ABSTRACT

Objective: Biomedical researchers tend to choose semiparametric methods to model time-to-event data because they do not require any assumptions about the shape of the underlying hazard. An example is provided where parametric models are a desirable alternative.

Methods: Data were analyzed from a prospective cohort study of 195 adults receiving HIV care and highly active antiretroviral therapy in Baltimore, Md. They were followed for 1188 visits between February 2000 and December 2001. Kaplan-Meier estimation and Cox and Weibull regressions were performed.

Results: Illicit drug users experienced a greater hazard of clinically significant antiretroviral resistance as compared to non-users. Weibull regression demonstrated that a quarter and a half of illicit drug users developed resistance within 5 and 20 months of viral suppression, respectively, compared to 20 and 85 months, respectively, for non-users.

Conclusions: Both semiparametric and parametric methods demonstrated an increased hazard of clinically significant resistance associated with illicit drug use. The parametric model facilitated the estimation of elapsed time to resistance associated with illicit drug use.

INTRODUCTION

The semiparametric Cox proportional hazards model is more popular than parametric methods to analyze time-to-event data because no assumption is needed about the shape of the underlying hazard of the event over time. Examples of hazard distributions include exponential, Weibull, and log-logistic. Semiparametric and parametric methods both yield the relative hazard (RH) as the measure of association, allowing researchers to gain insight into the actual risk process from onset of exposure to an event of interest. Some distributions allow modeling of actual failure times. These accelerated failure time (AFT) models produce a “time ratio” (TR) as its measure of association, and the time when the nth percentile of subjects achieves the outcome of interest can be directly estimated.

Using time-to-event data in which the underlying hazard was assumed to fit a Weibull distribution, we illustrate the advantages of parametric modeling.

METHODS

The data come from a prospective cohort study of individuals receiving HIV care and highly active antiretroviral therapy (HAART) in Baltimore, Md. Patients who had no evidence of prior resistance to therapy and had achieved viral suppression with HAART were followed for 1 year to observe the occurrence of viral rebound with clinically significant resistance. Participants were classified as illicit drug users at any point in the study if they reported use of an illegal substance other than marijuana in the previous 30 days.

Time from viral suppression to rebound with clinically significant resistance was estimated using Kaplan-Meier estimation with staggered entry to accommodate unobserved time at risk between viral suppression and study recruitment. Subjects were administratively censored at the end of follow-up and censored early if they discontinued HAART, did not return to the clinic for 6 months, or died.

The Weibull model assumes the underlying hazard at any given point in time t is \( h_o(t) \) and equals \( pt^{p-1} \exp(\beta o) \) where p is the shape parameter estimated from the data, and the scale parameter is \( \exp(\beta o) \). Under a proportional hazards model, the hazard at time t for
an individual failing at the \( j \)th ordered failure time with a set of covariates \( x \) is: \( H(t|x) = \exp(\beta_0 + x \beta) \psi \) and survival at that point in time is \( S(t|x) = \exp[-\exp(\beta_0 + x \beta) \psi] \). Under an AFT model, \( S(t|x) = \exp[-\exp(-\beta_0 - x \beta) t^\psi] \) and \( t = (-\ln(q))^\psi/[\exp(\beta_0 + x \beta)] \) where \( q \) is any fixed probability of survival (eg, for median survival time, \( q = 0.5 \)).

We used a Weibull model with robust variance estimates in both the proportional hazards and AFT metrics to yield RH, TR, and their corresponding 95% confidence intervals (CIs). Interpretation of the HR is: if RH\(>1 \), then illicit drug use was associated with greater hazard of viral rebound with clinically significant resistance than non-use; if RH\(<1 \), then lower hazard; and if RH\(=1 \), then no change in hazard. Interpretation of the TR is: if TR\(<1 \), then illicit drug use was associated with a shorter time to rebound with resistance, if TR\(>1 \), then a longer time; and if TR\(=0 \), then no difference in time. We calculated model-based estimates of elapsed time from viral suppression to when 25% and 50% of subjects experienced rebound with resistance. We examined observed and fitted survivor estimates graphically, and constructed piecewise constant hazard models to determine if the Weibull distribution was appropriate in modeling the underlying risk. All analyses were performed using STATA 9 (Statacorp, College Station, Texas).

> RESULTS

Overall, 195 participants contributed 1188 study visits (median=7; interquartile range [IQR]:5, 9). Median time between visits was 49 days (IQR: 41, 77). Median time between viral suppression and recruitment was 9.4 months (IQR: 3.7, 22.1) for illicit drug users and 15.5 months (IQR: 4.7, 31.1) for non-users (Wilcoxon rank-sum test, \( P = 0.235 \)). Median time from viral suppression to rebound with clinically significant resistance predicted by our model was 63 months, which was slightly longer than the longest time observed in our cohort (61 months).

In both Cox and Weibull regression, illicit drug users had a greater hazard of rebound with clinically significant resistance compared to non-users (Table 1). A Weibull model in the AFT metric demonstrated that illicit drug users experienced rebound with resistance in about a quarter of the time that non-users did. One-quarter and one-half of illicit drug users developed resistance within 5 and 20 months of viral suppression, respectively, compared to 20 and 85 months, respectively, for non-users.

Weibull estimates of time to rebound with resistance superimposed on Kaplan-Meier estimates demonstrate an attenuation of the effect of baseline illicit drug use by the Weibull model (Figure 1). Nevertheless, the association was statistically significant by both estimates. A piecewise constant hazard model (not shown) and similarity in RH estimates obtained from Cox and Weibull models confirmed the appropriateness of the Weibull model (Table 1). Akaike’s Information Criterion supported the use of the Weibull over other distributions (not shown).

> DISCUSSION

The relative hazard produced in semiparametric and parametric proportional hazards modeling helps researchers identify risk factors for an outcome of interest. Parametric models in the accelerated failure time metric are not commonly used despite the time ratio being a more easily interpretable measure of association than the relative hazard. AFT models also facilitate the estimation of elapsed time between exposure and outcome, which has more clinical interpretability than a hazard ratio.

In our analysis, illicit drug use was associated with a doubling of the hazard of rebound with resistance even after adjustment by other factors (not shown). This finding, which was consistent with previous studies at the time of and since the original study, was not particularly surprising. One could even argue the analysis, as reported, would have little impact on HIV care. However, the finding that a quarter of illicit drug users were predicted to rebound with resistance within 5

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<th>Table 1. Cox and Weibull Models to Examine the Association between 30-day Illicit Drug Use and Rebound with Clinically Significant Resistance</th>
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\( \alpha \) Elapsed months between viral suppression and rebound with resistance among illicit drug users vs. non-users. Abbreviations: RH, relative hazard; TR, time ratio.
months of achieving viral suppression has important implications. This reveals the imminence of rebound with resistance among illicit drug users despite achieving treatment success and emphasizes a need for physicians to ascertain substance use among patients and schedule more frequent follow-up visits for these patients.

Researchers conducting survival analyses should consider the use of parametric models. When properly fitted to the data, these models produce inferences identical to those drawn from Cox regression. The estimation of time ratios and elapsed time are especially advantageous as they have interpretations that can directly translate to clinical and public health practice. Concerns about misspecification of the model, while valid, can be minimized by the use of broad classes of parametric models that encompass a wide variety of hazard shapes.1-5

**Figure 1.** Kaplan-Meier (K-M) and Weibull model estimates for time from viral suppression to rebound with clinically significant resistance for 27 current illicit drug users (past 30 days) and 168 non-current illicit drug users (did not use in the past 30 days) at baseline.

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**REFERENCES**

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