

SUPPLEMENTAL A

This online supplemental material provides further details regarding the methods outlined within the main text. The purpose is to provide more rigorous details regarding the methods that may be useful for some readers but felt to be too technical such that the main points would be obscured to others.

Cause-specific hazard approach

For the cause-specific hazard methods, it has been stated that individuals who have the competing event may be treated as censored. To see that this is the case, it is useful to examine the likelihood function. The likelihood function can be written in terms of the cause-specific hazards $h_j(t|\mathbf{z})$ where \mathbf{z} is a vector of covariates and can be arranged such that the likelihood is a product of components based upon each event j . The likelihood for the probability function for time to failure and the cause of failure is as follows (1):

$$\prod_{i=1}^n [h_{j_i}(t_i | \mathbf{z}_i)]^{\xi_i} \times \prod_{j=1}^k \exp \left[- \int_0^t h_j[u | \mathbf{z}(u)] du \right]. \quad (\text{A1})$$

Thus for individuals with the event of interest (indicated by $\xi_i=1$) contribute to the hazard term; whereas individuals without event contribute to all subsurvivorship functions (i.e. $j=1, \dots, k$ events) up to time t . Essentially only whether an individual had an event at time t , or survived all events past time t is necessary for this likelihood function. This means that the corresponding likelihood function for the j th event is precisely that if failures due to the other event are treated as censored (1).

The proportional hazards model was given in equation (2). The partial likelihood for this model can be written in a manner similar to the stratified proportional hazards model in which the underlying baseline hazard, h_{0j} , cancels and is described by Holt for estimating β_j (assuming no tied failure times) as:

$$\prod_{j=1}^2 \left[\prod_{v=1}^{d_j} \frac{\exp[\mathbf{z}_{j(v)}^T \beta_j]}{\sum_{l \in R(t_{j(v)})} \exp[\mathbf{z}_l^T \beta_j]} \right] \quad (\text{A2})$$

where $t_{j(v)}$, $v=1, \dots, d_j$ is the d_j times of failure for type j , $\mathbf{z}_{j(v)}^T$ is the corresponding transposed column vector of covariates of the individual failing at time $t_{j(v)}$, $R(t_{j(v)})$ is the corresponding risk-set just prior to time $t_{j(v)}$ (1, 2).

Lunn and McNeil used the stratified form of the partial likelihood to implement a data augmentation method that allows for estimation of competing events in one model (3). Previously, the standard method was to perform separate regression models for each event. Briefly, the data augmentation method duplicates each individual's record such that each record is represented k times (e.g. one record for initiation of HAART and one record for AIDS or death). Each record is given an indicator variable, δ , such that the first record is given $\delta=0$ and the second record is given $\delta=1$ such that each record now corresponds to a specific cause of failure ($J=1$ and $J=2$, respectively). A binary status indicator is 0 for all duplicated records except for individuals who have one of the competing events. For these individuals, the record that represents the specific cause of failure (as indicated by δ) that was observed for that individual is given a value of 1. Upon this augmented data set a stratified proportional hazards regression is conducted (stratified on the indicator variable) with \mathbf{z} covariate vector and an interaction between \mathbf{z}

and δ . Alternatively, one may code the covariates as $\delta\mathbf{z}$ and $(1-\delta)\mathbf{z}$ thus this re-parameterizes the model by failure type rather than by main effects with interaction. Note that if there are $k>2$ competing events, there would need to be $k-1$ indicator variables and an overall variable that summarizes the $k-1$ indicator variables to be used as the stratification variable. Furthermore, should a parameter be held to be equivalent across strata (i.e. events) then robust standard errors must be utilized because then the partial likelihood does not completely factor by event-type (3-5). This model can be easily implemented in most standard statistical software packages (e.g., SAS, STATA, R). If the covariate effects are not constrained to be similar across event 1 and event 2 (i.e., $_{cs}RH \neq_{cs}RH_j$) then the exact same results will be obtained by modeling each event in separate models in which the other event is treated as censored. By utilizing the Lunn and McNeil approach to jointly model the competing events, the analyst has the flexibility of evaluating the impact of a set of covariates on a completely composite outcome (restricting all covariates to be the same across both outcomes), fully separate competing events (all covariates allowed to interact with outcome strata), or somewhere in between (some covariates have a common effect, some are event-specific). Glynn and Rosner used a this approach when examining whether coronary heart disease and stroke should be treated as a composite endpoint that is different from venous thromboembolism (6).

While the cause-specific cumulative incidence is directly estimated from the $_{cs}RH$, the subdistribution cumulative incidence can also be estimated. However, to understand how to obtain the subdistribution cumulative incidence, one must understand the relationship between the subdistribution and the cause-specific hazards. The relationship between the subdistribution and the cause-specific hazards is:

$$\begin{aligned}
F_j^*(t) &= P(T \leq t, J = j) \\
&= \int_0^t P(T > u-) h_j(u) du \\
&= \int_0^t S(u-) h_j(u) du
\end{aligned} \tag{A3}$$

where $S(t)$ is the net survival function just prior to time t (7). This net survival, $S(t)$, is a function of all cause-specific hazards, i.e., $S(t) = \exp[-\int_0^t h(u) du] = \exp[-\int_0^t \sum_{j=1}^k h_j(u) du]$ and therefore the subdistribution CIF for the j th event is a function of all the cause-specific hazards via $S(t)$ and not just the corresponding $h_j(t)$. Therefore, to properly estimate the subdistribution from the $_{cs}RH$ for those without exposure, several steps must be taken (8, 9). First an estimate of the arbitrary baseline cumulative cause-specific hazard for both competing events must be obtained (using the Breslow estimator for the cumulative incidence (10, 11) for example). Second, the cumulative cause-specific hazards from the two competing events must then be summed at each time-point, such that the net survival curve is constructed. This net survival curve is then multiplied by the cause-specific hazard to obtain the subdistribution curve as in equation (A3). This may then be repeated at various levels of discrete covariates.

Subdistribution hazard approach

Unlike the cause-specific hazard, the j th subdistribution hazard can be used to estimate the subdistribution CIF for the j th event. The subdistribution of the j th event is (7, 12, 13):

$$\begin{aligned}
F_j^*(t) &= P(T \leq t, J = j) \\
&= 1 - \exp(-\int_0^t \lambda_j(u) du).
\end{aligned} \tag{A4}$$

Therefore, an analysis based upon the hazards of the subdistribution may be more directly interpretable with regards to the subdistribution than an analysis based upon the cause-specific hazard (7, 12).

When Fine and Gray proposed the subdistribution proportional hazards model, they proposed a weighted score function to obtain an unbiased estimating equation from the partial likelihood (13). They proposed utilizing an inverse probability of censoring weight (13) and therefore the partial likelihood is as follows:

$$L = \prod_{v=1}^{d_j} \frac{\exp[\mathbf{z}_{j(v)}^T \boldsymbol{\varphi}_j]}{\sum_{l \in R(t_{j(v)})} w_{lj} \exp[\mathbf{z}_l^T \boldsymbol{\varphi}_j]} \quad (\text{A5})$$

where $t_{j(v)}$, $v=1, \dots, d_j$ is the d_j failure times of event type j and $R(t_{j(v)})$ is the corresponding risk-set and l corresponds to each individual in the risk-set. Therefore, the weights need only to be calculated for individuals who remain in the risk-set. The weight is calculated as follows:

$$w_l(t_{j(v)}) = \frac{S_c(t_{j(v)})}{S_c(\min(t_{j(v)}, t_{lm}))} \quad l \in R(t_{j(v)}) \quad (\text{A6})$$

where t_{lm} is the individuals failure time, $t_{j(v)}$ is the time-point at which the risk-set is defined, and $S_c(t)$ corresponds to the Kaplan-Meier estimator for censoring (13, 14). Thus for individuals who have yet to experience any event the weight $w_l(t_{j(v)})=1$ and for individuals who had a competing event prior to time $t_{j(v)}$ is $w_l(t_{j(v)})<1$.

Covariates for the mixture model approach

Inclusion of covariates into a mixture model is not necessarily straightforward.

Covariates can be included either in the mixture probability or to either of the

distributions corresponding to event 1 and event 2. Furthermore, should a distribution that has shape and scale parameters be used to model either event, then the shape and scale could include parameters to accommodate covariates. To include covariates in the model, parameters corresponding to covariates may be included in the mixture probability (π_i), the distribution for event 1 ($f_1(t)$ and $S_1(t)$), or the distribution for event 2 ($f_2(t)$ and $S_2(t)$). The full set of covariates in \mathbf{z} may be included in all three; alternatively a subset of the covariates may be utilized for various portions of the mixture model. For instance the π_i is the likelihood from a logistic model and can be written as $\exp(\mathbf{z}_A^T \boldsymbol{\eta}) / [1 + \exp(\mathbf{z}_A^T \boldsymbol{\eta})]$, where \mathbf{z}_A is a subset of \mathbf{z} , and the distribution for event 1 may depend on subset \mathbf{z}_B (e.g. $f_1(t|\mathbf{z}_B)$ and $S_1(t|\mathbf{z}_B)$), and the distribution for event 2 on a third subset \mathbf{z}_C (e.g. $f_2(t|\mathbf{z}_C)$ and $S_2(t|\mathbf{z}_C)$). Thus for a three parameter generalized gamma distribution with location (β), scale (σ) and shape (τ) parameters may be a linear combination of the covariates. That is the $GG(\beta, \sigma, \tau)$ may be extended to $GG(\beta^* \mathbf{z}_1, \sigma^* \mathbf{z}_2, \tau^* \mathbf{z}_3)$ where \mathbf{z}_1 , \mathbf{z}_2 , and \mathbf{z}_3 are covariate subsets of \mathbf{z} . Furthermore, if scale and shape parameters are not allowed to vary by covariates, then these generalized gamma distributions are parameterized in a similar manner to a conventional regression model with $GG(\alpha + \beta^* \mathbf{z}, \sigma, \tau)$ which would assume proportional times and would be an accelerated failure time model (15).

SUPPLEMENTAL B

The following is the code that can be used to perform the cause-specific hazard and subdistribution hazard. The data is provided below the programming code. The following describes the example data included:

ID: participant id (this has been changed from original WIHS study id)

t: time to event in years

eventtype: 0- censoring; 1- HAART initiation; 2-AIDS/Death before HAART

ageatfda: age in years at the time of FDA approval of the first protease inhibitor
(centered at age of 36)

BASEIDU: 0- no history of IDU; 1- history of IDU

black: 0-not African-American; 1- African-American

cd4nadir: CD4 count nadir prior to the FDA date of approval for the first protease inhibitor (per 100 cells/ul)

artev and dthev: binary indicators for event type (HAART and death, respectively).

Cause-specific hazard (For R and SAS)

```
#####  
# R code #  
# R is available from the R website (http://www.r-project.org/) #  
#####  
  
# load the library "survival"  
library("survival")
```

```

# Bring in data from the folder pathway in which it is stored

cframe <- read.csv("C:\\[folder pathway here]\\cmprskdat.csv",header=T)


# Create two records for each individual

#     one record corresponds to event 1 and the other to event 2

cframe1 <- cframe      # records for HAART initiation
cframe2 <- cframe      # records for AIDS/Death


# create an indicator variable for event failure 0- HAART initiation
#     and 1 for AIDS/Death

cframe1$ftype <- rep(0,length(cframe1$t))
cframe2$ftype <- rep(1,length(cframe2$t))


# create a new status indicator for whether the corresponding
#     ftype event occurred

cframe1$status <- rep(0,length(cframe1$t))
cframe1$status[cframe1$eventtype==1] <- c(1)


cframe2$status <- rep(0,length(cframe2$t))
cframe2$status[cframe2$eventtype==2] <- c(1)


# Bring all the records together

lframe <- rbind(cframe1,cframe2)


# Create strata specific variables such that the output gives
#     main effects rather than main effects and interaction

lframe$bidu.f <- lframe$BASEIDU*lframe$ftype
lframe$black.f <- lframe$black*lframe$ftype
lframe$age.f <- lframe$ageatfda*lframe$ftype

```



```

lframe$cd4.f <- lframe$cd4nadir*lframe$ftype

lframe$bidu.h <- lframe$BASEIDU*(1-lframe$ftype)
lframe$black.h <- lframe$black*(1-lframe$ftype)
lframe$age.h <- lframe$ageatfda*(1-lframe$ftype)
lframe$cd4.h <- lframe$cd4nadir*(1-lframe$ftype)

# Run model

l.mod <- coxph(Surv(t,status)~bidu.h + black.h + age.h + cd4.h +
               bidu.f + black.f + age.f + cd4.f + strata(ftype), data=lframe)
print(summary(l.mod))

#####

# End R code                                     #

#####

/*****/
/* SAS code                                     */
/*****/

* Bring in Data from wherever it has been saved to;

data cmprskdat;

    infile "C:\[folder pathway inserted here]\CmpRskExplDset.txt";

    input id t eventtype ageatfda baseidu black cd4nadir artev dthev;

    keep id t eventtype ageatfda baseidu black cd4nadir;

run;

```

```

* Augment dataset - set two records per observation;

data augment;
    set cmprskdat cmprskdat;
run;

proc sort data=augment;by id;run;

data augment1;
    set augment;
    by id;
    if first.id then do;
        ftype=0;
        if eventtype=1 then status=1;
        if eventtype^=1 then status=0;
    end;
    if first.id^=1 then do;
        ftype=1;
        if eventtype=2 then status=1;
        if eventtype^=2 then status=0;
    end;
    bidu_f=baseidu*ftype;
    black_f=black*ftype;
    ageatfda_f=ageatfda*ftype;
    cd4nadir_f=cd4nadir*ftype;

    * reparametrize into interactions no main effects;
    bidu_h=baseidu*(1-ftype);
    black_h=black * (1-ftype);

```

```

    ageatfda_h=ageatfda*(1-ftype);

    cd4nadir_h=cd4nadir*(1-ftype);

run;

* Run model;

proc phreg data= augment1;

    model t*status(0) = bidu_h black_h ageatfda_h cd4nadir_h

        bidu_f black_f ageatfda_f cd4nadir_f / ties=efron;

    strata ftype;

run;

/*****/

/* End SAS code                                     */

/*****/

```

Hazard of Subdistribution (For R only)

```

#####

# R code                                                    #

#   Note you must have the library "cmprsk" to run this code      #

#   it is available from the R website (http://www.r-project.org/) #

#####

library(cmprsk)

# Bring in data from the folder pathway in which it is stored

cframe <- read.csv("C:\\[folder pathway here]\\cmprskdat.csv",header=T)

# create a matrix or data frame with the corresponding covariates

mat <- data.frame(idu=cframe$BASEIDU,cd4=cframe$cd4nadir,

```

```

black=cframe$black,age=cframe$ageatfda)

# Run a model for event 1 - Initiation of HAART
mod1 <- crr(cframe$t,cframe$eventtype,mat,failcode=1)

# Run a model for event 2 - AIDS/Death
mod2 <- crr(cframe$t,cframe$eventtype,mat,failcode=2)

# Resulting output from model
print(mod1)
print(mod2)

#####

# End R code                                     #

#####

```

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"id", "t", "eventtype", "ageatfda", "BASEIDU", "black", "cd4nadir", "artev", "dhev"

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