 1-year follow-up

	Standard of care <i>N</i> = 43	Drug-resistance genotyping <i>N</i> = 64
Drug-resistance genotyping	1,360 (454) [1,249–1,471]	1,719 (672) [1,554–1,884]
Drug dosage	287 (790) [213–362]	257 (240) [198–316]
Ambulatory (clinic visits + tests)	2,042 (4,738) [1,807–2,277]	2,158 (1,563) [1,775–2,541]
Total drugs ( $p = .07$ )	13,221 [11,453–14,989]	11,053 [9,455–12,652]
Nucleoside reverse transcriptase inhibitors	4,782 [4,122–5,442]	4,028 [3,442–4,613]
Protease inhibitors	7,583 [6,351–8,815]	6,112 [5,088–7,132]
Nonnucleoside reverse transcriptase inhibitors	856 [517–1194]	913 [662–1,165]
Hospitalizations	3,502 (7,382) [1,302–5,702]	3,297 (7,692) [1,413–5,381]
Total yearly cost ( $p = .35$ )	20,412 (10,129) [17,386–23,438]	18,484 (9,652) [16,119–20,849]
Total yearly cost excluding genotyping done after interim analysis	19,052	

the study group than in the control group (3,4). The mean two hospitalizations per patient in 1 year reflects that our patient population was highly drug-experienced and at an advanced stage of HIV disease. The major cost driver was drugs, which represent 55% of total costs. Among drugs, the most costly group were protease inhibitors (over 56% of total drug cost). In the genotype-guided treatment arm, treatment was more diverse, with less use of protease inhibitors (3). MegaHAART or gigaHAART with a high number of drugs, sometimes used as salvage regimen, are of relative poor efficacy, associated with a high number of side effects and toxicities, and a higher cost (10).

No statistically or economically significant difference was found in either total costs or total drug costs, which can be due in part to the magnitude of the standard deviation of costs. When the total mean costs in each group were considered, the additional cost of DRG appeared to be offset by the savings obtained by lower drug costs.

The total yearly cost of management for HIV-infected patients in France was found to be roughly \$19,000 in 1998. This cost is lower than the yearly \$22,000 to \$30,000 range found for the care of HIV-infected patients in the United States (11,12) due in part to the fact that this cost was computed before the beginning of triple combination therapy, which resulted in fewer hospitalizations and that health care spending has been, in relative terms, 30% lower in France than in the United States during the years 1990 to 1999 (OECD Health data). The cost of drugs and ambulatory care was similar in the French and in the U.S. studies. The French study was conducted in 1997 to 1998 at the time when protease inhibitors became available. The additional cost of DRG did not increase the total costs of care because the total costs were not different between groups despite the inclusion of the genotyping costs in that arm. Subtracting the costs of genotyping performed in the standard of care arm after the interim analysis did not substantially affect the results. The fact that patients in the standard of care arm benefited from genotyping after the interim analysis (6 months), and adaptation of their drugs treatments may underestimate the actual difference in costs.

If the cost of genotyping assays were lower (\$300 for example), the cost difference between genotyping and no genotyping might be pushed toward significance.

This trend in the reduction of drug costs and drug use is possibly of great interest for future trials involving genotype-resistance testing. The high cost of antiretroviral drugs could become a burden for health care budgets, and DRG may offer a possibility to better adapt treatments and reduce drug costs. The findings of this initial trial need to be confirmed in larger patient populations.

Our cost analysis presented several limitations. First, the short duration of the follow-up may have underestimated the benefit of viral load reduction and potential savings in nonantiretroviral drug use and HIV-related illnesses. Second, as in most clinical trials, the inclusion of patients in a protocol and the protocol-related information given to physicians may have influenced the management and the costs of patients. Excluding protocol-driven costs does not properly address this issue because other costs could be affected by the better management resulting from information not routinely available to the participating physicians. This does not affect the comparison between arms but limits the external validity of cost results. Third, standard AIDS therapy has changed since the initiation of the VIRADAPT study and guidelines for drug therapy evolve rapidly. This change in standard of care may have influenced the differences seen between the two groups. In our study, cost saving linked to use of resistance testing was mainly due to reduced use of protease inhibitors in the genotyping arm. Generalized use of protease-sparing regimens could blunt the drug-associated cost saving found in the genotyping arm. The cost-effectiveness of genotypic resistance testing could than only rely on better drug efficacy. Fourth, our small sample size does not allow us to draw further conclusions on the possible cost savings obtained from the reduction in drug use; larger databases should be built to examine more precisely the costs for the subgroups of patients treated with nonnucleoside reverse transcriptase inhibitors or protease inhibitors. The cost-effectiveness of genotypic resistance testing we observed could vary depending the population studied. Although the prevalence of drug-resistant HIV in newly infected patients is increasing (13), this prevalence varies widely according to the region considered and definition used for drug resistance. In situations in which the probability of finding a drug-resistant virus is actually quite low, the use of resistance testing could prove to be noncost-effective. The threshold prevalence of drug resistant HIV in antiretroviral-naïve patients rendering resistance testing cost effective has yet to be defined. The same is true for first line failure. On the contrary, genotype resistance testing in broadly drug-resistant HIV-infected patients could help to define "drug holidays" that are possibly associated with drug resensitization and better outcome (14).

This is, however, the first report of the actual costs of resources used by patients benefiting from DRG compared with standard of care. At the end of the study, patients who benefited from genotyping had not expended more health care resources than control patients and had a reduced viral load, which could possibly result

in better long-term outcome. Therefore, DRG may prove an outcome-maximizing strategy. Further studies are needed to confirm the trend in reduction of drug costs found in the genotyping arm.

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