Published in final edited form as:
J Acquir Immune Defic Syndr. 2013 August 15; 63(5): 653–659. doi:10.1097/QAI.0b013e3182976891.

HIV-1 disease progression during Highly Active Antiretroviral Therapy: An application using population-level data in British Columbia: 1996–2011

B Nosyk, PhD[1], **JE Min, MSc**[1], **VD Lima, PhD**[1,2], **B Yip, BSc**[1], **RS Hogg, PhD**[1,3], and **JSG Montaner, MD, FRCPC**[1,2] **on behalf of the STOP HIV/AIDS Study Group**

[1]BC Centre for Excellence in HIV/AIDS

[2]Division of AIDS, Faculty of Medicine, University of British Columbia

[3]Faculty of Health Sciences, Simon Fraser University

Abstract

Background—Accurately estimating rates of disease progression is of central importance in developing mathematical models used to project outcomes and guide resource allocation decisions. Our objective was to specify a multivariate regression model to estimate changes in disease progression among individuals on HAART in British Columbia, Canada, 1996–2011.

Methods—We used population-level data on disease progression and antiretroviral treatment utilization from the BC HIV Drug Treatment Program. Disease progression was captured using longitudinal CD4 and plasma viral load testing data, linked with data on antiretroviral treatment. The study outcome was categorized into {CD4 count ≥500 cells/mm^3, 500 to 350 cells/mm^3, 350 to 200 cells/mm^3, <200cells/mm^3, and mortality}. A five-state continuous time Markov model was used to estimate covariate-specific probabilities of CD4 progression, focusing on temporal changes during the study period.

Results—A total of 210,083 CD4 measurements among 7,421 individuals with HIV/AIDS were included in the study. Results of the multivariate model suggested current HAART at baseline, lower baseline CD4 (<200 cells/mm^3), extended durations of elevated plasma viral load were each associated with accelerated progression. Immunological improvement was accelerated significantly from 2004 onward, with 23% and 46% increases in the probability of CD4 improvement from the 4th CD4 stratum {CD4<200} in 2004–2008 and 2008–2011, respectively.

Conclusion—Our results demonstrate the impact of innovations in antiretroviral treatment and treatment delivery at the population-level. These results can be used to estimate a transition probability matrix flexible to changes in the observed mix of clients in different clinical stages and treatment regimens over time.

Address for Correspondence: Dr. Julio SG Montaner, MD, FRCPC, BC Centre for Excellence in HIV/AIDS, St. Paul's Hospital, 613-1081 Burrard Street, Vancouver, BC V6Z 1Y6, jmontaner@cfenet.ubc.ca.

Conflicts: Dr. Julio Montaner has received grants from Abbott, Biolytical, Boehringer Ingelheim, Bristol-Myers Squibb, Gilead Sciences, Janssen, Merck and ViiV Healthcare. He is also is supported by the Ministry of Health Services and the Ministry of Healthy Living and Sport, from the Province of British Columbia; through a Knowledge Translation Award from the Canadian Institutes of Health Research (CIHR); and through an Avant-Garde Award (No. 1DP1DA026182) from the National Institute of Drug Abuse, at the US National Institutes of Health. He has also received support from the International AIDS Society, United Nations AIDS Program, World Health Organization, National Institute on Drug Abuse, National Institutes of Health Research-Office of AIDS Research, National Institute of Allergy & Infectious Diseases, The United States President's Emergency Plan for AIDS Relief (PEPfAR), Bill & Melinda Gates Foundation, French National Agency for Research on AIDS & Viral Hepatitis (ANRS), Public Health Agency of Canada

Keywords

human immunodeficiency virus; acquired immune deficiency syndromes; multi-state Markov models; CD4; transition probabilities

1.0 Introduction

Once considered an acute condition resulting in mortality within 10–15 years in most cases (1,2), HIV disease has been transformed into a chronic condition as a result of highly active antiretroviral treatment (HAART). In high-income countries, life expectancy for HIV-positive individuals aged 20 years and receiving HAART is roughly two-thirds of that of the general population (3). This is a direct result of delayed HIV disease progression brought about by continual improvements in HIV treatment (4,5). A number of other factors have been noted to alter disease progression, including earlier HIV diagnosis and treatment initiation and improved treatment adherence (6,7).

Health economic evaluation plays a critical role in informing health resource allocation decisions (8). In most cases, these decisions are intended for long-term or lifetime time horizons, implying the health technologies or programs in question will be available to clients in need for an indefinite period. As such, these analyses are most often executed using simulation models capturing all relevant costs and benefits within clearly-defined health states according to the disease in question (9).

Accurately estimating rates of disease progression is of central importance in developing individual microsimulation and compartmental mathematical models, used to project outcomes and guide resource allocation decisions regarding HIV treatment and prevention initiatives. Modeling disease progression via transition between CD4-based health states is a near-universal trait of health economic evaluations in HIV (10–14) given the strong relationship between CD4 T-lymphocyte counts and the costs of health resource use (15–17), as well as health-related quality of life (18,19). In this context, accurate estimates of CD4 progression over time are required in order to reliably predict the current and future burden of disease for the HIV-infected population, a highly heterogeneous group of patients, as well as to perform cost-effectiveness analyses of HAART in selective groups or settings.

Generating these estimates using multiple regression models can account for heterogeneity in patient characteristics and allows for flexibility in assigning population-level distributions of individuals at different clinical stages, receiving different HAART regimens, or according to specific locations and contexts. The results may also be amenable to probabilistic sensitivity analysis accounting for the correlation in specified individual-level covariates (20). However, a variety of different methodologies have been applied to estimate probabilities of disease progression in HIV/AIDS. For instance, in economic evaluations alongside clinical trials, transition probabilities are often calculated in a univariate manner, often using trial data at the study endpoints (usually at 24 or 48 weeks) (21,22). Other standard approaches involve the use of Weibull regression models to estimate time-dependent probabilities of transition between health states (23).

Markov chains constitute an alternative means of modeling the progression of a chronic disease through various severity states. For these models, a transition matrix with the probabilities of moving from one state to another for a specific time interval is estimated from observational cohort data. Multi-state Markov models are suited to analyses that involve transitions between many disease stages, and have previously been applied to model HIV/AIDS disease progression via CD4 cell count deterioration. They may be used (i) to estimate the effects of covariates on the risk of transition from one disease stage to another,

(ii) to compare the effects of each factor on the different transitions, (iii) to estimate the probabilities of evolving from one stage to another, of particular interest for simulation modeling (24–26).

The objective of this study was to specify a multiple regression model to estimate individual disease progression among individuals on antiretroviral therapy in British Columbia, Canada, from 1995 to 2011. We hypothesize that our model would demonstrate improving rates of disease progression (ie. slowed CD4 decay over time) at the population-level, controlling for patient-level characteristics. We executed our analysis using population-level data on clinical progression of HIV among individuals on antiretroviral treatment.

2.0 Methods

2.1 Patient Population

We considered all individuals who had ever received antiretroviral therapy from October 1st, 1995 to September 30th, 2011, as observed in the BC Centre for Excellence in HIV/AIDS (BC-CfE) HIV Drug Treatment Program. The study cohort is followed in a unique environment characterized by universal free medical care, including free in- and out-patient care, laboratory monitoring, and antiretroviral drugs, without co-payments or deductibles. The antiretroviral drugs are centrally distributed by the BC-CfE according to the BC-CfE's treatment guidelines, which have remained consistent with those put forward by the International AIDS Society since the summer of 1996 and until the most recent guidelines (5).

We included individuals who initiated antiretroviral therapy naïve at ≥ 19 years old with at least two CD4 cell count measurements. Individuals were excluded from the analysis if therapeutic information, baseline CD4 or viral load values were missing. The study sample is comprised of individuals infected primary with HIV subtype B virus; a previous study estimated a prevalence of 4.4% non-B virus (27). The study was approved by the University of British Columbia/Providence Health Care research ethics board.

2.2 Measures

HIV disease progression among individuals ever engaged in antiretroviral therapy, represented by changes in longitudinally-collected CD4 measurements, was of primary interest in this study. All CD4 observations following treatment initiation were included in the analysis, including periods where individuals were not on antiretroviral treatment. CD4 cell count measurements were categorized into {CD4 ≥500 cells/mm^3; 500 to 350 cells/mm^3; 350 to 200 cells/mm^3; <200 cells/mm^3; and death}.

While we aimed to preserve as many observations as possible, given the implicit assumption of constant covariates between assessments, CD4 measurements following breaks exceeding 36 months were excluded. The data are assumed to represent snapshots of the process at arbitrary time periods. Survival was ascertained through a continuous linkage to provincial vital statistics data.

CD4 cell counts were measured by flow cytometry (Beckman Coulter Inc, Mississauga, ON, Canada). The CD4 metric is known to exhibit considerable variability, resulting from intra-person temporal fluctuation, for example diurnal variation, as well as from measurement error introduced by the process of blood collection or the method of collection itself (28). Statistical techniques to model such noisy data will result in estimated transition intensities that are too large. Following an analysis of four smoothing techniques to address this measurement error (29), we applied the 'ad hoc smoothing' technique, whereby transitions

between CD4 strata were only allowed when two consecutive CD4 measurements were observed.

We tested a number of additional covariates hypothesized to influence changes in HIV disease progression, including age at treatment initiation, baseline CD4 (latest CD4 measurement within 3 months prior to HAART initiation: <200 vs. ≥200 cells/mm^3), gender, injection drug use (IDU), Hepatitis C virus (HCV) antibody positivity, whether or not the contemporary standard of HAART was prescribed at baseline (two Nucleoside Reverse Transcriptase Inhibitor plus either a boosted Protease Inhibitor (PI) or a Non-Nucleoside Reverse Transcriptase Inhibitor or raltegravir), and current HAART treatment regimen (first-generation regimens including zidovudine, lamivudine, didanosine, stavudine, nevirapine, abacavir, nelfinavir and ritonavir; or second-generation regimens including lamivudine+tenofovir, emtricitabine+tenfovir, tipranavir, maraviroc, raltegravir, etravirine, atazanavir, enfuvirtide, efavirenz, ritonavir and other PI- or boosted-PI based regimens; multi-drug resistance regimens including five or more drugs; or off-therapy). As sustained periods of high plasma viral load (pVL) are associated with decreases in CD4, the area under the pVL curve was also included as a continuous covariate.

Further, as both policies regarding treatment initiation, and the available treatment regimens have evolved substantially since the initiation of HAART in 1996 (4,5), we included covariates on the temporal period of CD4 measurement (pre-2004; 2004–2007; post-2007). Finally, interaction terms between the temporal period of CD4 measurement CD4 at baseline was tested. Classifications for categorical variables were informed by clinical relevance, observed distributions, or otherwise calibrated in multivariate analysis.

2.3 Statistical Analysis

A parametric continuous-time, multi-state Markov model was implemented to estimate the impact of prognostic factors on CD4 disease progression, and estimate CD4 state transition probabilities over time. Markov chains constitute a common way of modeling the progression of a chronic disease through various severity states. For these models, a transition matrix with the probabilities of moving from one state to another for a specific time interval is usually estimated from observational cohort data. The time between CD4 measurements is inherently controlled for in this methodology. Multi-state Markov models have previously been applied to model HIV/AIDS disease progression via CD4 cell counts (29–34). These models efficiently handle heavily censored data, such as when the exact time of disease onset is unknown or when a subject is observed over a portion of his/her disease history (31).

In this model, a covariate is assumed to affect the baseline intensity by a proportional (constant over time) factor, so that a model with ten transitions requires ten different regression coefficients to be estimated for each covariate. The effects of the different covariates (fixed and time-varying) were assumed to be multiplicative and constant over time, both assumptions being consistent with the conventional proportional hazards model (35). Therefore, the interpretation of exponentiated coefficient estimates is similar to that of the adjusted hazard ratio in the Cox model. All baseline intensities and regression coefficients were simultaneously estimated via maximum likelihood estimation. Instantaneous transitions were only permitted between adjacent states or death from each health state. Covariates were included in the multivariate model if they had a statistically significant impact on any of the CD4 transitions specified in the model. For all hypotheses tested, a significance level of α=0.05 was used.

The likelihood function for this model assumes that the sampling times are ignorable. That is, the fact that a particular observation is made at a certain time does not implicitly give

information about the value of that observation. Sampling times are ignorable if they are fixed in advance, or otherwise chosen independently of the outcome of the process. Grujer et al (36) also showed that the sampling times are ignorable under a 'doctor's care' sampling scheme, where the next observation time (in our case a regularly-scheduled CD4 measurement) is chosen on the basis of the current state. Basing the current observation time on the current state constitutes a non-ignorable sampling scheme (37). While the majority of CD4 measurements typically occur at regular intervals as part of routine care, in some limited instances CD4 measurements are triggered by changes in symptomatology, in a 'doctor's care' sampling scheme. Analyses were executed using SAS version 9.3 and the R statistical software (38) msm package (39,40).

3.0 Results

The study sample consisted of 7,421 individuals and 210,083 observations, including deaths, with a median follow up of 5.1 years (Interquartile range (IQR): 2.1–10.4 years) and a median of 20 CD4 measurements (IQR 9–44, range 2–161). A total of 1573 patients (21%) died during follow-up. Of the 5848 survivors, 2715 (46%) had a CD4 count ≥ 500 cells/mm^3, 1415 (24%) between 500 - 350 cells/mm^3, 1092 (19%) between 350 - 200 cells/mm^3, and 626 (11%) <200 cells/mm^3 at baseline. Finally, 3266 (44%) clients discontinued treatment at least once.

Table 1 provides baseline characteristics on the study sample. The majority of subjects were males (83%), the median age at ART initiation was 39 (IQR: 33 – 46), a prior history of IDU was observed in for 38% of the sample and 39% were co-infected with HCV. Nearly half of the sample (45%) initiated treatment prior to the year 2000, and baseline CD4 measurements <200 cells/mm^3 were observed in 41% of the study sample.

We summarized the study outcome in two ways. First, in Table 2, we displayed the distribution of the total number of transitions between CD4 strata. The majority of pairs of observations remained within the same CD4 stratum, with relatively few observed transitions to death from each CD4 stratum. Second, in Figure 1, we showed the distribution of the durations between CD4 measurements. Nearly 90% of observed CD4 measurement pairs were ≤6 months apart, with <5% occurring over 9 months apart. The mean frequency of CD4 measurements has varied between 1.2 to 1.5 per person-quarter during the study period.

The five-state multivariable Multi-state Markov model was fitted with covariates to produce nine parameter estimates for each of the ten possible transitions modeled, for a total of 90 parameter estimates. Selected results of the multivariate MSM model were presented in Table 3. We present hazard ratios (HRs) on improvement in CD4 strata; HRs <1 therefore indicate delayed time-to-CD4 improvement. Baseline CD4 counts<200 cells/mm^3 were associated with delayed time-to CD4 improvement from each of the 2^{nd}, 3^{rd} and 4^{th} CD4 strata, compared with baseline CD4 counts ≥ 200 cells/mm^3 (transition from CD4<200 cells/mm^3 to 200–350 cells/mm^3: HR:0.52; 95% CI (0.49, 0.56)). Higher pVL levels as indicated by AUC pVL, resulted in progressively greater delays in CD4 improvement from each of the 2^{nd} (0.95 (0.87, 1.02)), 3^{rd} (0.64 (0.60, 0.69)) and 4^{th} CD4 strata (0.38 (0.35, 0.41)). Finally, baseline prescription of second-generation HAART regimens resulted in accelerated CD4 improvement from the 2^{nd}, 3^{rd} and 4^{th} strata, and baseline prescription of second-generation HAART regimens was also independently associated with accelerated CD4 improvement compared to baseline prescription of first-generation HAART regimens and periods off therapy.

Finally, in Figure 2 we present fitted values of CD4 transition probabilities, estimated on an annual basis, generated from results of the multivariate MSM model, and using observed

mean values of covariates observed during three specified time periods (pre-2004; 2004–2007; 2008–2011). Marked improvement was observed on transitions from the 3rd {CD4:200–349 cells/mm^3} and 4th {CD4 <200 cells/mm^3} CD4 strata; the probability of transitioning from the 3rd CD4 stratum {CD4:200–349 cells/mm^3} to the 1st and 2nd CD4 strata improved from (0.088, 0.256) pre-2004 to (0.120, 0.308) and (0.138, 0.343) in the 2004–2007 and 2008–2011 time periods, while the probability of deterioration to the 4th CD4 stratum {CD4 <200 cells/mm^3} declined modestly. The probability of improvement from the 4th CD4 stratum {CD4 <200 cells/mm^3} increased from (0.019, 0.088 and 0.295) for CD4 strata 1, 2 and 3, respectively, in the pre-2004 period to (0.033, 0.131 and 0.329) in 2004–2007 and (0.044, 0.171 and 0.371) in 2008–2011. Together, the probability of improvement from the 4th CD4 strata increased from (0.019, 0.088 and 0.295=0.402) pre-2004 to 0.493 and 0.586 in 2004–2007 and 2008–2011, respectively, representing 23% and 46% increases in the probability of CD4 improvement from the 4th CD4 stratum {CD4<200 cells/mm^3} after 2004.

4.0 Discussion

Our results illustrate the effect of innovation in HIV therapeutics on CD4 disease progression. We found that the probability of CD4 improvement during HAART increased over time, resulting in disease progression being significantly delayed among treatment recipients in recent years. This result was punctuated by 23% and 46% increases in the probability of CD4 improvement for individuals with CD4 cell counts below 200 cells/mm^3 from to 2004–2008 and 2008–2011, respectively. Diminishing HIV disease virulence could be posited as an alternative hypothesis for the temporal trend revealed in this article, however provincial and North American data do not support this hypothesis (41,42); Improving genotypic sensitivity scores further support the role of treatment in improvements in disease progression (41).

Prior studies have estimated CD4 transition probabilities using related methodologies (43), however this population-level analysis spanning over 15 years of treatment delivery is the first, to our knowledge, to demonstrate significant delays in disease progression among individuals on HAART at the population-level. These findings have important implications. Clearly, simulation models aiming to project outcomes into the future, which employ CD4 transition probabilities based on data from the early-HAART era will substantially underestimate the individual, as well as public health benefits of HAART. This is an important result to communicate as efforts to scale-up treatment unfold globally on a backdrop of constraints and decreases for funding (43,44).

While our estimated transition probabilities from the higher CD4 states to death were uniformly low, generally in the neighborhood of 1% over a 12-month period, the direction of some parameter estimates were contrary to our *a priori* hypotheses. While we believe the vast majority of CD4 measurements in our analysis were non-informative, it may be possible that the timing of measurements nearest to death may have been informative. Sweeting et al (37) describe a methodology used to resolve this problem by conditioning on a more regularly observed auxiliary variable – a solution which may not be feasible for modeling HIV progression, as CD4/pVL measurements are themselves regularly observed. Further methodological development is likely required to handle these scenarios in Multi-state Markov models of HIV disease progression.

Several limitations are worth noting. First, while the study was based on a population-level registry of antiretroviral treatment dispensation, initiated in 1992 (in the pre-HAART era), given patient characteristics (including virus subtype), the nature of the HIV epidemic in BC, and our healthcare delivery policies, caution must be exercised in applying these

estimates to other settings. Second, time-varying covariates capturing changing drug resistance profiles over time were not considered in this analysis, however previous studies reported low prevalence of multi-class resistance (45); a detailed examination of the effect of drug resistance is beyond the scope of this article. Third, current, or recent CD4 and pVL measurements were not always available in all time periods where treatment was delivered. CD4 markers have been noted to exhibit considerable variability as a result of intraperson temporal fluctuation, for example diurnal variation, as well as from measurement error introduced by the process of blood collection or the method of collection (flow cytometry) itself (27). Further, the IDU status and aboriginal ethnicity covariates were self-reported and had high levels of missing data, likely to be non-differential, resulting in coefficients attenuated towards the null hypothesis. Efforts to improve data quality on these critical indicators via triangulation with provincial registries and administrative databases are currently underway. We attempted to address threats to internal validity due to measurement error or confounding in the design of the study, as described above.

To conclude, this analysis has highlighted the magnitude of temporal variations in HIV disease progression among HIV-positive individuals on antiretroviral therapy. The results are cause for careful consideration of estimates of transition probabilities in economic models to project the costs and benefits of HAART scale-up in HIV ‘treatment as prevention’ programs.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Sources of support: National Institutes of Health; BC Ministry of Health

We acknowledge the assistance of David Milan and Suzanne Humphreys in early efforts towards this manuscript, as well as all BCMoH and Vancouver Coastal Health Decision Support Staff involved in data access and procurement, including Monika Lindegger, Clinical Prevention Services, BC Centre for Disease Control; Elsie Wong, Public Health Agency of Canada; Al Cassidy, BC Ministry of Health Registries, Bruce Brady, BC Ministry of Health and Joleen Wright and Karen Luers, Vancouver Coastal Health decision support. We further acknowledge Drs. Art FY Poon and P. Richard Harrigan for their input into the revision of this article. This study was funded by the BC Ministry of Health-funded ‘Seek and treat for optimal prevention of HIV & AIDS’ pilot project, as well as NIH/NIDA grant numbers 1DP1DA026182 and R01-DA032551.

Bohdan Nosyk is a CIHR Bisby Fellow and a Michael Smith Foundation for Health Research Scholar. Dr. Lima is funded by a Scholar Award from the Michael Institute for Health Research. Dr. Julio Montaner has received grants from Abbott, Biolytical, Boehringer Ingelheim, Bristol-Myers Squibb, Gilead Sciences, Janssen, Merck and ViiV Healthcare. He is also is supported by the Ministry of Health Services and the Ministry of Healthy Living and Sport, from the Province of British Columbia; through a Knowledge Translation Award from the Canadian Institutes of Health Research (CIHR); and through an Avant-Garde Award (No. 1DP1DA026182) from the National Institute of Drug Abuse, at the US National Institutes of Health. He has also received support from the International AIDS Society, United Nations AIDS Program, World Health Organization, National Institute on Drug Abuse, National Institutes of Health Research-Office of AIDS Research, National Institute of Allergy & Infectious Diseases, The United States President’s Emergency Plan for AIDS Relief (PEPfAR), Bill & Melinda Gates Foundation, French National Agency for Research on AIDS & Viral Hepatitis (ANRS), Public Health Agency of Canada.

References

1. Mellors JW, Munoz A, Giorgi JV, et al. Plasma viral load and CD4+ lymphocytes as prognostic markers of HIV-1 infection. Ann Intern Med. 1997; 126:946–954. [PubMed: 9182471]
2. Moss AR, Bacchetti P. Natural history of HIV infection. AIDS. 1989; 3(2):55–61. [PubMed: 2496720]

3. Antiretroviral Cohort Collaboration. Life expectancy of individuals on combination antiretroviral therapy in high-income countries: a collaborative analysis of 14 cohort studies. Lancet. 2008; 372(9635):293–9. [PubMed: 18657708]
4. Carpenter CJC, Fischl MA, Hammer SM, et al. Antiretroviral Therapy for HIV Infection in 1996. JAMA. 1996; 276 (2):146–154. [PubMed: 8656507]
5. Thompson MA, Aberg JA, Hoy JF, et al. Antiretroviral treatment of adult HIV infection: 2012 recommendations of the International Antiviral Society-USA panel. JAMA. 2012; 308(4):387–402. [PubMed: 22820792]
6. Binquet C, Le Teuff C, Abrahamovicz M, et al. for the Groupe InterCOrevih du Nord-Est (ICONE). Markov modeling of HIV infection evolution in the HAART era. Epidemiol Infect. 2009; 137:1272–82. [PubMed: 19134234]
7. Sterne J, et al. Long-term effectiveness of potent antiretroviral therapy in preventing AIDS and death: a prospective cohort study. Lancet. 2005; 366:378–84. [PubMed: 16054937]
8. Drummond, M.; McGuire, A. Economic Evaluation in Health Care: Merging Theory with Practice. Oxford, UK: Oxford University Press; 2001.
9. Ramsey S, Willke R, Briggs A, et al. Good research practices for cost-effectiveness analysis alongside clinical trials: The ISPOR RCT-CEA task force report. Value in Health. 2005; 8(5):521–33. [PubMed: 16176491]
10. Walensky RP, Freedberg KA, Weinstein MC, et al. Cost-effectiveness of HIV testing and treatment in the United States. Clin Infect Dis. 2007; 45:S248–54. [PubMed: 18190295]
11. Long EF, Brandeau ML, Owens DK. The cost-effectiveness and population outcomes of expanded HIV screening and antiretroviral treatment in the United States. Ann Intern Med. 2010; 153(12): 778–89. [PubMed: 21173412]
12. Long EF, Brandeau ML, Galvin CM, et al. Effectiveness and cost-effectiveness of strategies to expand antiretroviral therapy in St. Petersburg, Russia. AIDS. 2006; 20:2207–15. [PubMed: 17086061]
13. Sanders GD, Bayoumi AM, Sundaram V, et al. Cost-effectiveness of screening for HIV in the era of highly active antiretroviral therapy. N Engl J Med. 2005; 352:570–85. [PubMed: 15703422]
14. Mauskopf J, Kitahata M, Kauf T, et al. HIV Antiretroviral treatment: Early versus later. J Acquir Immune Defic Syndr. 2005; 39:562–9. [PubMed: 16044008]
15. Levy AR, James D, Johnston KM, et al. The direct costs of HIV/AIDS care. Lancet Infect Dis. 2006; 6(3):171–7. [PubMed: 16500598]
16. Barnett PG, Chow A, Joyce VR, et al. for the OPTIMA team. Determinants of the costs of health services used by veterans with HIV. Med Care. 2011; 49(9):848–56. [PubMed: 21610542]
17. Levy A, Johnston K, Annemans L, et al. The impact of disease stage on direct medical costs of HIV management: a review of the international literature. Pharmacoeconomics. 2010; 28 (Suppl 1):35–47. [PubMed: 21182342]
18. Kauf TL, Roskell N, Shearer A, et al. A predictive model of health state utilities for HIV patients in the modern era of highly active antiretroviral therapy. Value in Health. 2008; 11(7):1144–53. [PubMed: 18494750]
19. Anis AH, Nosyk B, Sun H, et al. for the OPTIMA Team. Quality of life of patients with advanced HIV/AIDS: measuring the impact of both AIDS-defining events and non-AIDS serious adverse events. J Acquir Immune Defic Syndr. 2009; 51(5):631–9. [PubMed: 19430303]
20. Briggs, A. Handling uncertainty in economic evaluation and presenting the results. In: Drummond, M.; McGuire, A., editors. Economic Evaluation in Health Care: Merging Theory with Practice. Oxford, UK: Oxford University Press; 2001. p. 172-214.
21. Mauskopf J, Annemans L, Hill AM, et al. A review of economic evaluations of darunavir boosted by low-dose ritonavir in treatment-experienced persons living with HIV infection. Pharmacoeconomics. 2010; 28 (Suppl 1):1–16. [PubMed: 21182340]
22. Sax PE, Losina E, Weinstein MC, et al. Cost-effectiveness of enfuvirtide in treatment-experienced patients with advanced HIV disease. J Acquir Immune Defic Syndr. 2005; 39(1):69–77. [PubMed: 15851916]
23. Drummond, M.; McGuire, A. Economic Evaluation in Health Care: Merging Theory with Practice. Oxford, UK: Oxford University Press; 2001.

24. Alioum A, Leroy V, Commenges D, et al. Effect of gender, age, transmission category, and antiretroviral therapy on the progression of human immunodeficiency virus infection using multistate Markov models. Groupe d'Epidémiologie Clinique du SIDA en Aquitaine. Epidemiology. 1998; 9:605–612. [PubMed: 9799168]
25. Nichol MB, Knight TK, Wu J, et al. Transition probabilities and predictors of adherence in a California Medicaid population using antihypertensive and lipid-lowering medications. Value Health. 2009; 12(4):544–50. [PubMed: 19138308]
26. Borg S, Persson U, Jess T, et al. A maximum likelihood estimator of a Markov model for disease activity in Crohn's disease and ulcerative colitis for annually aggregated partial observations. Med Decis Making. 2010; 30(1):132–42. [PubMed: 19605883]
27. Alexander CS, Montessori V, Wynhoven B, Dong W, Chan K, O'Shaughnessy MV, Mo T, Piaseczny M, Montaner JS, Harrigan PR. Prevalence and response to antiretroviral therapy of non-B subtypes of HIV in antiretroviral-naive individuals in British Columbia. Antivir Ther. 2002; 7(1):31–5. [PubMed: 12008785]
28. Hoover DR, Graham NM, Chen B, et al. Effect of CD4+ cell count measurement variability on staging HIV-1 infection. J Acquir Immune Defic Syndr. 1992; 5(8):794–802. [PubMed: 1355556]
29. Sypsa V, Touloumi G, Kenward M, et al. Comparison of smoothing techniques for CD4 data in a Markov model with states defined by CD4: an example on the estimation of the HIV incubation time distribution. Stat Med. 2001; 20(24):3667–76. [PubMed: 11782025]
30. Guihenneuc-Jouyaux C, Richardson S, Longini IM Jr. Modeling markers of disease progression by a hidden Markov process: application to characterizing CD4 cell decline. Biometrics. 2000; 56(3): 733–41. [PubMed: 10985209]
31. Mathieu E, Loup P, Dellamonica P, et al. Markov modelling of immunological and virological states in HIV-1 infected patients. Biom J. 2005; 47(6):834–46. [PubMed: 16450856]
32. Charitos T, de Waal PR, van der Gaag LC. Computing short-interval transition matrices of a discrete-time Markov chain from partially observed data. Stat Med. 2008; 27(6):905–21. [PubMed: 17579926]
33. Satten GA, Longini IM. Markov chains with measurement error: estimating the 'true' course of a marker of the progression of the human immunodeficiency virus disease. Appl Stat. 1996; 45(3): 275–309.
34. Craig BA, Sendi PP. Estimation of the transition matrix of a discrete-time Markov chain. Health Econ. 2002; 11:33–42. [PubMed: 11788980]
35. Cox D. Regression models and life tables. J Royal Stat Soc. 1972; B34:187–220.
36. Grujer J, Kay R, Schumacher M. The validity of inferences based on incomplete observations in disease state models. Biometrics. 1991; 47:595–605. [PubMed: 1912263]
37. Sweeting MJ, Farewell VT, De Angelis D. Multi-state Markov models for disease progression in the presence of informative examination times: an application to hepatitis C. Stat Med. 2010; 29(11):1161–74. [PubMed: 20437454]
38. R Development Core Team. R: A language and environment for statistical computing. Vienna, Austria: R Foundation for Statistical Computing; 2012.
39. Jackson CH. Multi-state models for panel data: the msm package for R. J Stat Softw. 2011; 38:1–29.
40. [Accessed: April 2nd, 2012] MSM: Multi-state Markov and hidden Markov models in continuous time. http://cran.r-project.org/web/packages/msm/index.html
41. Personal Communication unpublished data Dr Art FY Poon. Mar 12. 2013
42. Herbeck JT, Gottlieb GS, Li X, Hu Z, Detels R, et al. Lack of Evidence for Changing Virulence of HIV-1 in North America. PLoS ONE. 2008; 3(2):e1525. [PubMed: 18253479]
43. Granich R, Gupta S, Suthar A, et al. on behalf of the ART in Prevention of HIV and TB Research Writing Group. ART in prevention of HIV and TB: Update on current research efforts. Curr HIV Res. 2011; 9:446–69. [PubMed: 21999779]
44. Bland, S. [Accessed: Sept 6th, 2012] The Global Fund is alive and well, but global health progress is in peril. The Global Fund to fight AIDS, Tuberculosis and Malaria. http://www.theglobalfund.org/en/mediacenter/announcements/

2011-12-01_The_Global_Fund_is_alive_and_well_But_Global_Health_Progress_is_in_Peril_by_Simon_Bland_the_Chair_of_the_Board_of_the_Global_Fund/

45. Lima VD, Harrigan PR, Sénécal M, Yip B, Druyts E, Hogg RS, Montaner JS. Epidemiology of antiretroviral multiclass resistance. Am J Epidemiol. 2010; 172(4):460–8. [PubMed: 20667931]

The STOP HIV/AIDS Study Group is comprised of the following

Julio Montaner, MD, FRCPC, Director, BC Centre for Excellence in HIV/AIDS; Division of AIDS, Faculty of Medicine, University of British Columbia

Bohdan Nosyk, BC Centre for Excellence in HIV/AIDS

Viviane D. Lima, BC Centre for Excellence in HIV/AIDS; Division of AIDS, Faculty of Medicine, University of British Columbia

Kate Heath, BC Centre for Excellence in HIV/AIDS

Robert S. Hogg, BC Centre for Excellence in HIV/AIDS; Faculty of Health Sciences, Simon Fraser University

Rolando Barrios, MD, FRCPC, Vancouver Coastal Health Authority; School of Population and Public Health, University of British Columbia.

Patty Daly, MD, Vancouver Coastal Health Authority

Mark Gilbert, Clinical Prevention Services, BC Centre for Disease Control; School of Population & Public Health, University of British Columbia.

Reka Gustafson, MD, Vancouver Coastal Health Authority

Perry RW Kendall, OBC, MBBS, MSc, FRCPC. Provincial Health Officer, British Columbia Ministry of Health; Clinical Professor, Faculty of Medicine UBC

Ciro Panessa, British Columbia Ministry of Health

Nancy South, British Columbia Ministry of Health

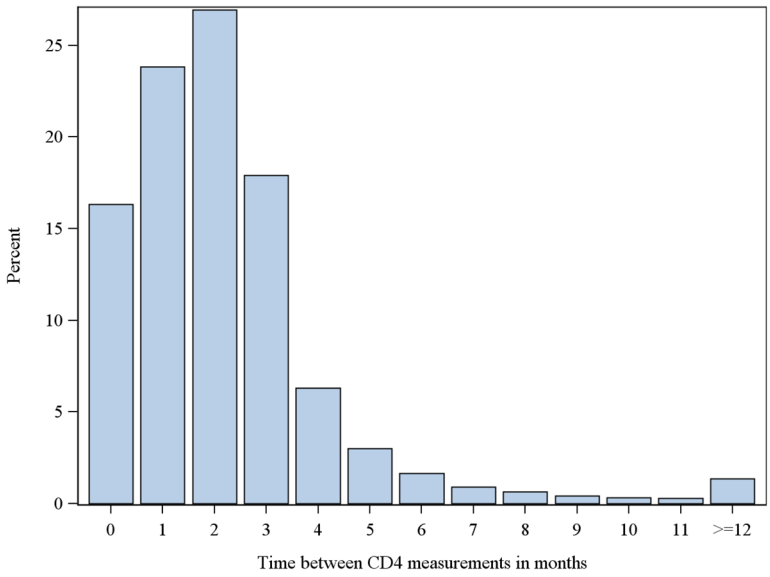
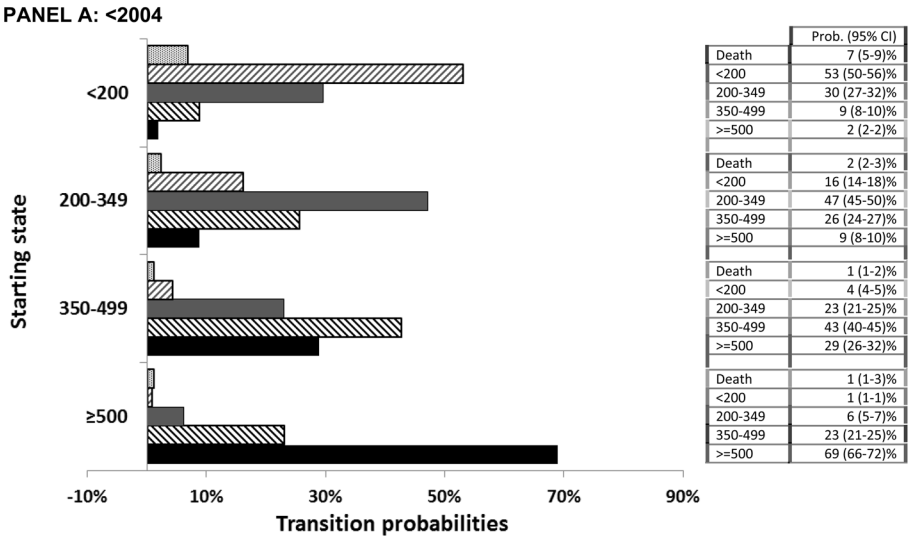
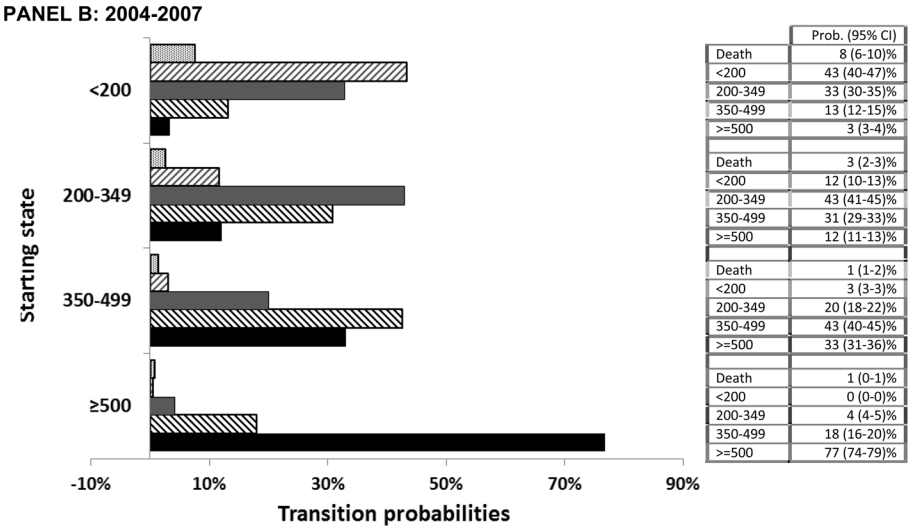


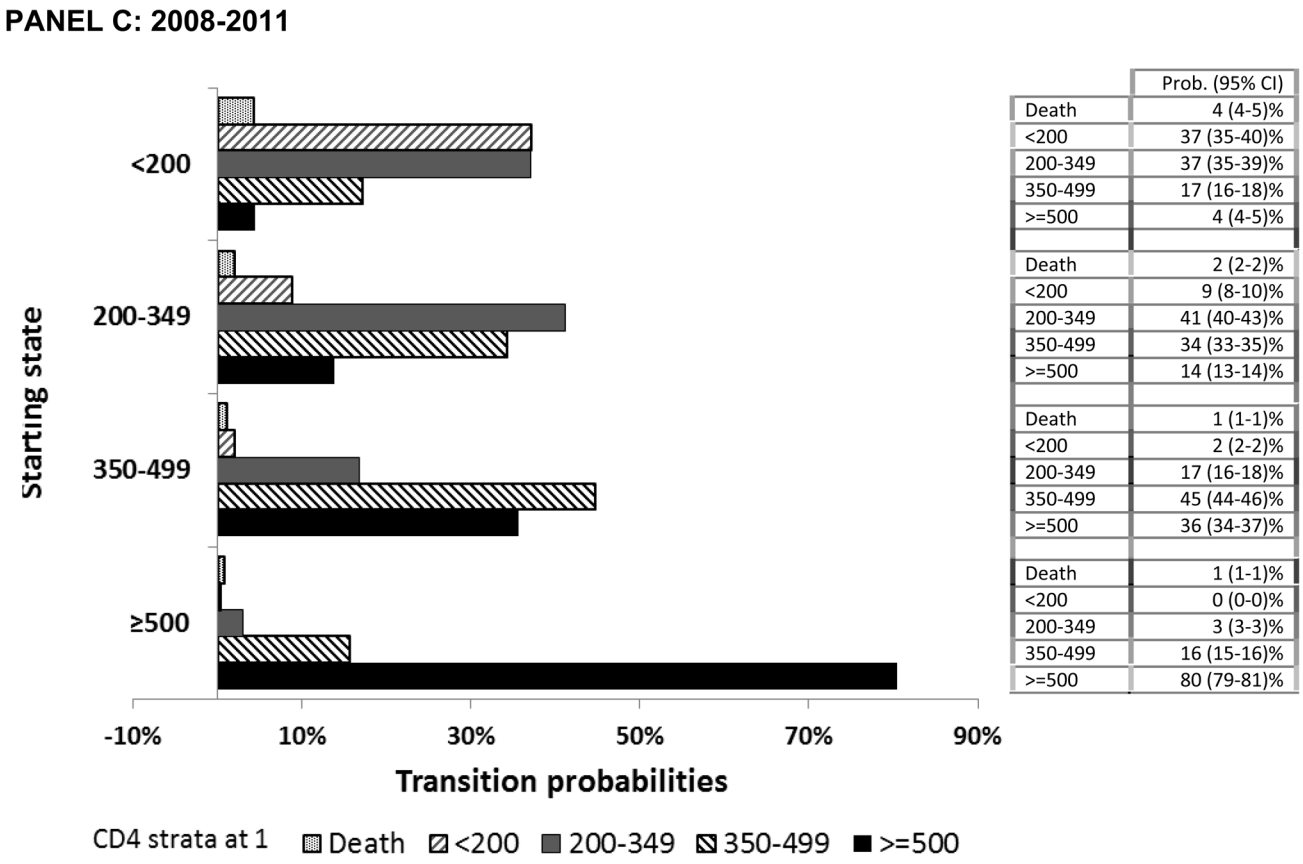
Figure 1.
Distribution of time between CD4 measurements



	Prob. (95% CI)
Death	7 (5-9)%
<200	53 (50-56)%
200-349	30 (27-32)%
350-499	9 (8-10)%
>=500	2 (2-2)%
Death	2 (2-3)%
<200	16 (14-18)%
200-349	47 (45-50)%
350-499	26 (24-27)%
>=500	9 (8-10)%
Death	1 (1-2)%
<200	4 (4-5)%
200-349	23 (21-25)%
350-499	43 (40-45)%
>=500	29 (26-32)%
Death	1 (1-3)%
<200	1 (1-1)%
200-349	6 (5-7)%
350-499	23 (21-25)%
>=500	69 (66-72)%



	Prob. (95% CI)
Death	8 (6-10)%
<200	43 (40-47)%
200-349	33 (30-35)%
350-499	13 (12-15)%
>=500	3 (3-4)%
Death	3 (2-3)%
<200	12 (10-13)%
200-349	43 (41-45)%
350-499	31 (29-33)%
>=500	12 (11-13)%
Death	1 (1-2)%
<200	3 (3-3)%
200-349	20 (18-22)%
350-499	43 (40-45)%
>=500	33 (31-36)%
Death	1 (0-1)%
<200	0 (0-0)%
200-349	4 (4-5)%
350-499	18 (16-20)%
>=500	77 (74-79)%



	Prob. (95% CI)
Death	4 (4-5)%
<200	37 (35-40)%
200-349	37 (35-39)%
350-499	17 (16-18)%
>=500	4 (4-5)%
Death	2 (2-2)%
<200	9 (8-10)%
200-349	41 (40-43)%
350-499	34 (33-35)%
>=500	14 (13-14)%
Death	1 (1-1)%
<200	2 (2-2)%
200-349	17 (16-18)%
350-499	45 (44-46)%
>=500	36 (34-37)%
Death	1 (1-1)%
<200	0 (0-0)%
200-349	3 (3-3)%
350-499	16 (15-16)%
>=500	80 (79-81)%

Figure 2.
12-month transition probabilities using current-valued covariates

Table 1

Baseline characteristics of the study sample (7,421 patients)

Characteristic	
Age (years) at the first ARV, median (IQR)	39 (33–46)
Males, N (%)	6132 (83)
Year of first ARV, N (%)	
1992–1996	883 (12)
1996–1999	2470 (33)
2000–2003	1193 (16)
2004–2007	1371 (18)
2008–2011	1504 (20)
Baseline CD4 (cell count/mm^3), N (%)	
≥ 500	792 (11)
350–499	1280 (17)
200–349	2313 (31)
< 200	3036 (41)
Baseline Viral Load (log_{10} copies/mL), median (IQR)	4.9 (4.4–5.0)
Injection drug use, N (%)	
No	3266 (44)
Yes	2812 (38)
Unknown	1343 (18)
HCV status, N (%)	
Negative	3555 (48)
Positive	2872 (39)
Unknown	994 (13)
First ARV therapy (current HAART), N (%)	
No	3512 (47)
Yes	3909 (53)

Table 2

Number of transitions between CD4-based strata (210,083 observations)

	CD4 stratum at time t+1				
CD4 stratum at time t	**≥500**	**350–499**	**200–349**	**< 200**	**Death**
≥ 500	64,904	3,617	676	153	146
350–499	5,319	40,082	3,705	381	170
200–349	565	5,496	39,956	2,638	280
< 200	51	275	3,500	29,771	977

Table 3

Multivariate multistate Markov model results: CD4 improvement during antiretroviral therapy in British Columbia, Canada: 1996–2011

	Transition between CD4 strata*		
Covariate	**350–499 to ≥500**	**200–349 to 350–499**	**<200 to 200–349**
	HR (95% CI)	**HR (95% CI)**	**HR (95% CI)**
Baseline Therapy: Not current standard	Ref	Ref	Ref
Current standard of care	1.30 (1.22,1.38)	1.34 (1.26,1.42)	1.28 (1.18,1.39)
AUC pVL	0.95 (0.88,1.03)	0.64 (0.60,0.69)	0.38 (0.35,0.41)
Current Therapy: 2nd generation	Ref	Ref	Ref
1st generation	0.79 (0.74,0.85)	0.73 (0.68,0.79)	0.78 (0.72,0.86)
Off therapy	0.32 (0.28,0.37)	0.36 (0.33,0.41)	0.46 (0.40,0.52)
At current year: <2004**			
Baseline CD4≥200	Ref	Ref	Ref
CD4<200	0.79 (0.71, 0.87)	0.59 (0.54, 0.64)	0.55 (0.50, 0.60)
At current year: 2004–2007**			
Baseline CD4≥200	Ref	Ref	Ref
CD4<200	0.77 (0.70, 0.85)	0.64 (0.59, 0.71)	0.52 (0.47, 0.57)
At current year: 2008–2011**			
Baseline CD4≥200	Ref	Ref	Ref
CD4<200	0.65 (0.59, 0.71)	0.52 (0.47, 0.57)	0.58 (0.50, 0.67)

Ref: reference group; HR (95%CI): Adjusted Hazard Ratio (95% Confidence Interval); AUC pVL: area under the pVL curve.

*Controlling also for age and gender.

**Statistical interaction between baseline CD4 (≥200 vs. <200) and current calendar year (<2004; 2004–2007; 2008–2011).