

Utilizing PHREG for Cox Proportional Hazards Regression Modeling with Time-Varying Covariates

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ABSTRACT

When conducting time-to-event analyses for prospective clinical studies (where data is collected at time intervals), it is appropriate to utilize all information available. Missing data issues can also arise when modeling data of this nature. Conventions such as Last Value Carried Forward (LVCF) may be used to account for the missingness in covariates.

In this paper, we describe an easy method in SAS® for setting up Cox Proportional Hazards models with time-varying covariates utilizing proc PHREG. We also describe the SAS® code used for construction of LVCF. An example of an application of these techniques from a Phase IIB randomized, multi-site HIV prevention trial conducted in the US from 1999 to 2003 (called EXPLORE), are illustrated and discussed.

INTRODUCTION

The EXPLORE study was a multi-site, two-arm randomized controlled screening trial. It tested the efficacy of a ten-session behavioral counseling program in preventing the acquisition of HIV among 4,295 HIV-negative Men Who Have Sex with Men (MSM). Study recruitment occurred between January 1999 and February 2001. Participants completed semi-annual follow-up visits through July 2003. At each follow-up visit staff collected behavioral risk data and blood specimens that were tested for HIV. The behavioral risk data collected included frequency of substance use and sexual behaviors in the past six months [1].

From this study, we conducted an analysis examining the influence of combinations of sexual risk behaviors among MSM associated with HIV acquisition. We exhausted all 64 possible patterns of risky sexual behavior (unprotected insertive or unprotected receptive anal sex with HIV-positive (HIV+), HIV-negative (HIV-), or HIV-unknown (HIV?) partners), and then chose the most prevalent to be included in Cox Proportional Hazards models. Adjusted models controlled for selected sexual patterns, race, amphetamine, and heavy alcohol use, self-reported gonorrhea, depressive symptomatology, drug and/or alcohol use before or during sex, and numbers of male sex partners (these were additional covariates found to be most predictive of HIV acquisition in Koblin, et al., 2006 [2]). All covariates apart from race were collected at six-month intervals (time-varying).

This paper covers the methods we used for conducting the Cox Proportional Hazards modeling utilizing the time-varying covariates with proc PHREG. Because the data was collected over a 4.5 year interval and contained missing values at various time points, we also show the SAS® code used to employ the LVCF convention.

EXPLORE STUDY DATA

Participants reported their demographic data such as age, race, ethnicity, education level, and household income at the baseline visit. In addition, each participant completed a risk assessment via an audio-computer assisted interview. This assessment asked questions pertaining to the amount and frequency of alcohol use, frequency of drug use including marijuana, poppers or inhaled nitrites, smoked crack or cocaine, snorted or sniffed cocaine, swallowed, snorted or smoked amphetamines such as speed, crystal, or crank, snorted or smoked heroin, hallucinogens, and any other non-injectable drugs in the last six months. Sexual behavior questions pertained to the partners HIV status (positive, negative or unknown) and the types of sexual behaviors practiced with this partner (insertive, receptive and/or oral sex) and whether these sexual acts were condom-protected or not. Additionally, the number of male sex partners, depression symptomatology, and whether or not the participant got high or drank alcohol immediately before or during sex were collected.

We set up the data file for the Cox Proportional Hazards modeling with one record per participant. For each six-month period completed by a participant in the study, a new variable was assigned to represent the data for that interval. Depending on the duration the participant was on the study (up to the point in which he became HIV+, dropped out of the study, or was censored because of the study ending), he could have had up to eight measurements for a given covariate.

LISTING OF DATA USED FOR COX PROPORTIONAL HAZARDS MODELING ANALYSIS

The indicator variable names (0=no, 1=yes) and labels for the data set used in this analysis are shown below.

Table 1: Indicator Variable Names and Labels from Data File Used for Cox Proportional Hazards Models

VARIABLE	VARIABLE LABEL
ptid	Participant ID
censor	Indicator for HIV+ or not (0=censored, 1=event)
visit2m	Indicator for month of last study visit (6,12,18,...,48)
arm	Randomization arm
siteid	Site ID
black	Black race
spdever06,...,spdever48	Amphetamine use in the last 6 months
heavy06,...,heavy48	Heavy alcohol use in the last 6 months
fstgonmisi06,...fstgonmisi48	Self-reported Gonorrhea in last 6 months
Depressquartile0_2506,...,depressquartile0_2548	Depression symptomatology at 0-25 th tile in the last 6 months
depressquartile26_5006,...,depressquartile26_5048	Depression symptomatology at 26-50 th tile in the last 6 months
Depressquartile51_7506,...,depressquartile51_7548	Depression symptomatology at 51-75 th tile in the last 6 months
Depressquartile76_10006,...,depressquartile76_10048	Depression symptomatology at 76-100 th tile in the last 6 months
drugalc06,...,drugalc48	Whether or not participant got high or drank alcohol immediately before or during sex in the last 6 months
msexpart0106,...,msexpart0148	0-1 male sex partners in the last 6 months
msexpart2306,...,msexpart2348	2-3 male sex partners in the last 6 months
msexpart4906,...,msexpart4948	4-9 male sex partners in the last 6 months
msexpart10ormore,...,msexpart10ormore	10+ male sex partners in the last 6 months
unprnegonly06,...,unprnegonly48	Unprotected receptive anal sex with HIV- partner(s)
unpinegonly06,...,unpinegonly48	Unprotected insertive anal sex with HIV- partner(s)
unprunkonly06,...,unprunkonly48	Unprotected receptive anal sex with HIV? Partner(s)
unpiunkonly06,...,unpiunkonly48	Unprotected insertive anal sex with HIV? Partner(s)
unprposonly06,...,unprposonly48	Unprotected receptive anal sex with HIV+ partner(s)
unpiposonly06,...,unpiposonly48	Unprotected insertive anal sex with HIV+ partner(s)
unprnegineg06,...,unprnegineg48	Unprotected receptive anal sex with HIV- partner(s) and unprotected insertive anal sex with HIV- partner(s)
unprunkiunk06,...,unprunkiunk48	Unprotected receptive anal sex with HIV? partner(s) and unprotected insertive anal sex with HIV? partner(s)
unprposipos06,...,unprposipos48	Unprotected receptive anal sex with HIV+ partner(s) and unprotected insertive anal sex with HIV+ partner(s)
unpinegunk06,...,unpinegunk48	Unprotected insertive anal sex with HIV- partner(s) and HIV? partner(s)
unprnegunk06,...,unprnegunk48	Unprotected receptive anal sex with HIV- partner(s) and HIV? partner(s)
unprneginegunk06,...,unprneginegunk48	Unprotected receptive anal sex with HIV- partner(s) and unprotected insertive anal sex with HIV- and HIV? partner(s)
unpinegrnegunk06,...,unpinegrnegunk48	Unprotected insertive anal sex with HIV- partner(s) and unprotected receptive anal sex with HIV- and HIV? partner(s)

VARIABLE	VARIABLE LABEL
unpinegposunk06,...,unpinegposunk48	Unprotected insertive anal sex with HIV- , HIV+ and HIV? partner(s)
unprposunkiposunk06,...,unprposunkiposunk48	Unprotected receptive anal sex with HIV+ and HIV? partner(s), and unprotected insertive anal sex with HIV+ and HIV? partner(s)
unprnegunkinegunk06,...,unprnegunkinegunk48	Unprotected receptive anal sex with HIV- and HIV? partner(s), and unprotected insertive anal sex with HIV- and HIV? partner(s)
unprnegposunkinegposunk06,...,unprnegposunkinegposunk48	Unprotected receptive anal sex with HIV-, HIV+ and HIV? partner(s), and unprotected insertive anal sex with HIV-, HIV+ and HIV? partner(s)

Table 2: Example of First Twenty Records for Time-Varying Covariate of Heavy Alcohol Use

ptid	heavy06	heavy12	heavy18	heavy24	...	heavy48	visit2m	ensor
001	0	.	0	.	...	.	18	1
002	0	0	0	0	...	0	48	0
003	0	.	0	0	...	.	36	0
004	0	0	1	.	...	1	48	0
005	0	.	.	0	...	.	30	0
006	0	0	1	0	...	.	24	1
007	1	0	0	1	...	1	48	0
008	0	.	1	.	...	0	48	0
009	1	.	0	0	...	.	42	0
010	0	0	0	0	...	.	36	0
011	0	0	.	0	...	0	48	0
012	0	0	.	.	...	.	12	1
013	0	0	0	0	...	1	48	0
014	1	.	0	1	...	0	48	1
015	0	0	0	1	...	.	24	0
016	0	1	.	.	...	0	48	0
017	0	.	0	0	...	.	42	0
018	0	1	0	0	...	1	48	0
019	0	0	0	0	...	.	36	0
020	0	.	.	0	...	0	48	0

LAST VALUE CARRIED FORWARD

When constructing models using proc PHREG utilizing time-varying data, it is essential to consider intermittent missingness in the data set. For any covariate in the model that is missing data at any event time, the data record is dropped from the analysis at that event time when using proc PHREG. This could potentially result in biased estimates. With this in mind, we adopted a common statistical convention called Last Value Carried Forward to account for missing values for the time-varying covariates where the assumption that the previous six-month period is congruent with the next is applicable.

Table 3: Example of First Twenty Records for Time-Varying Covariate of Heavy Alcohol Use Utilizing LVCF

ptid	heavy06	heavy12	heavy18	heavy24	...	heavy48	visit2m	ensor
001	0	0	0	.	...	.	18	1
002	0	0	0	0	...	0	48	0

003	0	0	0	0	...	.	36	0
004	0	0	1	1	...	1	48	0
005	0	0	0	0	...	.	30	0
006	0	0	1	0	...	.	24	1
007	1	0	0	1	...	1	48	0
008	0	0	1	1	...	0	48	0
009	1	1	0	0	...	.	42	0
010	0	0	0	0	...	.	36	0
011	0	0	0	0	...	0	48	0
012	0	0	.	.	...	.	12	1
013	0	0	0	0	...	1	48	0
014	1	1	0	1	...	0	48	1
015	0	0	0	1	...	.	24	0
016	0	1	1	1	...	0	48	0
017	0	0	0	0	...	.	42	0
018	0	1	0	0	...	1	48	0
019	0	0	0	0	...	.	36	0
020	0	0	0	0	...	0	48	0

SAS® SYNTAX

The SAS® macros used for to construct new covariates with the LVCF convention applied is shown below.
Note: &variable.00 represents the value of the variable at the baseline visit.

```
%macro lvcf (variable);
```

```
  if &variable.06 = . then do;
    &variable.062 = &variable.00;
  end;
  else do;
    &variable.062 = &variable.06;
  end;
```

```
  if &variable.12 = . then do;
    &variable.122 = &variable.06;
    if &variable.122 = . then &variable.122 = &variable.00;
  end;
  else do;
    &variable.122 = &variable.12;
  end;
```

```
  if &variable.18 = . then do;
    &variable.182 = &variable.12;
    if &variable.182 = . then &variable.182 = &variable.06;
    if &variable.182 = . then &variable.182 = &variable.00;
  end;
  else do;
    &variable.182 = &variable.18;
  end;
```

```

if &variable.24 = . then do;
&variable.242 = &variable.18;
if &variable.242 = . then &variable.242 = &variable.12;
if &variable.242 = . then &variable.242 = &variable.06;
if &variable.242 = . then &variable.242 = &variable.00;
end;
else do;
&variable.242 = &variable.24;
end;

```

```

if &variable.30 = . then do;
&variable.302 = &variable.24;
if &variable.302 = . then &variable.302 = &variable.18;
if &variable.302 = . then &variable.302 = &variable.12;
if &variable.302 = . then &variable.302 = &variable.06;
if &variable.302 = . then &variable.302 = &variable.00;
end;
else do;
&variable.302 = &variable.30;
end;

```

```

if &variable.36 = . then do;
&variable.362 = &variable.30;
if &variable.362 = . then &variable.362 = &variable.24;
if &variable.362 = . then &variable.362 = &variable.18;
if &variable.362 = . then &variable.362 = &variable.12;
if &variable.362 = . then &variable.362 = &variable.06;
if &variable.362 = . then &variable.362 = &variable.00;
end;
else do;
&variable.362 = &variable.36;
end;

```

```

if &variable.42 = . then do;
&variable.422 = &variable.36;
if &variable.422 = . then &variable.422 = &variable.30;
if &variable.422 = . then &variable.422 = &variable.24;
if &variable.422 = . then &variable.422 = &variable.18;
if &variable.422 = . then &variable.422 = &variable.12;
if &variable.422 = . then &variable.422 = &variable.06;
if &variable.422 = . then &variable.422 = &variable.00;
end;
else do;
&variable.422 = &variable.42;
end;

```

```

if &variable.48 = . then do;
&variable.482 = &variable.42;
if &variable.482 = . then &variable.482 = &variable.36;
if &variable.482 = . then &variable.482 = &variable.30;
if &variable.482 = . then &variable.482 = &variable.24;
if &variable.482 = . then &variable.482 = &variable.18;
if &variable.482 = . then &variable.482 = &variable.12;

```

```

if &variable.482 = . then &variable.482 = &variable.06;
if &variable.482 = . then &variable.482 = &variable.00;
end;
else do;
&variable.482 = &variable.48;
end;

%mend;

*** Create missing values for results after the last study visit (visit2m);

%macro deletedata(var);

if visit2m = 0 then do;

&var.062 = .;
&var.122 = .;
&var.182 = .;
&var.242 = .;
&var.302 = .;
&var.362 = .;
&var.422 = .;
&var.482 = .;

end;

else if visit2m = 6 then do;

&var.122 = .;
&var.182 = .;
&var.242 = .;
&var.302 = .;
&var.362 = .;
&var.422 = .;
&var.482 = .;

end;

else if visit2m = 12 then do;

&var.182 = .;
&var.242 = .;
&var.302 = .;
&var.362 = .;
&var.422 = .;
&var.482 = .;

end;

else if visit2m = 18 then do;

&var.242 = .;
&var.302 = .;
&var.362 = .;
&var.422 = .;
&var.482 = .;

end;

else if visit2m = 24 then do;

```

```

&var.302 = .;
&var.362 = .;
&var.422 = .;
&var.482 = .;

end;

else if visit2m = 30 then do;

&var.362 = .;
&var.422 = .;
&var.482 = .;

end;

else if visit2m = 36 then do;

&var.422 = .;
&var.482 = .;

end;

else if visit2m = 42 then do;

&var.482 = .;

end;

%mend;

```

Examples of calls to the above SAS® macros for heavy alcohol, amphetamine, and drug and alcohol use before sex variables are shown below.

```

%lvcf (heavy);
%lvcf (spdever);
%lvcf (drugalc);

%deletedata (heavy);
%deletedata (spdever);
%deletedata (drugalc);

```

COX PROPORTIONAL HAZARDS MODELING USING PROC PHREG

Considering the data structure above, we used programming statements within the proc PHREG procedure to account for the time-varying covariates in our model. Because each participant was observed at six-month intervals, we chose to use the discrete logistic model [3]. Also, given that the EXLORE cohort was randomized to either an intervention or standard treatment arm, and HIV+ incidence rates were found to differ across sites in previous analyses, we allowed for different baseline hazard functions by stratifying the analysis by treatment arm and site.

SAS® SYNTAX

The SAS® macro used for the analysis is shown below.

```

%macro phreg_multi(covar0,covar1,covar2,covar3,covar4,covar5,covar6,covar7,covar8,
covar9,covar10,covar11,covar12,covar13,covar14,covar15,covar16,
covar17,covar18,covar19,covar20,covar21,covar22,covar23,covar24,

covarname1,covarname2,covarname3,covarname4,covarname5,covarname6,covarname7,
covarname8,covarname9,covarname10,covarname11,covarname12,covarname13,covarname14,
covarname15,covarname16,covarname17,covarname18,covarname19,covarname20,covarname21,
covarname22,covarname23,covarname24,

filename=,dataset=,time=,censorvar=,stratavar=,lastval=,titttype=,new=) ;

```

```

%if &new ne %then %do;

PROC PRINTTO PRINT =
"/trials/behav/p015/analysis/manuscripts/main/Husnik/code/&filename..lst" new;
RUN;

%end;

%else %do;

PROC PRINTTO PRINT =
"/trials/behav/p015/analysis/manuscripts/main/Husnik/code/&filename..lst";
RUN;

%end;

title1 "EXPLORE - Predictors of HIV Seroconversion";
title2 "Follow-up (Time-Dependent) Covariates";
title3 "Multivariate comparison of HIV incidence on discrete time scale";
title4 "Stratified by arm & site";
title5 "&tittype";

proc phreg data= &dataset;

model &time*&ensorvar(0) =

&covar0

&covar1 &covar2 &covar3
&covar4 &covar5 &covar6
&covar7 &covar8 &covar9 &covar10
&covar11 &covar12 &covar13 &covar14
&covar15 &covar16 &covar17 &covar18
&covar20 &covar21 &covar22 &covar23
&covar24 /ties=discrete RL;

strata &stratavar;

%if &lastval ne %then %do;

array &covarname1{8} &covar1.062 &covar1.122 &covar1.182 &covar1.242 &covar1.302
&covar1.362 &covar1.422 &covar1.48;
array &covarname2{8} &covar2.062 &covar2.122 &covar2.182 &covar2.242 &covar2.302
&covar2.362 &covar2.422 &covar2.48;
array &covarname3{8} &covar3.062 &covar3.122 &covar3.182 &covar3.242 &covar3.302
&covar3.362 &covar3.422 &covar3.48;
.
.
.

array &covarname22{8} &covar22.062 &covar22.122 &covar22.182 &covar22.242
&covar22.302 &covar22.362 &covar22.422 &covar22.482;
array &covarname23{8} &covar23.062 &covar23.122 &covar23.182 &covar23.242
&covar23.302 &covar23.362 &covar23.422 &covar23.482;
array &covarname24{8} &covar24.062 &covar24.122 &covar24.182 &covar24.242
&covar24.302 &covar24.362 &covar24.422 &covar24.482;

%end;

%else %do;

array &covarname1{8} &covar1.06 &covar1.12 &covar1.18 &covar1.24 &covar1.30

```

```

&covar1.36 &covar1.42 &covar1.48;
array &covarname2{8} &covar2.06 &covar2.12 &covar2.18 &covar2.24 &covar2.30
&covar2.36 &covar2.42 &covar2.48;
array &covarname3{8} &covar3.06 &covar3.12 &covar3.18 &covar3.24 &covar3.30
&covar3.36 &covar3.42 &covar3.48;
.
.
.
array &covarname22{8} &covar22.06 &covar22.12 &covar22.18 &covar22.24 &covar22.30
&covar22.36 &covar22.42 &covar22.48;
array &covarname23{8} &covar23.06 &covar23.12 &covar23.18 &covar23.24 &covar23.30
&covar23.36 &covar23.42 &covar23.48;
array &covarname24{8} &covar24.06 &covar24.12 &covar24.18 &covar24.24 &covar24.30
&covar24.36 &covar24.42 &covar24.48;

%end;

if visit2m = 6 then do;

&covar1 = &covarname1{1};
&covar2 = &covarname2{1};
&covar3 = &covarname3{1};
.
.
.
&covar22 = &covarname22{1};
&covar23 = &covarname23{1};
&covar24 = &covarname24{1};

end;

else if visit2m = 12 then do;

&covar1 = &covarname1{2};
&covar2 = &covarname2{2};
&covar3 = &covarname3{2};
.
.
.
&covar22 = &covarname22{2};
&covar23 = &covarname23{2};
&covar24 = &covarname24{2};

end;

else if visit2m = 18 then do;

&covar1 = &covarname1{3};
&covar2 = &covarname2{3};
&covar3 = &covarname3{3};
.
.
.
&covar22 = &covarname22{3};
&covar23 = &covarname23{3};
&covar24 = &covarname24{3};

end;

else if visit2m = 24 then do;

&covar1 = &covarname1{4};
&covar2 = &covarname2{4};
&covar3 = &covarname3{4};
.

```

```

.
.
&covar22 = &covarname22{4};
&covar23 = &covarname23{4};
&covar24 = &covarname24{4};

end;

else if visit2m = 30 then do;

&covar1 = &covarname1{5};
&covar2 = &covarname2{5};
&covar3 = &covarname3{5};
.
.
.
&covar22 = &covarname22{5};
&covar23 = &covarname23{5};
&covar24 = &covarname24{5};

end;

else if visit2m = 36 then do;

&covar1 = &covarname1{6};
&covar2 = &covarname2{6};
&covar3 = &covarname3{6};
.
.
.
&covar22 = &covarname22{6};
&covar23 = &covarname23{6};
&covar24 = &covarname24{6};

end;

else if visit2m = 42 then do;

&covar1 = &covarname1{7};
&covar2 = &covarname2{7};
&covar3 = &covarname3{7};
.
.
.
&covar22 = &covarname22{7};
&covar23 = &covarname23{7};
&covar24 = &covarname24{7};

end;

else do;

&covar1 = &covarname1{8};
&covar2 = &covarname2{8};
&covar3 = &covarname3{8};
.
.
.
&covar22 = &covarname22{8};
&covar23 = &covarname23{8};
&covar24 = &covarname24{8};

end;
run;

```

```
%mend;
```

&covar0 is the only non-time-varying covariate in this model. Thus, it is not represented in the programming statements as conditional on time. Note that in the macro call, there is no &covarname indicator for this variable because an array is not needed for it. For all other time-varying covariates, however, we created an array with the indicators at each of the six-month time points (&covarname1,...,&covarname24). As the proc PHREG procedure evaluates the risk sets at each time point, it pulls in the appropriate value of the time-varying covariates. In the MODEL statement, the &time variable (visit2m) = 6,...,48 denotes the discrete time variable, and TIES=discrete indicates the discrete logistic model. &sensorvar denotes the indicator variable for HIV+ (1) or censored (0). RISKLIMITS request output of confidence limits for the hazard ratios. &stratavar indicates the stratification variable(s) for allowing differing baseline hazard functions. &lastval allows for a condition to be met for whether the covariates will be based on the LVCF convention. &titttype is a macro variable for an additional title describing the type of analysis (LVCF or not), and &new allows for the output file to be replaced, if desired.

The model created from this example uses the LVCF convention on all time-varying covariates in the model. The call for this macro is as follows:

```
%phreg_multi(black,spdever,heavy,fstgonmisi,depressquartile26_50,
drugalc,msexpart49,msexpart10ormore,unprnegonly,unpineonly,unprunkonly,
unpiunkonly,unprposonly,unpiposonly,unprnegineg,unprunkiunk,unprposipos,
unpinegunk,unprnegunk,unprneginegunk,unpinegrnegunk,unpinegposunk,
unprposunkiposunk,unprnegunkinegunk,unprnegposunkinegposunk,

spdevera,heavya,fstgonmisia,depressquartile26_50a,
drugalca,msexpart49a,msexpart10ormorea,unprnegonlya,unpineonlya,unprunkonlya,
unpiunkonlya,unprposonlya,unpiposonlya,unprneginega,unprunkiunka,unprposiposa,
unpinegunka,unprnegunka,unprneginegunka,unpinegrnegunka,unpinegposunka,
unprposunkiposunka,unprnegunkinegunka,unprnegposunkinegposunka,

filename=testcode_phreg_pnwsug_lvcf,dataset=adata3.phreg_combo_partial20,
time=visit2m,censorvar=censor,stratavar=arm siteid,lastval=yes,
titttype=Last-value-carried-forward convention used,new=yes);
```

RESULTS OF COX PROPORTIONAL HAZARDS MODEL

The SAS® output below shows the results of the analysis using the above macro.

EXPLORE - Predictors of HIV Seroconversion
Follow-up (Time-Dependent) Covariates
Multivariate comparison of HIV incidence on discrete time scale
Stratified by arm & site
Last-value-carried-forward convention used

The PHREG Procedure

Model Information

Data Set	ADATA3.PHREG_COMBO_PARTIAL20	Month of Semi-Annual Visit for Last Visit
Dependent Variable	visit2m	Indicator of Seroconversion
Censoring Variable	censor	
Censoring Value(s)	0	
Ties Handling	DISCRETE	

Number of Observations Read	4113
Number of Observations Used	4112

Summary of the Number of Event and Censored Values

Stratum	arm	siteid	Total	Event	Censored	Percent Censored
1	I	Boston	336	2	334	99.40
2	I	Chicago	289	14	275	95.16
3	I	Denver	348	10	338	97.13
4	I	NY Blood Center	348	17	331	95.11
5	I	San Francisco	348	15	333	95.69
6	I	Seattle	362	16	346	95.58
7	S	Boston	351	13	338	96.30
8	S	Chicago	300	24	276	92.00
9	S	Denver	356	14	342	96.07
10	S	NY Blood Center	355	23	332	93.52
11	S	San Francisco	357	11	346	96.92
12	S	Seattle	362	11	351	96.96
Total			4112	170	3942	95.87

Convergence Status

Convergence criterion (GCONV=1E-8) satisfied.

Model Fit Statistics

Criterion	Without Covariates	With Covariates
-2 LOG L	1667.347	1458.719
AIC	1667.347	1506.719
SBC	1667.347	1581.978

Testing Global Null Hypothesis: BETA=0

Test	Chi-Square	DF	Pr > ChiSq
Likelihood Ratio	208.6276	24	<.0001
Score	387.6942	24	<.0001
Wald	236.4890	24	<.0001

Analysis of Maximum Likelihood Estimates

Variable	DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio	95% Hazard Ratio Confidence Limits
black	1	0.82198	0.24212	11.5259	0.0007	2.275	1.415 3.657
spdever	1	0.67536	0.18791	12.9179	0.0003	1.965	1.359 2.840
heavy	1	0.79483	0.23037	11.9035	0.0006	2.214	1.410 3.478
fstgonmisi	1	0.75344	0.36754	4.2024	0.0404	2.124	1.034 4.366
depressquartile26_50	1	0.26488	0.16735	2.5050	0.1135	1.303	0.939 1.809
drugalc	1	0.36387	0.20552	3.1345	0.0767	1.439	0.962 2.153

Analysis of Maximum Likelihood Estimates

Variable	Variable Label
black	Black, non-hispanic
spdever	
heavy	
fstgonmisi	Self-Reported GC (0=no,1=yes)
depressquartile26_50	
drugalc	

EXPLORE - Predictors of HIV Seroconversion
Follow-up (Time-Dependent) Covariates
Multivariate comparison of HIV incidence on discrete time scale
Stratified by arm & site
Last-value-carried-forward convention used

The PHREG Procedure

Analysis of Maximum Likelihood Estimates

Variable	DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio	95% Hazard Ratio Confidence Limits
msexpart49	1	0.66438	0.22297	8.8782	0.0029	1.943	1.255 3.008
msexpart10ormore	1	0.80873	0.22049	13.4534	0.0002	2.245	1.457 3.459
unprnegonly	1	0.67661	0.29655	5.2058	0.0225	1.967	1.100 3.518
unpinegonly	1	-0.81137	0.52063	2.4287	0.1191	0.444	0.160 1.233
unprunkonly	1	1.29041	0.29461	19.1842	<.0001	3.634	2.040 6.474
unpiunkonly	1	-0.56084	0.47190	1.4125	0.2346	0.571	0.226 1.439
unprposonly	1	1.42161	0.61141	5.4062	0.0201	4.144	1.250 13.735
unpiposonly	1	-0.00414	0.72803	0.0000	0.9955	0.996	0.239 4.149
unprnegineg	1	-0.15863	0.30427	0.2718	0.6021	0.853	0.470 1.549
unprunkiunk	1	0.93111	0.31280	8.8610	0.0029	2.537	1.374 4.684
unprposipos	1	2.14515	0.45255	22.4692	<.0001	8.543	3.519 20.741
unpinegunk	1	-1.47798	1.01311	2.1282	0.1446	0.228	0.031 1.661
unprnegunk	1	1.03012	0.48247	4.5586	0.0328	2.801	1.088 7.212
unpinegrnegunk	1	0.71215	0.60999	1.3630	0.2430	2.038	0.617 6.738
unpinegposunk	1	0.70817	0.61746	1.3154	0.2514	2.030	0.605 6.810
unprposunkiposunk	1	2.88309	0.38029	57.4763	<.0001	17.869	8.480 37.654
unprnegunkinegunk	1	0.24293	0.38622	0.3956	0.5294	1.275	0.598 2.718
unprnegposunkinegposunk	1	1.58395	0.41710	14.4210	0.0001	4.874	2.152 11.039

Analysis of Maximum Likelihood Estimates

Variable	Variable Label
msexpart49	
msexpart10ormore	
unprnegonly	
unpinegonly	
unprunkonly	
unpiunkonly	
unprposonly	
unpiposonly	
unprnegineg	
unprunkiunk	
unprposipos	
unpinegunk	
unprnegunk	
unpinegrnegunk	
unpinegposunk	
unprposunkiposunk	
unprnegunkinegunk	
unprnegposunkinegposunk	

CONCLUSION

When analyzing data from longitudinal studies, it is important to consider appropriate methods to account for the time-varying aspects of reported data. Incorporating time-varying covariates into Cox Proportional Hazards models using programming statements proved to be an easy method with the SAS[®] proc PHREG procedure. The macro tool in SAS[®] also proved very useful in constructing the LVCF variables to account for intermittent missingness in the dataset.

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REFERENCES

1. The EXPLORE Study Team. Effects of a behavioural intervention to reduce acquisition of HIV infection among men who have sex with men: the EXPLORE randomised controlled study. *Lancet* 2004; 364:41-50.
2. Koblin B, Husnik M, Colfax G, et al. Risk factors for HIV infection among men who have sex with men. *AIDS* 2006; 20:731-739.
3. SAS Institute Inc. SAS/STAT User's Guide, Version 8, Volume 3, Cary, NC: SAS Institute Inc., 1999. 3884 pp.

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