

Prediction of AIDS Defining Illnesses or Death after the Initiation of HAART

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Abstract

Background: HAART has dramatically reduced the incidence of AIDS defining illnesses (ADI) and mortality in HIV infected individuals, yet these events continue to occur after initiating therapy. Developing and evaluating prediction models for the development of an individual's first ADI or death after HAART remains an important goal. Utilizing extensive data from persons at the Johns Hopkins HIV Clinical Cohort (Baltimore, MD), we develop a new prediction model and compared it to published models.

Methods: Utilizing data from persons who initiated HAART from 1996 through 2004, we constructed proportional hazards prediction models for the development of first ADI or death. We assessed discrimination using time-varying area under the receiver operating characteristic curve (AUC). Analyses were conducted on both a composite (death or ADI) and cause-specific competing risks endpoint. Variables evaluated at the time of HAART initiation (time-stationary) included CD4 count, HIV RNA, total lymphocyte count (TLC), hemoglobin (Hb), albumin (Alb), creatinine (Cr), prior ADI, PCP prophylaxis, sex, race, age, injection drug use (IDU), history of heavy alcohol use, heroin and/or cocaine use, and a medical history of personality disorder, anxiety, depression, schizophrenia, or suicide attempt.

Results: 2961 individuals initiated HAART and contributed 1235 events (772 ADI, 463 deaths) over 10728 person-years of follow-up. Our prediction model gave a mean AUC over 5 years of 0.73. Variables associated with shorter time to 1st ADI or death included CD4, HIV RNA, TLC, Hb, Cr, Age, sex, prior ADI, IDU, PCP prophylaxis, cocaine use, anxiety and depression. This model provided better discrimination at 6 months (AUC=0.73) as compared to a published prediction model (AUC=0.65) that used CD4, HIV RNA, anemia, BMI, age, antiretroviral use prior to HAART, IDU, and prior ADI. Splitting the composite outcome into competing events resulted in similar 6 month discrimination estimates with the exception of candidiasis (AUC=0.65).

Conclusions: We have developed a prediction model for ADI and death that has improved ability to discriminate these serious events relative to a published algorithm. As our model retained non-laboratory measures, this suggests their importance in predicting HAART response. This framework highlights an important goal for future clinical research of identifying and validating new measures that improve clinical prediction of competing events.

Introduction

Highly active antiretroviral therapy (HAART) has led to dramatic decreases in the incidence of AIDS defining illnesses (ADI) and death. Despite the advancement of HIV treatment individuals continue to have ADI and death after initiating therapy. It is therefore desirable to be able to evaluate the risk of further disease progression after the initiation of HAART.

Previously, predictive models of ADI or death have been examined as either a composite outcome (Moocrot A, AIDS 2007) or specifically examining one event ignoring (censoring) others. Composite outcome: this assumes an equal weight and equal censoring pattern for different events (i.e. death is equivalent to ADI). Censoring other outcomes: This has been shown to overestimate the probability of the event (Kim EJ, Statist Med 1992).

Alternatively, a competing risk framework may be used to predict disease progression to the first of several outcomes (specific ADIs and death).

Competing risk: When individuals are at risk for multiple events and can only fail due to one of the events, a competing risk framework exists. Typical examples include analyses of cause specific mortality (cardiovascular vs. cancer vs. other causes of death). Goal: To develop a new prediction model that allows for competing risk methods.

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Methods

- 2961 individuals initiating HAART between 1996 and 2005 in the John Hopkins HIV Clinical Cohort were identified.
- All covariate data was from prior to (up to one year) or at the time of HAART initiation.
- Laboratory measures included CD4 count, HIV RNA, total lymphocyte count (TLC), hemoglobin (Hb), albumin (Alb), and creatinine (Cr) levels.
- Non-laboratory measures: prior ADI, PCP prophylaxis, sex, race, age, history of injection drug use (IDU), history of heavy alcohol use, heroin and/or cocaine use, and a medical history of personality disorder, anxiety, depression, schizophrenia, or suicide attempt were included.
- The outcome of time to disease progression was defined in two ways:
 - Composite outcome - time to first occurrence of:
 - ADI or
 - death
 handled as one outcome
 - Competing risk outcomes - time to first occurrence of:
 - Candidiasis,
 - Pneumocystis Jiroveci Pneumonia (PCP)
 - other ADI or
 - death
 each handled as separate outcomes while allowing for the other events to occur

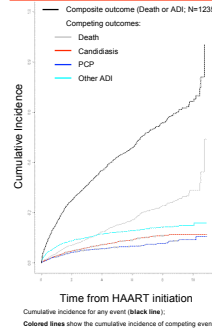
Statistical Methods

- Proportional hazards models allowing for competing risks were utilized (Fine J, JASA 1999)
- Non-linearity of continuous variables were allowed by including restricted cubic splines
- Several covariates violated the proportionality assumption of the model and therefore an appropriate interaction with time was included
- A full model was built utilizing all covariates and a stepdown method utilizing Akaike's information criteria to generate a final model (Cramer G, Statist Med 2002)
- Time-varying area under the receiver operating characteristic curve was calculated to evaluate model discrimination (Chambless LE, Statist Med 2006)
- Internal model validation was done via bootstrap methods (Harrell F, Statist Med 1998)

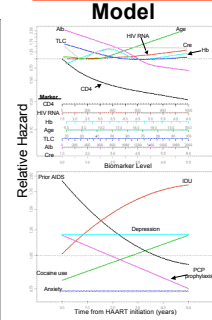
Study Population (N=2961)

Male - N (%)	2043 (69)
Race - N (%)	
African-American	2161 (73)
White	733 (25)
Median Age - years (IQR)	40 (35-45)
Median CD4 count - cells/mm ³ (IQR)	173 (46-325)
Median Log ₁₀ HIV RNA (IQR)	4.62 (3.55-5.23)
Median Hemoglobin - g/dl (IQR)	12.70 (11.07-14.10)
Median Total Lymphocyte Counts - cells/mm ³ (IQR)	1215 (783-1800)
Median Albumin - g/dl (IQR)	4.0 (3.6-4.4)
Median Creatinine - mg/dl (IQR)	0.9 (0.7-1.0)
Prev AIDS defining illness - % (n)	1832 (62)
PCP prophylaxis - N (%)	1607 (54)
IDU risk factor - N (%)	1197 (40)
Heavy alcohol use - N (%)	325 (11)
History of Heroin use - N (%)	718 (24)
History of Cocaine use - N (%)	875 (30)
Medical History of:	
Personality Disorder - N (%)	57 (2)
Anxiety - N (%)	102 (3)
Depression - N (%)	867 (29)
Schizophrenia - N (%)	70 (2)
Suicide attempt - N (%)	310 (10)
Median Date of HAART initiation (IQR)	November 1999 (August 1997 - October 2001)

Cumulative Incidence

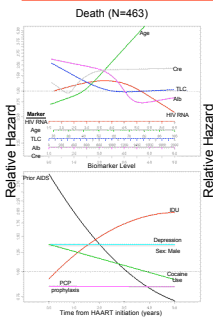


Composite Model



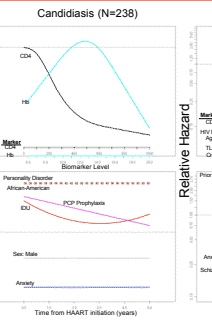
Top panel: Continuous variables were modeled without assuming a linear relationship. Thus, the non-linearity of the RH is shown (e.g. RH for CD4 counts begins to level off with higher cell counts).
Bottom panel: Binary exposure variables were sometimes modeled as an interaction with time, thus the RH for prior AIDS diagnosis results in an initial increased hazard for death or subsequent ADI that attenuates over time.

Death (N=463)



The relative hazards for the different events represent the increased (or decreased) risk of having the cause-specific outcome for individuals who have not experienced one of the alternative outcomes. Therefore, the interpretation of these models needs to be interpreted by examining the covariates across all outcomes. For instance the risk of Candidiasis decreases with lower hemoglobin values (relative to the median of 12.7), however other ADI has an increased risk with lower hemoglobin suggesting that individuals with low hemoglobin values are more likely to have some other ADI rather than Candidiasis. Interestingly, while CD4 has a decreased RH with higher levels of cells among Candidiasis, PCP, and other ADI, the pattern of association is not the same nor well reflected to be in the model for death. Whereas low HIV RNA was included in the model for death and suggested that the RH was higher with greater levels of HIV RNA but only to a point. This may be in part due to the increased risk of PCP and other ADI with the highest levels of HIV RNA. This suggests that individuals with extremely high levels of HIV RNA are more likely to have an ADI event prior to death.

Competing Risk Model



The relative hazards for the different events represent the increased (or decreased) risk of having the cause-specific outcome for individuals who have not experienced one of the alternative outcomes. Therefore, the interpretation of these models needs to be interpreted by examining the covariates across all outcomes. For instance the risk of Candidiasis decreases with lower hemoglobin values (relative to the median of 12.7), however other ADI has an increased risk with lower hemoglobin suggesting that individuals with low hemoglobin values are more likely to have some other ADI rather than Candidiasis. Interestingly, while CD4 has a decreased RH with higher levels of cells among Candidiasis, PCP, and other ADI, the pattern of association is not the same nor well reflected to be in the model for death. Whereas low HIV RNA was included in the model for death and suggested that the RH was higher with greater levels of HIV RNA but only to a point. This may be in part due to the increased risk of PCP and other ADI with the highest levels of HIV RNA. This suggests that individuals with extremely high levels of HIV RNA are more likely to have an ADI event prior to death.

Model Discrimination

Composite Outcome (Death or ADI, N=1235)		EuroSIDA risk score Composite Outcome	
Mean AUC	0.748	0.5 year AUC*	0.698
Optimism	0.656	1.0 year AUC*	0.618
Optimism-Corrected AUC	0.703		
0.5 year AUC	0.729		
1 year AUC	0.754		

Death Outcome (N=463)		ADI Outcome (N=772)	
Mean AUC	0.692	Mean AUC*	0.795
Optimism	0.614	Optimism	0.686
Optimism-Corrected AUC	0.684	Optimism-Corrected AUC*	0.735
0.5 year AUC	0.704	0.5 year AUC*	0.783
1 year AUC	0.737	1 year AUC*	0.731

Candidiasis Outcome (N=238)		Other ADI Outcome (N=534)	
Mean AUC	0.678	Mean AUC	0.674
Optimism	0.623	Optimism	0.678
Optimism-Corrected AUC	0.647	Optimism-Corrected AUC*	0.708
0.5 year AUC	0.692	0.5 year AUC*	0.747
1 year AUC	0.652	1 year AUC*	0.747

PCP Outcome (N=185)		Other ADI Outcome (N=349)	
Mean AUC	0.717	Mean AUC	0.628
Optimism	0.624	Optimism	0.528
Optimism-Corrected AUC	0.681	Optimism-Corrected AUC*	0.701
0.5 year AUC	0.781	0.5 year AUC*	0.745
1 year AUC	0.767	1 year AUC*	0.742

Conclusion

- The final model for the composite outcome has a slightly improved ability to discriminate as compared to a published algorithm
- The models retained non-laboratory measures including history of mental illness suggesting their importance in predicting HAART response
- Comparing the discriminatory ability of the models examining the competing cause-specific outcomes vs. composite outcome
 - With the exception of Other ADI, the models were slightly less capable of discriminating between those who did and did not develop the outcomes
 - This suggests that the need to identify measures that are more targeted to the cause-specific outcomes in order to improve prediction within a competing risk framework
- In the competing-risk framework:
 - It is apparent that not one variable was useful in predicting all competing outcomes
 - Furthermore, the curvature and magnitude of the relative hazard was not necessarily consistent across each outcome
 - Therefore a composite outcome could potentially mask a particular relationship between a specific outcome and variable
- A limitation of the analyses thus far is the ability to translate the results into a clinically useful prediction
 - Creation of a nomogram may resolve this

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