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The Costs of Full Suppression of Plasma HIV RNA in Highly Antiretroviral-Experienced Patients

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Abstract

The aim of antiretroviral treatment is long-term suppression of plasma HIV RNA < 50 copies/ml. The DUET, BENCHMRK, and MOTIVATE trials evaluated the efficacy of etravirine, raltegravir, and maraviroc, respectively, versus placebo, each given with an optimized background regimen of nucleoside reverse transcriptase inhibitors, protease inhibitors, and/or enfuvirtide. These trials were conducted in treatment-experienced patients, where complex and expensive drug combinations are typically required.
Rates of plasma HIV RNA suppression < 50 copies in different treatment groups by week 48 were combined with drug costs to calculate the costs per patient with undetectable viremia. These results were compared with two recent pilot studies of novel triple combination treatment. The average annual per patient cost of antiretrovirals for the active plus optimized background regimen arm versus placebo plus optimized background regimen was US$ 47,324 vs. 38,267 in the DUET Trials, US$ 45,484 vs. 34,585 in BENCHMRK, and US$ 46,633 vs. 36,404 in MOTIVATE. In the three trials, the highest treatment costs were from nucleoside analogs (29-30% of total costs) and enfuvirtide (22-25% of total costs). In the two pilot studies, the total cost of raltegravir/etravirine/darunavir/ritonavir was US$ 32,208, while use of raltegravir/etravirine/maraviroc cost US$ 30,952 per patient-year. The mean cost per patient with HIV RNA < 50 copies/ml at week 48 ranged from US$ 62,268 in the etravirine plus optimized background regimen arm of DUET, to US$ 214,141 in the placebo arm of MOTIVATE. In the pilot studies, the cost per patient with HIV RNA < 50 copies/ml was US$ 33,204 for raltegravir/etravirine/darunavir/ritonavir and US$ 33,603 for raltegravir/etravirine/maraviroc.
In summary, when treating highly treatment-experienced patients, cost-savings could be made by using combinations of newer antiretrovirals in preference to recycled nucleoside analogs and enfuvirtide.
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Key words

HIV. Antiretroviral. Health economics. Nucleoside analog. Protease inhibitor. Nonnucleoside. CCR5 antagonist. Fusion inhibitor. Integrase inhibitor.

Introduction

There is increasing pressure to lower the cost of treating people with HIV infection for three main reasons. Firstly, new treatment guidelines recommend earlier initiation of treatment, with CD4 counts of 350-500 cells/μl[1]; this increases the number of patients eligible for treatment. Secondly, with antiretroviral treatment improving survival, but infection rates remaining constant, an increasing number of patients are responding to and staying on antiretroviral treatment every year. Thirdly, with economic pressures there is little additional funding to cover the increasing number of patients requiring treatment. Strategies to lower costs of HIV treatment and care are clearly necessary.

There is substantial cross-resistance for drugs within the nucleoside analog, nonnucleoside, and protease inhibitor drug classes[2]. Emergence of HIV

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drug resistance can lead to rebound in HIV RNA levels during treatment, which in turn can lead to progressive losses in CD4 counts and eventual clinical disease progression to AIDS or death[3]. More intensive treatments may be needed to sustain HIV RNA suppression for patients with multidrug resistance.

There is a range of new drugs available for highly treatment-experienced patients, which could suppress HIV RNA to < 50 copies/ml if used in combination. The nonnucleoside etravirine was evaluated in the DUET trials[4-6], the integrase inhibitor raltegravir was evaluated in the BENCHMRK trials[7-9] and the CCR5 antagonist maraviroc was evaluated in the MOTIVATE trials[10-12]. These new antiretroviral drugs showed higher levels of efficacy when used in combination with either the protease inhibitor darunavir/ritonavir or the fusion inhibitor enfuvirtide. However, the cost of complex, multidrug combinations could limit their affordability.

Full HIV RNA suppression to < 50 copies/ml is an accepted efficacy outcome for clinical trials of antiretroviral treatment[13] and is used routinely in clinical practice for making decisions on whether to continue or modify treatment[1]. Patients with HIV RNA levels > 50 copies/ml on treatment have a higher risk of drug resistance and will eventually need to use new treatments with combinations of novel antiretrovirals to achieve full HIV RNA suppression. Other studies have evaluated the value of antiretroviral treatment as measured by the cost per patient with full HIV RNA suppression[14-16]. HIV RNA suppression < 50 copies/ml was therefore used as the basis for the economic calculations in this analysis.

Table 1. Baseline characteristics: DUET, BENCHMRK, and MOTIVATE trials

Characteristic	DUET	BENCHMRK	MOTIVATE*
Number (n)	1,203	699	635
% Male	90%	88%	89%
% Caucasian	70%	69%	84%
Median age (years)	46	46	46
Median CD4 count (cells/µl)	105	121	169
Median plasma HIV RNA (log	4.8	4.8	4.9
Use of enfuvirtide	46%	38%	42%
Use of darunavir/r	100%	41%	0%
PSS† = 0	17%	17%	13%
PSS = 1	38%	31%	23%
PSS = 2	27%	30%	26%
PSS = 3 or more	18%	19%	37%
Serious adverse events‡	20/23%	18/19%	18/18%

PSS: phenotypic sensitivity score.
*Only the twice daily maraviroc and placebo arms were included in the analysis.
†PSS score is of the OBR. Data on PSS at baseline were missing from 3% of patients in the BENCHMRK trials.
‡Serious clinical adverse events shown first for the investigational arm, and then for the placebo arm of each trial.

Design of the DUET, BENCHMRK, and MOTIVATE trials

DUET 1 and 2 were multicentre, randomized, controlled, double-blinded phase III clinical trials, which recruited HIV-1-infected subjects with documented genotypic evidence of resistance to currently available nonnucleoside reverse transcriptase inhibitors (NNRTI), at least three primary protease inhibitor mutations at screening, prior nucleoside reverse transcriptase inhibitor (NRTI) experience and screening HIV RNA levels > 5,000 copies/ml[4-6]. Patients were randomized to receive either etravirine or matching placebo treatment. Between screening and randomization, the NRTI and T-20 components of the background regimen were selected by the investigator, based on genotypic and phenotypic resistance testing. In addition, all patients received darunavir/ritonavir at the dosage of 600/100 mg twice daily.

The BENCHMRK[7-9] and the MOTIVATE trials[10-12] were also placebo controlled evaluations of a new antiretroviral drug, and were similar in design and baseline characteristics to the DUET trials (Table 1). In all three trials, background antiretrovirals were selected based on resistance testing before randomization.

In each trial, randomized treatment was for 48 weeks. The intent-to-treat population was used for analysis, including all randomized patients. The primary efficacy endpoint was HIV RNA suppression (measured either as log reductions from baseline or HIV RNA < 50 copies/ml). In each trial, the data were analyzed and reported by a standardized intent-to-treat, switch equals failure analysis. In the DUET trials, the efficacy data for patients fully susceptible to etravirine at baseline were used[5] because it would be normal clinical practice to test patients for resistance and to use etravirine in patients with full susceptibility. In the

Table 2. US costs of antiretrovirals per-patient year*

Class	Drug	Dose	Annual cost (US$)
NRTIs	Lamivudine	300 mg QD	4,384
	Emtricitabine	200 mg QD	4,431
	Zidovudine	300 mg BID	4,584
	Didanosine	400 mg QD	3,988
	Tenofovir	300 mg QD	7,822
	Stavudine	40 mg BID	4,447
	Abacavir	300 mg BID	5,271
NNRTIs	Etravirine	200 mg BID	8,884
Protease inhibitors	Ritonavir	100 mg QD†	624‡
	Atazanavir/r	300/100 mg QD	10,950 (11,574)
	Fosamprenavir/r	700/100 mg BID	8,318 (9,567)
	Indinavir/r	800/100 mg BID	3,724 (4,972)
	Saquinavir/r	1,000/100 mg BID	8,827 (10,075)
	Lopinavir/r	400/100 mg BID	8,541
	Nelfinavir	1,250 mg BID	8,085
	Tipranavir/r	500/100 mg BID	12,045 (14,542)
	Darunavir/r	600/100 mg BID	11,176 (12,425)
Entry inhibitor	Enfuvirtide	90 mg BID	26,089
Integrase inhibitor	Raltegravir	400 mg BID	10,899
CCR5 antagonist	Maraviroc	300 mg BID	11,169

QD: once daily; BID: twice daily; NRTIs: nucleoside reverse transcriptase inhibitors; NNRTIs: non-nucleoside reverse transcriptase inhibitors.
*Wholesale Acquisition Costs in the USA (Medspan Price Check PC, May 2010).
†The boosting dose of ritonavir is shown. For the protease inhibitors, the cost of drugs when boosted with ritonavir is shown in brackets.
‡Public payer price of ritonavir.

BENCHMRK trials, raltegravir was evaluated as a new class of antiretrovirals, with no preexisting resistance expected. In the MOTIVATE trials, patients were tested for viral tropism at screening and only the patients with CCR5 tropic virus (indicating sensitivity to maraviroc) were enrolled.

In addition, two pilot studies have been conducted, evaluating new triple combination treatments in highly treatment-experienced patients. A Spanish trial has evaluated the 24-week efficacy of raltegravir/etravirine/darunavir/r[17], while an Italian trial has evaluated raltegravir/etravirine/maraviroc[18].

Calculation of treatment costs

Data on the actual usage of antiretroviral treatments in the DUET, BENCHMRK, and MOTIVATE trials[4-12] were used to calculate the total annual cost of treatment for the different treatment arms. The annual costs of antiretrovirals are shown in table 2, and are based on the Wholesale Acquisition Costs in the USA (MedSpan Price Check PC, May 2010).

Patients were assumed to continue taking all treatments assigned at baseline for a full 52 weeks for this analysis. A very small number of patients received dideoxycytidine (ddC), which is no longer marketed. The cost of ddC was set to lamivudine, which is a similar nucleoside analog. The public payer price of ritonavir was used in these calculations; in the USA, ritonavir is significantly more expensive if prescribed privately.

In all three trials, there was use of genotypic resistance testing at screening to select the most appropriate background nucleoside analogs. In the MOTIVATE

trials, the published data on use of individual nucleoside analogs was compared with the DUET trials and was very similar. Given these similarities, the cost of nucleosides was assumed to be the same in the BENCHMRK trials as for the DUET trials.

In the DUET trials, all patients received the PI darunavir/ritonavir. Resistance testing was used to select the most appropriate protease inhibitor in the BENCHMRK and MOTIVATE trials. In the BENCHMRK trial, 41% of patients used darunavir/ritonavir; the remainder was assumed to be lopinavir/ritonavir (the most widely prescribed alternative protease inhibitor for treatment-experienced patients). In the MOTIVATE trials, published data on the use of different protease inhibitors was used to calculate costs. In each trial, the cost of enfuvirtide was calculated from the published percentage of patients using this fusion inhibitor.

The cost of using each class of antiretrovirals was compared between trials. In addition, the total cost of antiretrovirals was divided by the overall efficacy to calculate the mean cost for each patient with HIV RNA suppression < 50 copies/ml at week 48. These costs were compared in the investigational and placebo arms of each trial. The incremental cost-efficacy ratio (ICER) was calculated in each trial. This was the additional cost of treatment in the investigational versus placebo arm, divided by the improvement in efficacy for the investigational arm (Tables 3 A, B, C).

There is an additional cost component for maraviroc: testing for viral tropism. Maraviroc is only active against CCR5-tropic virus. Maraviroc needs to be used in combination with a test for viral tropism to identify patients with CCR5 tropic virus. In this analysis, we did not account for the additional costs of viral tropism testing because new genotype-based algorithms are being introduced, which could lower the costs of this testing technique.

Finally, the cost of using novel combinations of antiretrovirals was calculated for the two pilot studies of novel triple combination treatments in Spain and Italy[17,18]. The costs of these treatments and summary efficacy were compared with the most efficacious treatments used in the DUET, BENCHMRK, and MOTIVATE trials. In these trials, the highest efficacy was seen for patients who took the investigational drug with enfuvirtide, optimized protease inhibitors, and nucleoside analogs.

Treatment costs in trials conducted in antiretroviral-experienced patients

Table 1 shows the baseline characteristics of the patients enrolled in the DUET, MOTIVATE, and BENCHMRK trials. The trials were comparable in terms of baseline age, gender, race, $CD4^+$ cell counts, and HIV RNA levels.

The phenotypic sensitivity score (PSS) shows the number of drugs the patient is taking to which the HIV is susceptible. The percentage of patients with a PSS of the background of zero (i.e. no other active antiretrovirals) was similar between the three trials. The MOTIVATE trials included a higher percentage of patients with at least three active drugs used in the optimized background treatment. The percentage of patients using enfuvirtide was similar between the trials. However, there was a clear difference in use of darunavir between the trials, ranging from 100% in the DUET trials to 41% in the BENCHMRK trials and 0% in the MOTIVATE trials.

The two pilot studies of novel antiretrovirals also recruited patients with prior use of nucleoside analogs, nonnucleosides, and protease inhibitors[17,18].

Table 2 shows the unit costs of antiretrovirals per patient-year of treatment. The nucleoside analogs have the lowest unit costs (ranging from US$ 3,988 to 7,822 per patient-year of treatment), but patients often receive combinations of two or three of these drugs, which raises the overall costs. The nonnucleoside etravirine had a unit cost of US$ 8,884. This was lower than most ritonavir-boosted protease inhibitors, which cost between US$ 8,541 and 14,542 per patient-year. The unit costs of raltegravir and maraviroc (US$ 10,899 and 11,169, respectively) were far lower than the cost of the fusion inhibitor enfuvirtide, which was the most expensive antiretroviral at US$ 26,089 per patient-year.

Tables 3 A, 3 B, and 3 C show the mean annual cost of antiretroviral treatment in the investigational and placebo arms of the DUET, BENCHMRK, and MOTIVATE trials respectively. In all three trials, the costs of nucleoside analogs accounted for the highest percentage of overall treatment costs. For example, in the DUET trials, 30% of the cost of the etravirine plus optimized background arm was for nucleoside analogs; in the maraviroc plus optimized background arm of the MOTIVATE trials, this percentage was 29%. The cost of protease inhibitors ranged from US$ 10,562 per patient-year in the MOTIVATE trials to US$ 12,501 in the DUET trials. The cost of enfuvirtide reflected the percentage of patients receiving this drug, from US$ 9,914 in the BENCHMRK trials, where 38% of patients received it, to US$ 11,886 in the DUET trials, where 46% of patients received it. The cost of the new investigational drug was 19% of the total cost

Table 3. Annual per-patient costs of antiretroviral treatment and outcomes at week 48

A. DUET 1 and 2 trials of etravirine versus placebo (etravirine-sensitive patients)		
Costs (US$)/outcomes	**Etravirine + OBR**	**Placebo + OBR**
Total annual cost	47,324	38,267
Nucleoside analogs	14,053 (30%)	13,708 (36%)
Protease inhibitors	12,501 (26%)	12,379 (32%)
Enfuvirtide	11,886 (25%)	12,181 (32%)
Etravirine	8,884 (19%)	
HIV RNA < 50 copies/ml (%)	76%	42%
Cost per response	62,268	91,112
ICER	26,638	
B. BENCHMRK 1 and 2 trials of raltegravir versus placebo		
Costs (US$)/outcomes	**Raltegravir + OBR**	**Placebo + OBR**
Total annual cost	45,484	34,585
Nucleoside analogs	13,881(31%)	13,881 (40%)
Protease inhibitors	10,790 (24%)	10,790 (32%)
Enfuvirtide	9,914 (22%)	9,914 (29%)
Raltegravir	10,899 (24%)	
HIV RNA < 50 copies/ml (%)	62%	33%
Cost per response	73,361	104,803
ICER	37,582	
C. MOTIVATE 1 and 2 trials of maraviroc versus placebo		
Costs (US$)/outcomes	**Maraviroc + OBR**	**Placebo + OBR**
Total annual cost	46,633	36,404
Nucleoside analogs	13,756 (29%)	14,148 (39%)
Protease inhibitors	10,562 (23%)	10,897 (30%)
Enfuvirtide	11,146 (24%)	11,359 (31%)
Maraviroc	11,169 (24%)	
HIV RNA < 50 copies/ml (%)	46%	17%
Cost per response	101,376	214,141
ICER	38,513	

OBR: optimized background regimen; ICER: incremental cost-efficacy ratio.

of treatment for etravirine in the DUET trials, 24% of the total cost for raltegravir in the BENCHMRK trials, and 25% of the total cost for maraviroc in the MOTIVATE trials.

In all three trials, the cost per patient with HIV RNA < 50 copies/ml at week 48 was lower in the investigational arms compared with the control arms; the higher cost of the new antiretrovirals was more than offset

Table 4. Trials of novel triple combination treatments: summary efficacy and estimated costs

Combination	Plasma HIV RNA < 50 copies/m	Annual cost (US$)	Week
Spanish pilot study: RAL + ETR + DRV/r	97% (30/32)	32,208	24
Italian pilot study: RAL + ETR + MVC	92% (26/28)	30,952	24
DUET trial: NRTI + DRV/r + ENF + ETR	85% (75/88)	60,615	48
BENCHMRK trial: NRTI + DRV/r + ENF + RAL	89% (39/44)	62,555	48

RAL: raltegravir; ETR: etravirine; DRV/r ritonavir boosted darunavir; MVC: maraviroc; NRTI: nucleoside reverse transcriptase inhibitor; ENF: enfuvirtide.

by the improvements in efficacy seen (Tables 3 A, B, C). The ICER (the additional cost for each patient with HIV RNA < 50 copies/ml at week 48) was US$ 26,638 for etravirine in the DUET trials, US$ 37,582 for raltegravir in the BENCHMRK trials, and US$ 38,513 for maraviroc in the MOTIVATE trials.

Table 4 shows the mean cost of antiretrovirals in two recent pilot studies[17,18], as well as the costs and efficacy for the most intensive treatments used in the DUET and BENCHMRK trials (efficacy data on these subsets of patients have not been published for the MOTIVATE trial). In the Spanish pilot study, a combination of raltegravir, etravirine, and darunavir/ritonavir led to full HIV RNA suppression in 30/32 patients (97%) by week 24; this combination treatment would have a US cost of $ 32,208 per patient-year. In the Italian pilot study, another novel triple combination treatment (raltegravir, etravirine, maraviroc) showed efficacy of 92% (26/28 patients) at week 24, with a total cost of US$ 30,952 per patient-year. These two pilot studies used only new antiretrovirals, with no recycling of nucleoside analogs based on resistance testing, and no enfuvirtide. The costs of treatment were approximately 50% lower than in the most intensive combinations used in the DUET and BENCHMRK trials, which led to full HIV RNA suppression in 85-89% of patients by week 48. The higher costs of these treatments in DUET and BENCHMRK are caused mainly by the use of enfuvirtide and recycled nucleoside analogs.

Therapeutic implications based on value

In the DUET, BENCHMRK, and MOTIVATE trials, the new investigational drugs all showed significant efficacy benefits over the control arms. In each trial, the cost per patient with HIV RNA < 50 copies/ml at week 48 was lower in the investigational arm compared to the placebo arm. In all three trials, the cost of the investigational drugs (etravirine, raltegravir, or maraviroc) was a relatively small percentage of the total cost of treatment. The additional cost per patient with HIV RNA suppressed < 50 copies/ml using either etravirine, raltegravir, or maraviroc was similar between the trials.

The highest value drugs are those which provide the greatest improvements in HIV RNA suppression rates for the lowest cost. Using combinations of newer antiretrovirals, with the lowest risk of underlying drug resistance, should maximize value. In the two pilot studies, using combinations of three newer antiretrovirals led to HIV RNA suppression rates higher than those seen in the DUET, BENCHMRK, or MOTIVATE trials, and at a lower total cost.

The strengths of this analysis include the standardized efficacy endpoint used in the DUET, BENCHMRK, and MOTIVATE trials: HIV RNA suppression at week 48. All the trials were analyzed using the 50 copy endpoint for HIV RNA, from testing using the Roche Amplicor ultrasensitive PCR assay. All three trials were placebo-controlled and used a similar type of optimized background treatment, including nucleoside analogs, protease inhibitors, and optional enfuvirtide. The pilot studies only had efficacy data to week 24, but HIV RNA suppression is normally sustained to week 48 in adherent patients who show full suppression by week 24.

This analysis has some limitations. Firstly, several antiretrovirals will soon receive generic approval, which could lower their costs substantially. For example, the nucleoside analog lamivudine and the protease inhibitor saquinavir will lose patent protection by 2011; zidovudine is already off patent in several countries. These changes may affect the affordability of drugs for treatment-naive patients, but most of the drugs used for highly experienced patients are still several years from

patent expiry. Second, there is no data available from the trials about the drugs taken after discontinuation of trial medication. The costs of these salvage drugs could affect the economic calculations.

The cost of adverse events was not accounted for in the economic analysis. Fortunately, there was not an increase in the percentage of patients experiencing adverse events in the investigational versus placebo arms of any of the three trials (summary results were shown in Table 1). There were a few exceptions: the risk of Grade 3 or 4 rash was higher in the etravirine arm of the DUET trials (2.2%) versus the placebo arm (0%)[4]. Also, in the BENCHMRK trials there was a trend for more cancers in the raltegravir arm (3.5%) versus the placebo arm (1.7%)[7]. By contrast, there was a trend for fewer AIDS-defining events and deaths in the etravirine arms of the DUET trials compared with the placebo arms, which can also directly affect costs. In the DUET trials, the total number of days spent in hospital up to week 48 was 1,702 in the etravirine arm versus 2,747 in the placebo arm. This lower time in hospital was estimated to have saved between US$ 1.4 and 2.5 million in healthcare costs for the etravirine arm versus the placebo arm[19].

There is evidence from the TORO trials that nucleoside analogs provide little efficacy benefit for highly treatment-experienced patients, even when they are selected based on resistance testing[20]. The two pilot studies using novel triple combinations without nucleoside analogs are showing encouraging short-term efficacy, but larger, longer-term trials are needed. The ACTG 5241 "OPTIONS" trial is evaluating this approach. In this trial, more than 350 highly treatment-experienced patients are randomized to receive two or more newer antiretrovirals, either with or without additional nucleoside analogs[21].

There may be other measures of the long-term efficacy of treatment that have not been included in this analysis. For example, virologic failure may lead to different rates of development of drug resistance. In the DUET trials, patients with virologic failure in the etravirine arm were less likely to show resistance to protease inhibitors than those in the placebo arm[22]. Also, there may be different rises in CD4 counts between treatments. Across clinical trials of maraviroc, rises in CD4 counts have been greater than in the active control arms[23].

Healthcare agencies require evidence of value for treatments using the measure of costs per quality adjusted life-year (QALY) saved. These analyses have also been conducted for etravirine[24], raltegravir[25,26], and maraviroc[27]. However, these analyses can be hard for clinicians to interpret, given the complexities of Markov modeling and the assumptions made about long-term life expectancy and other outcomes after trials are completed. Full suppression of HIV RNA is a widely accepted marker of the success of antiretroviral treatment. It may be easier for decision makers to assess value using disease-specific outcome measures, such as suppression of HIV RNA, as a simple guide to support formal judgments based on cost per QALY.

In summary, the cost per patient with plasma HIV RNA suppression < 50 copies/ml was assessed across the DUET, BENCHMRK, and MOTIVATE trials. Etravirine use in the DUET trials yielded the lowest average cost per patient with HIV RNA < 50 copies/ml at week 48 and the lowest ICER; however, in all three trials, the cost per patient with HIV RNA < 50 copies/ml at week 48 was lower in the investigational arms compared with the control arms, implying that the higher cost of the new antiretrovirals was more than offset by the improvements in efficacy seen. These basic economic analyses of cost versus HIV RNA suppression rates can be used as a guide to selecting combinations of antiretrovirals that could maximize HIV RNA suppression rates while minimizing treatment costs. The results suggest that the highest value is from the use of new drugs in combination, while minimizing the use of recycled nucleoside analogs or enfuvirtide.

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