SUPPLEMENTAL DIGITAL CONTENT 1

Appendix to: Cost-effectiveness of Etravirine Combination Antiretroviral Therapy in Treatment-Experienced Adults With HIV-1 Infection in Canada

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The following sections provide additional detail on the model structure, input parameter values, and results of model validation and sensitivity analyses.

Section 1: Calculation of Rate of CD4 Decline After Virologic Failure on the Switch Regimen

After individuals experienced virologic failure on the switch regimen, the model assumed that they experienced declining CD4 cell counts for the remainder of their lifetimes. The rate of this decline was computed using an equation that estimated the relationship between annual rate of CD4 cell-count decline and viral load, derived from data observed among untreated individuals in the Multicenter AIDS Cohort Study [1]:

$$\text{Annual rate of CD4 cell-count decline} = -21.3 - 33.5 \log_{10}(\text{vRNA} \div 1{,}000),$$

where *vRNA* is the level of viral ribonucleic acid in the bloodstream, measured in units of copies per milliliter.

The model assumed that viral loads of individuals who experienced virologic failure on the switch regimen would return to levels observed at baseline in the DUET 1 and DUET 2 clinical trials. Substituting the mean baseline viral load of 4.83 $\log_{10}$ copies/mL into the equation gave an annual CD4 cell-count rate of decline of 82.61 cells for those individuals not taking any treatment. However, the model assumed individuals would

continue on treatment for the remainder of their lifetimes, and stable CD4 cell counts have been observed for individuals on treatment with viral loads of 4.00 $\log_{10}$ copies/mL (or 10,000 copies/mL) [2]. Substituting 4.00 $\log_{10}$ copies/mL into the equation above gave an annual CD4 cell-count rate of decline of 54.8 cells for those individuals not taking any treatment. Therefore, we adjusted the untreated annual rate of CD4 cell-count decline of 82.61 cells downward by 54.8 cells per year to give an estimated annual decline of 27.81 cells while on treatment for individuals with a mean viral load of 4.83 $\log_{10}$ copies/mL. This yields a rate of decline of 6.93 cells per 3-month cycle. This rate of decline was used for all individuals with virologic failure in the switch regimen.

Section 2: Calculation of First-Year Probabilities of Transitioning to the Death State

In the first 48 weeks of the DUET 1 and DUET 2 clinical trials, there were 6 HIV-related deaths in the etravirine arm and 16 HIV-related deaths in the control arm [3]. The model assumed all HIV-related deaths occurred from the 0-50 cells/mm^3 CD4 cell-count range and that the proportion of the population in the 0-50 cells/mm^3 CD4 cell-count range in the first year of the model was a weighted average of the proportion observed in the trials at baseline, week 24, and week 48 (12.7% in the etravirine arm and 18.5% in the control arm) [3]. The resulting 3-month transition probabilities from the 0-50 cells/mm^3 CD4 cell-count range to the death state were 0.0221 in the etravirine arm and 0.0410 in the control arm.

In the DUET trials, there were also six non–HIV-related deaths in the etravirine arm and four non–HIV-related deaths in the control arm [3]. The model assumed non–HIV-related deaths occurred with equal likelihood from each CD4 cell-count range; the resulting 3-

month transition probabilities from all CD4 cell-count ranges to death were 0.0027 in the etravirine arm and 0.0018 in the control arm.

Section 3: Estimation of Antiretroviral Drug Use and Cost in the Initial and Switch Regimens

Antiretroviral drug use in the model was based on observed drug use in the relevant clinical trials, with several adaptations to account for unavailable drugs, drugs not covered on formularies, and the replacement of older drugs with newer drugs. Specifically, all trial use of emtricitabine was assumed to be via fixed-dose tenofovir/emtricitabine because emtricitabine is not available in Canada as a single agent. Also, all trial use of zidovudine was assumed to be via fixed-dose zidovudine/lamivudine because zidovudine is not covered as a single agent in the Ontario Drug Benefit Formulary (ODBF). Finally, all trial use of amprenavir was converted to fosamprenavir, and all trial use of zalcitabine was converted to lamivudine.

For the raltegravir-based switch regimen, antiretroviral drug use was based on published data from the pooled BENCHMRK 1 and BENCHMRK 2 populations [4,5]. Data were available on the use of darunavir (39.8%), tipranavir (21.2%), and enfuvirtide (37.9%). The model assumed that 100% of participants in the BENCHMRK trials used a protease inhibitor (PI), but the combined use of darunavir and tipranavir (61.0%) did not sum to 100%. Therefore, for individuals not receiving tipranavir or darunavir, the model assumed a distribution among the remaining PIs that matched the distribution of PI use observed in the control arms of the pooled POWER 1 and POWER 2 trials [6].

Ritonavir use was estimated assuming that all participants received ritonavir, either in Kaletra (lopinavir/ritonavir) or separately, unless they received atazanavir 400 mg once

daily or nelfinavir. Participants who received tipranavir received ritonavir 400 mg daily, participants who received atazanavir 300 mg daily received ritonavir 100 mg daily, and participants who received all other PIs received ritonavir 200 mg daily.

Because no information was available on nucleoside/nucleotide reverse transcriptase inhibitor (NRTI) use by participants in the BENCHMRK trials, the model assumed that the same percentage of participants used each NRTI as in the pooled DUET 1 and DUET 2 trials [3].

Unit costs for antiretroviral drugs were obtained from the ODBF [7], except when costs were not available from the ODBF. The cost of enfuvirtide was obtained from the Association Québécoise des Pharmaciens Propriétaires pharmacist list in Quebec [8], and the costs of tipranavir and maraviroc were obtained from Canadian Expert Drug Advisory Committee recommendations [9,10].

Section 4: Further Information About the British Columbia Center for Excellence in HIV/AIDS Resource Use Study

Results of an unpublished resource use study from the British Columbia Centre for Excellence in HIV/AIDS were used to estimate medical costs in the model [11]. The study estimated resource use for a sample of 1,736 adults aged 18 years or older when starting antiretroviral therapy. Resource use was measured from October 1, 1997, through March 31, 2001. For each CD4 cell-count range for each month, the study estimated the average number of intensive care unit and non-intensive care unit hospital days, general practitioner and specialist physician visits, laboratory tests (CD4, plasma viral load, and genotypic resistance testing), and emergency department visits. The unpublished study was similar to an earlier study that presented resource use by CD4 cell-count range and

by viral load subgroup [12]. Unit costs for each type of health care service were obtained from the earlier study [12], except costs for emergency department visits, which were obtained from the London Health Science Centre in Canada for all individuals with an HIV diagnosis (*International Classification of Diseases and Related Health Problems, 10th edition,* codes B20-B24) visiting the emergency department during the 2006-2007 fiscal year [13]. All costs were inflated to 2009 Canadian dollars as necessary, using the health and personal care component of the consumer price index [14].

Section 5: Ranges and Distributions Used in the One-Way and Probabilistic Sensitivity Analyses

Table 1. List of Parameters Tested in the Sensitivity Analyses

Variable	Base Case	Ranges for One-Way Sensitivity Analyses	Distribution for PSA
Gender distribution	DUET trials values [3,15]	95% confidence limits for males	Beta
Age distribution	DUET trials values [3]	95% confidence limits for 65+ years age group	Dirichlet
Baseline CD4 cell-count distribution	DUET trials values [3]	95% confidence limits on the < 50 cells/mm^3 CD4 cell-count group	Dirichlet
Year 1 cost of hospitalizations	Mean days hospitalized from DUET trials for etravirine and control [3]; unit costs from Canadian cohort study [12]	95% confidence limits of mean hospitalized days	Normal
Year 1 probability of death	DUET trials values for etravirine and control [3]	95% confidence limits	Beta
Virologic response at 24 weeks: etravirine and control regimens	DUET trials values with and without enfuvirtide for etravirine and control [3]	95% confidence limits of the < 50 copies/mL group	Dirichlet
Virologic response at 24 weeks: switch regimen	BENCHMRK trials values [5,16-18]	95% confidence limits of the < 50 copies/mL group	Dirichlet

Variable	Base Case	Ranges for One-Way Sensitivity Analyses	Distribution for PSA
Rate of rapid CD4 cell-count increase: etravirine and control regimens	DUET trials values by viral load response [3]	95% confidence limits	Normal
Rate of rapid CD4 cell-count increase: switch regimen	BENCHMRK trials values imputed by viral load response [5,16,17]	95% confidence limits	Normal
Rate of slow change or stable CD4 cell count: etravirine and control regimens	DUET trials values by viral load response [3]	95% confidence limits	Normal
Rate of slow change or stable CD4 cell count: switch regimen	BENCHMRK trials values imputed by viral load response [5,16,17]	95% confidence limits	Normal
Rate of CD4 cell-count decline	Calculated using observational cohort data: –27.8 cells/mm^3 per year [1,2]	Estimated 95% confidence limits [2]	Normal
Duration of rapid CD4 cell-count increase	0.5 years [3,15,19,20]	Base-case value ± 3 months	Discrete triangle
Duration of slow change or stable CD4 cell count	3.25 years (etravirine), 1.75 years (control), or 2 years (switch regimen) for those with < 50 copies/mL 0.5 years for those with 50 copies/mL to ≥ 1-log10 drop 0 years for those with < 1-log10 drop [3,21-25]	95% Poisson confidence limits with mean equal to the base-case value	Poisson
Utility values	Utility weights converted from EuroQol responses from 21,000 participants in HIV clinical trials [26]	Estimated 95% confidence limits [27]	Normal
HIV-related mortality by CD4 cell count	Probabilities converted from EuroSIDA observational cohort rates [28]	95% confidence limits	Normal
Non–HIV-related mortality by age	Statistics Canada general population mortality rates for 2006 [29], multiplied by French increased risk factor of 2.5 [30]	Varied relative risk factor using 95% confidence limits	Lognormal

Variable	Base Case	Ranges for One-Way Sensitivity Analyses	Distribution for PSA
Use of enfuvirtide	DUET and BENCHMRK trials values [3,5]	95% confidence limits	Beta
Cost of ART: etravirine and control regimens	Standard dosing, Canadian prices, and drug use from DUET trials [3,7-10]	Not varied	Not varied
Cost of ART: switch regimen	Both initial regimen arms switch to raltegravir + OBR[a], based on BENCHMRK trials [4,5,7-10]	Lower bound: cost based on all PI use shifted to fosamprenavir/r Upper bound: cost based on all PI use shifted to tipranavir/r	Triangle
Non-ART medical costs by CD4 cell count	British Columbia Centre for Excellence in HIV/AIDS resource use study [11] with Canada-specific unit costs [12,13]	95% confidence limits for health care resource use; unit costs are not varied	Normal for resource use
Non-ART drug costs by CD4 cell count	Canadian cost study [31]	95% confidence limits estimated using the standard error to mean ratio for outpatient resource use from British Columbia resource use study [11]	Normal

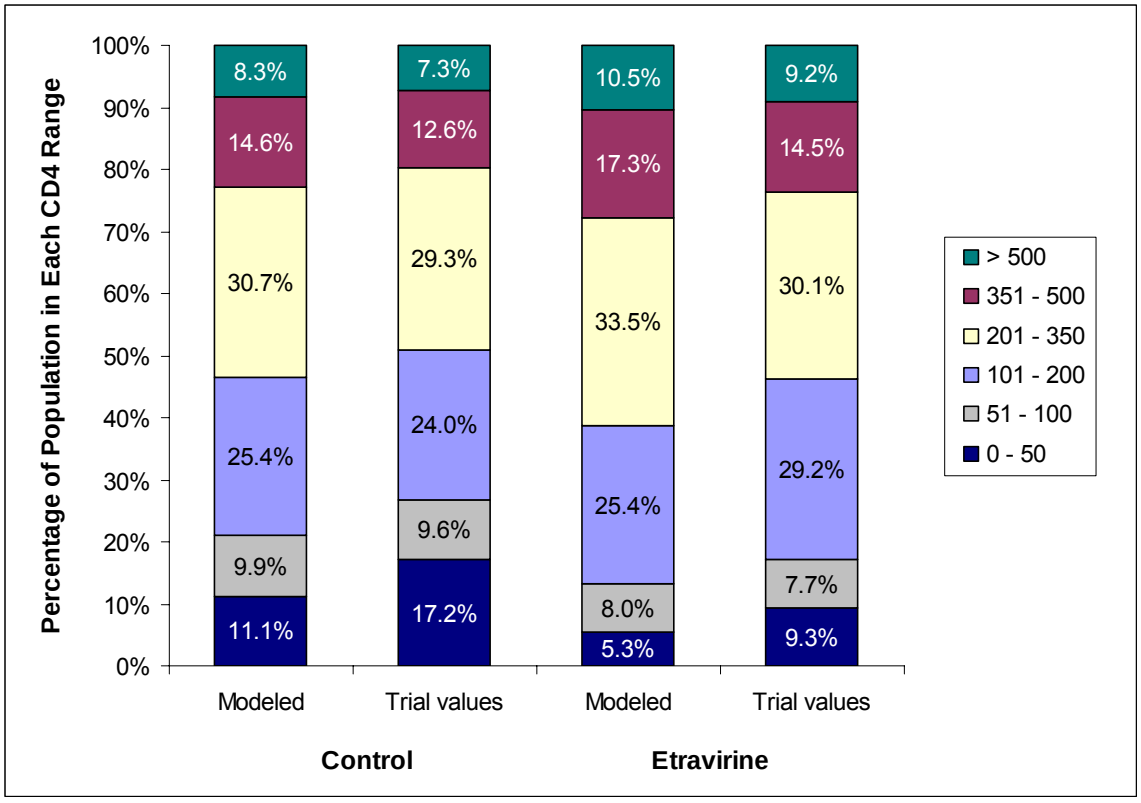
ART = antiretroviral therapy; FI = fusion inhibitor; NRTI = nucleoside/nucleotide reverse transcriptase inhibitor; OBR = optimized background regimen; PI = protease inhibitor; PSA = probabilistic sensitivity analysis; /r = boosted with ritonavir.

[a] OBR for the raltegravir-based switch regimen included optimized PIs, NRTIs, and FIs. PIs in the choice set included darunavir/r, tipranavir/r, and older PIs.

Section 6: Model Validation

Various outcomes of the economic analysis were compared with results from other data sources or models to determine the validity of the model. First, the distribution of individuals in the CD4 cell-count ranges predicted by the model at 1 year was compared with the actual distribution observed at 48 weeks in the DUET 1 and DUET 2 clinical trials (Figure 1) [3]. Although the match is not exact for either the etravirine or the control regimens, the distributions are similar in magnitude, and the differences between the two treatment regimens are consistent with those observed in the trial.

Figure 1. Modeled and Actual CD4 Cell-Count Distributions at 48 Weeks[a]



[a] In order to appropriately compare the modeled CD4 cell-count distributions to the trial distributions, deaths estimated by the model were added back into the modeled distribution, assuming that all HIV-related deaths occurred from the 0-50 CD4 cell-count range and that non–HIV-related deaths occurred from all ranges proportionately to the percentage of people in each range. The adjustment was needed because the trial distributions were based on a last-observation-carried-forward analysis; participants who died still contributed CD4 values to the distributions.

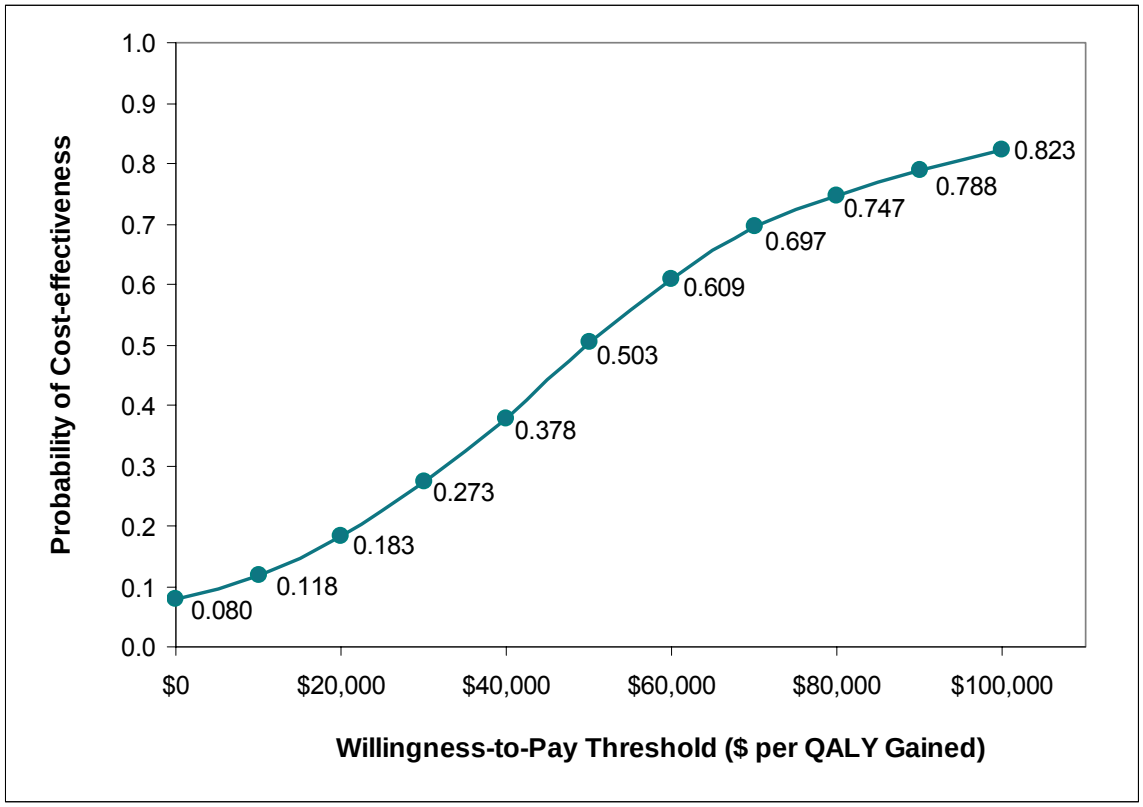
Next, the model predictions of the proportion of deaths that were related and unrelated to HIV were compared with estimates from southern Alberta for 1997-2003 [32]. The southern Alberta study found that 67% of all deaths in people with HIV infection were related to HIV. In our analysis, the proportion of HIV-related deaths was estimated to be 63% for the control group and 57% for the etravirine group. These estimates also were similar to recent calculations using a simulation model that estimated that approximately 59% of deaths from the time of diagnosis were related to HIV [33].

Finally, model-predicted life expectancies after HIV diagnosis and after starting treatment were compared with other published estimates. The model-predicted life expectancy after HIV diagnosis for participants in the control arm of the DUET 1 and DUET 2 trials was 31.0 years, which was computed as the sum of 14.2 years (average time since diagnosis for the control group entering the trial) plus 16.8 years (undiscounted life expectancy for the control arm from the model estimates). A recent paper based on the British Columbia Centre for Excellence in HIV/AIDS observational cohort estimated life expectancy for someone with HIV infection diagnosed at age 20 years to range between 19.1 years and 38.9 years, depending on risk group, hepatitis C serostatus, and multidrug antiretroviral treatment [34]. A recent life-cycle model estimated a median life expectancy of 20.4 years [33]. Model-predicted life expectancy after starting treatment (16.8 years) also was compared with estimates from two cost-effectiveness studies of enfuvirtide, which reported life expectancies of 7.4 years [35] and 6.3 years [36] for the enfuvirtide arm. Either of these estimates would be for an equivalent population to that found in the pooled DUET 1 and DUET 2 control arms. For both life expectancy after HIV diagnosis and after starting treatment, our model estimates tended to be higher than previously published estimates. This trend would be expected because our model included new drug regimens that are more efficacious than regimens available when previous analyses were conducted.

All of the validation steps indicated that the model results were similar to those observed in the DUET 1 and DUET 2 clinical trials and were consistent with prior estimates from observational database studies and other HIV disease-progression models.

Section 7: Graphical Results of Probabilistic Sensitivity Analysis

Figure 2. Cost-effectiveness Acceptability Curve for Lifetime Cost-Utility Analysis



QALY = quality-adjusted life-year.

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