

Predicting HIV Care Costs Using CD4 Counts From Clinical Trials

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Objective: To predict the effects of a new antiretroviral agent on the costs of care in a US HIV care setting.

Methods: Recent data on costs of patient care by CD4 count from 2 US cohorts (the HIV Research Network cohort and patients receiving primary care at the University of Alabama at Birmingham HIV clinic) were combined with CD4 count data from the POWER trials of the protease inhibitor darunavir. Patients in the POWER trials received either darunavir plus low-dose ritonavir (darunavir/r) or selected control protease inhibitors. The effects of rising CD4 counts with darunavir/r 600/100 mg twice daily on healthcare costs were predicted by using the US cohort data and published US antiretroviral drug prices.

Results: In the POWER trials, the overall cost of antiretroviral treatment including darunavir/r was \$427 (1.4%) higher than that of combination treatment including control protease inhibitors. However, this increase may be offset by lower predicted costs of HIV care, leading to predicted net savings in overall costs of HIV treatment and care of \$3613 per person-year based on data from the HIV Research Network cohort and \$2836 per person-year based on data from the University of Alabama cohort. The prediction of cost savings is limited to the 12-month duration of the trial.

Conclusion: By raising the CD4 count, new antiretrovirals could lower healthcare costs for HIV-infected people. This type of analysis could be used for other antiretrovirals, for a short-term assessment of overall budget impact.

(Am J Manag Care. 2007;13:524-528)

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Patients with persistently low CD4 counts on antiretroviral treatment have a higher risk of progression to AIDS and related death.^{1,2} The introduction of highly active antiretroviral treatment (HAART), which raised CD4 counts, led to reductions in costs of patient care.^{3,4} Costs of patient care in the United States by CD4 count recently were analyzed in the HIV Research Network (HIV RN) cohort⁵ and the University of Alabama cohort.⁶

For treatment-naïve patients, a range of combination treatments are available, which can lead to a high proportion of patients achieving undetectable HIV RNA levels, followed by long-term rises in CD4 counts.^{7,8} However, the proportion of treatment-experienced patients who respond to treatment is limited by drug resistance. Treatment-experienced patients take a wide range of complex combinations of antiretroviral drugs.⁸

This analysis was conducted to predict the effects of a new antiretroviral agent, darunavir, on the costs of care in a US HIV care setting. Darunavir is an HIV protease inhibitor with activity against protease inhibitor-resistant HIV.⁹ The costs of antiretroviral treatment from the POWER trials, where patients were treated either with darunavir plus low-dose ritonavir (darunavir/r) or selected control protease inhibitors, were compared with costs of patient care using cost data from the 2 US cohort studies.

METHODS

The costs of patient care from 2 US cohorts were combined with antiretroviral costs and CD4 count data from the POWER trials. The effects of rising CD4 counts with darunavir/r treatment on healthcare costs were predicted using the US cohort data and published US antiretroviral drug prices.

During 2003, 635 adult patients (age >18 years) who were in longitudinal HIV primary care at one of 14 HIV RN sites participated in face-to-face interviews. Comprehensive data were obtained regarding all medications used (prescription and nonprescription), as well as inpatient, outpatient, and emergency department utilization. Computation of costs was based on nonantiretroviral medications (Red Book average wholesale price—15%), inpatient days, outpatient visits, and emergency department utilization (HIV Cost & Services Utilization Study costs).¹⁰

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All encounters (except emergency department visits) of University of Alabama at Birmingham HIV clinic patients with the University of Alabama at Birmingham hospital system from March 1, 2000, to March 1, 2001, were analyzed. Medication expenditures were determined on the basis of 2001 average wholesale prices. Hospitalization expenditures were determined on the basis of 2001 Medicare diagnostic-related group reimbursement rates. Clinic expenditures were determined on the basis of 2001 Medicare current procedural terminology reimbursement rates.

Costs from both cohorts were inflation adjusted to 2005 values by using standard consumer price index assumptions.

POWER Trials: CD4 and Cost Data

The POWER 1 and 2 trials recruited patients with >1000 copies of HIV RNA per milliliter; prior exposure to nucleoside reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors, and protease inhibitors; and at least 1 primary protease inhibitor mutation.¹¹ Patients were given either darunavir/r or investigator-selected control protease inhibitors.^{9,11,12} In addition, all patients were given optimized background antiretrovirals: nucleoside analogues and in some cases the fusion inhibitor enfuvirtide (T-20).

Of the 4 dosages of darunavir/r studied, the 600/100 mg twice-daily dosage showed the strongest efficacy and was selected for further development. Therefore, data from the darunavir/r 600/100 mg twice daily ($n = 131$) and control protease inhibitor ($n = 124$) arms of the POWER trials were used in this analysis. The baseline mean HIV RNA and median CD4 counts were 4.6 \log_{10} copies per milliliter and 153 cells per microliter, respectively, for the darunavir/r group, versus 4.5 \log_{10} copies per milliliter and 163 cells per microliter, respectively, for the control protease inhibitor group. Darunavir/r 600/100 mg twice daily led to a rise in CD4 count of 102 cells and to 45.5% of patients having fewer than 50 copies of HIV RNA per milliliter at Week 48, compared with a rise in CD4 count of 19 cells and 10% of patients having fewer than 50 copies of HIV RNA per milliliter at Week 48 in the control protease inhibitor arm. There was no overall difference in the incidence or severity of adverse events by treatment arm.

In the POWER trials, the proportion of patients with CD4 counts in the categories used in the HIV RN and University of Alabama cohorts was assessed by treatment arm for patient visits from baseline to Week 48 (Table). The cost of antiretrovirals in the POWER trials was calculated using the most recent US prices (March 2006, Medi-Span, Indianapolis, Ind). For darunavir, the list price at launch in June 2006 was used. A weighted average of the antiretroviral treatment use

by arm was used to calculate mean annual per patient costs of antiretrovirals. For this analysis, patients were assumed to continue taking all treatments assigned at baseline for a full 52 weeks. The cost of ritonavir 100 mg daily was increased from US \$624 per patient-year to US \$3128 per patient-year in late 2003. However, public payers in the United States were not affected by this price increase. Therefore, the original cost of ritonavir 100 mg daily (US \$624 per patient-year) was retained for this analysis.

The CD4 data from the POWER trials were combined with the antiretroviral cost data, plus the estimates of costs of patient care by CD4 category from the 2 US cohorts. This analysis was used to calculate the predicted costs of antiretroviral treatment and patient care associated with the CD4 count distribution at Week 48 in the darunavir/r and control protease inhibitor arms of the POWER trials. In the HIV RN cohort classification of CD4 counts, the CD4 200-500 and >500 categories were used. However in the POWER trials, fewer than 1% of patients had CD4 counts above 500, so the categories of CD4 200-500 and >500 were merged into one category of CD4 >200.

A sensitivity analysis was conducted, assuming that the control protease inhibitor was lopinavir/ritonavir, which is a standard treatment for this population.⁸ This analysis produced very similar results to the main analysis (data not shown).

RESULTS

Overall costs of patient care were higher for the HIV RN cohort than for the University of Alabama cohort. In both cohorts, the majority of patient care cost was from inpatient hospitalization or nonantiretroviral medications, particularly in the lowest CD4 categories. For the HIV RN cohort, mean annual costs of patient care were \$44 311, \$22 441, \$15 690, and \$11 090 for the CD4 categories of <50, 50-200, 200-500 and >500 cells per microliter, respectively. For the University of Alabama cohort, the mean costs were \$30 421, \$14 219, \$7510, and \$5305 for the CD4 categories of <50, 50-200, 200-350 and >350 cells per microliter, respectively.

The POWER trial patients had more advanced HIV disease than those in the cohorts, with lower baseline CD4 counts and higher HIV RNA levels.^{5,6,11} However, there was significant overlap between the cohorts and the trial patients in terms of CD4 count categories at baseline.

The total cost of antiretroviral treatment for the darunavir/r arm, \$31 252 per person-year, was \$427 (1.4%) per person-year higher than the total cost in the control protease inhibitor arm, which was \$30 825 per person-year. In the control protease inhibitor arm, the total annual per person

■ TRENDS FROM THE FIELD ■

■ **Table.** Changes in CD4 Counts From Week 0 Through Week 48 in the POWER 1 and 2 Trials

Treatment Arm	CD4 Cells per Microliter, %			
	0-49	50-199	200-349	350+
DRV/r 600/100 mg twice daily				
Week 0	22.1	45.1	19.1	13.7
Week 8	6.9	39.7	30.5	22.9
Week 16	8.4	39.7	25.1	26.7
Week 24	6.9	36.6	32.1	24.4
Week 48	7.2	36.3	29.1	27.3
Control PI				
Week 0	24.2	33.8	19.4	13.7
Week 8	22.6	26.5	22.6	28.2
Week 16	20.9	34.3	20.9	23.8
Week 24	23.4	28.1	21.8	26.6
Week 48	23.3	27.4	27.5	21.7

DRV/r indicates darunavir plus low-dose ritonavir; PI, protease inhibitor.

treatment cost was comprised of 32% protease inhibitors, 37% nucleoside analogues, and 31% T-20. The darunavir/r arm involved a higher cost of protease inhibitors (\$749 per person-year more than the cost in the control arm), with the combined costs of nucleoside analogues and T-20 similar to those in the control arm.

The change in CD4 counts between baseline and Week 48 in the POWER trials is shown in the Table. In the darunavir/r arm, the proportion of patients whose CD4 counts were higher than 50 cells per microliter rose from 78% at baseline to 93% at Week 48, whereas this percentage was 76% at baseline and 77% at Week 48 in the control protease inhibitor arm. A consistent benefit was shown for darunavir/r over the control protease inhibitor, for both patients using enfuvirtide and those not using enfuvirtide.

For the HIV RN cohort, the CD4 changes at Week 48 were predicted to lower annual costs of patient care to \$20 125 per patient-year for the darunavir/r arm versus \$24 165 for the control protease inhibitor arm, a saving of \$4040 per patient year (Figure, panel A). Given that darunavir/r treatment cost a mean \$427 extra per patient, the net predicted saving in overall costs was \$3613 per person treated with darunavir/r-based HAART compared with control protease inhibitor-based HAART. Similar findings were seen with analysis of the University of Alabama cohort. For this cohort, the mean cost of patient care was calculated as \$10 910 for the darunavir/r arm versus \$14 173 for the control protease inhibitor arm, a saving of \$3263 per patient-year

(Figure, panel B). Adjusting for the additional \$427 cost of darunavir/r, the net saving in overall costs would be \$2836 per patient treated with darunavir/r versus a control protease inhibitor.

DISCUSSION

In the POWER trials, the overall cost of antiretroviral treatment including darunavir/r was \$427 (1.4%) higher than that of combination treatment including control protease inhibitors. However, this increase in antiretroviral drug cost may be offset by lower predicted costs of HIV care, leading to a predicted net saving in overall costs of HIV treatment and care of \$3613 per person-year based on data from the HIV RN cohort and \$2836 per person-year based on data from the University of Alabama cohort.

This analysis is based on data from antiretroviral-experienced patients, in whom darunavir/r treatment showed a significant efficacy benefit over alternative protease inhibitors. Clinical trials are under way to evaluate darunavir/r compared with other protease inhibitors in less experienced or treatment-naïve patients, and it is currently unknown whether efficacy benefits also will be seen in these populations. Patients in the POWER trials had relatively low CD4 counts at baseline. For populations with higher overall baseline CD4 levels, the same efficacy benefits may not be seen. In addition, the analysis does not take into account second-line treatments taken after initial failure of the randomized treatment. The

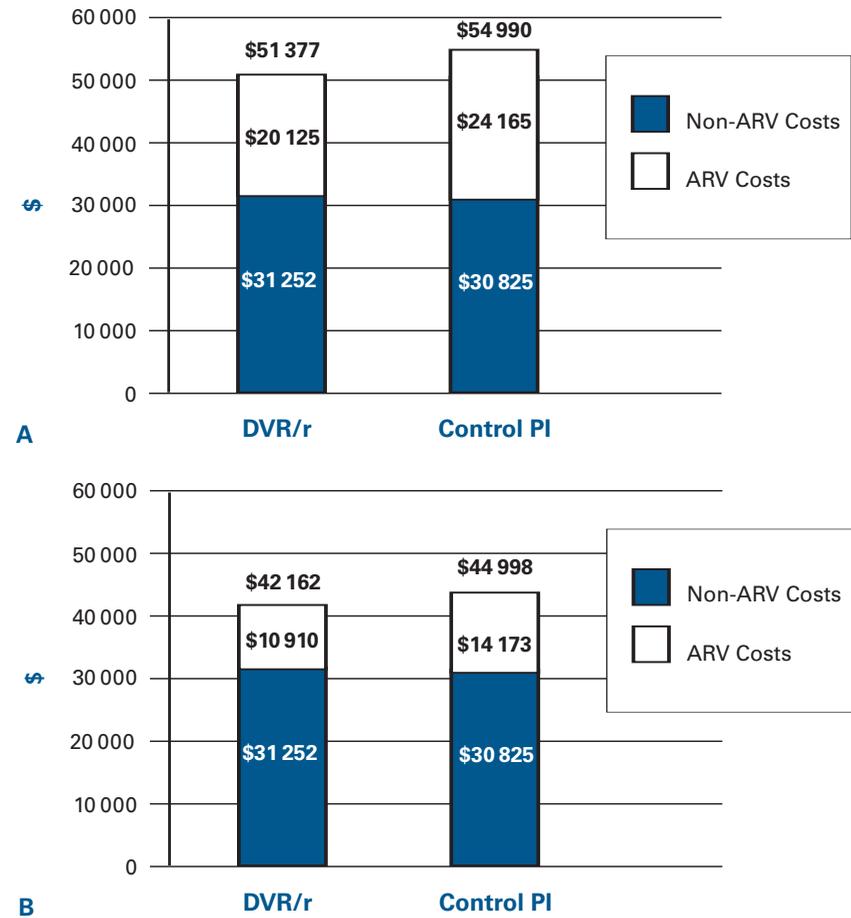
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rate of virologic failure was higher in the control protease inhibitor arm than in the darunavir/r arm. Virologic failure is a persistently detectable HIV RNA level despite good adherence to antiretroviral treatment. Treatments that lead to higher rates of resistance development at treatment failure may compromise future treatment options.^{13,14} Treatment-experienced patients with virologic failure may need more complex and expensive salvage options over the longer term, potentially involving more use of enfuvirtide, which could increase costs for the control protease inhibitor arm.

The prediction of cost savings is limited to the 12-month duration of the trial during which information on CD4 counts was available. Longer-term follow-up is needed to make predictions of subsequent benefits, and this analysis could be repeated once these results are available. However, the proportion of patients with CD4 counts above the most expensive category of <50 cells per microliter rose within 8 weeks of treatment initiation and remained stable in both treatment arms from Weeks 8 to 48 of the trial (Table). Another limitation of this analysis is that the data on costs of patient care and treatment efficacy were combined from different sources. New clinical trials of darunavir are under way, with integrated analysis of healthcare utilization and clinical efficacy during randomized treatment.

Other treatments may have benefits in terms of safety rather than efficacy. These differences are normally independent of treatment effects on CD4 count and would need to be calculated separately. For example, the nucleoside analogue tenofovir showed efficacy similar to that of stavudine in a large randomized trial, in combination with 3TC (lamivudine) and efavirenz.¹⁵ However tenofovir-based HAART led to lower rates of lipodystrophy, which could itself lower patient care costs. In the POWER trials, there were no clear differences between the treatment arms in terms of laboratory or clinical adverse events; these Phase 2 safety results need to be confirmed in larger, long-term clinical trials.

■ **Figure.** Total Predicted Costs for Antiretroviral Treatment and Patient Care, Based on the HIV Research Network Cohort (A) and the University of Alabama Cohort (B)



ARV indicates antiretroviral; DVR/r, darunavir plus low-dose ritonavir; PI, protease inhibitor.

In summary, the analysis suggests that the efficacy benefits of darunavir/r versus control protease inhibitor in the POWER trials may lead to reductions in overall US healthcare budgets for the population of highly treatment-experienced patients evaluated. However, this is a short-term prediction based on results from a 12-month randomized trial, and it is unknown whether these benefits would be seen during longer-term follow-up, or for patient populations with higher baseline CD4 counts, a wider range of other treatment options, or both. This method could be applied to other clinical trials of new antiretrovirals to predict their effects on patient care costs compared with increases in antiretroviral costs.

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Author Disclosure: Dr Hill receives grant funding and consultant fees from Tibotec BVBA. Dr Gebo reports receiving grant funding from Tibotec.

Take-away Points

By raising the CD4 count, new antiretrovirals could lower healthcare costs for HIV-infected people.

- Effects of rising CD4 counts with the protease inhibitor darunavir plus low-dose ritonavir (darunavir/r) on healthcare costs in a US HIV care setting were predicted by using US cohort data, published US antiretroviral drug prices, and CD4 count data from the POWER trials of darunavir/r.
- The higher cost of darunavir/r was offset by lower predicted costs of HIV care over the 12-month duration of the trial.
- This type of analysis could be used for other antiretrovirals, for a short-term assessment of overall budget impact.

Author Information: Concept and design (AH); acquisition of data (AH, KG); analysis and interpretation of data (AH); drafting of manuscript (AH); critical revision of the manuscript for important intellectual content (AH, KG); statistical analysis (AH); obtaining funding (AH, KG); administrative, technical, or logistic support (AH).

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