

# Combivir vs. Generic Zidovudine and Epivir: An Economic Modeling Study

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## Abstract

**Background:** Generic zidovudine will become available in the near future. A cost-effectiveness analysis was performed comparing generic zidovudine plus Epivir (ZDV/3TC) to Combivir, a fixed-dose combination of ZDV and 3TC, in antiretroviral treatment naïve patients on a protease regimen. Effectiveness was measured in quality-adjusted life years (QALYs).

**Methods:** A previously validated Markov model was updated and populated with CD4 and viral load (VL) data reflecting 48-week adherence differences reported in the literature for Combivir vs. ZDV/3TC, combined with data on the effects of adherence on VL. The base case mean adherence difference was 5% favoring Combivir. In sensitivity analyses, the effect of Combivir on VL suppression after 1 year was varied between 4% and 20% superiority. The effects of differences in daily drug costs were also tested. Utility values were based on a published study of HIV patients in the HAART era.

**Results:** The base model estimated mean survival to be 0.33 years longer with Combivir than with ZDV/3TC. Those on Combivir spent a median of 4.3 years on their initial regimen, versus 3.5 years for patients on ZDV/3TC. The incremental cost-utility ratio for Combivir was \$39,547 per QALY gained versus ZDV/3TC. Lifetime cost per patient was \$13,916 greater for patients receiving Combivir, \$7,469 of which is due to costs accrued by patients over the additional survival time. Sensitivity analysis around generic price of ZDV/3TC found favorable cost utility ratios for the Combivir arm under most conditions (\$8,258 to \$70,836 per QALY gained).

**Conclusion:** As part of an initial treatment regimen, use of Combivir rather than generic zidovudine plus Epivir was estimated to prolong the duration of the first regimen and extend survival. Combivir is cost effective when judged against the cost/QALY threshold used by most developed countries.

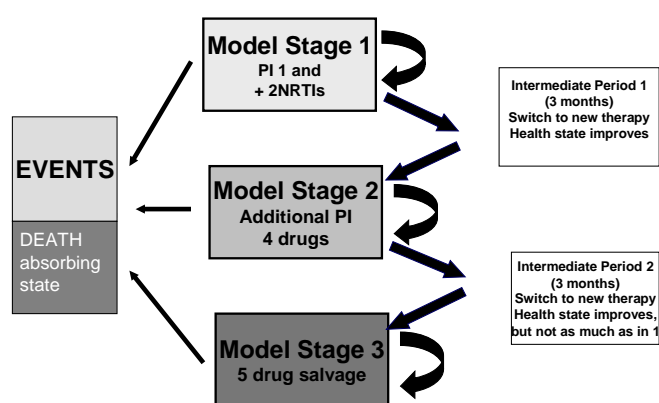
## Introduction

Patent protection for Zidovudine, the first antiretroviral approved for the treatment of HIV, has recently expired. Generic zidovudine (ZDV) may soon be available at a lower price than branded zidovudine (Retrovir®, GlaxoSmithKline), with resultant cost savings for antiretroviral regimens that contain this drug. However, for patients where Retrovir® is part of a combination tablet, such as for those receiving Combivir® (zidovudine + lamivudine combination tablet) or Trizivir® (zidovudine + lamivudine + abacavir combination tablet), the decision to replace Retrovir® with generic zidovudine is not straightforward because the daily pill burden will change if drugs are provided as separate components. Pill burden has been shown to be the most important single factor affecting adherence to a therapeutic regimen[1]. Before adopting a substitution approach, the antiretroviral cost savings from the use of generic ZDV must be weighed against the effect on adherence expected from the added pill burden. Furthermore, we must examine how much the expected decrement in adherence increases virologic progression, and the associated added healthcare costs, morbidity and mortality. We describe here a modeling study that explicates the interaction of these factors to help inform decisions on adoption of the use of generic zidovudine for patients who would otherwise receive Combivir.

## Methods

- A previously published Markov model [2], updated to reflect current treatment guidelines, was used to compare two theoretical treatment groups assigned to one of the following initial HIV regimens
  - Combivir + a protease inhibitor (Combivir Group)
  - Generic zidovudine + branded Epivir + a protease inhibitor (generic ZDV group)
- Treatment, while it is initially successful, is assumed to suppress viral load and increase CD4. Following failure of the first regimen, as indicated by viral load >400 copies/ml and CD4<200 cells, patients switch to a second regimen and eventually to a salvage regimen (Figure 1). After failure of the salvage treatment regimen, CD4 count generally declines, leading to AIDS events and ultimately death. The model is partitioned into 3 stages to reflect first, second, and salvage treatments.

Figure 1. Diagram of Model Structure



- The model contains 12 health states stratified by CD4 count and viral load ranges. Three transition probability matrix sets that direct transition through the health states are specific to each of the 3 stages and were derived from epidemiologic observational studies of first, second, and salvage therapies.
- Based on published literature, the Combivir group was assumed to have a 5% higher rate of adherence [3] and a 20% higher rate of viral load suppression <400 copies/ml during the first year of initial treatment than the ZDV group[4]. After the 1st year of initial therapy, adherence was assumed to be the same for the two treatment groups during all subsequent years modeled. In this model, any outcomes differences between treatment groups in terms of progression to AIDS events, death, and overall cost are therefore driven by the adherence and viral load suppression difference during the first year of treatment.
- Treatment group CD4 cell distribution at baseline, antiretrovirals used in second line and salvage regimens, and viral load suppression rates were based on observational data from 236 South Carolina patients who recently started HAART.
- Cost for AIDS events are based on average costs calculated from the analysis of U.S. Medicaid payments as well as hospital all-payer discharge data for patients with AIDS diagnoses.
- Drug costs are based on the US daily wholesale acquisition costs in 2004. Since the cost of generic ZDV was not known at the time of this study, we assumed that it would be 50% of the price of branded ZDV, Retrovir®. Drug regimens used in second and salvage therapies were derived from epidemiologic observational studies.
- Based on expected frequency of CD4 cell decline, AIDS events and survival, the model estimates time on first regimen, average length of survival, quality adjusted life years (QALY), lifetime costs, and the incremental cost effectiveness ratio. Both costs and life year benefits were discounted at 3% annually.
- One way sensitivity analysis was conducted to evaluate uncertainty in certain key model assumptions, including generic ZDV cost as well as the magnitude of differential impact of Combivir vs generic zidovudine + Epivir on viral load suppression.

## Results

- The model estimates the Combivir group to remain 0.6 years longer on the first regimen and have a mean survival that is 0.33 years longer than the Generic ZDV group [Table 1]. Lifetime total cost was also \$13,916 greater for the Combivir group.

Table 1. Summary of Model Outcomes

Estimate	Combivir	Generic ZVD+Epivir	Difference
Total Lifetime Cost per patient	\$326,642	\$312,726	\$13,916
Mean years survival	9.23	8.90	0.33 years gain
Median time on 1 <sup>st</sup> regimen	4.1 years	3.5 years	0.6 years gain

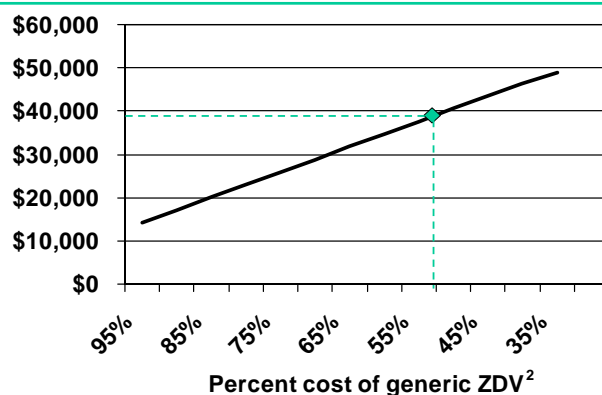
- The model estimates a substantially higher total cost of \$2,003 in the first year for those in the Combivir group and lesser premiums in years 2, 8, 9, and 10 [Table 2]. By contrast, in years 3 through 7, those in the Combivir group experience a net savings in total costs, with maximal savings of \$799 seen in year 4.

Table 2. Annual Total Cost per Patient

Year	Total Annual Cost/Pt.		Cost Increase or (Savings)
	Combivir	Generic ZVD+Epivir	
1	\$25,540	\$23,537	\$2,003
2	\$19,875	\$19,376	\$499
3	\$19,172	\$19,751	(\$579)
4	\$21,291	\$22,090	(\$799)
5	\$22,192	\$22,667	(\$715)
6	\$22,178	\$21,688	(\$490)
7	\$21,560	\$21,786	(\$226)
8	\$21,367	\$21,353	\$14
9	\$20,211	\$20,050	\$161
10	\$18,094	\$17,799	\$295

- The incremental cost effectiveness ratio (ICER) for using Combivir when the generic zidovudine price is 50% of the price of Retrovir, is \$39,547 per QALY gained [Figure 2]. Sensitivity analysis evaluating alternative costs of generic ZDV reveal that so long as costs were >35% of Retrovir price, ICER values for Combivir were <\$50,000 per QALY.
- Analysis of alternative values for the difference between Combivir and generic ZDV plus Epivir in the proportion of patients with undetectable VL at the end of the first year of treatment indicate that the ICER value is \$43,774 for a 15% difference; \$51,691 for a 10% difference; and \$64,384 for a 5% difference.

Figure 2. Generic ZDV Price Effect on Combivir ICER<sup>1</sup>



- ICER = Incremental Cost Effectiveness Ratio
- Percent cost relative to Retrovir

## Discussion

- This study has examined an important issue of making trade-offs between potential savings in drug budget versus using a HAART regimen that maximizes patient adherence.
- In the model, the adherence advantage associated with Combivir translates into the Combivir group remaining on the initial regimen longer, surviving longer, and generating a greater number of quality adjusted life years than the generic zidovudine group.
- Our model estimated an acceptable ICER of \$39,547 per QALY for the base-case assumptions wherein Combivir is utilized instead of generic ZDV plus Epivir. Judged against current ICER standard threshold values of < \$50,000/QALY for healthcare technology decisions, this estimate generally indicate that starting with Combivir rather than generic zidovudine plus Epivir is a cost effective strategy.
- The total healthcare cost estimated in the model was \$13,916 greater for the Combivir group. However, \$7,469 of the additional cost is directly attributable to the 0.33 years longer survival that the Combivir group experiences over the generic ZDV group.
- Economic modeling studies are only as good as the structure of the model and the validity of the parameters used to populate the model. While the structure of a model cannot be completely validated, our use of a previously published model that has been shown to predict 5-year death rates similar to those reported for epidemiological cohorts supports our confidence in the model's structure.
- Sensitivity analysis of key model input parameters, namely the magnitude of viral load suppression difference favoring Combivir and the cost of generic ZDV revealed that under most parameter values studied, Combivir was found to be a cost-effective strategy.

## Conclusion

- It is critical for decision makers to recognize the importance of very high adherence to HAART, its long term implications for survival, and the contribution that co-formulated drugs can make to achieving this objective.
- If one weighs the additional benefits against the cost of using branded Combivir vs generic zidovudine plus Epivir, (as we have done here in a structured model using established ICER thresholds), one would conclude that Combivir is worth the additional expense.

## References

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