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Cost Effectiveness Analysis of Abacavir/Lamivudine Versus Tenofovir/Emtricitabine Combination Therapy as Part of Highly Active Antiretroviral Therapy in Treatment Naïve HIV-Infected Patients

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Cost effectiveness analysis of abacavir/lamivudine versus tenofovir/emtricitabine combination therapy as part of highly active antiretroviral therapy in treatment naïve HIV-infected patients.

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Thesis submitted to the Faculty of Graduate and Postdoctoral Studies in partial fulfillment of the requirements for the MSc degree in Epidemiology

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Abstract

Introduction: Current recommendations for the treatment of HIV include the use of dual nucleoside reverse transcriptase inhibitors, namely abacavir/lamivudine or tenofovir/emtricitabine. This study is to compare the cost-effectiveness of these two alternatives in the treatment of HIV treatment-naïve patients.

Methods: A review of the literature was performed to identify relevant randomized controlled trials and economic models. The economic model described by Richter using maximal virologic response and rate of failure as efficacy parameters was adapted to take into consideration the effect of HLA-B*5701 genotyping. Indirect comparison technique was used to ascertain the estimate of efficacy parameters. Sensitivity analyses were performed on costs, efficacy parameters and utilities.

Results: Abacavir/lamivudine was dominant over tenofovir/emtricitabine. Efficacy parameters, but not costs and utilities, was very sensitive with a small variation leading to tenofovir/emtricitabine dominance.

Conclusion: Abacavir/lamivudine is dominant over tenofovir/emtricitabine in treatment-naïve HIV-infected patients. Results are extremely sensitive to efficacy parameters.

1. Introduction

1.1. History and Epidemiology

In 1981, a cluster of Pneumocystis Carinii pneumonia, an infection related to decreased immunity, among five homosexual men in Los Angeles triggered medical and public health agencies attention[1]. In the following months, more clusters were identified. These cases shared common characteristics, suggesting that sexual transmission, intravenous drug use and haemophilia were associated with the disease[2, 3]. The Centers for Disease Control gave the name of Acquired Immunodeficiency Syndrome (AIDS) to this phenomenon[4]. Later, the Human immunodeficiency virus (HIV)[5] was discovered by French[6] and American[7] researchers as the etiology of this syndrome.

Since the first reported cases, HIV infection has become pandemic. According to the 2007 report of the United Nations Programme on HIV/AIDS (UNAIDS)[8], HIV has spread in all five continents. In 2007, an estimated 33.2 million of people live with HIV/AIDS. For the same year, 2.1 million died from AIDS. UNAIDS also confirmed that the HIV infection epidemic is not over, with 2.3 million new infection in one year.

Geographically, HIV infection is not uniformly distributed. The vast majority, 25 of the 40 million (62.5%) of infected individuals, are located in sub Saharan Africa. North Americans accounts only for a small percentage of the global epidemic, with an estimated 1.4 million (3.5%) HIV-seropositive individuals.

In Canada, the Public Health Agency of Canada publishes an annual report of the HIV surveillance. As of June 2007, 63 000 HIV positive tests have occurred since 1995. The incidence of new infections remains stable with 2500 new positive tests annually. The representation of the HIV epidemics has remained unchanged for the last 3 years. The risk factors of unprotected sex between men and illicit intravenous drug use account for 39% and 19% respectively of all positive tests[9]. Ninety-nine percent are adults and 83% male, which is consistent with trends in other industrialized countries.

Nonetheless, despite the incidence of newly infected individuals remaining steady, the AIDS complication rate is declining. The number of newly reported cases of AIDS reached its lowest level in 2007 with 269 cases while in 1993, it reached its apogee with 1827 cases[9] (Table 1).

Table 1

Surveillance table for the number of reported AIDS cases by year of diagnosis (all ages).

Source: Public Health Agency of Canada

Year of diagnosis of AIDS	*Number of cases reported*
1979	1
1980	3
1981	8
1982	26
1983	64
1984	162
1985	402
1986	688
1987	1012
1988	1181
1989	1406
1990	1463
1991	1517
1992	1752
1993	1827
1994	1791
1995	1648
1996	1193
1997	723
1998	645
1999	555
2000	498
2001	419
2002	406
2003	382
2004	316
2005	331
2006	269
June 2007	109

This observation is the consequence of the wide uptake of newer antiretrovirals, which lead to a better virological control and immunological response.[10-14] As a result, while the incidence remains steady and the mortality due to AIDS decreases, the net effect is an increase number of patients living with HIV/AIDS.

1.2. Pathophysiology and Treatment

HIV is a retrovirus and belongs to the group of lentiviruses. The characteristics of such viruses are their long incubation and duration of infection. Typically, after infection, HIV is asymptomatic for many years (up to 10 years) before clinical signs and symptoms start to manifest[15]. This factor contributes to the epidemics of the infection as many infected individuals are unaware of their diagnosis and become vectors for the disease[16].

The knowledge about HIV replication has constantly evolved. It is now known that HIV needs to go through many essential steps in order to replicate effectively. First, entry into the host cell requires attachment to the receptor, to co receptors and fusion to the host cell. Reverse transcriptase enters in action to transcribe single strand RNA to double strand DNA. The penetration into the host nucleus and integration into host DNA is facilitated by the integrase. Finally, the protease cleave large polypeptides from transcribed mRNA into functional HIV proteins and enzymes allowing maturation of the virus[17]. The thorough understanding of the HIV replication cycle helped to identify potential targets for antiviral drugs.

At present, there are 19 antiretrovirals from 6 different classes available in Canada. Their combination is referred as triple therapy or highly active antiretroviral therapy (HAART). The results of clinical trials were incorporated in a number of local and international treatment guidelines to assist clinicians in the selection of antiretrovirals. The Department of Health and Human Services (DHHS) in USA annually publishes HIV treatment guidelines[18]. Similarly, the European AIDS Clinical Society (EACS) provides guidelines[19] for the clinical management of HIV infected Adults in Europe. For the management of treatment-naïve HIV-infected patients, three classes of antiretrovirals are recommended. HAART consists of the use of two nucleoside reverse transcriptase inhibitors (NRTIs) with either a protease inhibitor (PI) or a non-nucleoside reverse transcriptase inhibitor (NNRTI) (Table 2).

Table 2

Antiretroviral Components Recommended for Treatment of HIV-1 Infection in Treatment-Naïve Patients (Updated January 29, 2008)

To Construct an Antiretroviral Regimen, Select 1 Component from Column A + 1 from Column B				
	Column A NNRTI or PI Options – in alphabetical order)			**Column B** (Dual-NRTI Options)
Preferred Components	**NNRTI or PI** **efavirenz[1] (AII)** **atazanavir + ritonavir (AIII)** **fosamprenavir + ritonavir (2x/day) (AII)** **Lopinavir/ritonavir[2] (2x/day) (AII)** (coformulated)	+	**Preferred Components** (alphabetical order)	**abacavir/lamivudine[3]** (for patients who test negative for HLAB*5701) (coformulated) **(AII); or tenofovir/emtricitabine[3]** (coformulated) **(AII)**
Alternative to Preferred Components	**NNRTI or PI** **nevirapine[4] (BII)** **atazanavir[5] (BII)** **fosamprenavir (BII)** **fosamprenavir + ritonavir (1x/day) (BII)** **lopinavir/ritonavir (1x/day) (BII)** (coformulated) **saquinavir + ritonavir (BII)**		**Alternative to Preferred Components** (order of preference)	**zidovudine/lamivudine[3]** (coformulated) **(BII); or didanosine + (emtricitabine or lamivudine) (BII)**

NRTIs are analogs of natural nucleosides cytadine, thymidine, guanosine and adenosine. They exert antiretroviral activity by inhibiting the prolongation of the newly formed RNA chain by the viral reverse transcriptase[20]. Anti-HIV therapy includes two NRTIs, which is also known as the backbone. The combinations of abacavir/lamivudine or tenofovir/emtricitabine, which are coformulated as

Kivexa® and Truvada® in Canada, are the favoured NRTIs in DHHS and EACS guidelines.

Unlike NRTIs, NNRTIs are not nucleoside analogs. They attach to a hydrophobic pocket on the polymerase site which results in a conformational change of the reverse transcriptase and blockage of DNA synthesis[20]. Two NNRTI are indicated for treatment-naïve HIV-infected patients: efavirenz and nevirapine. Efavirenz is considered the drug of choice due to numerous clinical trials showing excellent virological efficacy[18]. Nevirapine is relegated to an alternative because of incidence of severe liver and skin toxicity that could be fatal[18].

PIs are an alternative to NNRTI-based therapy. The protease is an enzyme responsible to cleave large polyprotein precursors into functional proteins and enzymes required for viral assembly and maturation. Protease inhibitors will bind to the active site of the protease to prevent cleavage, leading to the production of immature and non-infectious HIV[21]. Several protease inhibitors are available. Practice guidelines recommend atazanavir/ritonavir or lopinavir/ritonavir as preferred PIs in treatment-naïve patients. The decision to pair PI or NNRTI with dual NRTI therapy is based on pharmacokinetic, toxicity and efficacy considerations.

1.3. Measures of effectiveness

As described earlier, the effectiveness of HAART is associated with clinical outcome such as mortality and/or the development of AIDS. Recent advances allowed quantification of viral replication which predicts clinical outcome. A valid surrogate outcome must correlate with clinical outcome and account for the full effect of the treatment on the clinical outcome. Scientific literature is comprised of several clinical trials that confirmed the correlation between decrease in HIV viral load and disease progression and death[22]. Since, HIV viral load is part of standard practice and is used as an indicator to change therapy in anticipation of clinical complications[23-25].. Although controversy exists with the use of surrogate endpoints[26], it may be ethically difficult to justify the conduct of a trial using clinical outcome such as survival [27]. Because HIV takes so long to result in disease and death, and because the window of benefits to treatment is critical, the practicality and ethics of conducting trials based on these usual endpoints has been addressed. It is recognized that the need to design trials that do not keep participants on a therapy for longer than the period of benefits justify shorter studies with clinical endpoints[28].

The guidelines published by U.S. DHHS, Food and Drug Administration and the Center for Drug Evaluation and Research (CDER) recommend to use plasma HIV RNA for the primary measure of efficacy[27]. CD4 response, AIDS defining illnesses and death should also be included in clinical trials. Use of intent-to-treat analysis called TLOVR (time to loss of virological response) is also encouraged

since it considers patients who die, are lost to follow-up, or introduce new study treatment due to toxicity/intolerance (or any other reason) as treatment failures[27]. The use of HAART in treatment-naïve patients is associated with virological response at one year in up to 80 percent of patients on an intend-to-treat TLOVR analysis[29].

1.4. Toxicity

Greater use of HAART improved survival but the benefits were quickly tempered by findings on long term toxicity[30]. NRTIs induce mitochondrial toxicity through inhibition of the polymerase gamma of the host cell[31]. As a result, toxicity such as lactic acidosis, loss of subcutaneous fat (lipoatrophy), neuropathy and pancreatitis became more prevalent[32]. Thus, treated HIV-infected individuals were stigmatized through important morphologic changes and their quality of life impaired consequently[33, 34].

Recently, advances in the pharmacotherapy of HIV were made in order to address the problems of toxicity and complexity of treatment regimen.

The 2008 revision of the DHHS and EACS guidelines addressed the toxicity concerns and changed the selection of the NRTI component of HAART. Both panels relegated zidovudine and stavudine based therapy as alternatives due to lipodystrophy concerns and favored lamivudine/abacavir and tenofovir/emtricitabine[18, 19].

Side effect profiles of abacavir and tenofovir are quite distinct. Abacavir is known to cause hypersensitivity reaction characterized as rash, fever and flu-like syndrome. The reaction occurs in up to five to eight percent of the Caucasian

population within six weeks after the initiation of therapy. The reaction is reversible after discontinuation of the drug but can be lethal if rechallenged[35]. HLA B*5701 genotyping has recently been used to identify individuals at risk for the reaction and is currently being implemented in major HIV centers throughout Canada. Randomized trials[36, 37] and cohort analysis[38-41] showed a marked decrease of abacavir hypersensitivity if prior genotyping is done. The PREDICT trial[36, 37] was a large diagnostic randomized double blind controlled trial involving 1956 patients with the objective of assessing the clinical effectiveness of HLA B*5701 genotype for the prevention of abacavir hypersensitivity. This study concluded that avoidance of abacavir in patients with the presence of HLA B*5701 prevented confirmed hypersensitivity to abacavir and also led to a reduction of discontinuations due to adverse events compared to the arm that was unaware of the HLA status. Details on this study will be presented later in the Methods section. Since the publication of PREDICT, HLA B*5701 has become standard of care in patients starting abacavir-based therapy[18].

Many cases of renal dysfunction have been reported with tenofovir use[42-57]. The reaction is described as Fanconi's syndrome, characterized by a transport defect in the proximal tubules, leading to renal losses of glucose, phosphate, calcium, uric acid and amino acids[58]. Clinical trials using tenofovir in treatment-naïve patients report a low incidence of nephrotoxicity, described as a change in serum creatinine or calculated creatinine clearance.

1.5. Economics

The HIV cost and Services Utilization Study Consortium[59] presented data on the total expenditure for the care of HIV-infected patients in the US. The consortium looked at the total costs before (1996) and after (1998) HAART. The mean annual costs per patient were reduced from US $20300 to US $18300. The majority of the costs were associated to inpatient and outpatient care costs, although drugs accounted for a higher proportion of the overall costs after HAART. Nonetheless, the 33 percent increase in drug expenditure led to a net 16 percent decrease in the overall costs.

A Canadian group also looked at the costs of HIV care between 1995 until 2001[60]. The mean annual costs were estimated to CAN $13428, comparable to the American estimate. Their conclusions were quite different though. Although the same trends were noticed, the reduction in the inpatient/outpatient costs did not offset the increase in the drug costs. The relative contribution of HAART costs at the end of the observation period accounted for 95 percent of the total drug costs and 69 percent of total costs. These data contrast with another report which estimated the contribution of drug costs to represent 10 to 24 percent of the total Health Care Costs[61]. This group estimated that the total direct costs of HIV care in Canada were CAN $600 million per year. Including indirect costs into the equation led to an estimated CAN $36.3 billion total economic burden of

HIV/AIDS in Canada to date. They also estimate the future economic burden associated with the current HIV population at CAN $27.3 billion.

Clearly, the impact of HIV on society is gaining in importance. As the prevalence of people living with HIV/AIDS is increasing secondary to longer survival, so are the costs[62]. The benefits of lifelong therapy are balanced between effectiveness of HAART and its toxicity. Since there are no clear demonstrated benefits between abacavir/lamivudine and tenofovir/emtricitabine in clinical trials, it is imperative to look closely not only at effectiveness but also at toxicity differences and the direct and indirect economical impact.

Several cost-effectiveness studies have been conducted in the HIV area. They are limited by their inability to apply to current practice, since practice guidelines are changing at least annually[63]. In addition, several economic models are available using surrogate markers such as CD4 and/or plasma HIV RNA differently. These factors contribute to add heterogeneity to the body of economic evidence. Given current treatment and knowledge, an economic model must represent the actual practice such as prevention of abacavir hypersensitivity reaction using HLA B*5701 genotyping. Model structure has to take into consideration the details of all appropriate outcomes (such as the composite outcome of clinical and virological outcomes included in TLOVR analysis).

The objective of this thesis is to conduct a cost-effectiveness study, which will include the following components:

1) The selection and adaptation of an existing economic model for HIV progression.

2) The integration of a decision tree for HLA B*5701 status.

3) A systematic review assessing the efficacy between abacavir/lamivudine and tenofovir/emtricitabine in treatment-naïve patients; with an indirect comparison to account for the possibility of no direct comparison study

4) Analysis based on the adapted model with probabilistic sensitivity analysis representing the degree of uncertainty in all input parameters.

Ultimately, this study is aimed to assist clinical health care providers as well as decision makers in obtaining a better understanding of the clinical and economical differences between the two newly recommended NRTI (abacavir/lamivudine and tenofovir/emtricitabine) for the treatment of HIV-infected individuals naïve to treatment.

2. Methods

2.1. Introduction

The ability to estimate the comparative effectiveness of the two selected NRTIs combination therapy requires modeling of HIV progression. The design of the economic model involves 4 different stages. First, it is necessary to characterize the stages of the disease, usually through the determination of health states. Second, it is necessary to determine the length of time in each health state by assigning transition probabilities relative to the progression from each health state. Thereafter, resources are allocated to each health state and a unit cost is obtained for each resource[64]. Finally, utility values can be integrated into the analysis. Utilities are weights than can be applied to weigh time in a specific health state to account for quality of life. Ideally, the model should reflect the current practice and should correlate with clinical HIV cohort databases.

The first step is then to identify economic model for HIV disease. Following this step, each section of the model will be populated. A systematic review will be performed to find estimates for health states transition probabilities. Costs and utility estimates will subsequently be appraised and inserted.

2.2. Review of Economic Models

Several economic models are available in the field of HIV. Since treatment has considerably evolved over time, the selected model must be in line with current practices. A literature search was conducted in order to identify the characteristics of HIV economic models. This section will discuss HIV economic models and HLA B*5701 genotyping modeling separately.

2.2.1. HIV Economic Model

2.2.1.1. Literature Review

2.2.1.1.1. Search strategy

A Medline search was performed from 1996 to the first week of April 2008 in order to identify all available models (appendix 1). Major international HIV conferences from 2005 to Feb 2008 were reviewed by searching through their respective websites or abstract books. These include the Conference on Retroviruses and Opportunistic Infections (CROI), Interscience Conference on Antimicrobials and Antiinfectives Chemotherapy (ICAAC), International AIDS Society (IAS), World AIDS Conference (WAC), European AIDS Conference Society (EACS) and Canadian AIDS and HIV Research (CAHR). The search included the generic and trade names of each drugs as well as the terms economic$, OR model OR cost$. The search strategy is intended to be non-specific. Studies that were developed after 1998, the year in which HAART started to be standard of care, were included. In addition, studies looking at

other reasons than comparing drug therapies (for example: time to initiate therapy, reduction of vertical transmission) were excluded.

2.2.1.1.2. Description of models

Ten published pharmacoeconomic studies[63, 65-73] were retained for further analyses. From these ten studies, six different models were identified (Appendix 2, 3).

2.2.1.1.2.1. CEPAC

The most reported model is *The Cost-effectiveness of Preventing AIDS Complications* (CEPAC) model[63]. This model is supported by several American regulatory agencies such as the CDC and the National Institute of Allergy and Infectious Diseases. CEPAC is a Monte Carlo simulation model simulating HIV progression using state transitions. It compares clinical outcomes and cost-effectiveness of different strategies using CD4, HIV viral load, adherence, resistance, and HIV testing. The model includes three health states categories (chronic, acute and death) in which individuals move according to the risk of developing opportunistic infections. Basically, individuals enter into the simulation in a CD4 and viral load category randomly assigned by user-specified probability distributions. CD4 and HIV viral load are stratified into six and five levels respectively. The rate of decline of CD4 count is modulated by virological activity as found by Mellor[24] (Table 3).

Table 3

Mean monthly decline in CD4 cell count according to HIV viral load as per CEPAC model[24]

HIV Viral Load	n	Decline in CD4 cell count (cells/mm3)	95% Confidence Interval
30,001-100,000 copies/ml	394	6.375	5.875, 6.908
10,001-30,000 copies/ml	383	5.400	4.967, 5.833
3,001-10,000 copies/ml	386	4.600	4.225, 4.983
501-3,000 copies/ml	250	3.733	3.258, 4.208
≤ 500 copies/ml	118	3.025	2.533, 3.525

Loss of immunological function is associated with an increased risk of opportunistic infections. The probability of having opportunistic infections is based on the Multicenter AIDS Cohort Study (MACS) Public Dataset (Table 4).

Table 4

Monthly risk of acquiring opportunistic infections by CD4 stratum as per CEPAC model

CD4 count	0-50/mm3	51-100/mm3	101-200/mm3	201-300/mm3	301-500/mm3	>500/mm3
Pneumocystis Carinii Pneumonia	0.037	0.031	0.0096	0.00373	0.00085	0.00041
Mycobacterium avium Complex	0.0122	0.00375	0.00101	0.00022	0.000055	0.000059
Toxoplasmosis	0.0027	0.0014	0.00067	0.00042	0.000092	0.000029
Cytomegalovirus	0.01857	0.00523	0.00214	0.00058	0.000129	0.000059
Fungal infection	0.01123	0.00591	0.00135	0.00029	0.000276	0.000088
Other	0.0394	0.0246	0.00716	0.00224	0.00087	0.00047

The Drug Topics Red Book is used to input the costs of drugs. Other health costs were estimated from cross-sectional data collected by the HIV Research Network. The utility function is taken from a study by Shackman[74] and is based on four categories of CD4 levels. A more thorough discussion of utility function will be presented later in the methods section. The model was programmed in C and compiled in Visual C++ 6.0 (Microsoft).

CEPAC is widely cited into the HIV economic literature[63, 66, 67, 75, 76]. Progression of HIV is modeled through data from the MACS cohort published by Mellor. This cohort was composed of 4954 homosexual men who were 18 years of age or older and enrolled between 1984 and 1985 throughout the USA[24, 77]. The MACS cohort led to the finding of the association between plasma HIV viral load[24] and it also includes population data on the rate of opportunistic infections and death. While homosexual men encompass the majority of Canadian infected individuals[9], this model assumes that the same dynamic exists between a rather homogeneous group of American homosexuals and the actual Canadian HIV mixed demographics. Two major assumptions were made for CEPAC. First, antiretroviral therapy ceased to confer benefits after two years. Second, subsequent lines of therapy are less effective than first-line therapy. Although the latter seems to still hold true due to the reduced sensitivity of antiretrovirals to HIV resistant strains, the former has been proven to be incorrect. Efavirenz-based[78] and PI-based[79] regimens have durability data for up to 7 years.

Medical services were extracted from seven American sites affiliated to the HIV Research Network representing academic (6) and community-based (1) facilities. Outpatient visits and hospitalizations were captured in the database but not emergency room visits. Instead, the data was imputed by using the ratio of emergency room visits to outpatient visits reported in the HIV Cost and Services Utilization Study. Inpatient costs came from the University Health System Consortium, which represents 117 academic and affiliated hospitals in the US. Antiretroviral regimen was set a priori for the different lines of treatment as per the latest clinical information. Costs for antiretrovirals as well as for the treatment of opportunistic infections were discounted average wholesale prices plus a fixed dispensing fee. Although quite diverse and detailed, the costs are specific to US health economic structure. Its adaptation and validation to Canadian health care system was not identified in the literature search.

2.2.1.1.2.2. Simpson's model

Simpson et al[73] developed a model based on 3 treatment stages (first line, second line and third line therapy) and twelve health states based on CD4 counts and HIV viral load. Transitions into these health states were extrapolated through US and Dutch cohorts published by Ghani[80, 81]. The first stage included patients starting on either nelfinavir-based or lopinavir/r-based therapy. Transition to the next stage is based on the results of the 98-863 clinical trial comparing these two drugs along with zidovudine/lamivudine[82]. The transition probabilities for the next two stages were derived from the Medical University of South Carolina (MUSC).

In subsequent studies[83, 84], the model was refined to incorporate the impact of dyslipidemia as per the Framingham cohort.

This model differs from CEPAC in several ways. First, the relationship between HIV viral load and CD4 decline is not based on the same source. In CEPAC, changes in viral load modulates CD4 decline, which leads to occurrence of opportunistic infections. In Simpson's, a composite measure of CD4 count and viral load is associated to development of opportunistic infections. Given that different cohorts were used, it is difficult to determine which of the two methods is more accurate.

Second, the risk for specific opportunistic infection is not modulated by the degree of immunosuppression. While CEPAC takes into consideration this factor through the MACS cohort, Simpson's model reports the inability to find such correlation into his cohort, which is against the current evidence from practice guidelines.

Finally, this model ignores the recurrence of opportunistic infections and assumes no differences in treatment efficacy after 48 weeks. These assumptions may limit external validity.

2.2.1.1.2.3. Richter's model

Richter et al[85] developed a Monte Carlo simulation to model outcomes of AIDS treatments. In summary, this model takes into consideration survival data, number of patients with AIDS, number of deaths, accrued quality-adjusted life years (QALYs), costs and duration of effectiveness for each regimen. The effectiveness of the first regimens were estimated by looking at maximum percentage of patients achieving virological suppression. For these patients, clinical trials' data was used to calculate the virologic failure rate. To achieve this, failure rate was modeled using a uniform distribution for the time to achieve maximum suppression and the time at which all patients have failed. Kolmogorov-Smirnov statistic was used to find the best fit for the model. Second and third line therapy effectiveness data were adapted from Baxter[86]. Risk of AIDS and mortality is derived from cohort data based on CD4 level. This model is run on Microsoft Excel© software.

Richter's model makes a number of assumptions. It considers that an individual experiencing treatment failure will have a return of viral load back to its baseline. This assumption is acceptable when antiretroviral therapy is discontinued. In reality, when failing therapy is continued, antiviral pressure is maintained and resistant HIV strains , which is characterized by a reduced replication capacity[87], leads to lower viral load than when the patient is off treatment.

From an immune reconstitution standpoint, CD4 was increased after the first initial 3 months of successful therapy based on clinical trial data. Thereafter, individuals cease to benefit any additional increase in CD4 for successful therapy. It also ignores other interventions such as primary prophylaxis aimed at preventing clinical complication of HIV progression. However, it is a model easy to operate and to adapt to different comparators.

2.2.1.1.2.4. Caro's model

Caro et al[68] created a model in which five health states were found. The model started with naïve-to-treatment state, followed by a state called RTW. RTW stands for Responding, Tolerating and Willing to adhere. The following health states would be antiretroviral failure, followed by AIDS but alive and then Death. RTW stage is defined as the proportion of patients still on treatment at 24 weeks from clinical trial data. Failure rate was defined as the number of participants in the RTW state who developed AIDS or met the criteria for virological failure at week 72. Other outcomes of interest included survival, time to AIDS, time with AIDS, time to treatment failure and health care costs. Second and third line therapy are extracted from published cohort sources. Although quite similar to Richter's[85] model, this model differs as it assumes that reversal from the AIDS stage is not possible. It also assumes that the maximum response is achieved at 6 months. Lastly, the risk of AIDS was calculated by adjusting the MACS cohort for the antiretroviral failure as per the patient's initial viral load, CD4 count and

duration of disease. It does not model the CD4 count decline like other models based on Mellor's data[24].

2.2.1.1.2.5. Cook's model

In 1999, Cook[72] developed an economic model based on the data of the first clinical trial involving a protease inhibitor, indinavir. The main goal was to incorporate viral load measure into an economic model. This model set up several assumptions such as failure of therapy after two year due to the lack long follow-up clinical trials. It also used adapted formula from the MACS cohort to simulate disease progression. It did not allow for future line of therapy. Although Cook's model was published in the era of HAART, it represents the transition between the pre and post HAART era and will not be discussed further.

2.2.1.1.2.6. Sendi's model

The Swiss HIV cohort is one of the largest HIV cohort worldwide with over 9000 participants. Sendi et al[71] used the cohort to look at the cost-effectiveness of HAART. The Markov model includes three stages: No AIDS, AIDS and death. The transition occurs from No AIDS to either death or AIDS and from AIDS to death. Reversion to No AIDS is not possible. Three levels of CD4 count group are available. Viral load data was not used to model HIV natural progression. Data from the cohort was used to derive transition probabilities and costs. This detailed cohort allows to look at HIV and non HIV-related mortality and captures costs through micro-costing system. However, it only relies to local practices and reflects uses of antiretroviral up to January 1998.

2.2.1.1.2.7. *Models from Non peer reviewed publication*

Four published cost effectiveness studies[88-91] based on abstracts were also retrieved during the search strategy. The abstract format provides very limited information on the characteristics of the models. Two of these models were specific to treatment-experienced patients. Boril et al[88] looked at the same comparison as the one in this study. The economic model used in the Borrill study was a simple model elaborated by Chancellor[92], which include four health states. Further details on these studies can be found in appendix 4.

2.2.2. HLA B*5701 Economic Model

2.2.2.1. Background

The most notable side effect of abacavir is a hypersensitivity reaction (HSR) that occurs in 5 to 8 percent of patients. This reaction is a multi-organ systemic illness that occurs within the first 6 weeks of HIV-infected patients who initiate therapy with abacavir[93]. Rechallenging abacavir in patients with previous HSR could be fatal. This reaction can be prevented by screening for an ancestry gene called HLA B*5701. Absence of this gene eliminates the risk of immunologically proven abacavir HSR. Since the publication of the PREDICT study in 2007, it has become standard of care to use this test before initiating abacavir[18].

PREDICT[36, 37] is a double-blind randomized diagnostic trial looking at the efficacy of preventing abacavir HSR by screening for HLA B*5701 genotype. The study randomized 1956 HIV-infected patients from 19 countries who had not previously received abacavir. One group was assigned randomly to the prospective HLA B*5701 genotyping while the other group had the same test performed retrospectively after the window period for the reaction expired. On the prospective genotyping arm, patients who tested positive for the presence of HLA B*5701 were not administered abacavir and were offered an alternative NRTI. HSRs to abacavir were diagnosed by the principal investigator at the site, without the use of predefined clinical criteria. Assessments were performed at the time of study entry, on day 1 (baseline), and at weeks 1, 2, and 6. Clinically diagnosed HSR to abacavir was confirmed immunologically using epicutaneous patch testing 6 to 10 weeks after the onset of the reaction. The patch test was validated on the first 100 patients tolerant to abacavir.

On the prospective arm, 55 patients out of 980 patients tested positive and did not receive abacavir. Of the 858 patients eligible for outcome measurement, 802 patients were evaluated. In the control arm, 847 of the 976 randomized patients were eligible for outcome evaluation. The number of clinically diagnosed HSR to abacavir was 27/803 (3.4%) in the prospective arm and 66/847 (7.8%) in the controlled arm with an odds ratio of 0.40 (95% CI: 0.25–0.62). Immunologically confirmed cases in the prospective arm compared to the control arm were 0/802 and 23/842 (2.7%) with an odds ratio of 0.03 (95% CI 0.00–0.18). As a measure of performance to prevent HSR to abacavir, HLA B*5701 genotyping obtained a

negative predictive value of 100% for immunologically confirmed HSR (95% CI: 99.5%–100%) and 95.5% (95% CI: 93.8%–96.8%) for clinically diagnosed HSR. Given the effectiveness of the HLA B*5701 genotyping to decrease the discontinuation of abacavir toxicity, because genotyping test is now considered standard of care and because none of the clinical trials have yet included genotyping in their design, it is mandatory to adapt the current known economic models to reflect the current practice. Therefore, a decision tree will be designed to account for the relative efficacy of HLA B*5701 genotyping.

2.2.2.2. Literature search

The same strategy as the one used for identification of economic model was performed. The only change was the addition of the search terms 'HLA*' and 'genotyp*' restricted to the titles for the MedLine search. For conference searches, the term abacavir captured with good sensitivity the economic analyses related to HLA B*5701. Three cost effectiveness studies of HLA B*5701 screening were identified[76, 94, 95]

2.2.2.3. Models for HLA B*5701

Hughes et al[94] assessed the cost-effectiveness of HLA genotyping (appendix 5). The model assumes that patients start first-line antiretroviral therapy with a triple NRTI therapy (abacavir/zidovudine/lamivudine), which is currently not recommended anymore due to inferior efficacy[18]. Different scenarios were tested as alternative therapies for tolerance of failure to abacavir. The model took into

account the probability of hypersensitivity, the probability of positive for HLA B*5701 testing, the cost of treating a HSR and the costs of alternative treatments to abacavir. Because the publication of this work pre-dates the PREDICT trial, the performance of genotyping was assessed using pooled data from previously published cohorts and the author's cohort. One major assumption applied to the model was that alternatives to abacavir were considered as being equally effective.

Schackman et al[76] presented an abstract looking at the cost-effectiveness of HLA genotyping (appendix 6). The model follows actual recommendations from practice guidelines as it models abacavir in comparison to tenofovir. Schackman's decision analytic tree accounts for level of genotype testing (universal or none), occurrence of nephrotoxicity or abacavir HSR, and effectiveness of alternative therapy should a substitution be needed. It is then attached to the CEPAC Markov model discussed earlier. This model used recent data from RCT and cohort published literature. It makes several assumptions:

1) equal efficacy between abacavir and tenofovir-based treatment in first-line therapy;

2) probability of an unconfirmed HSR diagnosis is not affected by the prevalence of HLA-B*5701;

3) patients with unconfirmed HSR incur the same cost and quality of life effects as patients with confirmed mild HSR.

No information is available with regards to the duration of the decision tree analysis.

The last model was presented in the summer of 2008 during the International AIDS Conference by Farkouh et al[95] (appendix 7). The design of this cost effectiveness study includes a decision analysis tree attached to a Markov model for HIV disease progression (ADVANCE). This model suggests that once treatment is indicated, patient starts efavirenz with either tenofovir/emtricitabine or abacavir/lamivudine. HLA B*5701 genotype is only performed on patient starting abacavir arm. If the genotype result is positive, treatment is changed to tenofovir/emtricitabine. If negative, then a proportion of subjects will experience suspected HSR, which needs to be clinically confirmed before change to tenofovir/emtricitabine occurs.

2.3. Selection, justification and adaptation of the Economic Model Design

Identified economic models can be grouped into two categories. A model can be based on clinical trial results relating to virologic response. In these models, virological data (i.e. viral suppression) is extracted. The virologic response is then translated into immunologic suppression (CD4 count decline), which is in turn associated with AIDS and death. These associations are epidemiological in nature. Second and third line therapies are modeled from cohort data for the

most part[96]. They are derived based on the clinical progression from local small databases to international large cohorts.

Other models use data extrapolated directly from large databases such as the HIV Swiss cohort[71]. Complication and use of resources are calculated according to pre-set categories such as CD4 count categories. These models ignore specific interventions and represent a mixture of therapies (mix of NNRTI- and PI-based therapy for instance).

It has been recognized that a variety of levels of evidence is used in decision models[97]. It was suggested that for parameters that can strongly influence results (e.g. efficacy data, safety), high quality evidence should be used. RCTs and meta-analyses of RCTs are considered being the best level of evidence for these parameters[97, 98]. However, whether choosing RCTs or epidemiological data, each of them has their own pros and cons[99, 100]. RCTs are considered the best evidence and should be selected for assessment of clinical effectiveness[101]. Randomization, allocation concealment and blinding are all factors that help to maximize the internal validity and minimize biases[102]. However, RCTs may not generalize well to the population. First, eligibility criteria are set a priori in a RCT. This selection of patients may lead to a different response from the intervention. Second, controlled environment usually aims for the optimal care and maximum compliance, which is usually not the case in the day-to-day clinical practice. Cohort data are exempt from this controlled environment but suffers from several limitations[103]. First, epidemiologic studies consider the degree of association between factors. So this type of evidence is geared toward hypothesis testing,

but may be weak to predict future incidence. It is also highly dependant of the location and time at which the data was assembled. External validity can be considered valid only if there is homogeneity in treatment response across time and location[103]. Because HIV treatment evolves rapidly, some of the cohort may provide data that do not translate current treatments. Despite these limitations, cohort data takes into account the overall survival of the population rather than modeling through mathematical functions[103]. It can therefore better reflect the actual use and effectiveness of an intervention.

I believe that the accuracy and up-to-date information from RCTs are important. Consequently, the approach of using RCTs for the first-line therapy is selected for this study.

2.3.1. Selection and Justification

I used a two-step approach to address the research question. Because HLA B*5701 genotyping is changing the risk associated to initiating therapy with abacavir-based regimens, the first part of the model will include a decision analysis tree taking into account the benefits of performing this test. Second, a Markov model will simulate HIV progression throughout two different lines of treatment.

2.3.1.1. HIV Progression Markov Model

An important component of economic models is the modeling of the clinical disease progression. Interventions meant to alter disease progression can then be incorporated in order to measure its effectiveness. In HIV, surrogate markers such as CD4 and viral load were shown to predict mortality and morbidity due to AIDS[24].

From the identified models, the design of the models used by Sendi[71] and Caro[68] are dismissed as they ignore the value of HIV viral load in disease progression. Cook's[72] does consider HIV viral load but the numerous assumptions on the duration of viral load suppression are not in alignment with current knowledge and practices. Simpson's[73], CEPAC[63] and Richter's[85] models consider the value of HIV viral load. Simpson's uses individual patient (IPD) data from clinical trials for changes in CD4 count. Although IPD allows for a more in-depth analysis, it is more time consuming and the data required are generally unavailable. More research is needed to establish the additional value of IPD over cohort data.[98]. CEPAC uses a specific program with the underlying coding not freely accessible. The Richter model is both flexible and intuitive as it accounts for the long-term failure rate based on the rate of failure after the maximum virological response was achieved. Clinical data from published RCT can be input easily. The reporting of the Richter model is transparent and the basic structure can be replicated within a standard spreadsheet software such as Excel. Thus, the basic

structure of the Richter model will be employed in this analysis, although the model itself was constructed specifically for this thesis.

The model will simulate the progression of HIV as follows. First, patients will enter into the simulation with CD4 count and viral load reflective of a recent clinical trial in treatment-naïve patients. Cycle length will be 6 months. The first cycle will simulate the probability of responding to treatment, which is related to the maximal virologic response. Subsequent cycles in the first-line therapy will account for failure cases as per failure rate. At time of failure, patients will then move to second-line therapy. The same pattern will take place in subsequent lines of therapy until a maximum of three lines of therapy fail. At this time, natural progression of the disease will resume as per the baseline HIV viral load. The time horizon will be limited to 30 years.

The model is constructed on a first-order Monte Carlo simulation in that it simulates the progression each individual patient within a cohort of 1000 patients. Progression is simulated based on the probability of events obtained from the literature. For each individual patient at each cycle, the model provides CD4 count, line of therapy, HIV/AIDS status, survival, specific opportunistic infections, and the associated costs and utility. Random numbers were generated for the following parameters: treatment failure, mortality, CD4 changes and AIDS events. The same random numbers are used for both treatment options leading to differences occurring due to treatment specific data rather than random chance. These random numbers allow for the modeling of the variability in patient progression in terms of events at each cycle.

The relationship between CD4 count and viral load will come from CEPAC data. CD4 reconstitution will be simulated using the UK-CHIC observational cohort study. It showed that CD4 count increases over a 5-year period of the study, though the rate is slower after the first year of therapy. The rate was also modified as per baseline CD4 count (Table 5).

Table 5

UNADJUSTED ESTIMATES OF MEAN YEARLY INCREASES IN CD4 COUNT FROM START OF HAART TO 5 YEARS, ACCORDING TO BASELINE CD4 COUNT, AMONG PATIENTS WITH CONTINUOUS VIRAL SUPPRESSION

Baseline CD4 count (cells/mm^3)	Estimated mean yearly increase in CD4 count (cells/mm^3)[95% CI]				
	Number of years since start of HAART				
	0-1 year	1-2 years	2-3 years	3-4 years	4-5 years
<25	181 [169,192]	83 [77,89]	55 [49,62]	40 [33,47]	30 [23,37]
25-49	181 [166,195]	69 [61,76]	43 [35,51]	29 [21,38]	21 [12,29]
50-99	175 [164,186]	64 [59,70]	41 [35,47]	29 [23,36]	22 [15,28]
100-199	172 [163,180]	56 [52,60]	34 [30,38]	23 [19,28]	17 [12,21]
200-349	184 [175,193]	54 [49,58]	31 [26,36]	20 [15,25]	13 [8,18]
350-499	180 [157,203]	52 [41,62]	30 [19,41]	19 [8,31]	13 [2,24]
≥500	98 [61,135]	30 [13,48]	19 [1,37]	13 [-5,31]	10 [-8,28]

Since no data is available after 5 years, no further increase in CD4 count is going to be assumed. At time of failure, a penalty on CD4 count equivalent to the loss of the gain obtained in the precedent year will be applied.

CD4 count will be correlated to the risk of the onset of AIDS and the associated opportunistic infection. CEPAC transition probabilities include a specific risk for

acquiring AIDS. Both the probability of developing AIDS and the related risk of opportunistic infections is a function of CD4 count and is based on published data within CEPAC.

Each opportunistic infection is assigned a utility value. Richter's model applies a utility value for AIDS regardless to the type of opportunistic infections. Therefore, my model will include the disutility associated with opportunistic infections by incorporating the CEPAC probabilities of opportunistic infection.

Death will be linked to CD4 level. EuroSIDA study group[104] analyzed data for 9803 patients in 70 European HIV centres including ones in Israel and Argentina. Incidence rates of AIDS or death were calculated for overall and most recent CD4 count in three treatment eras (pre-HAART, early-HAART, and late-HAART). The late-HAART overall mortality will be used in this study (Table 6).

Table 6

All Cause mortality per CD4 count[104]

CD4 count	All cause mortality per 100 PY (95% CI)
≤20	34,6 (28,6– 40,6)
21–50	25,7 (20,5– 30,9)
51–100	8,3 (6,3– 10,3)
101–200	4,0 (3,3– 4,7)
201–350	1,4 (1,1– 1,7)
>350	0,7 (0,6– 0,8)

First-line therapy will consist of the comparison between tenofovir/emtricitabine and abacavir/lamivudine in treatment-naïve individuals. Use of direct and indirect evidence will provide an estimate of relative efficacy between the 2 comparators.

After consultation with clinical experts at the immunodeficiency clinic at The Ottawa Hospital, a consensus was reached for a common treatment pathway that represents the recent advances in the treatment of HIV. Second and third line therapies are selected a priori. Lopinavir/ritonavir-based therapy is selected for second-line therapy. Data from the TITAN study[105, 106] comparing 2 protease inhibitors (darunavir/ritonavir versus lopinavir/ritonavir) with optimized background is considered reflecting trends in actual practice for early treatment-experienced patients. I will consider subjects failing this line of treatment to evolve to more advanced treatment-experienced stage. DUET is a recent study in the advanced treatment-experienced patients. It compares the use of etravirine, which is a recent NNRTI, to placebo with optimized background regimen including darunavir. Maximum response and treatment failure rate will be calculated using the same method as in the first-line therapy. After failure of the third-line, we will assume that the viral load returns to the baseline value and that the natural progression will resume[107]. This pathway will be identical for both arms of this cost-effectiveness study.

Use of resources and selection of the utility factor will be discussed later in the Methods section.

2.3.1.2. HLA B*5701 Models

The models from Schackman and Farkouh represent current trends in the treatment of HIV disease as per clinical guidelines. They attempt to simulate the relative cost effectiveness between the two recommended treatments and share the same general objective of comparing abacavir-based versus tenofovir-based regimes. However, they differ on the following points:

- Nephrotoxicity: Nephrotoxicity is considered in Schackman's decision analytic tree, assuming that nephrotoxicity occurs early in the treatment. Clinical reports support that nephrotoxicity from tenofovir is cumulative and happens several months after starting therapy[46]. Furthermore, lack of homogeneity for its definition (change in serum creatinine, calculated creatinine clearance using either Cockroft and Gault or MDRD methods) as well as other confounders[47, 56] (e.g. diabetes, duration of infection, CD4 count, age and concomitant nephrotoxic drugs) makes it extremely difficult to estimate precisely. The clinical significance of nephrotoxicity in treatment-naive patients starting tenofovir is minimal[46]. Farkouh's model captures nephrotoxicity in the Markov model.

- Outcome from abacavir HSR: Schackman assumes that death can occur following abacavir HSR. Although this is a serious potential

complication from abacavir HSR seen in the early days of abacavir, it was not reported in any cohort and RCT using HLA B*5701 pre-screening strategies. Farkouh's does not consider mortality as an outcome.

The decision analytic tree used in this analysis will be similar to that used in the Farkouh study.

In summary, my model is configured as follows. All patients who will receive abacavir will have a HLA B*5701 testing. This modification is made necessary due to the fact that the selection of antiretroviral agents involves the consideration of several factors, with HLA genotyping being one of them. Then, based on the results of the test, patients will go on one of the two arms, i.e. abacavir/lamivudine or tenofovir/emtricitabine. In patients on the abacavir/lamivudine, if HLA B*5701 is present, then the subject will go automatically on tenofovir/emtricitabine treatment. Otherwise, subjects will receive abacavir/lamivudine as planned. These subjects can then be tolerant or suspect of an abacavir HSR. In suspected patients, some of them will be false positive HSR while others will be confirmed after an outpatient consultation with a HIV specialist. Only those with confirmed HSR will change abacavir/lamivudine to tenofovir/emtricitabine.

Unlike Farkouh, the performance of the HLA B*5701 test will come from the PREDICT trial. It will be assumed that the patient-suspected reactions

in the model are representative of the clinically suspected HSR in the study. Similarly, the clinically diagnosed in the model will be equivalent to what the study called immunologically confirmed HSR. Details are found in the cost section.

The assumptions of no mortality imputed to abacavir HSR and no discontinuation due to nephrotoxicity are acceptable based on recent evidence from cohort trials using HLA B*5701 genotyping. Unlike Farkouh's model, the duration of this decision analytic tree will be 30 days to be in accordance with the median onset of HSR seen in PREDICT[36] [10 days (interquartile range, 3 to 14)].

2.3.2. Parameters for the Economic Model

The economic model requires two parameters to approximate HIV disease progression while on treatment, namely: Maximal virologic response and virologic failure rate. In addition, the model accounts for HLA B*5701 genotyping. Beside effectiveness, costs and utility values will be discussed in the next sections.

2.3.2.1. Effectiveness of comparative co-formulated NRTIs

When this project of comparing the cost effectiveness of abacavir/lamivudine and tenofovir/emtricitabine was initiated in early 2007, HIV drug development was mainly focused on dug classes other than NRTIs. From January 2003 to July 2008, Health Canada issued notice of compliance to eight new HIV drugs[108]. Only two of them are NRTIs, namely emtricitabine and tenofovir[109]. Interestingly, NRTIs are indicated in all patients initiating therapy. Given the widespread use of NRTIs, the paucity of comparative clinical data in the literature is surprising. Therefore, it was expected that few comparative NRTIs RCT would be available. An exhaustive systematic review was conducted. In the eventuality that no direct comparison studies were available, it was planned to explore the effect of each combination independently (i.e. tenofovir/emtricitabine and abacavir/lamivudine) compared to recommended dual NRTIs backbone therapy and apply indirect comparison methods to derive comparative efficacy. DHHS reports clinical trials in their guidelines. Along with personal and other experts' opinions, it is conceivable to address the question through 3 pathways: head-to-head comparison between abacavir/lamivudine and tenofovir/emtricitabine and two indirect comparisons using zidovudine/lamivudine and stavudine/lamivudine as common comparators. This section describes the search strategy, sets the eligibility criteria and provides a discussion of the efficacy measurements. It will be followed by a description of the identified studies. Details on extraction of

effectiveness measures relevant to the economic model (maximal virological response [MVR] and virological failure rate) will also be discussed.

Indirect comparison will be further discussed in the Methods section.

2.3.2.1.1. Literature Systematic Review

2.3.2.1.1.1. Question Formulation

The literature search was configured to look at this specific question: In HIV-infected patients with no prior treatment, does abacavir/lamivudine have similar antiretroviral activity as tenofovir/emtricitabine?

2.3.2.1.1.2. Literature Search

The literature search was performed through MedLine and Embase databases. The strategy is described in Appendix 8. The search was done from 1995 until July 13, 2008. Because there was a chance for missing recent evidence, the latest conference abstracts were included in the search strategy. Major international HIV conferences from 2005 to August 2008 were searched through their respective websites or abstract books. These include CROI, ICAAC, IAS, WAC, EACS and CAHR meeting. A search engine was available on the website for all conferences except ICAAC and recent CAHR abstracts. Search engines on website are limited in term of capacity to combine search terms. Therefore, a simplified search was performed using the following terms in titles and abstracts: abacavir, Kivexa®, Epzicom®, emtricitabine, FTC, tenofovir and Truvada®. For

ICAAC and CAHR, the abstract book index was used to search manually for the same keywords.

2.3.2.1.1.3. Eligibility criteria

This review looked at HIV-infected individuals aged at least 18 year-old. In an attempt to ensure the treatment of wild type HIV strains, the participants needed to be naïve to treatment. The intervention included the use of lamivudine/abacavir combination in comparison to tenofovir/emtricitabine with the same third antiretroviral as recommended per DHHS Guidelines[18]. In the eventuality that no direct comparison studies were available, we planned to explore the effect of each combination independently (i.e. tenofovir/emtricitabine and abacavir/lamivudine) compared to recommended dual NRTIs backbone therapy.

Only randomized controlled trials were included in this review. No time limits were applied. French and English articles were considered.

2.3.2.1.1.4. Study selection & Data Collection process

Studies were identified and a first screen was conducted eliminating all studies without the mention randomized control trial, HIV infection, or those referring to experienced patients (terms: experienced, salvage, rescue, advanced). In the second step, studies were checked to confirm eligibility. These two first steps were performed by myself. Extraction of the data was done by myself through a non-validated three-page instrument that records the methodology, desired outcome and quality. Problems in the extraction of the results were to be resolved by consensus with the thesis supervisors.

2.3.2.1.1.5. Summary measures

The economic model requires two important efficacy measurements: The maximum percentage of patients who achieved viral suppression and the virological failure rate. The latter is calculated by dividing the percentage of individuals who lost virological suppression since maximum response by the follow up time.

The maximum virological response was calculated by looking at the maximum proportions of patients reaching undetectable HIV viral load. This measure can be estimated either from table in the publication or extracted from graphs. The virological failure rate was calculated by calculating the slope between the MVR and follow-up observations. Multiple point estimate response at various time points was recorded. The slope was estimated by regression analysis. All these data were collected using the reported ITT analysis. If several ITT definitions were reported (missing equals failure, lost observation carried forward, etc), the strictest definition was used. Virological suppression cut-offs of less than 50 copies/mL was selected.

In the situation where efficacy data is reported only by graphics, extrapolation was performed using Acrobat measuring function (Adobe Acrobat professional 7.0).

If pre-screening patients for HLA genotyping is not used in the design of the identified studies using abacavir, the number of discontinuation due to HSR was also extracted to enable the correction of the maximal response. This correction was also applied to the comparative arm if the study is blinded to the researchers and patients.

2.3.2.1.1.6. Risk of Bias in included studies and across studies

It is possible to introduce bias into this review, mainly publication bias. Publication bias may result from the likelihood for a study to be published in function of the significance of the results regardless of its quality. In addition, most of these studies are industry-sponsored, and therefore the likelihood to release the information as well as the promptness to make the information available is variable depending of the outcome. A funnel plot (effect size versus inverse of the variance) would be used in an attempt to capture this phenomenon.

2.3.2.1.1.7. Results of identified studies

Nine studies fulfilled the inclusion and exclusion criteria and are summarized in appendix 9[29, 110-120]. They are categorized by NRTIs combinations. Only one study directly compares abacavir/lamivudine and tenofovir/emtricitabine[120]. All others use two common comparators: zidovudine/lamivudine or stavudine/lamivudine, and are used to derive indirect estimates of relative

efficacy. The following text provides a summary of these studies. Greater details are available in appendix 10.

Direct Comparison

HEAT was presented at two major HIV conferences in February [120] and August[121] 2008. It is the first and only published double-blind placebo-control RCT comparing abacavir/lamivudine to tenofovir/emtricitabine in combination with lopinavir/ritonavir. The primary objectives were to establish comparative virological efficacy at 48 weeks and to compare the safety and tolerability at 96 weeks. Three hundred and forty three participants were assigned to the abacavir/lamivudine while 345 were in the tenofovir/emtricitabine arm. Substituting zidovudine/lamivudine for abacavir/lamivudine or tenofovir/emtricitabine was also allowed for suspected abacavir HSR or renal toxicity. These changes were not counted as failures in the primary analysis using intent-to-treat missing equals failure (M=F) definition. The primary objective was calculated using M=F, thus allowing changes. At week 48, 68% of subjects on abacavir/lamivudine versus 67% in tenofovir/emtricitabine achieved viral load < 50 copies/mL (95% CI for the difference: -6.63%, 7.40%). At week 96, the difference in efficacy was maintained (95% CI for the difference: -5.41%, 9.32%).

However, allowed switches for toxicity to NRTIs (14 in abacavir/lamivudine and 3 in tenofovir/emtricitabine) may bias the results. It is impossible to isolate the relative contribution of the substitutes over the allocated NRTIs.

2.3.2.1.2. Indirect Comparison

Without a doubt, a RCT is the design of choice to evaluate comparative efficacy between two or more interventions. Indirect comparisons can be used in specific circumstances. Glenny et al[122] has produced an excellent review on indirect comparisons of competing interventions (appendix 11). Their objective was to survey the frequency of use of indirect comparisons in systematic reviews and evaluate and critic the statistics used in such analysis. They suggest that: 'However, in many areas, available trials may not have directly compared the specific treatments or regimens of interest. A common example is where there is a class of several drugs, each of which has been studied in placebo-controlled RCTs, but there are no trials (or very few) in which the drugs have been directly compared with each other.' A few years ago, comparison between the two recommended NRTI combinations abacavir/lamivudine and tenofovir/emtricitabine was fulfilling these criteria. Despite the publication of recent head to head trial, it was decided to contrast the result of the HEAT study with other studies using indirect comparison technique.

The nature of indirect comparison involves the comparison of studies using different treatment comparison. It is similar to using two meta-analyses to calculate an estimate for a specific comparison. Thus, statistical methodological components of meta-analysis are analogous to the ones encountered for indirect

comparison. The common form of indirect comparison includes the comparison of A vs B, for which the only evidence is for A vs C and B vs C.

The adapted method was the classical method using aggregate data. This method is an extension from the classical meta-analysis statistical methods. The meta-analysis method involves a standard 2-step approach, whereas a summary statistic for each study is calculated and then weighted to provide an overall estimate. Standard methods include Mantel-Haenszel methods and the generic inverse variance method. Added to this approach, indirect comparison adds a final step which is the combination of the two distinct meta-analysis. A standard statistical result is that the variance (θ) of the difference between two independent estimates is the sum of the two variances. Given two estimated effects θ_{AB} and θ_{AC} for comparisons of A vs B and A vs C (common comparator A), the effect for the comparison B vs C is estimated as $\theta_{BC} = \theta_{AB} - \theta_{AC}$, and var $(\theta_{BC}) = var(\theta_{AB}) + var(\theta_{AC})$. A 95% confidence interval for θ_{BC} is obtained as $\theta_{BC} \pm 1.96\sqrt{[var\ (\theta_{BC})]}$. Fixed effect meta-analysis is the method of choice selected by all authors identified in their search.

2.3.2.1.2.1. Selection and justification of indirect comparison

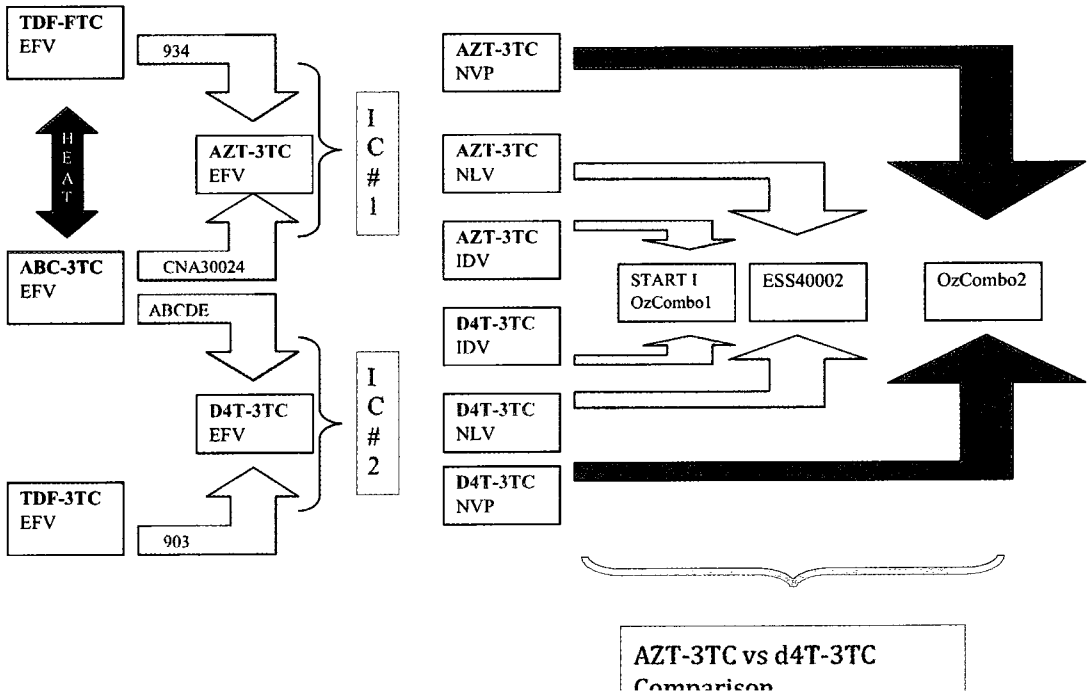
There are few studies in each of our scenarios to derive an estimate on the comparative effectiveness of abacavir/lamivudine and tenofovir/emtricitabine. In most of the cases, only two studies are available which prevents us from using a

random effect model. Because of the limited number of trials, adjusted indirect with fixed effect will be selected. Endpoints of interest will be in accordance with selected endpoints needed for the economic analysis: failure rate and maximum virological suppression.

Two indirect comparison pathways can be looked at (figure 1). First, zidovudine/lamivudine combination was used in both GS-934 and CNA30024 (Indirect Comparison #1). Second, stavudine/lamivudine combination was common in GS-903 and ABCDE study (Indirect Comparison #2). The results of the indirect comparison will serve to verify the findings in the HEAT study. Finally, we can compare the relative efficacy of both common comparators, i.e. zidovudine/lamivudine and stavudine/lamivudine. This comparison will be made to strengthen the previous indirect comparison using proportion of patients with viral load < 50 copies/mL at week 48.

Figure 1

Schematic representation of indirect comparisons



comparison through zidovudine/lamivudine

GS-934[29] and CNA30024[117] compared zidovudine/lamivudine to tenofovir/emtricitabine and abacavir/lamivudine respectively.

GS-934

GS-934 is a multicenter international non-inferiority RCT comparing zidovudine/lamivudine to tenofovir/emtricitabine[29]. Five hundred and seventeen patients were randomized to one of the two arms. The primary objective was to assess the non-inferiority as measured by HIV viral load < 400 copies/mL through week 48, using ITT-TLOVR algorithm.

At week 48, 84% reached and maintained a viral load < 400 copies/mL in the tenofovir arm compared to 73% in the zidovudine arm (95% CI for the difference: 4, 19; P = 0.002). The same conclusion was reached using the most stringent assay with 80% of the tenofovir-treated and 70% of the zidovudine-treated subjects reached a viral load < 50 copies/mL (95% CI for the difference: 2, 17; P = 0.02).

The difference in response was partly explained by the rate of virological failure and discontinuations due to side effects. There was nearly twice as much virological failures (23 vs 12) in the zidovudine-lamivudine group than in the tenofovir/emtricitabine group, although this difference did not reach statistical significance.

With a Jadad's score of 3 and despite lack of blinding, GS-934 is a good quality study. Despite criticism from regulatory agencies on methodology weaknesses associated to early divulgation of efficacy data[123], this study proved that considering tolerance and efficacy, tenofovir/emtricitabine exerts superior activity than zidovudine/lamivudine, which was the reference for dual NRTIs backbone during this era. Extended follow-up to week 96[112] and 144[110] were published since the original publication. Tenofovir-based treatment maintained superior antiviral activity throughout week 144, with 64% vs. 56% in zidovudine/lamivudine arm achieving a viral load <50 copies/mL (95% CI of the difference -0.8, 17; p=0.08)[110].

In summary, despite some methodology concerns associated to the release of effectiveness data early in the study, tenofovir/emtricitabine was shown to be superior to zidovudine/lamivudine. The difference in efficacy was maintained after 3 years of follow-up.

CNA30024

Abacavir and zidovudine has been compared in a head-to-head RCT along with lamivudine and efavirenz. CNA30024 was a double-blind placebo non-inferiority RCT involving 628 subjects[117]. The primary efficacy measure was the proportion of subjects with plasma HIV viral load < 50 copies/mL at week 48. Secondary efficacy measures included ITT-TLOVR. Similar to previous studies, CNA30024 scored 3 as per Jadad's scale.

Abacavir and zidovudine were shown to have equivalent efficacy, with 70% vs. 69% of subjects achieving HIV viral load < 50 copies/mL in the abacavir vs. zidovudine arms (95% CI for the difference: -6.3, 7.9). Generally, the incidence of adverse events was comparable between arms. However, fatigue and gastrointestinal intestinal side effects were more frequent in the zidovudine group. Due to the blinded design of the study, suspected abacavir HSR was reported in both arms, 9% in the abacavir group and 3% in the zidovudine group.

GS934 to CNA30024 are comparable in many points from a population perspective. Age, gender and race are relatively similar. Immunologic and virologic baseline characteristic may suggest that GS934 population was more advanced since CD4 count was lower and median viral load was higher at baseline. No subjects discontinued tenofovir due to renal toxicity. Abacavir discontinuation due to suspected HSR was 9%. The difference in these major signature toxicities may explain the difference observed between the common comparator.

Indirect comparison through stavudine/lamivudine

Tenofovir and abacavir were compared to a common comparator, stavudine. Herein, tenofovir was associated with lamivudine rather than emtricitabine. However, lamivudine and emtricitabine exert similar activity against HIV and are considered by the scientific community to be interchangeable[18, 124].

GS-903

Tenofovir and stavudine were compared in a head-to-head trial with lamivudine and efavirenz. GS-903 was an international non-inferiority double-blind RCT involving 602 HIV-infected subjects[111]. The primary endpoint was the proportion of patients with viral load < 400 copies/mL at week 48 on an ITT M=F switch=failure analysis, while a more sensitive assay (50 copies/mL) was used in a secondary analysis. The switch=failure considers all addition or change to antiretrovirals as failure. The publication of this study also included 96 and 144 week data.

At week 48, 79.9% versus 84.1% and 76.3% versus 79.7% of subjects reached a viral load < 400 copies/mL (95% CI for the difference: −10.4, 1.5) and < 50 copies/mL (95% CI for the difference: −9.8, 3.0) for tenofovir and stavudine respectively. At week 144, the study discontinuation rate was slightly higher in the stavudine group than in the tenofovir group (27% versus 33%) due to a higher incidence of adverse events/intercurrent illness.

ABCDE

Abacavir and stavudine were compared in the ABCDE study[118, 119]. ABCDE was an open-label multicenter RCT done in Spain. Participants were randomized to receive abacavir (n=115) or stavudine (n=122) with lamivudine and efavirenz. The study was planned and powered to assess metabolic changes such as lipodystrophy. The comparison of the efficacy was a secondary objective.

Efficacy data were presented using ITT switch=failure using a viral load threshold of 50 copies/mL.

Of the 237 patients, more patients discontinued prematurely study drugs in the stavudine arm compared to the abacavir arm (59 versus 40 patients respectively), mainly due to toxicity. Thirteen patients in the abacavir group experienced HSR while 23 stopped stavudine due to mitochondrial toxicity. Overall, after 96 weeks, a trend favoring abacavir in the proportion of patients with a viral load < 50 copies/mL was observed (60.9% versus 47.5% [95% CI for the difference: 0.8, 26.0]).

Summary:

Tenofovir and abacavir along with lamivudine and efavirenz have been compared to stavudine. The tenofovir trial was powered to look at efficacy and provide a more precise estimate of comparative efficacy. It was also less prone to bias due to the double-blind design.

In contrast, the open-label design abacavir study can be a threat to the internal validity[125]. In fact, the elevated discontinuation rate due to toxicity observed in the stavudine group was possibly influenced by the open-label design.

Nonetheless, using two distinct comparators (zidovudine/lamivudine and stavudine/lamivudine) in the indirect comparison will strengthen the comparison between abacavir/lamivudine and tenofovir/emtricitabine.

Comparison of zidovudine/lamivudine and stavudine/lamivudine

Zidovudine/lamivudine and stavudine/lamivudine are the two common comparators used for the estimation of efficacy between abacavir/lamivudine and tenofovir/emtricitabine. In order to strengthen the relationship between these different NRTI combinations, we will look at the RCTs comparing zidovudine to stavudine.

In the late 90s and early 2000, 4 studies were conducted to directly compare zidovudine to stavudine along with lamivudine. The common third drug comparators were the PIs indinavir and nelfinavir and the NNRTI nevirapine. As described earlier in this section, a pooled efficacy measure will be determined using a common outcome (the proportion of patients with viral load < 50 copies/mL) on three of the four studies (using RevMan 5.0). The risk ratio using fixed-effect Mantel-Haenszel method is selected.

2.3.2.1.3. Extraction of clinical data for the decision model

For the decision model, two parameters are required: maximal virologic response and virological failure rate. In addition to the latter, because HLA B*5701 genotyping affects the rate of maximum virologic response, adjusted maximal response will be calculated for abacavir-based antiretroviral therapy as well as for the comparator arm whenever a double-blind RCT design was used. The following provides details on data extraction for each study.

HEAT

Since the comparison of the NRTIs is at the heart of the research question, it is suitable to use an ITT definition that fits the best to the selected economic model. Thus, it seems inappropriate to use the ITT definition used in the primary analysis which allows switches for abacavir HSR or proximal renal tubule dysfunction. Since our economic model includes HLA B*5701 genotyping, correction for abacavir HSR needs to be applied. Fortunately, ITT MD=F analysis, which considers all switches as failures, was also presented. Personal communication with one of the authors (P Patel, March 10, 2008) led to obtaining detailed breakthrough of the data for the abacavir HSR and virological response using MD=F analysis for assays with a cut-off at 50 copies/mL. Using these data, we can input the number of failure cases accounted by abacavir HSR. Assuming that all abacavir HSR would have been avoided by screening for HLA B*5701 and that all avoided cases of HSR will reach MVR, the adjusted maximal virological response will be adjusted by considering the abacavir HSR suspected cases as reaching undetectable viral load. Therefore suspected abacavir HSR will be added to the numerator. Looking at the HEAT dataset, week 24 is the maximal virological response for viral load <50 copies/mL. Because we cannot assume that all the added suspected abacavir HSR will maintain virological suppression throughout the follow up period, the virological failure rate will be calculated using the unadjusted MVR data provided in the publication. The virological failure rate will be calculated by using regression analysis. This provides a virological failure rate for subjects with viral load < 50 copies/mL equal to 1.8% and 1.7% per

three-month cycle for tenofovir/emtricitabine and abacavir/lamivudine respectively (Table 7).

Table 7

Summary of virologic and immunologic efficacy for the direct comparison between lamivudine/abacavir and tenofovir/emtricitabine

	Efficacy (VL< 50 copies/mL)				Number of HSR	Adjusted maximal Response	Virological Failure Rate per 3 months
	wk	n	N	%			(95% CI)
HEAT [120]							
LPVr- TDF/FTC	12	167	345	48.4%			
LPVr -ABC/3TC	12	151	343	44.0%			
	24	227	345	65.8%	3	66.7%	
	24	227	343	66.2%	14	70.3%	
	48	215	345	62.3%			
	48	220	343	64.1%			
	96	190	345	55.1%			0.0179 (0.0168,0.0190)
	96	192	343	56.0%			0.0175 (0,0023,0.0326)

LPVr=lopinavir/ritonavir, TDF/FTC=tenofovir/emtricitabine, ABC/3TC=abacavir/lamivudine, VL=HIV viral load. HSR=Hypersensitivity reactions

GS-934

Complete information could be retrieved from the 4 publications sources[29, 110, 112, 126] for this study. Because the primary endpoint was selected to be the proportion of subjects with a viral load < 400 copies/mL, extensive details on table format as well as a graphic representing virological suppression over time were presented using this cut-off. For viral load < 50 copies/mL, week 48 data was used as the maximum viral response. Number of subjects was calculated from given percentages available in all three references (table 8).

CNA30024

In CNA30024, maximal virologic response can be determined for the analysis using viral cutoff of 50 copies/mL. In this analysis, extrapolation from the graph provided an estimated 71.5% of treated subjects with an undetectable viral load at 24 weeks for the abacavir arm (appendix 12). Using the same method for extrapolation, the precision of the estimate calculated by dividing the measure obtained with Acrobat and the reported estimate at week 48 was 1.1%. For the zidovudine arm, the maximal response was achieved at week 48, which is the final follow-up time point.

The virological failure rate could be calculated only for the abacavir group using the week 48 data. The results are summarized in **Table 8**.

Table 8

Summary of virologic and immunologic efficacy for the indirect comparison between lamivudine/abacavir and tenofovir/emtricitabine using zidovudine/lamivudine as a common comparator

		Efficacy (VL< 50 copies/mL)			Number of HSR	Adjusted maximal Response	Virological Failure Rate per 3 months
	wk	n	N	%			
Study 934[29]							
EFV-FTC-TDF	48	194	244	79.5%		79.5%	
EFV-AZT-3TC	48	171	243	70.4%		70.4%	
	96	163	244	66.8%			
	96	148	243	60.9%			
	144	156	244	64.0%			0.019
	144	136	243	56.0%			0.018
CNA30024[117]							
EFV-ABC-3TC	24	232	324	71.6%	28	80.2%	
EFV-AZT-3TC	24	na	325	na			
	48	226	324	69.8%			0.020
	48	224	325	68.9%		68.9%	Na

EFV=efavirenz, FTC=emtricitabine, TDF=tenofovir, AZT=zidovudine, 3TC=lamivudine, ABC=abacavir, VL= HIV viral load, HSR=Hypersensitivity reactions

GS 903

Maximal virologic response from GS903 is only available from the graph provided into the publication for the primary endpoint selection, i.e. viral load < 400 copies/mL. No data is available for a virological cutoff of 50 copies/mL. Following personal communication with the manufacturer, data was obtained for this virological cutoff at week 24. This was chosen to be our MVR. The number of subjects was calculated backward from percentages.

The virological failure rate can be calculated using the week 48, 96 and 144 data from the publication using ITT switch=failure analysis (table 9).

Table 9

Summary of virologic and immunologic efficacy for the indirect comparison between lamivudine/abacavir and lamivudine/tenofovir using stavudine/lamivudine as a common comparator

	Efficacy (VL< 50 copies/mL)				Number of HSR	Adjusted maximal Response	Virological Failure Rate per 3 months
	wk	n	N	%			
Study 903 [111]							
EFV-3TC-TDF	24	250	299	83.6%		83.6%	
EFV-3TC-d4T	24	268	301	89.0%		89.0%	
	48	228	299	76.3%			
	48	240	301	79.7%			
	96	217	299	72.6%			
	96	204	301	67.8%			
	144	203	299	67.9%			0.016
	144	188	301	62.5%			0.027
ABCDE [118, 119]							
EFV-ABC-3TC	24	85	115	73.7%	13	85.0%	
EFV-3TV-d4T	24	98	122	80.2%		80.2%	
	48	82	115	71.4%			
	48	90	122	73.8%			
	96	70	115	60.9%			0.021
	96	58	122	47.5%			0.055

EFV=efavirenz, 3TC=lamivudine, TDF=tenofovir, d4T=stavudine, ABC=abacavir
VL= HIV viral load, HSR=Hypersensitivity reactions

ABCDE

The maximal virologic response could be extrapolated using the graph from the conference abstract (appendix 13). It occurred at week 24 for both drugs and was slightly higher for the stavudine. Correction for the rate of abacavir HSR was made to reflect the impact of HLA B5701 pre-screening of our model. The error rate between reported and measured estimates at week 48 was less than 1%.

The virological failure rate was extracted from the same graph. Week 48 data will be extrapolated from the graph. Final 96 week data presented in the final manuscript was also used in the regression model.

OzCombo1-2, START 1, ESS40002

Two common problem associated with these studies are the selection of the primary endpoint and the reporting of the results. Few studies presented extended virological data, showing only the proportion of subjects with a viral load under the selected level of detection. Only START I and ESS40002 presented their data in a way to allow data extraction. Due to this inconsistency, only comparison of the proportion of subjects with a viral load less than 50 copies/mL will be presented. This process excludes START 1 from the pool of studies. Estimation of this outcome was reported in the publications (table 10).

Table 10

Summary of virologic and immunologic efficacy for the direct comparison between zidovudine/lamivudine and stavudine/lamivudine

	Efficacy			
	wk	n	N	VL < 50
OzCombo1[113]				
IDV-AZT-3TC	52	23	35	65.7%
IDV-3TC-d4T	52	20	34	58.8%
OzCombo2[114]				
AZT-3TC-NVP	52	11	15	73.3%
D4T-3TC-NVP	52	13	19	68.4%
ESS40002[115]				
AZT-3TC-NLV	96			39.0%
D4T-3TC-NLV	96			33.0%

AZT=zidovudine, 3TC=lamivudine, IDV=indinavir, NVP=nevirapine, d4T=stavudine, NLV=nelfinavir, VL= HIV viral load

2.3.2.1.4. Indirect Comparison estimates:

Two measurements can be estimated using indirect comparison techniques described earlier. They are the maximum virologic response and the virological failure rate.

Using the direct comparison study, the relative risk for the maximum virological response adjusted for the rate of HSR avoided from HLA B*5701 genotyping was estimated to be 1.054 (95% CI :0.952, 1.167) in favor for abacavir/lamivudine.

Indirect comparison using zidovudine/lamivudine (Indirect comparison #1) or stavudine/lamivudine (Indirect comparison #2) gave an estimate of 1.027 (95% CI: 0.894, 1.178) and 1.130 (95% CI: 0.989, 1.190) in favor of abacavir/lamivudine (table 11).

Table 11

Direct and Indirect Comparison summary measures for maximal virologic response and virological failure rate

Efficacy measures	Maximal virologic response (VL< 50 copies/mL)		Virological Failure Rate per 3 months (VL< 50 copies/mL)	
		RR (95% CI)		RR (95% CI)
Direct Comparison				
ABC/3TC	241/343 (70.3%)		0.0175	0.9799
TDF/FTC	230/345 (66.7%)	1.054 (0.952,1.167)	0.0179	(0.649,1.500)
Indirect Comparison #1 (common comparator = AZT/3TC)		1.027 (0.894,1.178)		Unable to calculate
Indirect Comparison # 2 (common comparator = d4T/3TC)		1.130 (0.989, 1.290)		0.685 (0.285,1.644)

ABC=abacavir, 3TC=lamivudine, TDF=tenofovir, FTC=emtricitabine, d4T=stavudine, VL = HIV viral load

The virological failure rate per 3-month cycle for viral load less than 50 copies/mL was estimated to 0.0175 (95% CI: 0.0023, 0.0326) and 0.0179 (95% CI: 0.0168, 0.0190) for abacavir/lamivudine and tenofovir/emtricitabine respectively. Although no evidence was found on the validity of using indirect comparison to rates, the same methodology is applied to the rate of virological failure, with the exception of the estimation of the standard deviation (SD) calculated for rates using the number of events[127]. For each individual study, the SD will be:

$SD(\ln IR) = \sqrt{(1/a + 1/c)}$,

95% CI = exp [lnIR ± 1.96 SD(ln IR)]

whereas a and c is the number of events (failures) in each comparative arms.

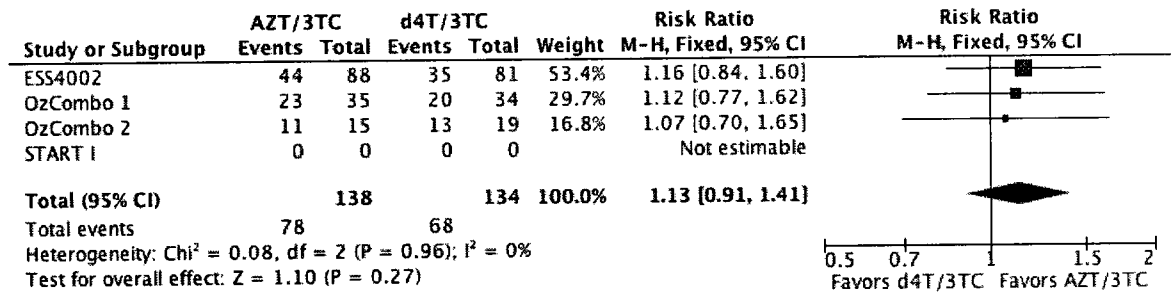
The rate ratio was 0.980 (95% CI: 0.6489, 1.4795) for the direct comparison and 0.6443 (95% CI: 0.3193,1.3003) for the indirect comparison with lamivudine and stavudine.

The results from the indirect comparison support the direct comparison estimates. The 95% CI for the three estimates for maximal virologic response overlaps. Using a validated method to assess the discrepancies between direct and indirect comparisons [122, 128], the difference (95% CI) between the direct and indirect comparisons with zidovudine/lamivudine is -0.0178 (-0.1890, 0.1712) and -0.0151 (-0.1822, 0.1670) with stavudine and lamivudine. Thus, there is no evidence to support that the indirect comparisons differs from the direct comparison.

The pooling of the common comparators zidovudine/lamivudine and stavudine/lamivudine for efficacy was also performed. The outcome of interest was the proportion of subjects with a viral load less than 50 copies/mL. The risk ratio was 1.13 (95% CI: 0.91, 1.41) in favor of zidovudine/lamivudine (figure 2).

Figure 2

Forest Plot of the AZT/3TC versus d4T/3TC trials for viral load < 50 copies/mL at week 48.



The wide confidence interval illustrates well the sample size limitation of the comparison. It supports the fact that both combinations exert similar antiviral efficacy, although it is impossible to assess the relative durability of the treatments.

Publication bias may distort this estimation as described in the systematic review method section. A funnel plot was planned to be done to capture this phenomenon. Unfortunately, only 3 studies were available, therefore it was not presented since a minimum of 10 studies are required to obtain meaningful information.[129]

2.3.2.2. Second and third-line efficacy measures

Second-line therapy consists of lopinavir/ritonavir plus optimal background therapy for both arms of this economic analysis. The estimates for maximal virologic response and the virological failure rate will come from one arm from the Titan study[105, 106]. The data will be extracted following the same methodology as for the first-line therapy.

Third-line therapy will include the combination of darunavir/etravirine plus optimal background therapy. Data from the DUET[130-132] study is used to derive the same two efficacy parameters.

2.3.2.2.1. TITAN

TITAN is a double-blind darunavir/ritonavir or lopinavir/ritonavir RCT plus non-blinded optimal background therapy in early experienced patients[105, 106]. Of the 595 patients randomized in a 1:1 ratio, significantly more darunavir/ritonavir than lopinavir-ritonavir patients achieved HIV viral load < 50 copies/mL (71% versus 60% respectively) at week 48. Week 96 data presented at an international conference was used to calculate the failure rate[106]. MVR and failure rate were 61% and 0,015 per 3 month respectively.

2.3.2.2.2. DUET

DUET 1 and 2[130-132] are two identical double-blind RCTs conducted in different geographic regions evaluating the efficacy of etravirine compared with placebo, in combination with optimized background therapy including darunavir, in patients with triple-class drug resistance in whom antiretroviral therapy had failed. The

primary endpoint was the proportion of patients with confirmed viral load < 50 copies per mL at week 24. The duration of the study was planned to be 96 weeks. Herein, 48-week data of the etravirine arm is summarized in Table 12.

Table 12

Efficacy, Maximal virologic response and probability of virological failure rate for second- and third-line therapy.

	Efficacy (VL < 50 copies/mL)				Maximal Virologic response	Virological Failure Rate per 3 months (95% CI)
	wk	n	N	%		
Second-Line						
Titan						
LPVr + OBR	48	181	297	61%	61%	
	96	163	297	55%		0.015 (0.009, 0.023)
Third-line						
DUET						
DRV-ETR-OBR	24	364	599	60.8%		
	32	372	599	62.1%	62.1%	
	48	362	599	60.4%		0.013 (0.006, 0.023)

LPVr= lopinavir/ritonavir, OBR=optimal background regimen, DRV=darunavir, ETR=etravirine, VL= HIV viral load

The virological failure rate was calculated from extrapolation of the week 32 data provided in a graphic format (appendix 14). The MVR and rate of failure is 62,1% and 0,013 per 3-month.

2.3.3. COSTS

In Section 2.1, a review of the economic models in HIV was undertaken. The characteristics of the identified models were described. In cost-effectiveness studies, clinical and economic data are the two essential components of a model. In this section, cost data will be presented. Data will be grouped as per the stages of the model.

The following cost parameters are required:

- Cost of the genotype test
- Toxicity costs: costs of abacavir HSR
- Costs of drugs for first, second and third-line therapy
- Costs associated with HIV/AIDS excluding drugs

Costs for HLA B*5701 test:

HLA typing for *HLA-B*5701* allele is done using a combination of Sequence Specific Primers (SSP). This system allows rapid *HLA-B*5701* low resolution PCR typing using a primer mix containing four specific primers that can be used to discriminate between HLA-B*5701 and the related B57 subtypes[133]. The costs associated to the test was estimated as US$68 in Schackman's cost effectiveness model[76] and US$88 in Farkouh's[95]. At The Ottawa Hospital, the overall cost including laboratory and clinical interpretation is CAN$100 (Personal communication, Dr Angel). Our local costing will be used for this assay.

Toxicity cost: abacavir HSR

The costs of toxicities are somewhat difficult to estimate precisely. Hughes et al[94] attempted to quantify the costs of abacavir hypersensitivity. They found a large variability in costs. Abacavir HSR was estimated to cost a median of £2611. Schackman was able to attribute a cost based on the severity of the reaction[76, 134]. It ranges from $103 for minor reaction, to $3666 for severe and $31999 for lethal cases. Farkouh[95] established a cost based on suspected abacavir HSR including phone call cost, outpatient clinic and emergency department visits, 1-day in-hospital admission and cost of drug treatment. The base-case value for a HSR is $800 (range $171-$1739).

Based on Farkouh[95], it is assumed that for patient-suspected HSR, all patients will call the physician, two-thirds will need an extra outpatient visit and 6.2% will need an emergency department visit. For clinically confirmed HSR, the same costs incur but a further 5.4% will have a 1-day hospitalization. Unit costs for each item were obtained from The Ottawa Hospital (TOH) institutional costs and Ontario physician fees. For telephone calls, it was assumed that the cost would be equivalent to 0.5 hour of a pharmacist hourly rate ($50). Daily hospital costs, excluding physician fees, for admitted patients are $1319, $348 for an emergency department visit and $279 for an outpatient visit (personal communication, TOH finance department, 2007). Physician fees for outpatient care are billed as a HIV primary care code ($51.70), for emergency visit as a consult for the emergency physician ($97.60) plus an Infectious Diseases

consultation ($132.50) for half of the cases (Table 13). Costs for the drug management are minimal and therefore not considered.

Table 13

Costs and probabilities of hypersensitivity associated with abacavir

	Utilization	Unit cost	Total cost per capita
Costs for Patient Suspected HSR			
Phone consultation	100%	0.5 h x $46/h	$ 23.00
Outpatient Visit	67%	$331	$ 221.77
Emergency Department Visit	6.2%	$512	$ 31.74
1-day hospitalization	0%	$1319	$ 0
Total			$ 276.51
Costs for Clinically Suspected HSR			
Phone consultation	100%	0.5 h x $46/h	$ 23.00
Outpatient Visit	67%	$331	$ 221.77
Emergency Department Visit	6.2%	$512	$ 31.74
1-day hospitalization	5.3%	$1319	$ 69,91
Total			$ 346.42
Costs for HLA B*5701 genotyping assay			$100
HLA B*5701 patient suspected negative predicted value			95.5 (95% CI: 93.8–96.8)
HLA B*5701 Clinically diagnosed negative predicted value			100 (95% CI: 99.5–100)
HLA B*5701 prevalence			109/1956 (5.6%; 95% CI: 4.55, 6.59)
Rate of HSR symptoms among patients who test negative for the allele and initiate abacavir			36/798 (4.5%; 95% CI: 3.07, 5.95)

Costs of drugs for first, second and third line therapy

Most of the RCTs in the review include either the use of efavirenz or lopinavir/ritonavir. Herein, first-line therapy will include the use of efavirenz. Costs for abacavir/lamivudine, tenofovir/emtricitabine, efavirenz and a $7 dispensing fees per prescription will reflect prices in Ontario as per the Ontario Drug Benefits formulary (edition 41). http://www.health.gov.on.ca/english/providers/program/drugs/odbf_eformulary.html).

For second-line therapy, lopinavir/ritonavir was selected to be the protease inhibitor. TITAN was a RCT looking at the comparative efficacy of darunavir/ritonavir to lopinavir/ritonavir in early treatment-experienced patients. A cost-effectiveness study of TITAN data was conducted using adjusted costs for UK, Belgium, Italy and Sweden. It was possible to obtain from the sponsor of the trial the composition of the optimal background regimen, so Canadian costs could be calculated for the lopinavir/ritonavir arm (Table 14).

Table 14

Average Drug Costs of Lopinavir/ritonavir arm of TITAN study in Canadian Dollars

Use of antiretrovirals in TITAN (N=297)	Usage n	Costs per day (Ontario Drug Benefits)	Total daily study costs (including $7 dispensing fees)
Lamivudine 300mg	18	$9.27	$0.56
Tenofovir/emtricitabine	45	$25.28	$3.83
Zidovudine/lamivudine	114	$19.75	$7.58
Didanosine 400mg	84	$10.74	$3.04
Tenofovir 300mg	116	$16.48	$6.44
Stavudine 40mg	36	$9.23	$1.12
Abacavir 300mg	78	$13.07	$3.43
Lopinavir/ritonavir 3 caps	297	$21.83	$21.83
Efavirenz 600mg	15	$14.06	$0.71
Nevirapine 400mg	8	$9.88	$0.27
		Total Daily Costs	$48.80

For third-line treatment, it was decided to use the darunavir/etravirine arms of the DUET study. An economic analysis was performed for DUET trials[135], with the objective to look at the costs per patient reaching and sustaining an undetectable viral load. The annual US costs for antiretrovirals was $46 740, representing 25% of NRTI, 34% of PI, 24% of enfuvirtide and 17% from etravirine costs. The publication provides a complete breakdown of antiretrovirals used. Once adapted for Canadian costs (Ontario Drug Benefits Formulary), the daily costs for antiretrovirals are $120 (Table 15).

Table 15

Average Drug Costs of Darunavir/ritonavir arm of DUET study in Canadian Dollars

Use of ARVs in DUET (N=599)	Usage n	COSTS per day (ODB)	Total daily study costs (including $7 dispensing fees)
Lamivudine 300mg	124	$9.27	$1.92
Tenofovir/emtricitabine	173	$25.28	$7.30
Zidovudine/lamivudine	221	$19.75	$7.29
Didanosine 400mg	117	$10.74	$2.10
Tenofovir 300mg	280	$16.48	$7.70
Stavudine 40mg	94	$9.23	$1.45
Abacavir 300mg	127	$13.07	$2.77
Etravirine 200mg	597	$22.03	$21.96
ENF	272	$79.75	$36.21
Darunavir/ritonavir 600/100mg	595	$30.95	$30.74
Atazanavir/ritonavir 300/100mg	3	$21.99	$0.11
Saquinavir/ritonavir 1000/100mg	1	$19.91	$0.03
Lopinavir/ritonavir 3 caps	3	$21.83	$0.11
		Total Daily Costs	$119.69

Costs associated with HIV/AIDS excluding drug costs

Estimating long-term costs of a HIV population can be quite complicated.

In most countries, health authorities are the main providers for derivation of the cost units. Countries such as Switzerland, Canada, United Kingdom and France are examples where local or national authorities provided data on unit costs. In the US, in addition to some local databases, most of the cost models originate from two surveys: AIDS Cost and Service Utilisation Survey[136] (ACSUS) and HIV Cost and Services Utilisation Study (HCSUS)[59]. In this section, an evaluation of the databases used for estimating unit costs will be presented.

ACSUS is a survey of 1949 patients at 26 HIV centers across US in 1991-1992. HCSUS is a random American survey of 2900 patients in 1996-1997. HCSUS interviewed patients three times and assessed medical care services, other health conditions, quality of life, ability to perform the activities of daily living, out-of-pocket expenses, income, disability status and housing situation. A sample of the HCSUS population was surveyed up until 1999. They were able to stratify by CD4 count, the strata overall expenditure by drug costs, inpatient, outpatient and hospitalization costs. Both surveys did not have sample size large enough to break the data by viral load strata, yet most of the cost-effectiveness studies ignore that fact.

In 2004, a group from Quebec came up with Canadian data for HIV expenditure[137]. An estimated average total cost per person-year was US $ 9445 (CAN $14 829) and US$11754 (CAN $18 454) for Non AIDS and AIDS

respectively in 2002 dollar. These estimates include costs of drugs (antiretrovirals and others), inpatient and outpatient visits.

Interestingly, the overall cost was lower than the one in HCSUS which ranges from $US 532 to $US 2344 monthly. The difference is greater in AIDS patients (CD<200 cells/mm^3) whereas American cost is $1361 to $2344 as opposed to $973 for the Canadian's. The sources of data (administrative database versus survey) may partly explain the disparity. There is no stratification for CD4 or viral load in the Canadian dataset, which limit the applicability to the selected model.

The Quebec data will be used for this analysis. The total cost reported is adjusted to remove the costs of antiretrovirals, which are already accounted for in the treatment pathway for second and third line therapy. After removal of antiretrovirals cost and adjustment to 2009 costs using a 2.12% average annual inflation rate (Bank of Canada website), yearly costs for AIDS and non AIDS are CAN$5674 and CAN$2664.

2.3.4. Discounting

Discounting costs and benefits is an important concept in cost-effectiveness studies. It accounts for time preference, which illustrates the advantage of receiving a benefit earlier. Three of the 6 studies took into account discounting, with rates ranging from 3 to 4%. As per convention, the rate of discounting is fixed at 5% for this analysis[101].

2.3.5. Utility values

Previous cost-effectiveness studies used utility values obtained after transformation of visual analogue scale, which ignores one of the fundamental principles of health value, namely uncertainty. Accepted methods for preference-based utilities include direct methods such as standard gamble and time trade off and indirect questionnaires such as the EQ-5D, HUI 2 and 3 and the SF-6D[101, 138].

The utilities used in the selected cost-effectiveness studies may not truly reflect health status due to changes to treatment within the new era of HAART. Therefore a Medline search was conducted to identify additional studies exploring utility values with respect to HIV and AIDS. The search identified 76 potential articles. Of these studies, many looked specifically at domains related to QoL instruments. Mental and Physical Health are dealt separately and many do not provide the overall QoL measures.

Schackman addressed specifically the issue of utility value in HIV[139]. The objective was to compare health state utilities derived from two different methods,

i.e. patients rating scale (patient-derived) and SF-6D (community sample) utilities from the HCSUS survey. This method to derive utility value is considered valid. Therefore, the community sample for patients with and without prior history of AIDS-defining illnesses, which is divided in 4 CD4 subgroups, will be used (Table 16).

Table 16

Utility Value Reviews

	CEPAC[140]	Holtgrave[141]	Tsevat[142]	Tsevat[142]	Schackman[139]
Method	TTO transformation from rating scale	Median of 6 various utility studies	Rating scale transformation	Quality of well-being scale	SF-6D
Categories	CD4	CD4	Asx: 0.69	Asx: 0.72	No AIDS
	201-300: 0.94	200-499: 0.76	Sx: 0.68	Sx: 0.66	CD4
	101-200: 0.87	<200 : 0.65	AIDS: 0.64	AIDS: 0.63	>500: 0.870
	51-100: 0.81	AIDS: 0.62			201-500: 0.860
	0-50: 0.79				51-200: 0.850
					0-50: 0.832
					AIDS
					PCP: 0.775
					MAC: 0.735
					Toxo: 0.731
					CMV: 0.760
					Fungal: 0.743
					Other: 0.770

Asx: Asymptomatic, Sx: symptomatic, TTO: time trade-off, PCP: Pneumocystis Carinii Pneumonia, MAC: Mycobacterium avium Complex, Toxo: Toxoplasmosis, CMV: Cytomegalovirus

2.3.6. Sensitivity Analysis:

Because many variables can have an effect on the results of the analysis, it is planned to carry out a wide range of deterministic sensitivity analyses. Important parameter values were varied to represent plausible variation of the estimates.

1) Effectiveness data are represented by the MVR and the rate of virological failure. Four distinct analyses were conducted. First, the lower and upper bound of the 95% confidence interval of these estimates were inputted. A combined best-case scenario (upper bound of the confidence interval [UCI] of the MVR and the lower bound confidence interval [LCI] of the failure rate) and worst-case scenario (LCI of the MVR and the UCI confidence interval of the failure rate) were conducted. Second, estimates derived from the indirect comparisons will be substituted. Third, analysis incorporated the latest data coming from ACTG 5202, suggesting the possibility that abacavir-lamivudine may have an increase risk of virological failure in the subset of patients with baseline viral load superior to 100 000 copies/mL. The adjustment equal to 1.053 and 1.094 was applied to MVR and rate of virologic failure (appendix 15).

2) Lastly, in a collaborative cohort study, abacavir based therapy was associated with an increase relative risk of myocardial infarction by 1.9, with a crude rate of 3.3 events per 1000 patient-year. Twenty-one percent of these MI were

fatal. In an attempt to correct for this data, a correction factor was applied to abacavir arm to account for any excess in mortality (appendix 16).

Uncertainty for the following parameters of the economic model will also be applied

- baseline CD4 (100, 400)
- baseline HIV viral load (log 4)
- discount factor (3%; 7%)
- Costs for hospitalization (LCI, UCI)
- Tenofovir or abacavir drug Costs (+10%, or similar)
- Utility values (LCI;UCI)
- Mortality (LCI;UCI)
- HLA B5701 test cost ($30)
- HLA B5701 negative predictive value (LCI;UCI)

2.3.7. Analysis

One thousand patients will be simulated through a first-order Monte Carlo model for 30 years. After completion of the simulation, the average of life expectancy, total costs, and quality of life adjusted year, which is measured by the product of utility value and time spent in a given state. To correct for the fact that events occur not solely at the beginning or the end of the cycle-interval, half-cycle

correction will be applied. Incremental cost-effectiveness ratio (ICER) and incremental net benefits (INB) for an ICER of $50 000 are the measures selected to compare the interventions[143, 144].

In addition to univariate sensitivity analysis as described above, multivariate (or probabilistic) analysis will be performed by allowing all model factors to vary as per the distribution of their estimates. One thousand random draws will be made from the probability distributions of each parameter. From this 1000 replications of the simulated 1000 cases within the cohort will be obtained and a set of 1000 outcome measures (average of life expectancy, costs, QALY) estimated. Data will be presented using Incremental costs versus Incremental QALY, a scatter plot and a cost effectiveness acceptability curve representing the probability of abacavir to be cost-effective.

2.3.8. Economic Evaluation Summary

For each arm, a population of 1000 subjects will enter a Monte Carlo simulation. This population will have the characteristics (age, baseline CD4 and HIV viral load) similar to HEAT study. They will enter into the first-line therapy health state transition based on their chance of achieving treatment response at 6 months (maximal virologic response) and thereafter their risk of failing therapy at each 6-month cycle. Treatment response is associated with a rise in CD4 count for the next 5 years, time after which CD4 will decline as per treatment response. CD4 count is associated with occurrence of opportunistic infections and death. Upon

failure to first-line treatment, a non-differential matrix is applied for effectiveness of second-line and third-line therapy. If failure occurs within the first 5 years, a correction for CD4 gain is applied to account for a diminished response due to virologic replication during the 6-month cycle. Hence, a subject failing in the first five years of HAART initiation will lose one cycle of CD4 reconstitution. Second and third-line treatment transition states are derived from TITAN and DUET studies respectively. After failure of the three lines of therapy, natural disease progression based on baseline viral load and associated CD4 decline will continue until the subject dies. Utility functions are applied based on the occurrence of opportunistic infections and CD4 level.

A summary table of the estimates and uncertainty of the model parameters is shown in Table 17. Uncertainty around parameters is depicted by their 95% confidence intervals. Uncertainty around probabilities will be characterized by beta distributions, around utility values by inverse lognormal distributions and around costs by gamma distributions.

Table 17

Model Parameters Estimates and Uncertainty

Effectiveness

	Adjusted Maximal Virologic Response		Failure rate	
	Estimate	95% CI	Estimate	95% CI
First-Line				
EFV-TDF-FTC	66.7%	61.42, 71.62	0.0179	0.0168, 0.019
EFV-ABC-3TC	70.3%	65.12, 75.05	0.0175	0.0023, 0.0326
Second-line				
LPV-OBR (TITAN)	46.3%	37.31, 55.56	0.025	0.014, 0.043
Third-line				
ETR - OBR (DUET)	62.1%	58.08, 66%	0.013	0.006,0.023

Mortality (6-month estimate)

		95 % CI	
<20	0.1913	0.1550	0.2293
21-50	0.1380	0.1084	0.1687
51-100	0.0424	0.0320	0.0529
101-200	0.0202	0.0166	0.0238
201-350	0.0070	0.0055	0.0085
>350	0.0035	0.0030	0.0040

HIV Disease Progression (monthly)

HIV Viral Load	Decline in CD4	95% CI	
30,001-100,000	6.375	5.88	6.93
10,001-30,000	5.4	4.99	5.87
3,001-10,000	4.6	4.23	4.98
501-3,000	3.733	3.27	4.23
< 500	3.025	2.52	3.49

Probabilities of AIDS (per 6-month)

	0-50	95 % CI	51-100	95 % CI	101-200	95 % CI
PCP	0.1647	0.0991, 0.2430	0.1556	0.0918, 0.2324	0.0545	0.0192, 0.1065
MAC	0.2190	0.1440, 0.3047	0.1744	0.1069, 0.2542	0.0603	0.0227, 0.1143
Toxo	0.2310	0.1542, 0.3180	0.1815	0.1127, 0.2624	0.0641	0.0251, 0.1194
CMV	0.3137	0.2270, 0.4075	0.2077	0.1344, 0.2920	0.0762	0.0330, 0.1354
Fungal	0.3637	0.2727, 0.4599	0.2374	0.1597, 0.3251	0.0839	0.0382, 0.1453
Other	0.5391	0.4414, 0.6354	0.3609	0.2701, 0.4570	0.1246	0.0677, 0.1957

	201-300	95 % CI	301-500	95 % CI	>500	95 % CI
PCP	0.0220	0.0031, 0.0583	0.0051	0.0000, 0.0253	0.0025	0.0000, 0.0169
MAC	0.0233	0.0036, 0.0605	0.0054	0.0000, 0.0261	0.0028	0.0000, 0.0183
Toxo	0.0257	0.0045, 0.0643	0.0059	0.0000, 0.0273	0.0030	0.0000, 0.0189
CMV	0.0292	0.0059, 0.0698	0.0067	0.0000, 0.0293	0.0033	0.0000, 0.0201
Fungal	0.0309	0.0067, 0.0725	0.0084	0.0001, 0.0332	0.0039	0.0000, 0.0217
Other	0.0440	0.0132, 0.0918	0.0136	0.0008, 0.0436	0.0067	0.0000, 0.0292

Table 17

Model Parameters Estimates and Uncertainty (cont'd)

CD4 gain post-HAART

	0-1 years	95% CI	1-2 years	95% CI	2-3 years	95% CI
<25	181	169, 192	83	77, 89	55	49, 62
25-49	181	166, 195	69	61, 76	43	35, 51
50-99	175	164, 186	64	59, 70	41	35, 47
100-199	172	163, 180	56	52, 60	34	30, 38
200-349	184	175, 193	54	49, 58	31	26, 36
350-499	180	157, 203	52	41, 62	30	19, 41
>500	98	61, 135	30	13, 48	19	1, 37

	3-4 years	95% CI	4-5 years	95% CI
<25	40	33, 47	30	23, 37
25-49	29	21, 38	32	12, 29
50-99	29	23, 36	33	15, 28
100-199	23	19, 28	17	12, 21
200-349	20	15, 25	13	8, 18
350-499	19	8, 31	13	2, 24
>500	13	-5, 31	10	-8, 28

Costs

Drugs

First line			
Abacavir/lamivudine	$6,672.20		
Tenofovir/emtricitabine	$7,179.55		
Second-line	$8,906.84		
Third line	$21,844.13		
Hospitalization			
AIDS	$2,959	$2,914.00	$3,017.50
No AIDS	$1,376	$1,329.00	$1,421.50
HLA B*5701Assay	$100		
Patient suspected HSR	$231.51		
Clinically suspected HSR	$301.41		

Utility values

AIDS	Estimate	95% CI	NO AIDS	CD4	Estimate	95% CI
PCP	0.775	0.748, 0.802		>500:	0.87	0.851, 0.888
MAC	0.735	0.703, 0.767		201-500:	0.86	0.843, 0.878
Toxo	0.731	0.685, 0.777		51-200:	0.85	0.835, 0.865
CMV	0.76	0.737, 0.783		0-50:	0.832	0.807, 0.857
Fungal	0.743	0.694, 0.789				
Other	0.77	0.751, 0.79				

Table 17

Model Parameters Estimates and Uncertainty (cont'd)

HSR Probabilities	Estimate	95% CI
Prevalence	0.058	
False negative	0.0022	
Patient susp	0.0407	0.032, 0.062

3. Results

This section is divided in three sections. The first part is the base case scenario; the second incorporates deterministic sensitivity analysis; and the last presents the full probabilistic sensitivity analysis. All data are presented discounted.

3.1. Base Case Analysis

The base characteristics are in accordance with baseline characteristics from the HEAT study. CD4 count and HIV viral load at initiation of treatment were 214 and 4.9 log respectively. The discount rate was set at 5%.

After 30 years, 21% of the cases were alive. Median time on first-line therapy was approximately 4 years.

Estimated average discounted life expectancy, costs and QALY for abacavir/lamivudine and tenofovir/emtricitabine were 12.36 years, $279275,10.62 and 12.28 years, $279997, 10.55 respectively. Abacavir/lamivudine is cheaper (discounted cost saving of $722), and provides better life expectancy (gain of 0.08 life years) and QALY (gain of 0.07 QALYs), and therefore is dominant compared to tenofovir/emtricitabine (Table 18**Error! Reference source not found.**). However, it is clear that differences in costs and outcomes are small.

Table 18

Discounted and undiscounted Life expectancy, Costs and QALYs of abacavir/lamivudine versus tenofovir/emtricitabine and its cost per QALY gained and cost per life year gained.

	Undiscounted			*Discounted*		
	Life expectancy	Costs	QALYs	Life expectancy	Costs	QALYs
Tenofovir/ emtricitabine	20.59	$479 199	17.663	12.28	$279 997	10.548
Abacavir/ lamivudine	20.77	$479 173	17.821	12.36	$279 275	10.615
Cost per QALY gained	Abacavir/lamivudine dominant					
Cost per life year gained	Abacavir/lamivudine dominant					

3.2. Deterministic Analysis

In order to asses the uncertainty of the results in Section 3.1, deterministic sensitivity analysis on each of the variables is presented in Table 19.

Table 19

Discounted Sensitivity analysis

	Tenofovir/emtricitabine			Abacavir/lamivudine			Abacavir/lamivudine – Tenofovir/emtricitabine			Cost per QALY	Cost per life Year Gained	INB
	LE	Costs	QALY	LE	Costs	QALY	LE	Costs	QALY			
Base Case	12.28	$279,997	10.5477	12.36	$279,275	10.6151	0.08	-$722	0.0674	ABC/3TC Dominant	ABC/3TC Dominant	$4,092
CD4=100	10.36	$239,894	8.8682	10.48	$240,320	8.9710	0.12	$426	0.1028	$4,153	$3,593	$4,712
CD4=400	13.45	$296,970	11.6294	13.50	$296,113	11.6735	0.05	-$856	0.0441	ABC/3TC Dominant	ABC/3TC Dominant	$3,062
VL=4,5 log	12.28	$279,997	10.5477	12.36	$279,275	10.6151	0.08	-$722	0.0674	ABC/3TC Dominant	ABC/3TC Dominant	$4,092
VL=4 log	12.50	$281,590	10.7404	12.57	$280,915	10.8010	0.07	-$675	0.0606	ABC/3TC Dominant	ABC/3TC Dominant	$3,704
Discount=3%	14.82	$340,445	12.7213	14.92	$339,990	12.8143	0.11	-$456	0.0931	ABC/3TC Dominant	ABC/3TC Dominant	$5,108
Discount=7%	10.40	$235,385	8.9351	10.46	$234,519	8.9850	0.06	-$866	0.0499	ABC/3TC Dominant	ABC/3TC Dominant	$3,360
Costs of Hospitalization = LCI	12.28	$278,863	10.5477	12.36	$278,133	10.6151	0.08	-$730	0.0674	ABC/3TC Dominant	ABC/3TC Dominant	$4,100
Costs of Hospitalization = UCI	12.28	$326,096	10.5477	12.36	$323,726	10.6151	0.08	-$2,370	0.0674	ABC/3TC Dominant	ABC/3TC Dominant	$5,740
Costs Drugs = +10%	12.28	$352,722	10.5477	12.36	$350,076	10.6151	0.08	-$2,646	0.0674	ABC/3TC Dominant	ABC/3TC Dominant	$6,016
Costs tenofovir = abacavir	12.28	$273,710	10.5477	12.36	$272,692	10.6151	0.08	-$1,018	0.0674	ABC/3TC Dominant	ABC/3TC Dominant	$4,388
Effectiveness LCI MVR	12.17	$280,896	10.4547	12.25	$280,266	10.5174	0.07	-$630	0.0628	ABC/3TC Dominant	ABC/3TC Dominant	$3,768
Effectiveness UCI MVR	12.39	$279,561	10.6408	12.46	$279,093	10.7043	0.07	-$468	0.0635	ABC/3TC Dominant	ABC/3TC Dominant	$3,640
Effectiveness Failure rate LCI	12.31	$278,577	10.5712	12.81	$266,421	11.0132	0.51	-$12,156	0.4420	ABC/3TC Dominant	ABC/3TC Dominant	$34,257
Effectiveness Failure rate UCI	12.24	$280,150	10.5138	12.14	$283,843	10.4274	-0.10	$3,693	-0.0863	TDF/FTC Dominant	TDF/FTC Dominant	-$8,010

	Tenofovir/emtricitabine			Abacavir/lamivudine			Abacavir/lamivudine – Tenofovir/emtricitabine			Cost per QALY	Cost per life Year Gained	INB
	LE	Costs	QALY	LE	Costs	QALY	LE	Costs	QALY			
Effectiveness	12.20	$279,781	10.4769	12.96	$267,017	11.1381	0.76	-$12,765	0.6611	ABC/3TC Dominant	ABC/3TC Dominant	$45,822
MVR UCI & Failure rate LCI	12.35	$279,972	10.6074	12.22	$283,806	10.4994	-0.12	$3,834	-0.1080	TDF/FTC Dominant	TDF/FTC Dominant	-$9,234
Effectiveness MVR LCI & Failure UCI	12.28	$279,997	10.5477	12.24	$280,259	10.5157	-0.04	$262	-0.0319	TDF/FTC Dominant	TDF/FTC Dominant	-$1,859
Effectiveness ACTG5202 correction	12.28	$279,997	10.5477	12.36	$279,272	10.6138	0.07	-$725	0.0661	ABC/3TC Dominant	ABC/3TC Dominant	$4,030
Effectiveness Abacavir MI	12.28	$279,997	10.5477	12.39	$278,469	10.6443	0.11	-$1,528	0.0966	ABC/3TC Dominant	ABC/3TC Dominant	$6,357
Effectiveness indirect comparison #1	12.28	$279,997	10.5477	12.68	$274,466	10.8973	0.40	-$5,531	0.3496	ABC/3TC Dominant	ABC/3TC Dominant	$23,011
Effectiveness indirect comparison #2	12.28	$279,997	10.3340	12.36	$279,275	10.4001	0.08	-$722	0.0660	ABC/3TC Dominant	ABC/3TC Dominant	$4,024
Utilities LCI	12.28	$279,997	10.7683	12.36	$279,275	10.8371	0.08	-$722	0.0688	ABC/3TC Dominant	ABC/3TC Dominant	$4,160
Utilities UCI	12.66	$287,019	10.8673	12.73	$286,382	10.9307	0.07	-$638	0.0634	ABC/3TC Dominant	ABC/3TC Dominant	$3,806
Mortality LCI	12.02	$275,068	10.3257	12.10	$274,356	10.3979	0.08	-$712	0.0722	ABC/3TC Dominant	ABC/3TC Dominant	$4,322
Mortality UCI	12.28	$279,997	10.5477	12.36	$279,135	10.6151	0.08	-$862	0.0674	ABC/3TC Dominant	ABC/3TC Dominant	$4,232
HLA B5701 costs=$30	12.28	$279,997	10.5477	12.36	$279,268	10.6151	0.08	-$729	0.0674	ABC/3TC Dominant	ABC/3TC Dominant	$4,099
HLA B5701 LCI	12.28	$279,997	10.5477	12.36	$279,282	10.6151	0.08	-$716	0.0674	ABC/3TC Dominant	ABC/3TC Dominant	$4,086
HLA B5701 UCI												

LE: Life expectancy; LCI: Lower bound of the 95% confidence interval; UCI: upper bound of the 95% confidence interval, MVR: Maximal virologic response; MI: Myocardial infarction; INB: incremental net benefit (Δ in QALYs *$50000 - Δ in Costs), ABC/3TC: abacavir/lamivudine; TDF/FTC: tenofovir/emtricitabine

3.2.1. Baseline CD4 count

CD4 count at initiation of treatment has an effect on the dominance of abacavir/lamivudine. At CD4 of 100, abacavir/lamivudine loses its dominance as it costs slightly more ($427) but maintains a better life expectancy and QALY. The cost per QALY and the cost per life year gained are $4153 and $3593. At CD4 of 400, abacavir/lamivudine is dominant.

3.2.2. Baseline HIV viral load

Lower HIV viral (4 log) was not associated with a change in abacavir/lamivudine dominance. Viral load about 4.9log was not performed as the base case already exceeds the ceiling of 30 000 (4.48 log), leading to no change in the natural progression of the disease.

3.2.3. Discounting

Discounting the costs and effectiveness of the interventions to 3% or 7% instead of 5% had no effect on the dominance of abacavir/lamivudine.

3.2.4. Costs of Hospitalization

Abacavir/lamivudine remains dominant regardless of the uncertainty around the costs of hospitalization, equivalent to the lower and upper bound of the 95% confidence interval.

3.2.5. Costs of abacavir/lamivudine and tenofovir/emtricitabine

The costs were changed in two ways. First, both were increased by 10%. Second, the cost for abacavir/lamivudine was increased to match the cost of tenofovir/emtricitabine. None of these changes alters the dominance of abacavir/lamivudine.

3.2.6. Effectiveness data

The first sensitivity analysis was comprised of standard variation associated with the 95% confidence interval of the HEAT study on the MVR and on the rate of failure. The uncertainty on the MVR does not reverse the dominance of abacavir/lamivudine. The rate of failure was associated with a different outcome though. While the lower confidence interval exaggerated the dominance of abacavir/lamivudine, the lowest rate of failure reversed the dominance, resulting in tenofovir/emtricitabine being dominant.

Not surprisingly, combining the MVR and the rate of failure, the lower bound 95% confidence interval is associated with dominance of abacavir/lamivudine while the higher bound 95% confidence interval makes tenofovir/emtricitabine dominant.

Indirect comparison method was used to adjust for the potential difference in effectiveness. For the indirect comparison #1, the effectiveness parameters were adjusted to inflate the maximal virologic response by 1.025. For the indirect

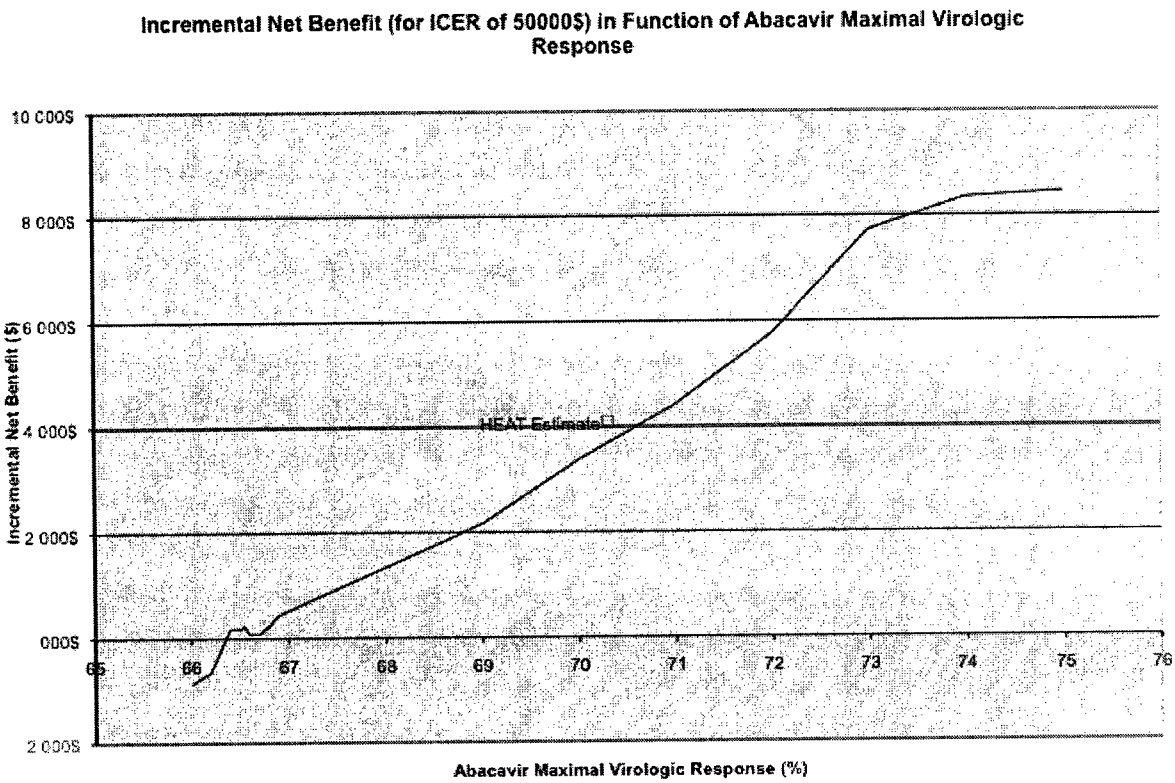
comparison #2, both parameters were adjusted. In the two separate analyses, abacavir/lamivudine remains dominant.

To consider the possibility that abacavir/lamivudine may be inferior to tenofovir/emtricitabine in the subset of patients with high baseline viral load as suggested in the ACTG 5202, the adjustment made was to decrease the MVR and increase the rate of failure. These changes remove the dominance of abacavir/lamivudine since it is associated with a decrease in QALY by 0,03 years and an increased in costs by $262. At that point, tenofovir/emtricitabine becomes dominant.

Finally, adjustment to account for the possibility of increased fatal MI was carried forward to increase the risk of mortality in the abacavir arm. This results in abacavir/lamivudine remaining the dominant option.

In figure 3, an exploration of the sensitivity of changing abacavir effectiveness parameters on the overall economic results is shown. For a fixed tenofovir/emtricitabine MVR of 66.7%, tenofovir/emtricitabine is dominant when maximal virologic response of abacavir/lamivudine drops from 70.3% to 66.2%. But when it reaches 66,8%, abacavir/lamivudine is dominant again.

Figure 3

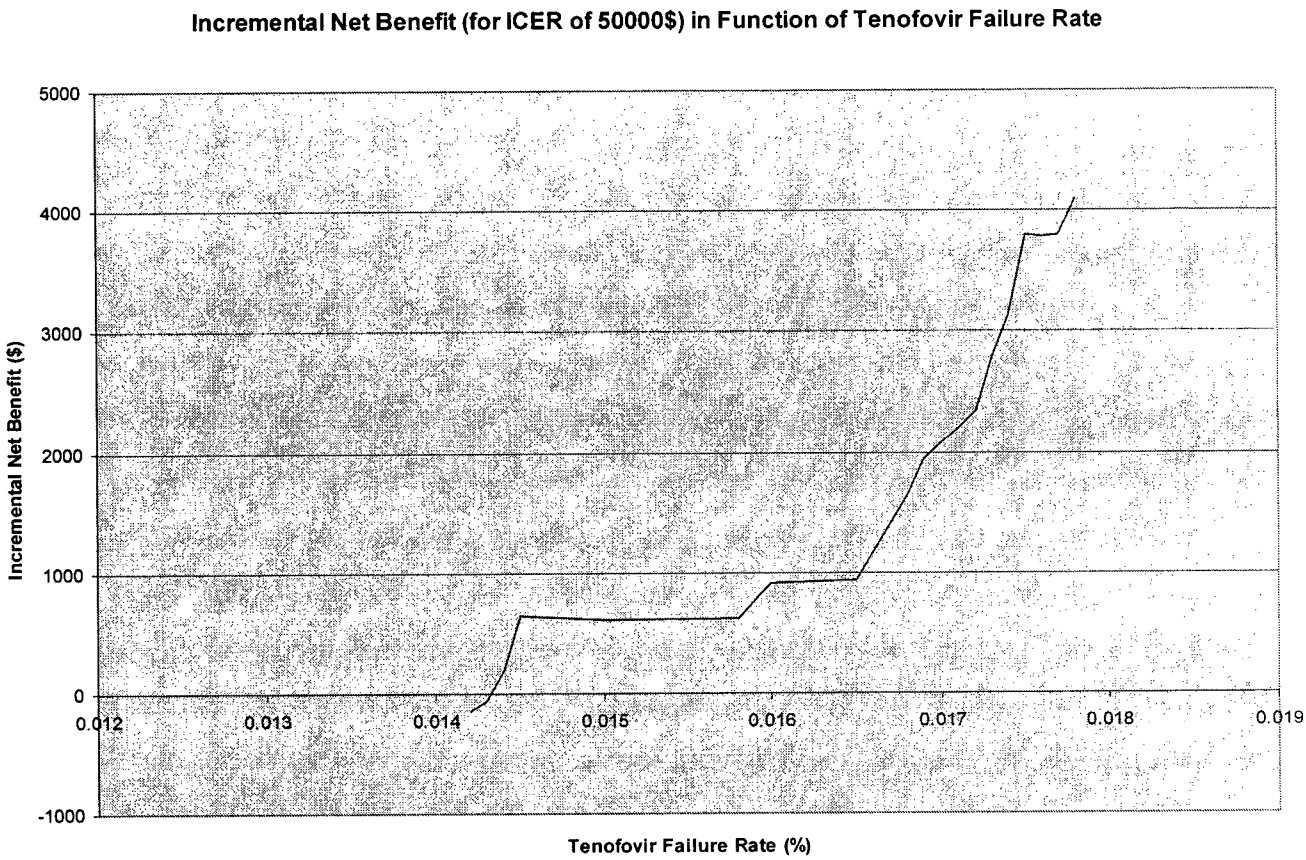


ICER and INB graphs emphasize that for maximal virologic response, abacavir/lamivudine is cost-effective or dominant as long until MVR are the same.

Conversely, for a fixed abacavir/lamivudine at 70.3%, tenofovir/emtricitabine becomes dominant when maximal virologic response is 71.5%.

For failure rate, for a fixed rate of 1.75% per cycle for abacavir/lamivudine, tenofovir/emtricitabine becomes dominant when failure rate is lower or equal to 1.41% (figure 4).

Figure 4



3.2.7. Utility value

Sensitive analysis for utility value using the 95% LCU and UCI confirmed the dominance of abacavir/lamivudine.

3.2.8. HLA B*5701 test

Since a different assay for HLA B*5701 genotyping may be cheaper, the analysis was run at a lower price of $30 with no change in the outcome. The negative predictive value for suspected HSR was also tested for sensitivity. Abacavir/lamivudine confirmed its dominance in all situations.

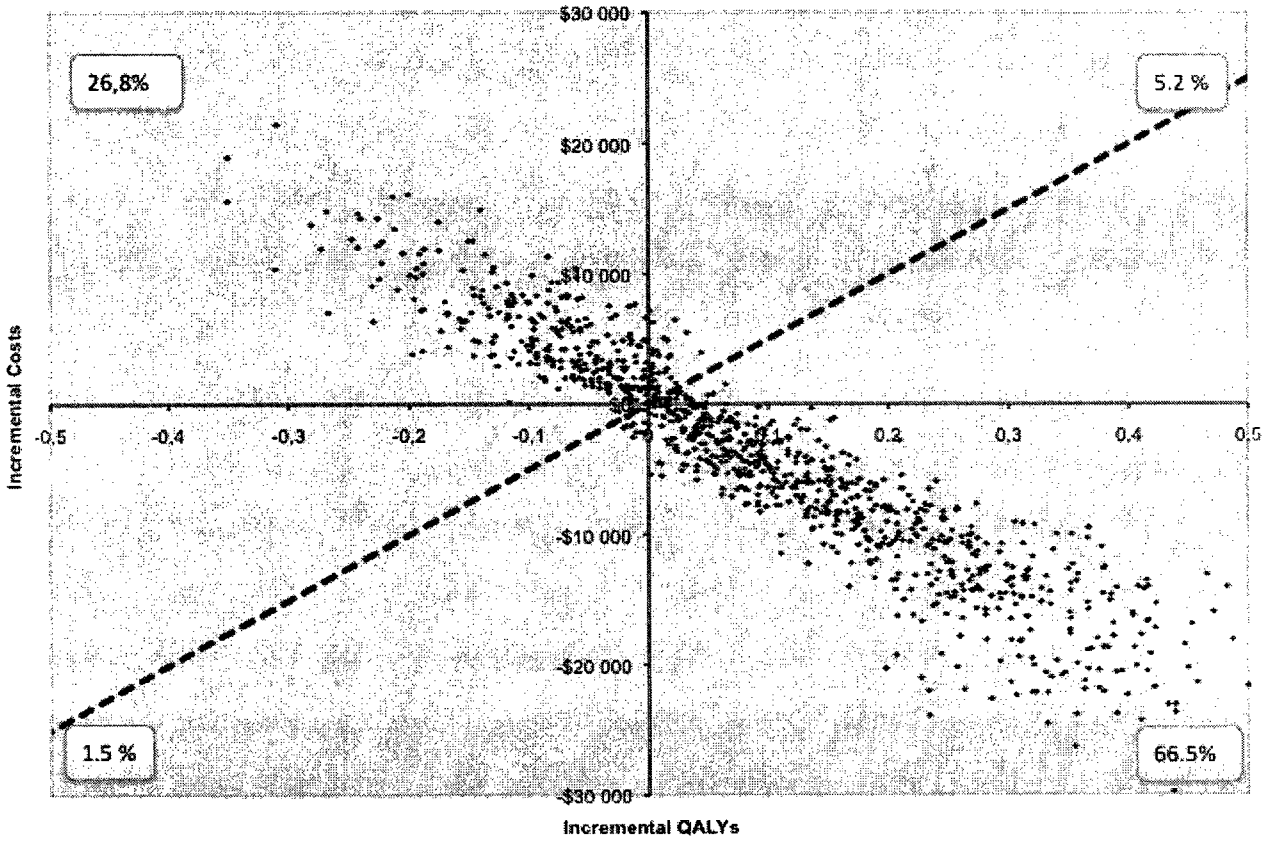
3.3. Probabilistic Analysis

Probabilistic analysis takes into account the variability of each variable of the economic model. After 1000 replication of the 1000 case cohort, the mean (25^{th}, 75^{th} percentile) life expectancy, costs and QALY is 12.02 (11.20, 12.75) years, $200 107 (170605, 228989) and 10.34 (9.41, 11.18) for tenofovir/emtricitabine and 12.15 (11.22, 12.93) years, $190360 (147 596, 235 246) and 10.45 (9.44, 11.35) for abacavir/lamivudine respectively.

The analysis reveals that 66% of all the simulations will lie in the abacavir/lamivudine dominance quadrant (figure 5).

Figure 5

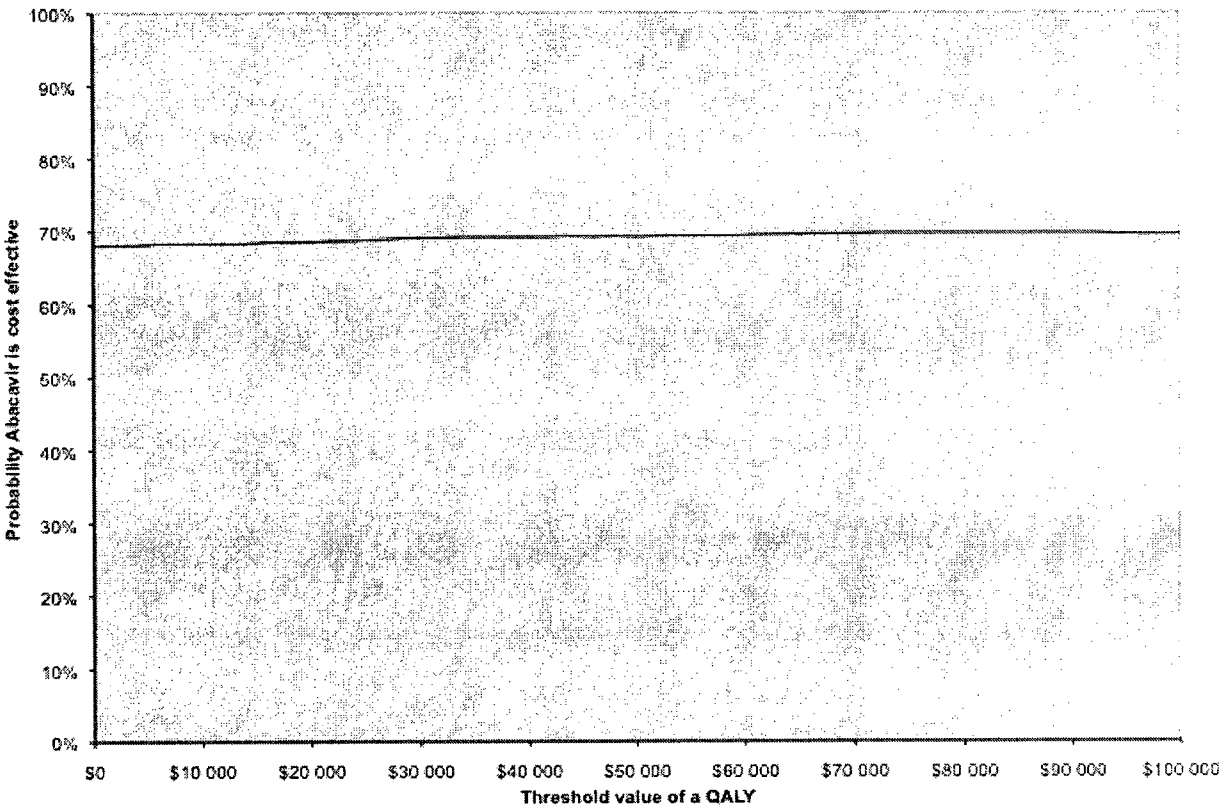
Probabilistic Analysis of Abacavir/lamivudine versus Tenofovir/emtricitabine



The probability that abacavir/lamivudine is cost-effective for an ICER of $50000 is around 70%, with little variations according to the threshold of cost-effectiveness acceptability (figure 6).

Figure 6

Probability of Abacavir/Lamivudine to be Cost-Effective in function of the Threshold of a QALY.



4. DISCUSSION

Very little is known when attempting to compare the effectiveness of abacavir/lamivudine and tenofovir/emtricitabine. The treatment guidelines from international organizations recommend using nucleoside analogs to every treatment-naïve HIV-infected individual. It is therefore expected that this class of drugs will be widely prescribed. In 2006, the overall annual sales for NRTIs were 6 billion, with a compound annual growth rate of 10% until 2010 in the 6 major world markets. According to this prediction, abacavir/lamivudine and tenofovir/emtricitabine will encompass 41% of the NRTI market in 2010[145].

Acceptance of this broad use of NRTI agents is also accompanied by limited evidence of superiority of one or the other. Only one RCT comparing abacavir/lamivudine and tenofovir/emtricitabine has been completed[121] and others are underway. Similarly, only one cost-effectiveness study was completed in the UK with different assumptions[88]. The later will be discussed later.

This chapter will be divided in 3 sections. The first will discuss the strengths and weaknesses of the economic model, followed by a critic of the clinical data. Finally, comparison to existing cost-effectiveness analysis between these 2 drugs and a thorough understanding of the limitations will be done.

4.1. Economic Model

A major determinant of this analysis lies on the validity of the economic model. An adaptation from Richter's model was used in this study. In Richter's model, the fact that two components of effectiveness were incorporated into the disease progression, namely the proportion of maximal virologic response and the rate of failure, was instrumental in the selection of the model. Consensus with clinical experts was reached on the fundamentals of the model.

Richter's paper[85] used 5 model parameters: HIV viral load progression, risk of having AIDS according to CD4 count, risk of mortality per CD4 count, costs and utilities. In my model, I use different estimates for all parameters with the exception of HIV viral load progression. I did not accept the assumptions that AIDS has an effect on utility function only. Furthermore, assuming a null mortality chance for a CD4 above 100 is not realistic. Lastly, the data was extracted from studies published in 1996, which does not take into account progresses achieved in the last decade. The mortality data was taken from studies looking at the effect of zidovudine in 1993. American rather than Canadian costs data were used and various utility values were inputted. Therefore, the adaptation of the Richter's Markov model in this study accounts for Canadian costs and update the mortality, AIDS and utility data. It also incorporates the effect of HLA B*5701 genotypic testing in the first cycle of the simulation.

Many factors may limit the validity of this adapted economic model. The most important one may be the overestimation of the true failure rate of drug

treatments. Failure rate in the randomized controlled trials include true virological failure and a mix of other factors like intolerance, loss to follow-up, protocol violations, etc. In this study, upon treatment failure, it was assumed that patients were virological resistant and were applied a probability of treatment success similar to advanced patients. The model was not able to distinguish the impact of intolerance versus virological failure. In this study, 21% of the population survived 30 years, with an average survival of 12 years. By contrast, in a recent publication from a collaboration of 14 cohorts, 81% of the patients survived between a period of 20 and 44 years[146]. A person starting HAART at 35 years of age could expect to live 32 years[146]. This difference may be explained in part by this failure rate overestimation. However, there is no evidence suggesting that the inflated effect on mortality could be differential between abacavir/lamivudine and tenofovir/emtricitabine, and it should not change the overall conclusion.

Only one study was available to estimate Canadian costs to the health care system from 1997-2001[137]. While it was adjusted for current dollars, changes in patients' management may be missed. Indirect costs were not accounted in this analysis. However, the impact of indirect costs is likely to be non-differential and therefore should not change the overall conclusions.

The structure of the economic model maintains some assumptions that may be inappropriate in some patients. For example, AIDS status is not reversible, meaning that once a patient has an AIDS-defining illness, it can not reverse it, resulting in a lifetime decrease in the utility value. Such an assumption may be adequate for cytomegalovirus complications leading to blindness, but may not

apply to a clinically cured Pneumocysis Carinii pneumonia. However, sensitivity analysis for utility values did not influence the results, and the likelihood that this factor being influential is low.

Finally, recent evidence showed that mortality in HIV-infected individual is a combination of traditional AIDS mortality and non-AIDS related events[147, 148]. Hence, mortality in this economic model is associated to the level of immunosuppression only. Non-AIDS complications may be categorized by other factors than CD4 count and are not considered from a health-related quality of life standpoint.

4.2. Efficacy data

It was anticipated that the availability of efficacy data comparing abacavir/lamivudine and tenofovir/emtricitabine was going to be limited. It was planned a priori to conduct an indirect comparison to provide an estimation of relative efficacy. Fortunately, one RCT (HEAT[121]) was published during the course of this thesis and it was decided to use this estimate. The indirect comparison was still performed as a measure of sensitivity analysis as well as to confirm the validity of the direct comparison estimate.

Data from HEAT became available during the conduct of the study. Like other RCTs, eligibility criteria carefully selected patients, excluding those with pre-existing liver or renal dysfunction and those with congestive heart failure and diabetes. According to this study, abacavir/lamivudine and

tenofovir/emtricitabine were non-inferior at 96 weeks as defined by the proportion of patients with HIV viral load less than 50 copies/mL on an intent-to-treat analysis in which switch may be allowed. The definition of treatment failure was rather conservative, defined as failure to achieve HIV viral load below 200 copies/mL or confirmed rebound to above or equal to 200 copies/mL after confirmed reduction to less than 50 copies/mL by Week 24[149]. For the purpose of this analysis, the parameters of efficacy were different. The MVR and rate of treatment failure were extrapolated. After adjustment for the reduction of abacavir HSR from HLA B*5701 genotype, and the removal of allowed substitution, the two efficacy measures were in favor of abacavir/lamivudine.

The additional information obtained from the indirect comparison failed in the attempt to provide better accuracy on the efficacy estimates. Because of limited number of trials, the uncertainty around the estimates was important. However, the ratio revealed a trend that was consistent with the direct comparison (table 11). By contrast, a retrospective cohort review of tenofovir-based treatment revealed a trend for tenofovir superiority compared to abacavir-based treatment (61.3% versus 52.7% of patients with undetectable viral load at week 48 respectively).

One major problem when attempting to compare trials over time is the heterogeneity of the definition of treatment failure. Earlier trials used a different viral load cutoff assay of 500 copies/mL instead of the contemporary assay detecting as little as 50 copies/mL. To add to the confusion, several intent-to-treat definitions such as M=F, LOCF, TLOVR are used. In some protocol, substitution

of drugs is allowed. Moreover, treatment failure definition also varies across trials, with the latest, as being used in HEAT, trending to be more conservative.

Furthermore, the MVR is rarely available in publications. Because the primary outcome is usually the proportion of patients responding to treatment at a specific time after the initiation of therapy, MVR is not available. For this study, the MVR was either obtained through personal communication with the pharmaceutical industry or leading author, or was extrapolated from the publication graph. When extrapolated, the error rate was no more than 1 to 2%, which was considered to be of minimal impact on the results.

Finally, the results of the systematic review are susceptible to biases. Despite a thorough literature search and consultations with experts in the field, a publication bias may be present. It is possible that efficacy estimates are based on incomplete evidence. Furthermore, the quality of the evidence was assessed with Jadad's scale. This instrument was shown to have many limitations[150]. Different tools are available and the SIGN 50 has been proposed to be better at assessing all domains pertinent to RCTs[151]. Finally, a data extraction bias cannot be ruled out since data extraction was performed by one person only.

ACTG5202 and ET-001 are ongoing RCT comparing abacavir/lamivudine and tenofovir/emtricitabine. Results of these studies will help to precise the effect size of each intervention on virological suppression.

4.3. Cost-Utility

The result of my analysis comes to the conclusion than abacavir/lamivudine is dominant compared to tenofovir/emtricitabine. However, the results are very sensitive to the rate of virological failure. A difference of 0.34% per 6-month cycle in the failure rates reverses the dominance of abacavir/lamivudine to its comparator. For the maximal virologic response, should abacavir/lamivudine be 3.5% less effective, tenofovir/emtricitabine would be dominant. In other words, relative small variations of effectiveness will lead to dominance of one or the other interventions in 93% of the time (quadrant 1 and 4 of the incremental QALY and costs graph in figure 5).

This sensitivity for effectiveness parameters does not offset the cost-effectiveness benefits of abacavir/lamivudine when adjustments were made to account for possible increased mortality. But tenofovir/emtricitabine turns out to be dominant should the concern of inferior efficacy raised in ACTG5202 becomes reality. Likewise, the adjustment using the 95% upper bound confidence interval leads to dominance for tenofovir/emtricitabine.

These results contrast with the one from Borrill. In Borrill's cost-effectiveness study, transition probabilities are different. First, the economic model is derived from an adaptation of Chancellor's model, in which patients transition from 3 health states categorized on CD4 count strata. Disease progression occurs only downstream, without CD4 recovery. Adjusted indirect comparison using GS934 and CNA30024 was applied on a disease progression matrix extracted from

internal data from the Royal Free Hospital in London between 1995 and 1996. HLA B*5701 genotyping was not taken into account. The conclusion was that tenofovir/emtricitabine was cost-effective with an ICER of £ 21 014.

The factors that may explain the difference in my analysis are multiple. First, the transition factor for the efficacy parameter is different. In the case of abacavir-based treatment, particularly when not adjusting for abacavir hypersensitivity, the rate of failure during the first cycle is higher since HSR occurs early after treatment[93]. To illustrate this phenomenon, using the same principles on the study GS934 for a viral load less than 50 copies/mL, the adjustment (relative risk) for tenofovir/emtricitabine using zidovudine/lamivudine as a common comparator is 0.693 at week 48, and 0.849 at week 96 and 0.819 at week 144. The application of the correction factor at week 48 exaggerates the difference between the interventions. Using two different efficacy parameters assessing efficacy at different time points will adjust for this phenomenon.

Considering HLA B*5701 genotype testing also will improve abacavir/lamivudine outcome. It is known that this test reduces the risk of clinically diagnosed HSR by 60%, therefore leading to less discontinuation for the abacavir/lamivudine arm.

Finally, the selected model in this analysis allows for immunologic recovery. In a clinic setting, patients improve significantly their CD4 level after successful HAART. Changes in the rate of failure between abacavir/lamivudine and tenofovir/emtricitabine will change the magnitude of CD4 recovery and impact their QALY.

5. CONCLUSION

The use of abacavir/lamivudine in first-line therapy for HIV disease is dominant compared to tenofovir/emtricitabine. However, this conclusion is very sensitive to the comparative effectiveness. A minor change in the rate of failure by 0.34% results in tenofovir/emtricitabine being dominant over its comparator. Additional RCT are required to further improve the precision of the comparative effectiveness of both competing interventions.

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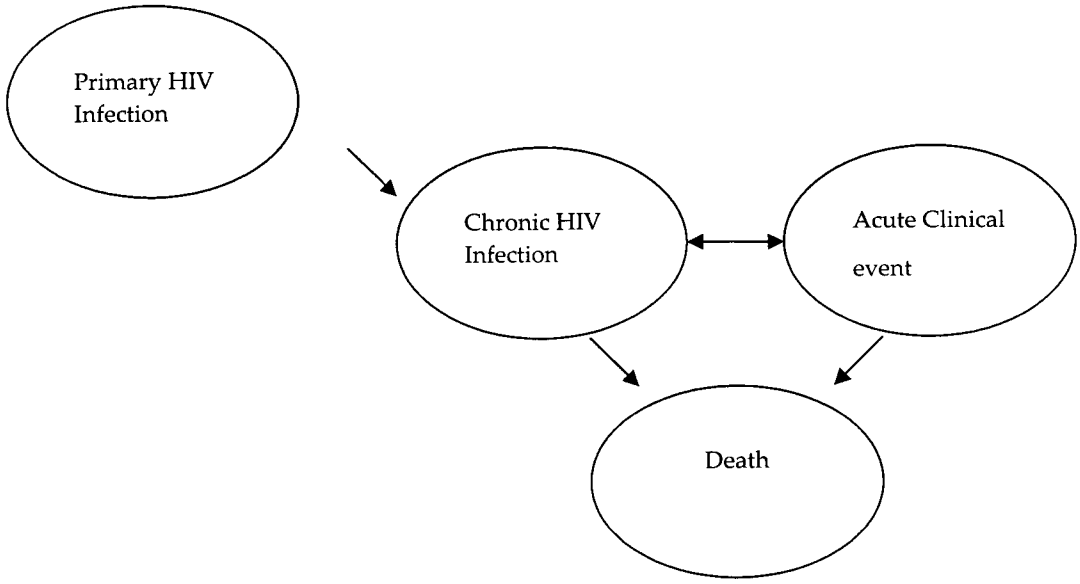
Appendix 1
Search Strategy for **HIV economic model**

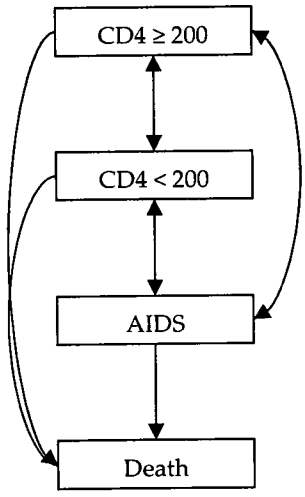
5	(wolf l or wolf lb or wolf ls).au.	50
6	"journal of acquired immune deficiency syndromes jaids".jn.	2659
7	5 and 6	1
8	cost-effectiveness.mp. or exp Cost-Benefit Analysis/	32492
9	anti-hiv agents/ec	943
10	model$.ab.	572992
11	(8 or 10) and 9	139
12	(hiv-1 or hiv-2).mp.	39813
13	human immunodeficiency virus.tw.	31165
14	AIDS.mp.	57308
15	AIDS/ or SIDA.mp. or AIDS.mp.	63689
16	acquir$ immunod$ syndrom$.mp.	24946
17	hiv.mp.	121004
18	or/12-17	147968
19	zidovudine.ab.	2876
20	didanosine.ab.	1017
21	lamivudine.ab.	3320
22	abacavir.ab.	577
23	emtricitabine.ab.	202
24	tenofovir.ab.	653
25	efavirenz.ab.	939
26	nevirapine.ab.	1281
27	etravirine.ab.	19
28	saquinavir.ab.	995
29	indinavir.ab.	1423
30	ritonavir.ab.	1745
31	amprenavir.ab.	430
32	fosamprenavir.ab.	73
33	atazanavir.ab.	267
34	darunavir.ab.	58
35	tipranavir.ab.	121
36	maraviroc.ab.	37
37	enfuvirtide.ab.	278
38	or/19-37	9534
39	11 and 18	139
40	from 39 keep 1, 3, 9-11, 13, 15, 25-26...	30

Appendix 2

Illustration of HIV Economic Models

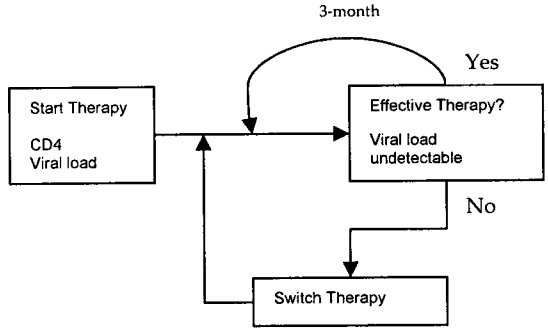
CEPAC



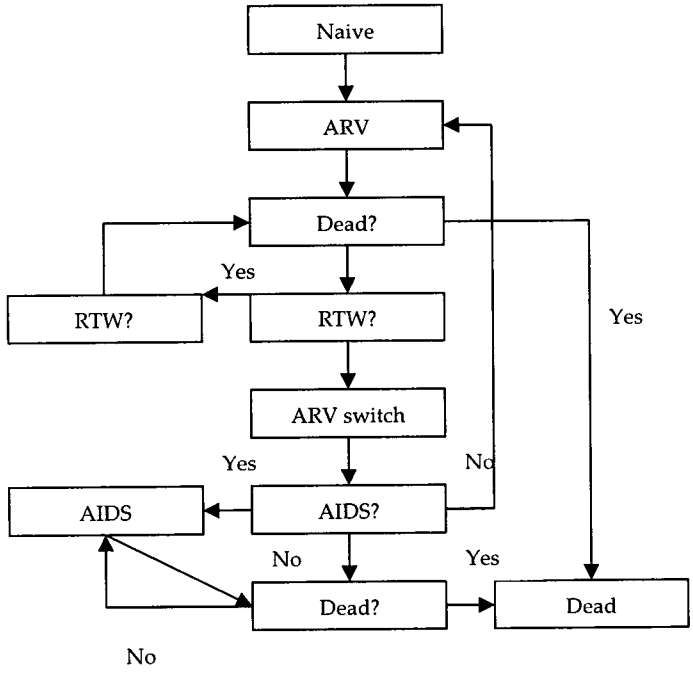


Chancellor

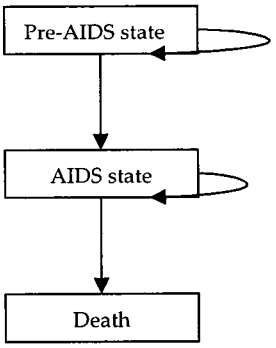
Richter's



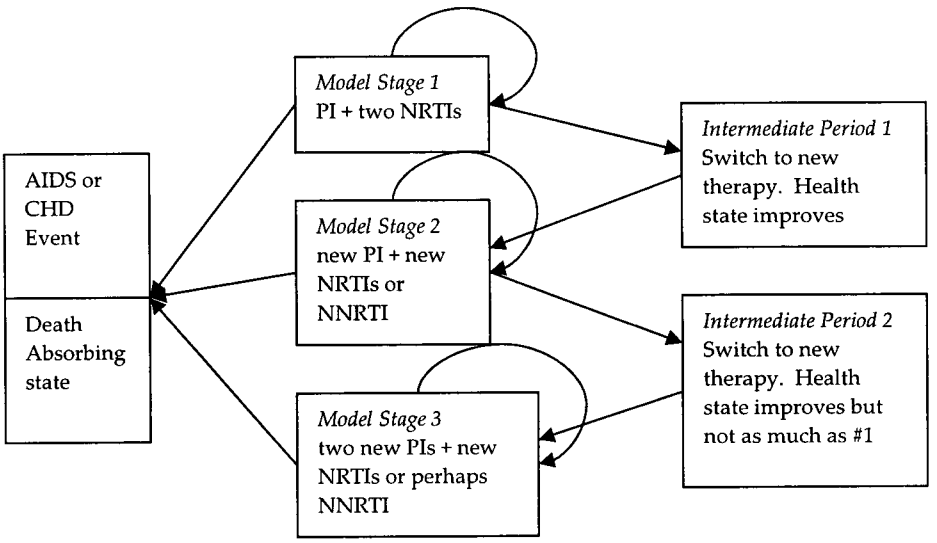
Caro's



Cook's



Simpson's



Appendix 3

Economic Model : CEPAC characteristics

	CEPAC[63]	
Horizon	Lifetime	
Parameters	CD4	
	Viral load	
Stratification	CD4:	Viral load
	>500	30 001-100 000
	301-500	10 001-30 000
	201-300	3001- 10 000
	101-200	501- 3 000
	51-100	≤500
	≤50	
Model stages	Chronic, Acute diseases, Death	
Assumptions	CD4 recovery = pre-treatment CD4	
	Virological failure: 2 consecutive increase by 0.5log	
	Treatment benefit ceased to confer benefits after 2 years	
	2nd line therapy less effective	
CD4 decline	MACS	
AIDS risk, mortality	MACS	
External Validation	YES (Enger JAMA 96)	
Costs	CSUS	
	Payment office	
	Red Book	
Utility	QOL transformed by Torrance	
	Pinkerton	
Discounting	3%	

Economic Model : Simpson's characteristics

	Simpson[73]			
Horizon	Up until 50% of cohort dead			
Parameters	CD4			
	Viral load			
Stratification	Combined health states		CD4	Viral load
	CD4	Viral load	201-350	≥400
	>500	<400	50-200	<400
	>500	≥400	50-200	400-19 999
	351-500	<400	50-200	20 000-100 000
	351-500	≥400	50-200	>100 000
	201-350	<400	<50	any level
Model stages	Stage1: Initial Therapy, Stage2: Second-line therapy			
	Stage3: Third-line therapy, Death			
	Transition Health state: 3-month improvement in health state with new therapy			
Assumptions	1 Opportunistic infection at a time and in a lifetime.			
	No differential weight for different OI per CD4 stratum			
	The magnitude of difference between arms is unchanged after 48 weeks			
	Stage 2 and 3 as per two large databases			
CD4 decline	Specific Clinical trial data			
AIDS risk, mortality	US and Dutch cohorts			
External Validation	YES			
	By 1456pts from Simpson cohort			
Costs	Medicaid from South Carolina			
	Wholesale acquisition costs			
Utility	Adjusted QOL transformed Dolan			
Discounting	3%			

Economic Model : Cook characteristics

	Cook[72]
Horizon	5-20 years
Parameters	CD4
	Viral load
Stratification	n/a
Model stages	Pre-AIDS, AIDS, Death
Assumptions	If Viral load within 0.3 log of baseline, CD4 declines.
	If VL>500, VL returns to baseline within 1 yr
	If VL<500, suppression is maintained for 2 yrs
CD4 decline	MACS formula
AIDS risk, mortality	Formula derived from local database
External Validation	No
Costs	Hellinger
Utility	No
Discounting	3%

Economic Model : Richter's characteristics

	Richter[85]	
Horizon	25 years	
Parameters	CD4, Viral load	
Stratification	CD4	Viral load
	>500	30 001-100 000
	351-500	10 001-30 000
	201-350	3001- 10 000
	50-200	501- 3 000
	<50	≤500
Model stages	Stage1: Initial Therapy	
	Stage2: Second-line therapy	
	Stage3: Third-line therapy	
	Death	
Assumptions	VL for Failure cases returns to baseline	
	Three lines of treatment, then natural progression.	
	Failure cases do not get any CD4 increase.	
	Only CD4 and VL are predictive of OI risks	
CD4 decline	MACS	
AIDS risk, mortality	Simpson's cohort	
External Validation	n/a	
Costs	CSUS (Costs of ARV omitted)	
Utility	Pinkerton	
	Tsevat	
	QOL transformed by Torrance	
Discounting	Not specified	

Economic Model : Sendi's characteristics

	Sendi[71]
Horizon	lifetime
Parameters	CD4
Stratification	CD4
	0-199
	200-499
	500+
Model stages	No AIDS
	AIDS
	Death
Assumptions	Reversion from the AIDS stage is not possible
CD4 decline	n/a
AIDS risk, mortality	Swiss cohort
External Validation	No
Costs	Swiss cohort
Utility	None
Discounting	3,5- 4%

Economic Model : Caro's characteristics

	Caro[68]
Horizon	15 years
Parameters	Treatment failure
Stratification	n/a
Model stages	Naive to treatment
	RTW state (responding, tolerating, willing)
	Antiretroviral failure
	AIDS
	Death
Assumptions	Reversion from the AIDS stage is not possible
	Maximum virological response at 6 months
CD4 decline	Adjusted MACS
AIDS risk	UK AIDS cohort
mortality	US life table
	Local state database
External Validation	No
Costs	HCFA
	Redbook
Utility	None
Discounting	3%

Appendix 4

Non Peer Review Economic Model Publication

Four published cost effectiveness studies[88-91] on abstract format were also retrieved during the search strategy

In the HOPE[91] model is a model in which individuals transit into three levels of CD4 counts. Transition probabilities were from CNAAB3001 and AVANTI II clinical trials. Unfortunately, very few details were available within the abstracts. Attempts to obtain further details were unsuccessful.

Mauskopf et al[90] looked at the cost-effectiveness of the latest PI darunavir in treatment-experienced patients in Canada. The model treatment pathway includes patients using darunavir or comparative PI as designed in POWER 1 and 2 trials. Patients were then switched to tipranavir if treatment failure or intolerance occurred. In summary, three health states were defined: first regimen, second regimen and death. Transition to death at each health state was extrapolated by Mocroft et al.

Maraviroc cost-effectiveness was assessed by Kuehne et al[89]. In this analysis, MOTIVATE clinical trials efficacy data were used in the 'AntiRetroviral Analysis by Monte Carlo Individual Simulation' (ARAMIS) model. It simulates the outcome of HIV viral load and CD4 count on the risk of opportunistic infections.

Both the Mauskopf and Kuehne studies address the treatment of HIV-experienced patients, which differs from treatment-naïve. However, the abstract format does not allow detailed information on assumptions and model structure.

Lastly, a cost-effectiveness analysis was performed comparing tenofovir/emtricitabine and lamivudine/abacavir in treatment-naïve patients. Borrill et al[88] used a common comparator (i.e. zidovudine and lamivudine) to contrast the costs per QALY. A simple model developed by Chancellor[92] including 4 health states (CD4≥200 cells/mm^3, CD4<200 cells/mm^3, AIDS and death) was used and adapted transition probabilities derived from local hospital UK cohort[70]. Direct and indirect comparison (using the ratio of tenofovir/emtricitabine and lamivudine/abacavir reaching a HIV viral load less than 400 copies/mL) were calculated. This study looks at the same question as this thesis does. However, several concerns need to be raised. First, the model is quite simple as it only addresses four health states. The transition probabilities were extracted from the Royal Free Hospital cohort in London for the zidovudine/lamivudine comparator arm. These data reflects the practice in 1995 while we were using dual NRTI therapy as standard of care. Today, this is considered suboptimal[18]. An estimate of the relative risk of disease progression for the FTC/TDF group versus AZT/3TC was derived using the proportion of patients who failed to achieve a viral load below 400 copies/ml at week 48:

$$\text{Relative Risk of Disease Progression} = \frac{\%\ \text{Patients}^{\text{FTC/TDF}}\ (\text{viral load} > 400\ \text{copies/ml})}{\%\ \text{Patients}^{\text{AZT/3TC}}\ (\text{viral load} > 400\ \text{copies/ml})}$$

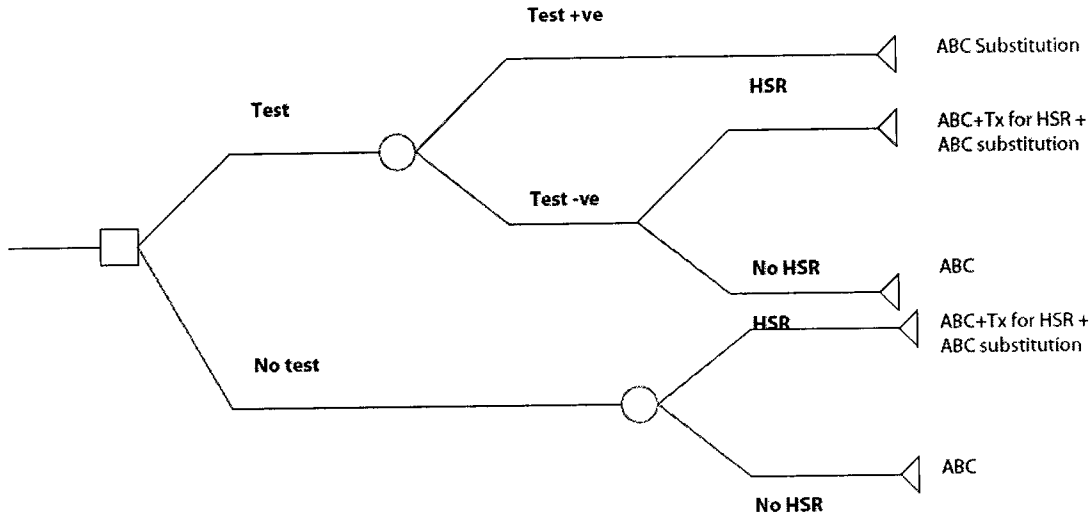
This correcting factor was then applied to the matrix for the tenofovir/emtricitabine arm. (personal communication).

As discussed earlier, HLA B*5701 genotyping is known to reduced the risk of abacavir hypersensitivity[36, 38, 40, 152]. The model ignores this fact and may therefore underestimate abacavir/lamivudine effectiveness.

Resource use data were accounted from a report published in December 2004 by the National Programme Monitoring System – HIV Health Economics Consortium (NPSMS-HHC). The NPSMS-HHC report provided resource data from 21,258 HIV-infected patients that were treated in 24 clinics across the UK. Standard unit costs, from a publication by Beck et al[153], were applied to the mean use of inpatient, outpatient and day ward services for asymptomatic, symptomatic, non-AIDS and AIDS patients.

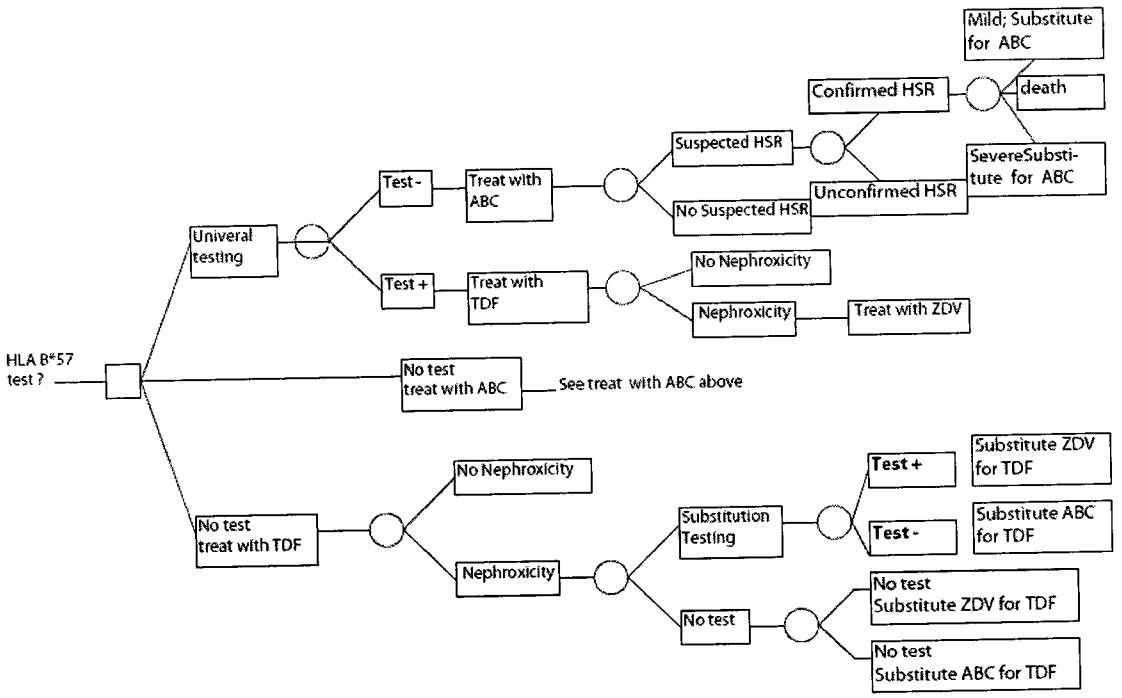
Appendix 5

Hughes Decision analytic framework



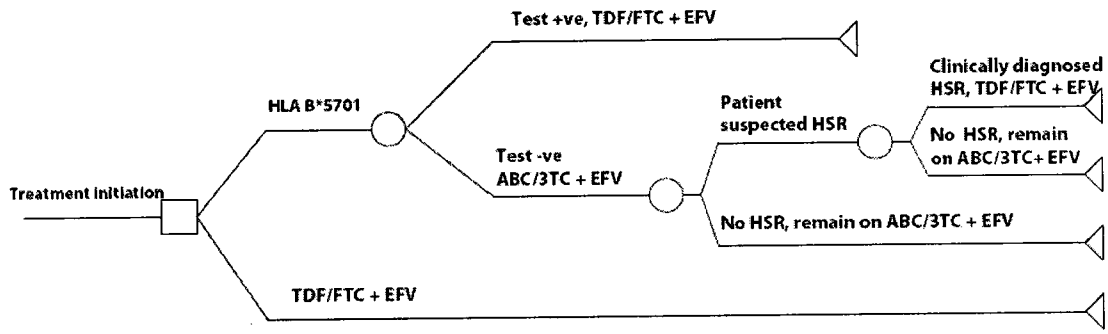
Appendix 6

Shackman's HLA B*5701 economic modeling



Appendix 7

Farkouh's HLA*B5701 Economic Model



Appendix 8

Search Strategy for **Effectiveness of comparative co-formulated NRTIs**

1. Lamivudine/
2. Cytosine/aa [Analogs & Derivatives]
3. Lamivudine.mp.
4. 3tc.mp.
5. epivir.mp.
6. or/1-5
7. abacavir.mp.
8. "1589".mp.
9. Ziagen.mp.
10. or/7-9
11. emtricitabine.mp.
12. Emtriva.mp.
13. or/11-12
14. kivexa.mp.
15. epzicom.mp.
16. or/14-15
17. tenofovir.mp.
18. Viread.mp.
19. or/17-18
20. truvada.mp.
21. 6 and 10

22. 21 or 16

23. 13 and 19

24. 20 or 23

25. exp HIV/

26. hiv.mp.

27. (hiv-1 or hiv-2).mp. [mp=title, original title, abstract, name of substance word, subject heading word]

28. human immunodeficiency virus.tw.

29. AIDS.mp. [mp=title, original title, abstract, name of substance word, subject heading word]

30. AIDS/ or SIDA.mp. or AIDS.mp.

31. acquir$ immunod$ syndrom$.mp. [mp=title, original title, abstract, name of substance word, subject heading word]

32. or/25-31

33. 22 and 32

34. Clinical trial/

35. Randomized controlled trial/

36. Single blind procedure/

37. Randomization/

38. Double blind procedure/

39. Crossover procedure/

40. Placebo/

41. Randomi?ed controlled trial$.tw.

42. Rct.tw.

43. Random allocation.tw.

44. Randomly allocated.tw.

45. randomi$.ab.

46. Allocated randomly.tw.

47. (allocated adj2 random).tw.

48. Single blind$.tw.

49. Double blind$.tw.

50. ((treble or triple) adj blind$).tw.

51. Placebo$.tw.

52. Prospective study/

53. or/34-52

54. Case study/

55. Case report.tw.

56. Abstract report/ or letter/

57. or/54-56

58. 53 not 57

59. 24 and 32

60. 58 and 59

61. 33 and 59

62. 60 and 61

63. 33 and 58

64. 60 and 63

65. 19 and 32 and 58

66. zidovudine.mp.

67. azt.mp.

68. retrovir.mp.

69. or/66-68

70. 69 and 6

71. 70 and 32 and 58

72. Child/

73. 71 not 72

74. limit 73 to randomized controlled trial

75. 62 not 72

76. 60 not 72

77. 65 not 72

78. or/74-77

Appendix 9

Tenofovir-based Randomized Controlled Trials

Study	design	Treatment	n	Baseline VL (log)	Baseline CD4 (/mm^3)	Duration (weeks)	VL<50 (%)
HEAT[120, 121]	RCT DB-PC	ABC-3TC-LPVr	343	4.9	214	48	68
		TDF-FTC-LPVr	345	4.84	193		67
		ABC-3TC-LPVr	343			96	56
		TDF-FTC-LPVr	345				55
934[154 112 110]	RCT OL	FTC-TDF-EFV	255	5	233	48	77
		AZT-3TC-EFV	254	5	241		68
		FTC-TDF-EFV				96	67
		AZT-3TC -EFV					61
		FTC-TDF-EFV				144	64
		AZT-3TC -EFV					56
903[111, 155]	RCT DB PC	TDF-3TC-EFV	299	4.91	276	48	76.3
		d4T-3TC-EFV	303	4.91	283		79.7
		TDF-3TC-EFV				96	72.6
		d4T-3TC-EFV					67.8
		TDF-3TC-EFV				144	67.9
		d4T-3TC-EFV					62.5

RCT = randomized control trial, DB=double-blind, PC=placebo control, OL=open-label. ABC=abacavir, 3TC=lamivudine, LPVr=lopinavir/ritonavir, TDF=tenofovir, FTC=emtricitabine, EFV=efavirenz, AZT=zidovudine, 3TC=lamivudine, d4T=stavudine

Abacavir-lamivudine-based Randomized Controlled Trials

Study	Design	Treatment	n	Baseline VL (log)	Baseline CD4 (/mm^3)	Duration (weeks)	VL<50 (%)	# HSR (%)
CNA30024[156]	RCT DB-PC	ABC-3TC-EFV	324	4.81 (median)	267 (median)	48	70	29 (9)
		AZT-3TC-EFV	325	4.76	258		69	10 (3)
ABCDE[118, 157]	RCT OL	ABC-3TC-EFV	115	5.23 (mean)	203	48	na	8 (7)
		d4T-3TC-EFV	122	5.21	223		na	
		ABC-3TC-EFV	115			96	60.9	
		d4T-3TC-EFV	122				47.5	

RCT = randomized control trial, DB=double-blind, PC=placebo control, OL=open-label. ABC=abacavir, 3TC=lamivudine, EFV=efavirenz, AZT=zidovudine, 3TC=lamivudine, d4T=stavudine. HSR = hypersensitivity reaction.

Zidovudine-lamivudine and stavudine-lamivudine based Randomized Controlled Trials

Study	Design	Treatment	n	Baseline VL (log)	Baseline CD4 ($/mm^3$)	Duration (weeks)	VL<50 (%)
START I[116]	RCT OL	D4T-3TC-IDV	101	4.57	424 (mean)	40-48	49
		AZT-3TC-IDV	103	4.46	422		47
OzCombo2[114]	RCT OL	AZT-3TC-NVP	20	4.52 (mean)	448	52	73
		D4T-ddI-NVP	23	4.74	357		80
		D4T-3TC-NVP	22	4.62	398		68
ESS40002[115]	RCT OL	AZT-3TC-NLV	88	4.46	355 (mean)	96	39
		D4T-3TC-NLV	81	4.46	357		33
		AZT-3TC-ABC	85	4.36	351		41
		AZT-3TC-NLV	89	4.46	320 (mean)	48	47
		D4T-3TC-NLV	83	4.46	315		39
		AZT-3TC-ABC	86	4.36	309		48
OzCombo1[113]	RCT OL	AZT-3TC-IDV	35	5.01	267	52	66
		D4T-3TC-IDV	34	5.21	313		59

RCT=randomized controlled trial, OL=open-label. AZT=zidovudine, d4T=stavudine, 3TC=lamivudine, ddI=didanosine, IDV=indinavir, NLV=nelfinavir, NVP=nevirapine, ABC=abacavir

Appendix 10

Details on the systematic review of studies for effectiveness of comparative NRTIs

HEAT Study:

HEAT was presented at two major HIV conferences in February [120] and August[121] 2008. It is the first and only published RCT comparing abacavir/lamivudine to tenofovir/emtricitabine in combination with lopinavir/ritonavir. The primary objectives were to establish comparative virological efficacy at 48 weeks and to compare the safety and tolerability at 96 weeks. This was a double-blind placebo-matched multicenter non-inferiority RCT performed in the US. Three hundred and forty three participants were assigned to the abacavir/lamivudine while 345 were in the tenofovir/emtricitabine arm. Virological failure was defined as failure to achieve HIV viral load < 200 copies/mL or confirmed rebound > 200 copies/mL after confirmed reduction to < 50 copies/mL after week 24. Substituting zidovudine/lamivudine for NRTIs for abacavir/lamivudine or tenofovir/emtricitabine was also allowed for suspected abacavir HSR or renal toxicity. These changes were not counted as failure in the primary analysis (M=F). Virological primary endpoint was presented using four different types of analysis. Intent to treat (ITT) missing=failure (M=F), ITT time to loss of virological failure (TLOVR), ITT missing/discontinuation=failure (MD=F) and observed data. The primary objective was calculated using M=F, thus allowing changes. Of note, HLA B*5701 screening was not part of the protocol and was not done.

Similar proportions of patients withdrew before week 96 (32% vs. 36% for abacavir/lamivudine and tenofovir/emtricitabine respectively). Main reasons for early discontinuations for abacavir/lamivudine and tenofovir/emtricitabine respectively were adverse events (6%, 6%) which included suspected abacavir HSR (4%, 1%), renal dysfunction (0%, 1%) , virological failure (2%, 2%), non-compliance (3%, 3%), lost to follow-up (13%, 15%), protocol violation (<1%, 0%), subject decision (4%, 7%) and other (3%, 3%).

At week 48, 68% of subjects on abacavir/lamivudine versus 67% in tenofovir/emtricitabine achieved virological suppression. The difference of subjects with HIV viral load < 50 copies/mL between abacavir/lamivudine and tenofovir/emtricitabine was 1% (95% CI: -6.63, 7.40) and therefore non inferiority was confirmed. Similar conclusions were confirmed regardless of the 4 types of analyses studied. At week 96, the difference in efficacy was maintained (difference 2%, 95% CI [-5.41, 9.32]). Stratified analysis for subjects with high baseline HIV viral load (defined as > 100 000 copies/mL) revealed the same relative efficacy, although reversed, with 56% versus 58% achieving undetectable viral load for abacavir/lamivudine and tenofovir/emtricitabine respectively at week 96.

Using Jadad's scale, the quality of this study is good. However, allowed switches for toxicity to NRTIs (14 in abacavir/lamivudine and 3 in tenofovir/emtricitabine) may bias the results. It is impossible to isolate the relative contribution of the substitutes over the allocated NRTIs.

GS-934

GS-934 was a multicenter international non-inferiority RCT comparing zidovudine/lamivudine to tenofovir/emtricitabine[29]. Five hundred and seventeen patients were randomized to one of the two arms. Patients were stratified according to baseline CD4 cell count (<200 vs. ≥200 cells/mm^3) but not HIV viral load. The primary objective was to assess the non-inferiority as measured by HIV viral load < 400 copies/mL through week 48, using ITT-TLOVR algorithm. Missing data or early termination of participation in the study was considered a failure.

At week 48, 84% reached and maintained a viral load < 400 copies/mL in the tenofovir arm compared to 73% in the zidovudine arm (95% CI for the difference: 4 % to 19 %; P = 0.002). The same conclusion applied using the most stringent assay with 80% of the tenofovir-treated and 70% of the zidovudine-treated subjects reached a viral load < 50 copies/mL (95% CI for the difference, 2 % to 17 %; P = 0.02).
The difference in response was partly explained by the rate of virological failure and discontinuations due to side effects. There was nearly twice as many virological failures (23 vs 12) in the zidovudine-lamivudine group than in the tenofovir/emtricitabine group although this difference did not reach statistical significance. Fourteen patients in the zidovudine/lamivudine arm had to discontinue treatment due to anemia, compared to none in the tenofovir/emtricitabine arm.

With a Jadad's score of 3 and despite lack of blinding, GS-934 is a good quality study. It proved that considering tolerance and efficacy, tenofovir/emtricitabine exerts superior activity than zidovudine/lamivudine, which was the reference for dual NRTIs backbone

during this era. Shortly after its publication, the conduct of the study highlighted open-label methodology weaknesses[123]. First, it was noted that there was a high proportion of discontinuations for reasons other than virological failure. Second, a press release published during an interim analysis at week 24 announcing superiority of the tenofovir/emtricitabine arm may have been a source of bias. The FDA conducted sensitivity analysis on the potential impact of such bias and concluded that the magnitude of the difference may be reduced but the overall conclusion was supported.

Extended follow-up to week 96[112] and 144[110] were published after the original publication. Tenofovir-based treatment maintained superior antiviral activity throughout week 144, with 78% of subjects with a viral load < 400 copies/mL compared to 58% for zidovudine/lamivudine[110].

In summary, despite some methodology concerns associated to the release of effectiveness data early in the study, tenofovir/emtricitabine was shown to be superior to zidovudine/lamivudine. The difference in efficacy was maintained after 3 years of follow-up.

CNA30024

Abacavir and zidovudine was compared head-to-head in a RCT along with lamivudine and efavirenz. CNA30024 was a double-blind placebo non-inferiority RCT involving 628 subjects randomized in a 1:1 fashion[117]. The primary efficacy measure was the proportion of subjects with plasma HIV viral load < 50 copies/mL at week 48, adjusted by randomization strata (baseline viral load <100,000 copies/mL vs. ≥100,000

copies/mL). Secondary efficacy measures included ITT-TLOVR. Similar to previous studies, CNA30024 scored 3 as per Jadad's scale.

Twenty-four percent of the patients discontinued treatment before week 48. Of those, the majority stopped because of loss to follow-up (41%) and adverse events (28%) regardless of treatment groups.

Abacavir and zidovudine were shown to have equivalent efficacy, with 70% vs 69% of subjects achieving HIV viral load < 50 copies/mL in the abacavir vs zidovudine arms (95% CI for the difference: -6.3% to 7.9%). Generally, the incidence of adverse events was comparable between arms. However, fatigue and gastrointestinal intestinal side effects were more frequent in the zidovudine group. Due to the blinded design of the study, suspected abacavir HSR was reported in both arms, 9% in the abacavir group and 3% in the zidovudine group.

GS934 to CNA30024 are comparable in many points from a population perspective. Age, gender and race were relatively similar. Immunologic and virologic baseline characteristic may suggest that GS934 population was more advanced since CD4 count was lower and median viral load was higher at baseline. No subjects discontinued tenofovir due to renal toxicity. Abacavir discontinuation due to suspected HSR was 9%. The difference in these major signature toxicities may explain the difference observed between the common comparator.

Indirect comparison through stavudine/lamivudine

Tenofovir and abacavir were compared to a common comparator, stavudine. Herein, tenofovir was associated with lamivudine rather than emtricitabine. However, lamivudine and emtricitabine exert similar activity against HIV and are considered by the scientific community to be interchangeable[18, 124].

GS-903

Tenofovir and stavudine were compared in a head-to-head trial with lamivudine and efavirenz. GS-903 was an international non-inferiority double-blind RCT involving 602 HIV-infected subjects[111]. Allocation to either group was stratified for baseline viral load (< 100 000 or ≥ 100 000 copies/mL) and CD4 count (<200 or ≥ 200 cells/mm^3). The primary endpoint was the proportion of patients with viral load < 400 copies/mL at week 48 on an ITT M=F switch=failure analysis, while a more sensitive assay (50 copies/mL) was used in a secondary analysis. The switch=failure considers all addition or change to antiretrovirals as failure. Though, the protocol allowed for efavirenz substitution in case of central nervous system side effects. The authors chose this analysis to protect against type II error due to possible cases in which antiretrovirals were changed during virological success. Non-inferiority would be declared if the lower bound of the 95% CI for the difference between the 2 groups did not exceed 10%. The publication of this study also included 96 and 144 week data.

At week 48, 79.9% versus 84.1% and 76.3% versus 79.7% of subjects reached a viral load < 400 copies/mL and < 50 copies/mL for tenofovir and stavudine respectively. At week 144, the study discontinuation rate was slightly higher in the stavudine group than

in the tenofovir group (27% versus 33%). This difference was accounted by the number of adverse events/intercurrent illness. Using the primary endpoint (VL<400 copies/mL at week 48, ITT switch=failure), non inferiority was missed as the lower 95% CI for the difference was -10.4%. However, at week 48, non inferiority criteria was met using a viral load cutoff of 50 copies/mL (lower 95% CI = -9.8%). All other analyses performed at week 96 and week 144 supported non-inferiority criteria, regardless of viral load cutoff assays.

Grade 3 and 4 adverse events were similar in both groups except for a greater proportion of increased triglyceride in the stavudine arm (14% versus 3%). The rate of virological failure was also similar. However, fewer cases of peripheral neuropathy and lipoatrophy were observed in the tenofovir arm. From a renal perspective, no difference in change in grade 3-4 creatinine and proteinuria was detected.

ABCDE

Abacavir and stavudine were compared in the ABCDE study[118, 119]. ABCDE was an open-label multicenter RCT done in Spain. Participants were randomized to receive abacavir (n=115) or stavudine (n=122) with lamivudine and efavirenz. Randomization was stratified for viral load > or ≤30,000 copies/mL and CD4 counts > or ≤200 cells/mm^3. The study was planned and powered to assess metabolic changes such as lipodystrophy. The comparison of the efficacy was a secondary objective. Efficacy data were presented using ITT switch=failure using a viral load threshold of 50 copies/mL. Two publications were found. The first one was presented at a conference on the 48

weeks data[119]. The second one is the official publication in a specialized AIDS journal[118].

Of the 237 patients, more patients discontinued prematurely study drugs in the stavudine arm compared to the abacavir arm (59 versus 40 patients respectively), mainly due to toxicity. Thirteen patients in the abacavir group experienced HSR while 23 stopped stavudine due to mitochondrial toxicity. Overall, after 96 weeks, a trend favoring abacavir in the proportion of patients with a viral load < 50 copies/mL was observed (60.9% versus 47.5% [95% CI for the difference: 0.8 to 26.0]).

Summary:

Tenofovir and abacavir along with lamivudine and efavirenz have been compared to stavudine. The tenofovir trial was powered to look at efficacy and provide a more precise estimate of comparative efficacy. It was also less prone to bias due to the double-blind design.

In contrast, the open-label design of the abacavir study can be a threat for internal validity[125]. In fact, the elevated discontinuation rate due to toxicity observed in the stavudine group was possibly influenced by the open-label design.

Nonetheless, using two distinct comparators (zidovudine/lamivudine and stavudine/lamivudine) in the indirect comparison will strengthen the comparison between abacavir/lamivudine and tenofovir/emtricitabine.

Comparison of zidovudine/lamivudine and stavudine/lamivudine

Zidovudine/lamivudine and stavudine/lamivudine are the two common comparators used for the estimation of efficacy between abacavir/lamivudine and tenofovir/emtricitabine. In order to strengthen the relationship between these different NRTI combinations, we will look at the RCTs comparing zidovudine to stavudine.

In the late 90s and early 2000, 4 studies were conducted to compare directly zidovudine to stavudine along with lamivudine. The common third drug comparators were the PIs indinavir and nelfinavir and the NNRTI nevirapine.

OzCombo 1 and 2

OzCombo 1 and 2 were two open-label RCT performed between 1997 and 1999[113, 114, 158]. The main objective was identical: compare three different NRTI combinations, i.e. zidovudine/lamivudine, stavudine/lamivudine and didanosine/stavudine. The difference between the two studies was the selection of the third antiretroviral: OzCombo 1 used indinavir and OzCombo 2 nevirapine. For the purpose of this work, only the first two arms of each study are going to be used. Eligibility criteria were identical with only few exceptions. OzCombo subjects needed to have baseline CD4 above 500 or a viral load greater than 30 000 copies/mL while OzCombo 2 required CD4 above 50 and no limitations on viral load. The primary endpoint was the change in viral load, which was the standard at the time during which the study was performed. In a secondary analysis, the proportions of patients with a viral load < 50 or 500 copies/mL was studied. In total,

Ozcombo 1 and 2 enrolled and randomized 35 and 20 participants in the zidovudine arm while 34 and 22 wererandomized to the stavudine arm.

Overall, 70% and 74% of the OzCombo 1 and 2 participants respectively completed week 52. The reasons for discontinuation included adverse events related to the study drugs and patient's withdrawal. There was no difference between arms for discontinuations.

In OzCombo1, there was no statistical difference between zidovudine and stavudine based therapy on the proportion of subjects with a viral load < 50 copies/mL (53% versus 60% respectively) at week 52 on an ITT analysis. In OzCombo2, 70% versus 68% achieved a viral load < 500 copies/mL and 73% versus 68% achieved a viral load < 50 copies/mL respectively. The author concluded that there was no statistical difference between stavudine and zidovudine but acknowledged small study size limitations.

START I

START 1 was an open-label RCT comparing zidovudine to stavudine[116]. In total, 204 participants were randomized to zidovudine (n=103) and stavudine (n=101) along with lamivudine and indinavir. Subjects had to have a viral load greater or equal to 5000 copies/mL and a CD4 greater or equal to 200 cell/mm^3. Previous use of zidovudine or stavudine for no more than 28 days was permitted. Percentage of patients with a viral load < 500 copies/mL at week 24 and 48 was the primary endpoint. Samples were

reanalyzed using a viral load assay with a limit of quantification of 50 copies/mL. The analysis was performed using a modified ITT analysis whereby missing data at week 48 were considered a failure for subjects with previous viral load ≥500 copies/mL but was excluded from the analysis if their viral load was < 500 copies/mL. A secondary analysis included all the patients and reflected a genuine ITT analysis.

Thirty five percent of the participants in each arm discontinued treatment before week 48 with no difference observed as for the reasons. Using a true ITT analysis, 48% and 47% of the zidovudine versus 55% and 49% of the stavudine reached a VL < 500 copies/mL and < 50 copies/mL at week 48 respectively.

Jadad's criteria applied to START I gives a score of 2, and therefore is considered of low quality.

ESS40002

ESS40002 was a RCT performed in the US and Central America[115]. The objectives were to assess the development of metabolic complications and evaluate safety and efficacy. The primary endpoint was the change in LDL-C at week 96. Efficacy data reported as the proportion of patients with a viral load < 50 copies/mL was shown. Three approaches were evaluated: triple NRTI therapy consisting of abacavir/lamivudine/zidovudine, PI-based therapy including nelfinavir and lamivudine with either stavudine or zidovudine. Only the PI-based approach was looked at for this analysis.

In total, 261 HIV-infected subjects were randomized and stratified according to their baseline CD4 and viral load. Of these, 254 received study drugs. Excluded were the patients with a viral load exceeding 200 000 copies/mL and CD4 less than 50. Subjects must have been ART-naïve or of limited experience (defined as ≤1 week of 3TC or a PI, ≤4 weeks of therapy with other NRTIs, and no experience with an NNRTI). Virological failure was defined as viral load >2000copies/mL on two occasions at least 2–4 weeks apart.

Forty-nine percent of the participants withdrew prematurely from the study. The majority (60-65%) of these were administrative (loss to follow up, withdrawal of consent, protocol violation). 14 vs 8 experienced virological failure in the zidovudine and stavudine arm respectively.

At week 96, 39% and 33% of the zidovudine and stavudine patients achieved a viral load undetectable on an ITT M=F analysis. Of note, TLOVR analysis was not applied into the virological success definition. Only 4% of the zidovudine subjects experienced anemia.

With a Jadad's score of 2, this study is of low quality. The high proportion of drop outs may also negatively impact the validity of the study.

Summary of zidovudine and stavudine comparative studies

The four studies[113-116], although performed in the same era, are quite diverse in many regards. First, the elibility criteria vary from excluding very low CD4 count at baseline to high CD4. The definition of treatment-naïve allows short term use of previous NRTIs in some trials[116]. The dose of zidovudine in two trials[113, 114] were lower compared to other trials and to today's standard. Finally, the primary endpoint for efficacy was variable. Some studies[113, 114] used changes in plasma viral load as their primary endpoint while others used proportion below detection[116]. The viral load cutoff assays were different than the one currently used which may inflate the proportion of patients reaching virological suppression. Whether or not this difference in virological cutoff may favour one NRTI combination in particular is unknown. Unlike most recent studies[29, 111, 117, 120], the quality of the studies as per Jadad's criteria is inferior.

Appendix 11

Systematic review summary of direct and indirect comparisons

Glenny et al performed a review of systematic reviews using direct and indirect comparisons. The search included Database of Abstracts of Reviews of Effects, Cochrane Database of Systematic Reviews, MEDLINE, CINAHL, Current Contents Clinical Medicine and BIOSIS from 1994 to 1998.

Thirteen reviews were identified to use both direct and indirect comparisons, while 23 included indirect comparisons only.

In the 13 studies that used both direct and indirect comparisons, two different techniques were used to pool the data. The adjusted indirect comparison, which consist at pooling the effect of each treatment against its comparator before comparing the 2 estimates, and the unadjusted technique that simply pools response rate regardless of its comparator. Ten reviews used adjusted indirect comparison. All of them had appropriate interpretation of the results. In 7 of them, there was agreement between indirect comparison and direct comparison (estimate of effect in the same direction) while 2 did not and 1 was uncertain. Three studies used unadjusted indirect comparison. Two were appropriate in the interpretation of the results and one uncertain. The agreement between indirect and direct comparison resulted in 1 study in each category.

For indirect comparison reviews only, 15 were adjusted and 8 were naïve. 6 of the adjusted and none of the naïve drew appropriate interpretation, versus 3 and 7 that did not respectively.

In summary, in 9.5% of the identified meta-analysis identified in this review, indirect comparisons were used. The analytic methods used include naïve indirect comparison in 31% of the reviews. Using the naïve method breaks the randomization process, leading to data that are at best equivalent to non-randomized studies. This review also highlights the lack of consistency between the results from indirect comparison compared to evidence from direct comparison.

Appendix 12

Indirect measures for extrapolation of efficacy data for CNA30024 study

	Y axis 100% measure		3TC-ABC		3TC-AZT	
	56.62		measure	% viral load suppression	measure	% viral load suppression
wk 24			40.48	71.5%		
wk48			39.95	70.6%	39.16	69.2%
from study				69.8%		69.0%
Error				1.011541		1.00236

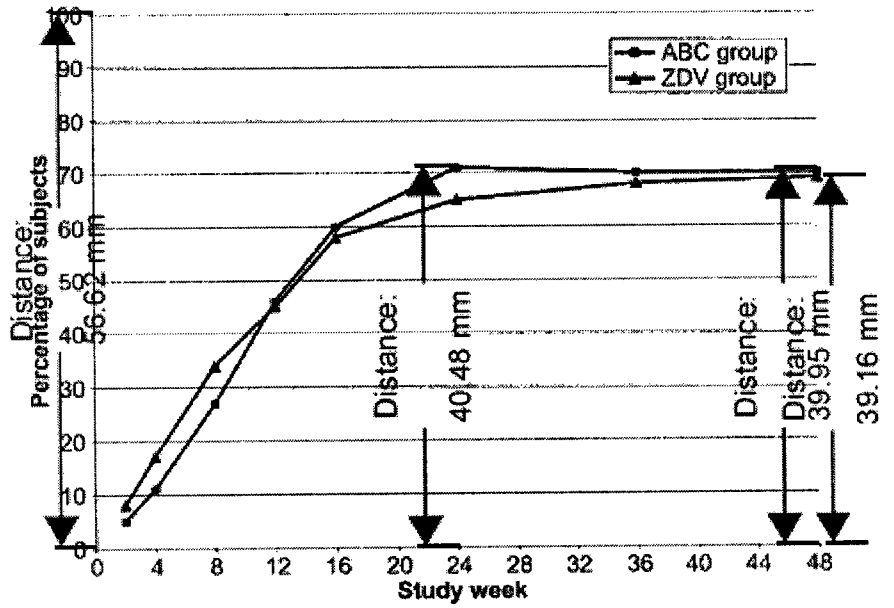


Figure 1. Percentage of subjects in the intent-to-treat exposed population of study CNA30024 receiving either a combination of abacavir (ABC), lamivudine, and efavirenz (the ABC group) or a combination of zidovudine (ZDV), lamivudine, and efavirenz (the ZDV group) with plasma HIV-1 RNA levels ≤50 copies/mL through study week 48. Data are based on results of an algorithm used to determine the time to loss of virologic response.

Appendix 13

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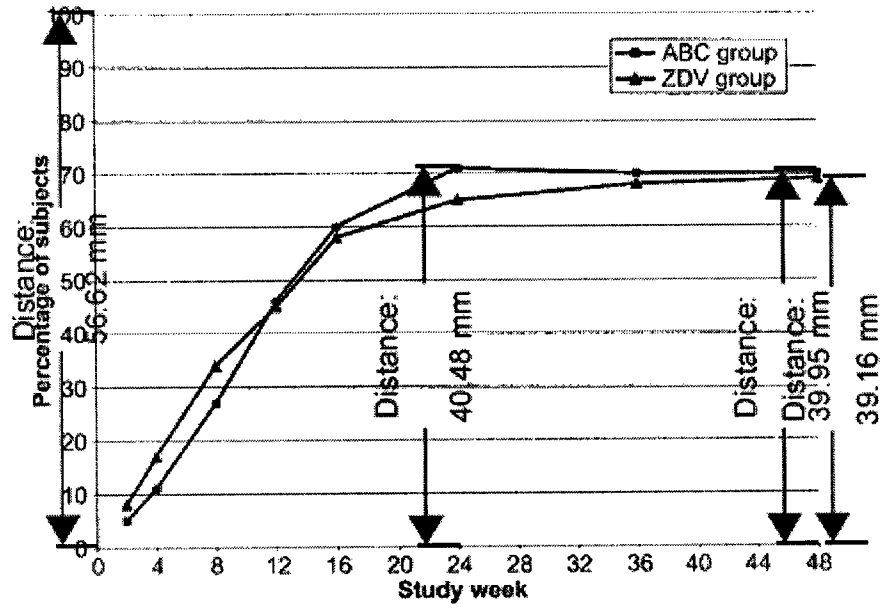

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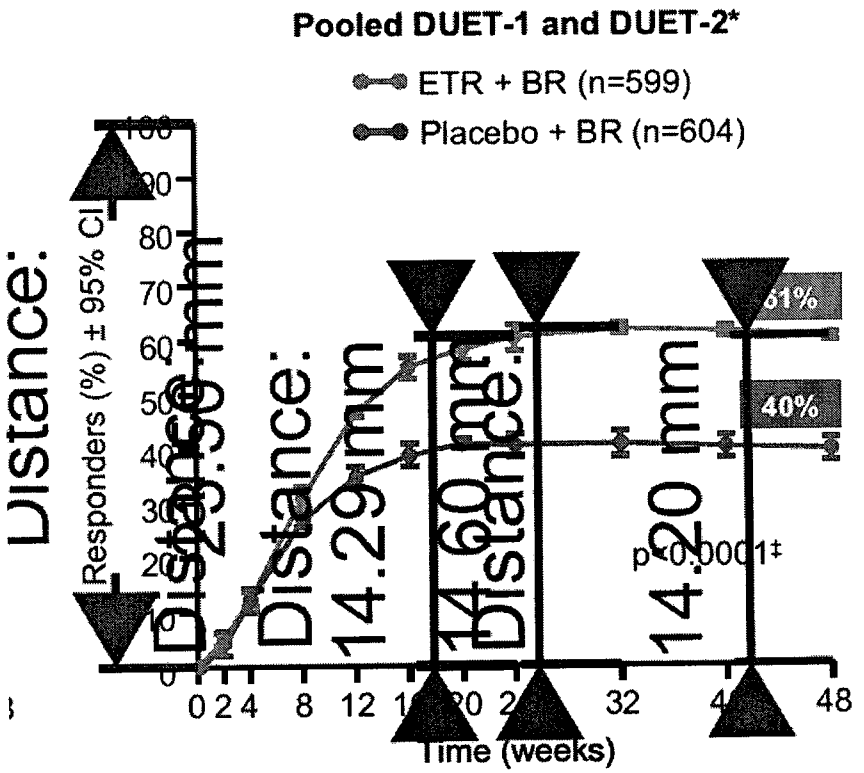
Appendix 14

Pooled DUET1-2 Extrapolation of efficacy data from graph

VL<50

	Y axis 100%	measure	%	from study	error rate
wk24	23.5	14.29	60.8%	61%	100.3%
wk32		14.6	62.1%		
wk48		14.2	60.4%	61%	101.0%



Appendix 15

Adjustment for the possibility of reduced virologic response to Abacavir/Lamivudine in ACTG5025

The calculation of the correcting factors is as followed:

1) proportion of patients with baseline viral load above 100 000 copies/mL: 45 %

2) ratio of proportion of patients with virological failure In ACTG 5142

   a) Never reached < 200 copies/mL : 3.76% for tenofovir-emtricitabine vs. 7.29% for abacavir-lamivudine; RR=1.94

   b) Failed after initial virological suppression: 2.76% for tenofovir-emtricitabine vs. 7.04% for abacavir-lamivudine; RR = 2.56

3) In HEAT study,

   a) 21/343 (6.10%) failed to achieve maximal response. The difference in total failure was due to intolerance and other factors associated with the conduct of the study.

   b) 28/343 (8.16%) lost virological failure after good initial response. This represents the rate of virological failure.

4) So the correction factor applied to each of the overall effectiveness parameter factors were the proportion of patients with baseline viral load > 100 000 copies/mL x RR of failure x proportion of patients with virological failure.

Therefore, the MVR is adjusted by dividing the estimate by the product of the proportion of subjects with baseline viral load > 100 000 copies/mL (1) x relative risk of failure in ACTG (2a) x proportion of failure due to virological failure (3a) which equals 1.053

The rate of virologic failure is the product of the proportion of subjects with baseline viral load > 100 000 copies/mL (1) x relative risk of failure in ACTG (2b) x proportion of failure due to virological failure (3b) which equals 1.094.

Appendix 16

Adjustment for the possibility of increased fatality from Myocardial Infarction to Abacavir/Lamivudine in D:A:D

- Crude rate x RR for abacavir x mortality associated to the event
- 0.0033 patient-year x 1.9 x 0.21
- = 1.0013167 per patient-year
- = 1.00065835 per patient per 6-month cycle