eAppendix:

RESTRICTED QUADRATIC SPLINES

A spline is a function of a continuous regressor ("independent variable") which allows the polynomial representing the regressor to change at specified values (knots) of the regressor. Splines may be linear or higher-order polynomials. For linear splines, the slope for the relationship between the variables of interest is allowed to change solely at the knots resulting in linear functions with inflection points at the knots.  Its fit can be improved by using quadratic or cubic spline functions which allow for smooth functions at the knots rather than inflection points. A spline may be unrestricted or restricted in the tails (i.e., the function before the first knot and after the last knot) of the spline. Unrestricted splines allow the tails to be non-linear, while restricted splines are linear in the tails. Restriction can prevent poor fit in the tails due to small sample size or outliers. Here we concentrate on quadratic splines and we restrict the tails of the spline to be linear.

Splines of any order or restriction can be used when fitting various regression models including generalized linear and Cox proportional hazards models. To fit any standard regression model with a spline, one must include the original continuous variable as well as a set of "basis functions", which are constructed variables that are added to the model. The number of basis functions is determined by the number of knots in the spline.

For unrestricted quadratic splines, if there are $k$ knots for continuous regressor $x$, in relation to the dependent variable $y$, then there are $k$ + 1 basis functions. The functional form for a quadratic spline regression model with $k$ knots is

$$y = f(x) = \beta_0 + \beta_1 x + \gamma_1 x^2 + \gamma_2 \left(x - \chi_1\right)_+^2 + \ldots + \gamma_{k+1}\left(x - \chi_k\right)_+^2 \qquad \text{(Equation 1)}$$

where $\chi_i$ corresponds to the location of the *i*th knot ($i = 1$ to $k$), the positive-part function $(\ldots)_+$ is defined by $(x-\chi_k)_+ = (x-\chi_k)$ if $(x-\chi_k) > 0$; $(x-\chi_k)_+ = 0$ if $(x-\chi_k) \le 0$, and $x^2$ as well as $(x-\chi_i)_+^{\,2}$ are the basis functions for the quadratic spline regression model.

For quadratic splines restricted in both tails, if there are $k$ knots for continuous regressor $x$, in relation to the dependent variable $y$, then there are $k$ - 1 basis functions. To restrict the quadratic spline to be linear before the first knot, the first quadratic term (i.e., $x^2$) in Equation 1 should be removed. To restrict the quadratic spline to be linear after the last knot, the quadratic term corresponding to the last knot (i.e., $(x-\chi_k)_+^{\,2}$) should be subtracted from all quadratic terms. Therefore, the functional form for the restricted quadratic spline regression model is

$$
\begin{aligned}
y = f(x) &= \beta_0 + \beta_1 x \\
&\quad + \beta_2\left[(x-\chi_1)_+^{\,2} - (x-\chi_k)_+^{\,2}\right] \\
&\quad + \beta_3\left[(x-\chi_2)_+^{\,2} - (x-\chi_k)_+^{\,2}\right] \\
&\quad + \cdots \\
&\quad + \beta_k\left[(x-\chi_{k-1})_+^{\,2} - (x-\chi_k)_+^{\,2}\right]
\end{aligned}
\qquad \text{(Equation 2)}
$$

where $\left[(x-\chi_i)_+^{\,2} - (x-\chi_k)_+^{\,2}\right]$ are the basis functions for the restricted quadratic spline regression model.

The restricted quadratic spline model with $k$ knots has the same model degrees of freedom (df) as the restricted cubic spline model with $k$+1 knots, perhaps counter to intuition. As demonstrated by the SAS output for the included example, when the model df are the same and the knots are placed at comparable locations (e.g., cubic: 16th, 33rd, 50th, 67th and 84th; quadratic: 20th, 40th, 60th, and 80th) restricted quadratic and cubic spline models yield similar results. This equivalence between the quadratic and cubic models likely occurs given that both models are allowed to be equally flexible at similar knot locations of the continuous regressor.

DESCRIPTION OF SAS CODE FOR ESTIMATION OF RESCTRICTED QUADRATIC SPLINES

To generate the restricted spline basis functions in Equation 2 the user can specify the dataset to be used (i.e., *data*). If a dataset is not specified, the provided code will automatically select the last dataset used in SAS. The user must specify the continuous variable for which the spline basis functions are to be constructed (i.e., *x*) as well as choose the number of knots (i.e., *k*) from 3, 4, 5, 6, or 7. A finite range for the potential number of knots was selected rather than allowing the user to specify any integer to keep the macro as simple as possible. The specific range of 3-7 was recommended by Harrell.[1] If the number of knots is not chosen, the provided code will automatically select 4 knots. The user must specify whether the knots should be placed at equally or unequally spaced percentile intervals. By default the macro generates knots at equally spaced percentile intervals. If the user specifies unequal intervals, then following Harrell[2] the knots will be placed at the symmetric, but unequally spaced percentile intervals summarized in the provided SAS macro.

The user must also specify whether the percentiles are to be based on the entire distribution of *x* or solely on the cases to maximize power when non-cases substantially outnumber cases.[3] The default is to estimate the percentiles using the entire data. The macro allows for the exploration of various knot specifications in terms of number and location to facilitate careful consideration during model selection. Finally, the macro prints to the SAS log the values corresponding to the specified knot locations.

The spline basis functions for variable *x* are automatically added to the data set *data* as variables _*x* , with the number of leading underscores coincident with the number of the basis function (i.e., if 4 unequal knots are chosen then basis function variables _*x*, __*x*, and ___*x* are returned where _*x*$=\left[(x-P5)_+^2-(x-P95)_+^2\right]\big/(P95-P5)$,

__*x*$=\left[(x-P35)_+^2-(x-P95)_+^2\right]\big/(P95-P5)$, ___*x*$=\left[(x-P65)_+^2-(x-P95)_+^2\right]\big/(P95-P5)$) ,

*P5* is the quantile for the 5$^{th}$ percentile of *x*, *P35* is the quantile for the 35$^{th}$ percentile, *P65* is the quantile for the 65$^{th}$ percentile, and *P95* is the quantile for the 95$^{th}$ percentile). Following Harrell,[2] our macro divides each basis function in Equation 2 by the difference of the outer knots (e.g., 5$^{th}$ and 95$^{th}$ percentiles) to ensure that the basis functions generated by the macro are in the original units of *x*. To generate splines with distinct specifications (e.g., different number of knots) or for more than one continuous variable, the user must re-call the SAS code with the specification or regressor *x* changed.

To fit any standard regression model with the restricted quadratic spline, the user must include the original continuous variable as well as the basis function variables constructed by the macro (e.g., _*x*, __*x*, and ___*x*) in the relevant regression model which can be any generalized linear (e.g., Poisson, logistic) or Cox proportional hazards model.

STRATEGIES FOR MODEL SELECTION

The provided code is intended to aid in selecting between various model specifications of the continuous regressor (e.g., linear, categorical, spline, fractional polynomial) as well as assessing robustness of inferences. Given that these different specifications correspond to non-nested models, the Akaike information criterion (AIC)[4] should be used to assess model fit. The AIC can also be used to inform selection regarding the number of knots (e.g., 3, 4, 5, 6, or 7) as well as knot location (e.g., equal versus unequal percentile intervals, percentiles intervals based on the entire distribution of *x* versus solely on the cases).

SAS (VERSION 9.2) CODE FOR ESTIMATION OF RESTRICTED QUADRATIC SPLINES (RQSMACRO)

```
*************************************************************************************************************
** 1. User names data set (e.g., data), single variable (e.g., var), outcome of interest (e.g., event)    **
** number of knots (3, 4, 5, 6, or 7), knots at equal intervals (e.g., 1 for equal), and percentiles      **
** based on cases (e.g., 1 for cases).                                                                     **
** 2. Macro adds k-1 restricted quadratic spline basis functions to data set.                              **
** 3. Basis functions are named _var, __var, etc.                                                          **
** 4. Multiple macro runs are required for multiple variables.                                             **
** 5. 3 knots at equal intervals or at: 5, 50, 95                                                          **
**    4 knots at equal intervals or at: 5, 35, 65, 95                                                      **
**    5 knots at equal intervals or at: 5, 28, 50, 73, 95                                                  **
**    6 knots at equal intervals or at: 5, 23, 41, 59, 77, 95                                              **
**    7 knots at equal intervals or at: 3, 18, 34, 50, 66, 82, 98                                          **
*************************************************************************************************************;

%macro rqspline(data=_last_,x=,event=,k=4,equal=1,cases=0);
	options nonotes;
	%local _p_ _z_;
	data &data;
		set &data;
		_z_=1;
	%if &equal=0 %then %do;
	%if &cases=0 %then %do;
	proc univariate data=&data noprint;
		var &x; output out=_p_ pctlpts=3 5 18 23 28 34 35 41 50 59 65 66 73 77 82 95 98 pctlpre=p;
	%end;
	%if &cases=1 %then %do;
	proc univariate data=&data noprint;
		where &event=1; var &x; output out=_p_ pctlpts=3 5 18 23 28 34 35 41 50 59 65 66 73 77 82 95 98 pctlpre=p;
	%end; %end;
```

```
%if &equal=1 %then %do;
%if &cases=0 %then %do;
proc univariate data=&data noprint;
        var &x; output out=_p_ pctlpts=12 15 16 20 24 25 29 33 37 40 43 50 57 60 63 67 71 75 76 80 84 85 88 pctlpre=p;
%end;
%if &cases=1 %then %do;
proc univariate data=&data noprint;
        where &event=1; var &x; output out=_p_ pctlpts=12 15 16 20 24 25 29 33 37 40 43 50 57 60 63 67 71 75 76 80 84 85
88 pctlpre=p;
%end; %end;
data _p_;
        set _p_;
        _z_=1;
        if &k=3 and &equal=0 then put "Knots for &x =" p5 p50 p95;
        else if &k=3 and &equal=1 then put "Knots for &x =" p25 p50 p75;
        if &k=4 and &equal=0 then put "Knots for &x =" p5 p35 p65 p95;
        else if &k=4 and &equal=1 then put "Knots for &x =" p20 p40 p60 p80;
        if &k=5 and &equal=0 then put "Knots for &x =" p5 p28 p50 p73 p95;
        else if &k=5 and &equal=1 then put "Knots for &x =" p16 p33 p50 p67 p84;
        if &k=6 and &equal=0 then put "Knots for &x =" p5 p23 p41 p59 p77 p95;
        else if &k=6 and &equal=1 then put "Knots for &x =" p15 p29 p43 p57 p71 p85;
        if &k=7 and &equal=0 then put "Knots for &x =" p3 p18 p34 p50 p66 p82 p98;
        else if &k=7 and &equal=1 then put "Knots for &x =" p12 p24 p37 p50 p63 p76 p88;

data &data;
        merge &data _p_;
        by _z_;
        drop _z_;
data &data;
        set &data;
        %if &equal=0 %then %do;
```

```
%if &k=3 %then %do;
	_&x=(max(0,&x-p5)**2-max(0,&x-p95)**2)/(p95-p5);
	__&x=(max(0,&x-p50)**2-max(0,&x-p95)**2)/(p95-p5);
%end;
%else %if &k=4 %then %do;
	_&x=(max(0,&x-p5)**2-max(0,&x-p95)**2)/(p95-p5);
	__&x=(max(0,&x-p35)**2-max(0,&x-p95)**2)/(p95-p5);
	___&x=(max(0,&x-p65)**2-max(0,&x-p95)**2)/(p95-p5);
%end;
%else %if &k=5 %then %do;
	_&x=(max(0,&x-p5)**2-max(0,&x-p95)**2)/(p95-p5);
	__&x=(max(0,&x-p28)**2-max(0,&x-p95)**2)/(p95-p5);
	___&x=(max(0,&x-p50)**2-max(0,&x-p95)**2)/(p95-p5);
	____&x=(max(0,&x-p73)**2-max(0,&x-p95)**2)/(p95-p5);
%end;
%else %if &k=6 %then %do;
	_&x=(max(0,&x-p5)**2-max(0,&x-p95)**2)/(p95-p5);
	__&x=(max(0,&x-p23)**2-max(0,&x-p95)**2)/(p95-p5);
	___&x=(max(0,&x-p41)**2-max(0,&x-p95)**2)/(p95-p5);
	____&x=(max(0,&x-p59)**2-max(0,&x-p95)**2)/(p95-p5);
	_____&x=(max(0,&x-p77)**2-max(0,&x-p95)**2)/(p95-p5);
%end;
%else %if &k=7 %then %do;
	_&x=(max(0,&x-p3)**2-max(0,&x-p98)**2)/(p98-p3);
	__&x=(max(0,&x-p18)**2-max(0,&x-p98)**2)/(p98-p3);
	___&x=(max(0,&x-p34)**2-max(0,&x-p98)**2)/(p98-p3);
	____&x=(max(0,&x-p50)**2-max(0,&x-p98)**2)/(p98-p3);
	_____&x=(max(0,&x-p66)**2-max(0,&x-p98)**2)/(p98-p3);
	______&x=(max(0,&x-p82)**2-max(0,&x-p98)**2)/(p98-p3);
%end; %end;
%if &equal=1 %then %do;
```

```
%if &k=3 %then %do;
        _&x=(max(0,&x-p25)**2-max(0,&x-p75)**2)/(p75-p25);
        __&x=(max(0,&x-p50)**2-max(0,&x-p75)**2)/(p75-p25);
%end;
%else %if &k=4 %then %do;
        _&x=(max(0,&x-p20)**2-max(0,&x-p80)**2)/(p80-p20);
        __&x=(max(0,&x-p40)**2-max(0,&x-p80)**2)/(p80-p20);
        ___&x=(max(0,&x-p60)**2-max(0,&x-p80)**2)/(p80-p20);
%end;
%else %if &k=5 %then %do;
        _&x=(max(0,&x-p16)**2-max(0,&x-p84)**2)/(p84-p16);
        __&x=(max(0,&x-p33)**2-max(0,&x-p84)**2)/(p84-p16);
        ___&x=(max(0,&x-p50)**2-max(0,&x-p84)**2)/(p84-p16);
        ____&x=(max(0,&x-p67)**2-max(0,&x-p84)**2)/(p84-p16);
%end;
%else %if &k=6 %then %do;
        _&x=(max(0,&x-p15)**2-max(0,&x-p85)**2)/(p85-p15);
        __&x=(max(0,&x-p29)**2-max(0,&x-p85)**2)/(p85-p15);
        ___&x=(max(0,&x-p43)**2-max(0,&x-p85)**2)/(p85-p15);
        ____&x=(max(0,&x-p57)**2-max(0,&x-p85)**2)/(p85-p15);
        _____&x=(max(0,&x-p71)**2-max(0,&x-p85)**2)/(p85-p15);
%end;
%else %if &k=7 %then %do;
        _&x=(max(0,&x-p12)**2-max(0,&x-p88)**2)/(p88-p12);
        __&x=(max(0,&x-p24)**2-max(0,&x-p88)**2)/(p88-p12);
        ___&x=(max(0,&x-p37)**2-max(0,&x-p88)**2)/(p88-p12);
        ____&x=(max(0,&x-p50)**2-max(0,&x-p88)**2)/(p88-p12);
        _____&x=(max(0,&x-p63)**2-max(0,&x-p88)**2)/(p88-p12);
        ______&x=(max(0,&x-p76)**2-max(0,&x-p88)**2)/(p88-p12);
%end; %end;
```

```
            drop p3 p5 p12 p15 p16 p18 p20 p23 p24 p25 p28 p29 p33 p34 p35 p37 p40 p41 p43 p50 p57 p59 p60 p63 p65 p66
p67 p71 p73 p75 p76 p77 p80 p82 p84 p85 p88 p95 p98;
     run; quit; run;
     options notes;
%mend rqspline;
```

## THE UNIVERSITY OF NORTH CAROLINA CENTER FOR AIDS RESEARCH HIV CLINICAL COHORT

In 1999 the University of North Carolina Center for AIDS Research (UNC CFAR) initiated a prospective clinic cohort study of HIV-infected patients attending the UNC HIV clinic. Details regarding this cohort are provided elsewhere.[5] The institutional review board at UNC approved all study forms. Written informed consent was obtained in English or Spanish from all enrolled participants. Here we analyze 557 male participants seen for a scheduled visit after 1 January 1999 in the clinic cohort who initiated combination antiretroviral therapy (henceforth, therapy) at or after their first visit to the UNC HIV clinic, and had CD4 and HIV-1 viral load measured at least once during the 12 months prior to therapy initiation. Patients were administratively censored at 31 May 2010. Therapy was defined as the concurrent use of three or more antiretroviral agents. Over the 2,537 person years of follow up 59 participants died. Given that therapy could have been initiated between entry into the UNC HIV clinic and cohort enrollment the person time included during this interval is immortal and may introduce a survival bias.[6] However, because the objective of this example is to demonstrate the use of RQS this issue was ignored in all corresponding analyses.

DATA USED IN EXAMPLES

| | | | | | |
|---|---|---|---|---|---|
| 1 | 15 | 3.5740300 | 0.000000000 | 10.143737166 | 0 |
| 2 | 339 | 1.8286600 | 0.000000000 | 4.559206023 | 0 |
| 3 | 35 | 3.0345400 | 0.000000000 | 8.164271047 | 1 |
| 4 | 203 | 2.4417700 | 0.000000000 | 2.231348392 | 1 |
| 5 | 67 | 3.5355900 | 0.000000000 | 5.947296372 | 0 |
| 6 | 22 | 3.1953300 | 0.000000000 | 9.927446954 | 0 |
| 7 | 5 | 3.3090900 | 0.000000000 | 9.333333333 | 0 |
| 8 | 11 | 3.1473000 | 0.000000000 | 9.982203970 | 0 |
| 9 | 10 | 3.5740300 | 0.000000000 | 9.114305270 | 0 |
| 10 | 447 | 2.7224700 | 0.000000000 | 9.429158111 | 0 |
| 11 | 266 | 1.7430400 | 0.000000000 | 8.060232717 | 0 |
| 12 | 5 | 3.0267700 | 0.000000000 | 10.080766598 | 0 |
| 13 | 35 | 2.5740400 | 0.000000000 | 7.718001369 | 0 |
| 14 | 209 | 2.2560300 | 0.000000000 | 8.944558522 | 0 |
| 15 | 237 | 2.9435500 | 0.000000000 | 3.064339493 | 0 |
| 16 | 26 | 2.8577400 | 0.000000000 | 0.643394935 | 1 |
| 17 | 27 | 2.1945100 | 0.000000000 | 5.708418891 | 0 |
| 18 | 398 | 0.0000000 | 0.000000000 | 10.083504449 | 0 |
| 19 | 384 | 1.7893700 | 0.000000000 | 6.697467488 | 0 |
| 20 | 265 | 0.0000000 | 0.000000000 | 1.853524983 | 0 |
| 21 | 136 | 2.5708900 | 0.000000000 | 8.222450376 | 0 |
| 22 | 69 | 3.3670800 | 0.000000000 | 5.527720739 | 1 |
| 23 | 350 | 2.5837700 | 0.000000000 | 2.738535250 | 0 |
| 24 | 131 | 1.1147800 | 0.000000000 | 8.777549624 | 0 |
| 25 | 207 | 2.9345000 | 0.000000000 | 9.122518823 | 0 |
| 26 | 168 | 2.9599300 | 0.000000000 | 10.231348392 | 0 |
| 27 | 67 | 2.1253700 | 0.000000000 | 10.146475017 | 0 |
| 28 | 456 | 2.3927300 | 0.000000000 | 7.874743326 | 0 |
| 29 | 13 | 3.2819000 | 0.000000000 | 10.036960986 | 0 |
| 30 | 545 | 1.5651400 | 0.000000000 | 9.875427789 | 0 |
| 31 | 202 | 2.2403700 | 0.000000000 | 3.491444216 | 0 |
| 32 | 193 | 3.1034100 | 0.000000000 | 3.543463381 | 0 |
| 33 | 119 | 3.2897800 | 0.000000000 | 4.388774812 | 1 |
| 34 | 146 | 1.4336900 | 0.000000000 | 2.932922656 | 0 |
| 35 | 5 | 3.5267700 | 0.000000000 | 0.260095825 | 1 |
| 36 | 150 | 1.9794300 | 0.000000000 | 6.639288159 | 1 |
| 37 | 529 | 1.9001800 | 0.000000000 | 8.704312115 | 0 |
| 38 | 311 | 2.5174800 | 0.000000000 | 2.952087611 | 0 |
| 39 | 106 | 2.5934000 | 0.000000000 | 9.943874059 | 0 |
| 40 | 227 | 3.0341700 | 0.000000000 | 9.842573580 | 0 |
| 41 | 12 | 3.5559400 | 0.000000000 | 10.165639973 | 0 |
| 42 | 203 | 2.2388700 | 0.000000000 | 9.667351129 | 0 |
| 43 | 363 | 2.7130800 | 0.000000000 | 5.120465435 | 0 |

| | | | | | |
|---|---|---|---|---|---|
| 44 | 47 | 2.0776600 | 0.000000000 | 3.712525667 | 1 |
| 45 | 309 | 1.7328800 | 0.000000000 | 10.015058179 | 0 |
| 46 | 44 | 3.3866500 | 0.000000000 | 10.053388090 | 0 |
| 47 | 415 | 2.4649600 | 0.000000000 | 9.946611910 | 0 |
| 48 | 634 | 2.3848300 | 0.000000000 | 9.880903491 | 0 |
| 49 | 5 | 3.2086100 | 0.000000000 | 9.831622177 | 0 |
| 50 | 58 | 3.3576000 | 0.000000000 | 9.708418891 | 0 |
| 51 | 14 | 3.2583200 | 0.000000000 | 9.524982888 | 0 |
| 52 | 449 | 2.6216600 | 0.000000000 | 9.273100616 | 0 |
| 53 | 37 | 2.9230200 | 0.000000000 | 7.986310746 | 1 |
| 54 | 5 | 3.5740300 | 0.000000000 | 9.560574949 | 0 |
| 55 | 50 | 2.2120400 | 0.000000000 | 9.152635181 | 0 |
| 56 | 5 | 3.5401300 | 0.000000000 | 7.759069131 | 1 |
| 57 | 181 | 3.1254700 | 0.000000000 | 9.275838467 | 0 |
| 58 | 103 | 3.5740300 | 0.000000000 | 9.253935661 | 0 |
| 59 | 44 | 3.4374200 | 0.000000000 | 9.382614648 | 0 |
| 60 | 5 | 0.0000000 | 0.000000000 | 9.327857632 | 0 |
| 61 | 5 | 2.6242200 | 0.000000000 | 9.360711841 | 0 |
| 62 | 62 | 3.1646400 | 0.000000000 | 9.267624914 | 0 |
| 63 | 150 | 2.2233000 | 0.000000000 | 9.002053388 | 0 |
| 64 | 52 | 3.5740300 | 0.000000000 | 8.441478439 | 0 |
| 65 | 5 | 1.9868200 | 0.000000000 | 2.494866530 | 0 |
| 66 | 542 | 2.2809200 | 0.000000000 | 8.843258042 | 0 |
| 67 | 235 | 2.7004100 | 0.000000000 | 8.884325804 | 0 |
| 68 | 169 | 2.4567500 | 0.000000000 | 1.468172485 | 0 |
| 69 | 5 | 3.3521500 | 0.000000000 | 8.583846680 | 0 |
| 70 | 239 | 2.4201000 | 0.000000000 | 7.819986311 | 0 |
| 71 | 5 | 2.5740400 | 0.000000000 | 6.919233402 | 0 |
| 72 | 201 | 2.2238200 | 0.000000000 | 4.536618754 | 0 |
| 73 | 692 | 1.8257500 | 0.000000000 | 9.670088980 | 0 |
| 74 | 176 | 2.8057800 | 0.000000000 | 9.806981520 | 0 |
| 75 | 62 | 1.9439400 | 0.000000000 | 3.616700890 | 1 |
| 76 | 5 | 3.5296200 | 0.000000000 | 1.848049281 | 1 |
| 77 | 111 | 2.5740400 | 0.000000000 | 8.908966461 | 0 |
| 78 | 555 | 2.4894700 | 0.000000000 | 0.950034223 | 0 |
| 79 | 203 | 0.9604700 | 0.000000000 | 10.135523614 | 0 |
| 80 | 28 | 2.2001400 | 0.000000000 | 9.462012320 | 0 |
| 81 | 99 | 2.6214600 | 0.000000000 | 4.982888433 | 1 |
| 82 | 712 | 2.5069900 | 0.000000000 | 9.639972621 | 0 |
| 83 | 5 | 3.5740300 | 0.000000000 | 6.004106776 | 1 |
| 84 | 107 | 3.5740300 | 0.000000000 | 3.127310062 | 0 |
| 85 | 48 | 3.5740300 | 0.000000000 | 5.913757700 | 0 |
| 86 | 5 | 3.1186200 | 0.000000000 | 2.237508556 | 0 |
| 87 | 160 | 2.3566500 | 0.000000000 | 8.711841205 | 0 |
| 88 | 128 | 3.1120300 | 0.000000000 | 7.926078029 | 0 |

| | | | | | |
|---|---|---|---|---|---|
| 89 | 11 | 3.4327700 | 0.000000000 | 1.785763176 | 0 |
| 90 | 113 | 2.2696300 | 0.000000000 | 9.390828200 | 0 |
| 91 | 195 | 3.4835000 | 0.000000000 | 9.618069815 | 0 |
| 92 | 407 | 1.6902800 | 0.000000000 | 9.716632444 | 0 |
| 93 | 548 | 2.3244200 | 0.000000000 | 5.544832307 | 0 |
| 94 | 5 | 2.9425100 | 0.000000000 | 6.611909651 | 1 |
| 95 | 16 | 3.0475700 | 0.000000000 | 8.777549624 | 0 |
| 96 | 47 | 3.5740300 | 0.000000000 | 8.804928131 | 0 |
| 97 | 279 | 2.2707500 | 0.000000000 | 4.533880903 | 0 |
| 98 | 17 | 3.5740300 | 0.000000000 | 7.798083504 | 0 |
| 99 | 504 | 1.1931200 | 0.000000000 | 0.911704312 | 0 |
| 100 | 89 | 2.7920800 | 0.000000000 | 7.685831622 | 0 |
| 101 | 303 | 2.1453100 | 0.000000000 | 5.079397673 | 0 |
| 102 | 90 | 2.5740400 | 0.000000000 | 8.758384668 | 0 |
| 103 | 94 | 3.4935600 | 0.000000000 | 2.904859685 | 1 |
| 104 | 123 | 2.4456000 | 0.000000000 | 8.733744011 | 0 |
| 105 | 5 | 2.5740400 | 0.000000000 | 8.709103354 | 0 |
| 106 | 90 | 3.5740300 | 0.000000000 | 6.009582478 | 1 |
| 107 | 651 | 3.4392000 | 0.000000000 | 2.787816564 | 0 |
| 108 | 12 | 3.4715500 | 0.000000000 | 8.616016427 | 0 |
| 109 | 86 | 3.5740300 | 0.000000000 | 4.832991102 | 0 |
| 110 | 544 | 2.0140600 | 0.000000000 | 2.809719370 | 0 |
| 111 | 288 | 2.9519000 | 0.000000000 | 4.255304586 | 0 |
| 112 | 17 | 2.7821200 | 0.000000000 | 8.659822040 | 0 |
| 113 | 264 | 1.7391400 | 0.000000000 | 8.177960301 | 0 |
| 114 | 214 | 1.4616500 | 0.000000000 | 2.308008214 | 0 |
| 115 | 5 | 3.5740300 | 0.000000000 | 0.561259411 | 1 |
| 116 | 275 | 3.0491500 | 0.000000000 | 0.232717317 | 1 |
| 117 | 95 | 3.4023800 | 0.000000000 | 3.581793292 | 0 |
| 118 | 197 | 0.0000000 | 0.000000000 | 8.487337440 | 0 |
| 119 | 161 | 2.5740400 | 0.000000000 | 8.216290212 | 0 |
| 120 | 266 | 2.6365500 | 0.000000000 | 7.488021903 | 1 |
| 121 | 162 | 2.8020900 | 0.000000000 | 1.160848734 | 0 |
| 122 | 286 | 2.3316600 | 0.000000000 | 0.720739220 | 0 |
| 123 | 21 | 3.1838100 | 0.000000000 | 2.270362765 | 0 |
| 124 | 290 | 2.4332300 | 0.000000000 | 7.129363450 | 0 |
| 125 | 262 | 3.3371400 | 0.000000000 | 7.126625599 | 0 |
| 126 | 33 | 2.6933400 | 0.000000000 | 5.402464066 | 0 |
| 127 | 235 | 1.4609000 | 0.000000000 | 5.670773443 | 0 |
| 128 | 176 | 2.1049800 | 0.000000000 | 1.251882272 | 0 |
| 129 | 388 | 2.3927000 | 0.000000000 | 6.225872690 | 0 |
| 130 | 157 | 2.9433000 | 0.000000000 | 6.533196441 | 0 |
| 131 | 269 | 2.8870100 | 0.000000000 | 8.079397673 | 0 |
| 132 | 23 | 3.3961100 | 0.000000000 | 8.227241615 | 0 |
| 133 | 332 | 2.9086600 | 0.000000000 | 4.652292950 | 0 |

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| 134 | 286 | 0.0000000 | 0.000000000 | 5.210130048 | 0 |
| 135 | 50 | 2.2577700 | 0.000000000 | 2.418206708 | 0 |
| 136 | 22 | 3.5740300 | 0.000000000 | 2.031485284 | 1 |
| 137 | 416 | 2.3179800 | 0.000000000 | 6.763175907 | 0 |
| 138 | 316 | 0.9867700 | 0.000000000 | 6.108145106 | 0 |
| 139 | 437 | 0.4337700 | 0.000000000 | 7.707049966 | 0 |
| 140 | 349 | 2.9458600 | 0.000000000 | 1.785763176 | 0 |
| 141 | 205 | 2.2019600 | 0.000000000 | 7.854893908 | 0 |
| 142 | 330 | 0.0000000 | 0.000000000 | 6.707734428 | 0 |
| 143 | 68 | 3.4721300 | 0.000000000 | 5.577686516 | 0 |
| 144 | 5 | 2.8882300 | 0.000000000 | 0.936344969 | 1 |
| 145 | 49 | 3.5740300 | 0.000000000 | 0.487337440 | 1 |
| 146 | 402 | 2.6989700 | 0.000000000 | 1.104038330 | 0 |
| 147 | 20 | 3.5740300 | 0.000000000 | 7.871321013 | 0 |
| 148 | 39 | 3.5740300 | 0.000000000 | 7.723477070 | 0 |
| 149 | 193 | 0.4321700 | 0.000000000 | 7.575633128 | 0 |
| 150 | 167 | 3.2056200 | 0.000000000 | 7.728952772 | 0 |
| 151 | 26 | 3.3865100 | 0.000000000 | 7.042436687 | 0 |
| 152 | 14 | 3.5328500 | 0.000000000 | 0.788501027 | 1 |
| 153 | 518 | 2.5498900 | 0.000000000 | 7.186858316 | 0 |
| 154 | 386 | 3.1440700 | 0.000000000 | 7.693360712 | 0 |
| 155 | 26 | 2.8724200 | 0.000000000 | 7.704312115 | 0 |
| 156 | 11 | 2.5159800 | 0.000000000 | 7.638603696 | 0 |
| 157 | 158 | 2.8572800 | 0.000000000 | 7.570157426 | 0 |
| 158 | 184 | 2.5256100 | 0.000000000 | 4.583846680 | 0 |
| 159 | 206 | 2.5868800 | 0.000000000 | 7.679671458 | 0 |
| 160 | 316 | 2.4133000 | 0.000000000 | 5.957563313 | 0 |
| 161 | 106 | 3.3362100 | 0.000000000 | 7.233401780 | 0 |
| 162 | 38 | 2.7136000 | 0.000000000 | 3.472279261 | 0 |
| 163 | 216 | 2.4788500 | 0.000000000 | 6.973305955 | 0 |
| 164 | 109 | 2.5911300 | 0.000000000 | 1.457221081 | 0 |
| 165 | 49 | 2.7042200 | 0.000000000 | 1.769336071 | 0 |
| 166 | 52 | 2.9641800 | 0.000000000 | 5.535934292 | 1 |
| 167 | 181 | 1.8952000 | 0.000000000 | 6.954140999 | 0 |
| 168 | 262 | 2.1653600 | 0.000000000 | 6.951403149 | 0 |
| 169 | 38 | 2.4397400 | 0.000000000 | 3.898699521 | 0 |
| 170 | 12 | 2.4625200 | 0.000000000 | 7.271731691 | 0 |
| 171 | 5 | 2.7976700 | 0.000000000 | 7.140314853 | 0 |
| 172 | 254 | 2.4756700 | 0.000000000 | 2.147159480 | 0 |
| 173 | 62 | 3.1430600 | 0.000000000 | 4.495550992 | 1 |
| 174 | 33 | 3.3878100 | 0.000000000 | 4.698836413 | 0 |
| 175 | 88 | 3.3936200 | 0.000000000 | 7.085557837 | 0 |
| 176 | 261 | 2.4281800 | 0.000000000 | 6.609171800 | 0 |
| 177 | 112 | 2.4460600 | 0.000000000 | 9.535934292 | 0 |
| 178 | 70 | 2.2236600 | 0.000000000 | 7.101984942 | 0 |

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| 179 | 64 | 2.4607700 | 0.000000000 | 6.984257358 | 0 |
| 180 | 120 | 3.4852700 | 0.000000000 | 6.666666667 | 1 |
| 181 | 42 | 3.2538400 | 0.000000000 | 7.063655031 | 0 |
| 182 | 5 | 3.3509700 | 0.000000000 | 1.344969199 | 0 |
| 183 | 307 | 1.8208300 | 0.000000000 | 6.891170431 | 0 |
| 184 | 17 | 3.5740300 | 0.000000000 | 1.311430527 | 1 |
| 185 | 247 | 2.3566400 | 0.000000000 | 1.761122519 | 0 |
| 186 | 181 | 3.0758500 | 0.000000000 | 4.958247775 | 0 |
| 187 | 5 | 3.3025700 | 0.000000000 | 0.342231348 | 1 |
| 188 | 13 | 2.8688300 | 0.000000000 | 1.160848734 | 1 |
| 189 | 131 | 2.6550700 | 0.000000000 | 1.295687885 | 0 |
| 190 | 401 | 1.7323900 | 0.000000000 | 1.623545517 | 0 |
| 191 | 5 | 2.3255500 | 0.000000000 | 3.674195756 | 0 |
| 192 | 69 | 3.4977400 | 0.000000000 | 6.877481177 | 0 |
| 193 | 123 | 2.9220100 | 0.000000000 | 0.747433265 | 1 |
| 194 | 250 | 2.6117200 | 0.000000000 | 3.843942505 | 0 |
| 195 | 61 | 2.6181800 | 0.000000000 | 6.819986311 | 0 |
| 196 | 301 | 0.9894500 | 0.000000000 | 4.533880903 | 0 |
| 197 | 5 | 3.5740300 | 0.000000000 | 6.850102669 | 0 |
| 198 | 59 | 3.5740300 | 0.000000000 | 6.376454483 | 0 |
| 199 | 51 | 2.2290300 | 0.000000000 | 6.773442847 | 0 |
| 200 | 108 | 3.4936700 | 0.000000000 | 5.405201916 | 0 |
| 201 | 51 | 2.2579100 | 0.000000000 | 6.718685832 | 0 |
| 202 | 276 | 2.0273500 | 0.000000000 | 6.050650240 | 0 |
| 203 | 16 | 3.5740300 | 0.000000000 | 6.707734428 | 0 |
| 204 | 198 | 2.6989700 | 0.000000000 | 3.247091034 | 0 |
| 205 | 184 | 3.5740300 | 0.000000000 | 6.669404517 | 0 |
| 206 | 276 | 2.8558500 | 0.000000000 | 6.625598905 | 0 |
| 207 | 157 | 0.0000000 | 0.000000000 | 6.644763860 | 0 |
| 208 | 63 | 3.5740300 | 0.000000000 | 6.475017112 | 0 |
| 209 | 129 | 3.4855200 | 0.000000000 | 6.631074606 | 0 |
| 210 | 249 | 2.5932900 | 0.000000000 | 3.031485284 | 0 |
| 211 | 88 | 3.1546800 | 0.000000000 | 6.532511978 | 0 |
| 212 | 116 | 2.6989700 | 0.000000000 | 2.280629706 | 0 |
| 213 | 518 | 1.4224300 | 0.000000000 | 5.338809035 | 0 |
| 214 | 5 | 2.3335000 | 0.000000000 | 6.245037645 | 0 |
| 215 | 394 | 1.6190900 | 0.000000000 | 3.236824093 | 0 |
| 216 | 118 | 3.5740300 | 0.000000000 | 6.198494182 | 0 |
| 217 | 130 | 3.5740300 | 0.000000000 | 6.401095140 | 0 |
| 218 | 254 | 1.4409100 | 0.000000000 | 6.015742642 | 0 |
| 219 | 428 | 1.5969800 | 0.000000000 | 3.000684463 | 0 |
| 220 | 46 | 2.2228900 | 0.000000000 | 6.439425051 | 0 |
| 221 | 73 | 3.4548400 | 0.000000000 | 5.831622177 | 0 |
| 222 | 5 | 2.9956400 | 0.000000000 | 0.945242984 | 0 |
| 223 | 361 | 2.8388500 | 0.000000000 | 2.034907598 | 0 |

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| 224 | 941 | 0.0000000 | 0.000000000 | 0.720054757 | 0 |
| 225 | 326 | 2.6989700 | 0.000000000 | 5.152635181 | 0 |
| 226 | 57 | 3.0700400 | 0.000000000 | 5.798767967 | 0 |
| 227 | 258 | 2.8059100 | 0.000000000 | 5.787816564 | 0 |
| 228 | 50 | 2.5194400 | 0.000000000 | 1.859685147 | 0 |
| 229 | 406 | 3.1089000 | 0.000000000 | 5.489390828 | 0 |
| 230 | 81 | 2.6989700 | 0.000000000 | 3.839151266 | 0 |
| 231 | 56 | 3.3128100 | 0.000000000 | 5.820670773 | 0 |
| 232 | 15 | 3.3453700 | 0.000000000 | 5.790554415 | 0 |
| 233 | 5 | 1.9754300 | 0.000000000 | 1.757700205 | 1 |
| 234 | 11 | 3.5740300 | 0.000000000 | 5.309377139 | 0 |
| 235 | 5 | 2.8162400 | 0.000000000 | 3.529774127 | 0 |
| 236 | 43 | 3.1258400 | 0.000000000 | 5.571526352 | 0 |
| 237 | 43 | 3.5740300 | 0.000000000 | 5.459274470 | 0 |
| 238 | 53 | 3.1687900 | 0.000000000 | 4.759069131 | 0 |
| 239 | 542 | 0.0000000 | 0.000000000 | 0.720054757 | 0 |
| 240 | 149 | 1.8388500 | 0.000000000 | 5.054072553 | 0 |
| 241 | 268 | 2.7708500 | 0.000000000 | 3.159479808 | 1 |
| 242 | 353 | 1.7593300 | 0.000000000 | 3.072553046 | 0 |
| 243 | 68 | 3.5740300 | 0.000000000 | 5.459274470 | 0 |
| 244 | 128 | 2.7520500 | 0.000000000 | 2.223819302 | 0 |
| 245 | 433 | 2.6811200 | 0.000000000 | 3.529089665 | 0 |
| 246 | 386 | 0.0000000 | 0.000000000 | 5.325119781 | 0 |
| 247 | 504 | 2.3819300 | 0.000000000 | 2.064339493 | 1 |
| 248 | 79 | 3.5740300 | 0.000000000 | 5.210130048 | 0 |
| 249 | 272 | 2.4690400 | 0.000000000 | 2.990417522 | 0 |
| 250 | 16 | 3.3032000 | 0.000000000 | 2.503080082 | 0 |
| 251 | 44 | 3.5740300 | 0.000000000 | 5.364134155 | 0 |
| 252 | 123 | 3.5740300 | 0.000000000 | 5.182751540 | 0 |
| 253 | 24 | 1.9684800 | 0.000000000 | 2.284052019 | 0 |
| 254 | 299 | 1.9545600 | 0.000000000 | 2.924709103 | 0 |
| 255 | 10 | 2.6369300 | 0.000000000 | 5.021218344 | 0 |
| 256 | 128 | 3.5450000 | 0.000000000 | 3.362080767 | 1 |
| 257 | 32 | 2.5247100 | 0.000000000 | 4.744695414 | 0 |
| 258 | 84 | 3.2625100 | 0.000000000 | 1.364134155 | 0 |
| 259 | 180 | 3.5740300 | 0.000000000 | 4.922655715 | 0 |
| 260 | 163 | 2.6190900 | 0.000000000 | 4.703627652 | 0 |
| 261 | 155 | 2.1222200 | 0.000000000 | 5.494866530 | 0 |
| 262 | 577 | 2.4848800 | 0.000000000 | 4.635181383 | 0 |
| 263 | 94 | 3.5740300 | 0.000000000 | 4.837782341 | 0 |
| 264 | 102 | 2.4649600 | 0.000000000 | 3.392881588 | 0 |
| 265 | 53 | 3.4511400 | 0.000000000 | 2.618069815 | 0 |
| 266 | 139 | 3.3774900 | 0.000000000 | 4.533880903 | 0 |
| 267 | 5 | 1.9365400 | 0.000000000 | 1.872689938 | 1 |
| 268 | 217 | 3.1268600 | 0.000000000 | 3.403832991 | 0 |

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| 269 | 22 | 2.0022500 | 0.000000000 | 4.700889802 | 0 |
| 270 | 381 | 2.0673500 | 0.000000000 | 2.335386721 | 0 |
| 271 | 311 | 2.1673600 | 0.000000000 | 5.338809035 | 0 |
| 272 | 311 | 2.0719400 | 0.000000000 | 3.830253251 | 0 |
| 273 | 39 | 2.6989700 | 0.000000000 | 3.510609172 | 0 |
| 274 | 388 | 2.2384900 | 0.000000000 | 3.156741958 | 0 |
| 275 | 260 | 1.4672400 | 0.000000000 | 3.802874743 | 0 |
| 276 | 591 | 1.9916200 | 0.000000000 | 2.927446954 | 0 |
| 277 | 370 | 2.5414400 | 0.000000000 | 4.465434634 | 0 |
| 278 | 5 | 3.2464800 | 0.000000000 | 4.479123888 | 0 |
| 279 | 28 | 3.2530600 | 0.000000000 | 4.421629021 | 0 |
| 280 | 207 | 3.2712600 | 0.000000000 | 3.023271732 | 0 |
| 281 | 53 | 3.5740300 | 0.000000000 | 5.314852841 | 0 |
| 282 | 463 | 0.4005400 | 0.000000000 | 1.383299110 | 0 |
| 283 | 361 | 1.7991300 | 0.000000000 | 4.167008898 | 0 |
| 284 | 466 | 2.8461600 | 0.000000000 | 4.347707050 | 0 |
| 285 | 239 | 2.5481200 | 0.000000000 | 4.331279945 | 0 |
| 286 | 262 | 2.4730300 | 0.000000000 | 4.331279945 | 0 |
| 287 | 104 | 2.1486600 | 0.000000000 | 4.446269678 | 0 |
| 288 | 118 | 3.5740300 | 0.000000000 | 4.342231348 | 0 |
| 289 | 304 | 2.6836900 | 0.000000000 | 4.386036961 | 0 |
| 290 | 622 | 0.0000000 | 0.000000000 | 2.283367556 | 0 |
| 291 | 179 | 2.2599300 | 0.000000000 | 4.290212183 | 0 |
| 292 | 477 | 2.2467800 | 0.000000000 | 3.316221766 | 0 |
| 293 | 49 | 3.5104900 | 0.000000000 | 1.368925394 | 1 |
| 294 | 234 | 2.6419700 | 0.000000000 | 4.112251882 | 0 |
| 295 | 294 | 2.1717300 | 0.000000000 | 2.201232033 | 0 |
| 296 | 99 | 3.4175300 | 0.000000000 | 4.136892539 | 0 |
| 297 | 273 | 1.4800100 | 0.000000000 | 4.169746749 | 0 |
| 298 | 187 | 2.4158100 | 0.000000000 | 4.057494867 | 0 |
| 299 | 309 | 2.6662500 | 0.000000000 | 3.250513347 | 0 |
| 300 | 468 | 1.9826600 | 0.000000000 | 3.961670089 | 0 |
| 301 | 342 | 0.9588000 | 0.000000000 | 3.928815880 | 0 |
| 302 | 152 | 3.5428300 | 0.000000000 | 1.448323066 | 0 |
| 303 | 227 | 2.3239800 | 0.000000000 | 3.805612594 | 0 |
| 304 | 106 | 2.3184300 | 0.000000000 | 3.405886379 | 0 |
| 305 | 345 | 3.2459800 | 0.000000000 | 3.860369610 | 0 |
| 306 | 5 | 3.3058800 | 0.000000000 | 3.947980835 | 0 |
| 307 | 37 | 2.7318600 | 0.000000000 | 3.616700890 | 0 |
| 308 | 27 | 2.3554800 | 0.000000000 | 3.967145791 | 0 |
| 309 | 385 | 0.7937900 | 0.000000000 | 3.926078029 | 0 |
| 310 | 182 | 1.3555500 | 0.000000000 | 3.693360712 | 0 |
| 311 | 32 | 3.5740300 | 0.000000000 | 4.427104723 | 0 |
| 312 | 23 | 2.4438100 | 0.000000000 | 3.843942505 | 0 |
| 313 | 564 | 0.0000000 | 0.000000000 | 1.705681040 | 1 |

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| 314 | 176 | 2.5005200 | 0.000000000 | 3.832991102 | 0 |
| 315 | 343 | 2.6000200 | 0.000000000 | 3.485284052 | 0 |
| 316 | 47 | 3.5740300 | 0.000000000 | 2.804243669 | 0 |
| 317 | 140 | 2.5332900 | 0.000000000 | 3.157426420 | 0 |
| 318 | 27 | 2.6192400 | 0.000000000 | 3.843942505 | 0 |
| 319 | 127 | 2.4357100 | 0.000000000 | 3.597535934 | 0 |
| 320 | 88 | 2.8479400 | 0.000000000 | 3.657768652 | 0 |
| 321 | 648 | 2.8508700 | 0.000000000 | 1.453798768 | 0 |
| 322 | 183 | 2.1666400 | 0.000000000 | 3.085557837 | 0 |
| 323 | 22 | 3.0636100 | 0.000000000 | 3.635865845 | 0 |
| 324 | 805 | 0.0000000 | 0.000000000 | 3.693360712 | 0 |
| 325 | 203 | 2.5924600 | 0.000000000 | 3.581108830 | 0 |
| 326 | 286 | 1.0993400 | 0.000000000 | 3.537303217 | 0 |
| 327 | 277 | 3.5740300 | 0.000000000 | 3.594798084 | 0 |
| 328 | 305 | 2.2627500 | 0.000000000 | 3.468856947 | 0 |
| 329 | 388 | 1.7075700 | 0.000000000 | 1.894592745 | 0 |
| 330 | 343 | 1.9469400 | 0.000000000 | 1.831622177 | 0 |
| 331 | 145 | 2.6509600 | 0.000000000 | 2.374401095 | 0 |
| 332 | 318 | 1.9216900 | 0.000000000 | 1.607118412 | 0 |
| 333 | 84 | 2.7823300 | 0.000000000 | 3.351129363 | 0 |
| 334 | 23 | 3.2686700 | 0.000000000 | 3.252566735 | 0 |
| 335 | 389 | 3.4694100 | 0.000000000 | 3.441478439 | 0 |
| 336 | 30 | 2.3858900 | 0.000000000 | 3.381245722 | 0 |
| 337 | 252 | 2.8895700 | 0.000000000 | 3.471594798 | 1 |
| 338 | 242 | 1.6758700 | 0.000000000 | 2.447638604 | 0 |
| 339 | 86 | 2.6078600 | 0.000000000 | 3.233401780 | 0 |
| 340 | 17 | 2.6110700 | 0.000000000 | 3.189596167 | 0 |
| 341 | 516 | 1.3580300 | 0.000000000 | 2.598220397 | 0 |
| 342 | 539 | 2.0320900 | 0.000000000 | 2.040383299 | 0 |
| 343 | 480 | 1.9258500 | 0.000000000 | 2.354551677 | 0 |
| 344 | 347 | 1.7157500 | 0.000000000 | 1.095824778 | 0 |
| 345 | 61 | 0.3909400 | 0.000000000 | 3.222450376 | 0 |
| 346 | 305 | 3.5484600 | 0.000000000 | 2.948665298 | 0 |
| 347 | 525 | 2.6455800 | 0.000000000 | 0.919917864 | 0 |
| 348 | 587 | 3.4748800 | 0.000000000 | 3.044490075 | 0 |
| 349 | 21 | 3.5740300 | 0.000000000 | 2.852840520 | 0 |
| 350 | 1012 | 3.5740300 | 0.000000000 | 2.981519507 | 0 |
| 351 | 5 | 2.3171600 | 0.000000000 | 2.770704997 | 0 |
| 352 | 696 | 1.4673100 | 0.000000000 | 2.872005476 | 0 |
| 353 | 363 | 1.8317400 | 0.000000000 | 2.702258727 | 0 |
| 354 | 272 | 1.9445600 | 0.000000000 | 2.447638604 | 0 |
| 355 | 5 | 2.1389800 | 0.000000000 | 2.485968515 | 0 |
| 356 | 225 | 1.8654900 | 0.000000000 | 1.402464066 | 0 |
| 357 | 30 | 3.5740300 | 0.000000000 | 0.796714579 | 1 |
| 358 | 414 | 2.3736200 | 0.000000000 | 2.464065708 | 0 |

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| 359 | 9 | 2.5665000 | 0.000000000 | 2.642026010 | 0 |
| 360 | 5 | 3.2718000 | 0.000000000 | 1.969199179 | 0 |
| 361 | 5 | 2.9878100 | 0.000000000 | 2.587268994 | 0 |
| 362 | 403 | 1.7155400 | 0.000000000 | 2.644763860 | 0 |
| 363 | 257 | 2.2594000 | 0.000000000 | 2.639288159 | 0 |
| 364 | 189 | 2.3074600 | 0.000000000 | 2.428473648 | 0 |
| 365 | 78 | 2.6989700 | 0.000000000 | 2.524298426 | 0 |
| 366 | 235 | 1.9559000 | 0.000000000 | 2.469541410 | 0 |
| 367 | 310 | 1.2430400 | 0.000000000 | 1.598904860 | 0 |
| 368 | 286 | 1.4771200 | 0.000000000 | 2.502395619 | 0 |
| 369 | 420 | 2.7103900 | 0.000000000 | 0.843258042 | 0 |
| 370 | 5 | 3.5740300 | 0.000000000 | 2.179329227 | 0 |
| 371 | 25 | 3.4773800 | 0.000000000 | 2.294318960 | 0 |
| 372 | 33 | 2.8755600 | 0.000000000 | 2.272416153 | 0 |
| 373 | 56 | 2.5963300 | 0.000000000 | 2.228610541 | 0 |
| 374 | 241 | 1.5422000 | 0.000000000 | 1.278576318 | 0 |
| 375 | 165 | 2.4083800 | 0.000000000 | 1.724845996 | 0 |
| 376 | 14 | 3.5740300 | 0.000000000 | 2.067077344 | 0 |
| 377 | 440 | 0.5415800 | 0.000000000 | 2.061601643 | 0 |
| 378 | 29 | 2.5860200 | 0.000000000 | 2.223134839 | 0 |
| 379 | 18 | 2.9777200 | 0.000000000 | 2.105407255 | 0 |
| 380 | 58 | 3.5740300 | 0.000000000 | 2.086242300 | 0 |
| 381 | 158 | 2.5927300 | 0.000000000 | 2.028747433 | 0 |
| 382 | 108 | 3.5740300 | 0.000000000 | 1.820670773 | 0 |
| 383 | 61 | 2.4661300 | 0.000000000 | 2.086242300 | 0 |
| 384 | 801 | 2.7921400 | 0.000000000 | 2.058863792 | 0 |
| 385 | 540 | 2.5085300 | 0.000000000 | 0.355920602 | 0 |
| 386 | 478 | 3.2870700 | 0.000000000 | 2.042436687 | 0 |
| 387 | 430 | 1.3953300 | 0.000000000 | 0.268309377 | 0 |
| 388 | 254 | 1.8481900 | 0.000000000 | 1.932922656 | 0 |
| 389 | 5 | 2.8162400 | 0.000000000 | 1.713894593 | 0 |
| 390 | 97 | 3.5740300 | 0.000000000 | 3.986310746 | 0 |
| 391 | 290 | 0.8388500 | 0.000000000 | 0.785763176 | 0 |
| 392 | 466 | 0.0000000 | 0.000000000 | 1.779603012 | 0 |
| 393 | 345 | 2.1861100 | 0.000000000 | 1.752224504 | 0 |
| 394 | 301 | 2.9493900 | 0.000000000 | 0.421629021 | 0 |
| 395 | 142 | 1.9956400 | 0.000000000 | 1.530458590 | 0 |
| 396 | 668 | 2.2342600 | 0.000000000 | 0.265571526 | 0 |
| 397 | 17 | 3.5740300 | 0.000000000 | 1.620807666 | 0 |
| 398 | 300 | 1.8779500 | 0.000000000 | 1.601642710 | 0 |
| 399 | 272 | 3.5740300 | 0.000000000 | 1.541409993 | 0 |
| 400 | 557 | 1.6932900 | 0.000000000 | 0.262833676 | 0 |
| 401 | 458 | 3.5740300 | 0.000000000 | 1.103353867 | 0 |
| 402 | 49 | 2.8721600 | 0.000000000 | 1.393566051 | 0 |
| 403 | 509 | 2.2002800 | 0.000000000 | 4.709103354 | 1 |

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| 404 | 444 | 2.7714900 | 0.000000000 | 7.030800821 | 1 |
| 405 | 16 | 2.5740400 | 0.000000000 | 8.323750856 | 0 |
| 406 | 90 | 3.1507700 | 0.000000000 | 10.825462012 | 0 |
| 407 | 195 | 2.3496400 | 0.000000000 | 10.694045175 | 0 |
| 408 | 268 | 2.2237700 | 0.000000000 | 3.026009582 | 0 |
| 409 | 502 | 2.4839100 | 0.000000000 | 10.480492813 | 0 |
| 410 | 5 | 2.9825100 | 0.000000000 | 6.844626968 | 1 |
| 411 | 576 | 1.3821100 | 0.000000000 | 9.100616016 | 0 |
| 412 | 20 | 2.7103500 | 0.000000000 | 2.209445585 | 1 |
| 413 | 353 | 2.5644400 | 0.000000000 | 10.291581109 | 0 |
| 414 | 9 | 3.4201000 | 0.000000000 | 11.011635866 | 0 |
| 415 | 81 | 3.2821300 | 0.000000000 | 10.721423682 | 0 |
| 416 | 410 | 1.8750000 | 0.000000000 | 7.696098563 | 0 |
| 417 | 402 | 0.5769200 | 0.000000000 | 3.069815195 | 0 |
| 418 | 57 | 2.6169400 | 0.000000000 | 9.900068446 | 0 |
| 419 | 305 | 0.0000000 | 0.000000000 | 10.209445585 | 0 |
| 420 | 137 | 2.7217700 | 0.000000000 | 4.603011636 | 0 |
| 421 | 19 | 3.5740300 | 0.000000000 | 10.138261465 | 0 |
| 422 | 292 | 2.2230300 | 0.000000000 | 0.673511294 | 1 |
| 423 | 241 | 2.4826800 | 0.000000000 | 1.109514031 | 0 |
| 424 | 402 | 2.0839100 | 0.000000000 | 11.052703628 | 0 |
| 425 | 278 | 2.6677800 | 0.000000000 | 10.039698836 | 0 |
| 426 | 12 | 3.5740300 | 0.000000000 | 10.733059548 | 0 |
| 427 | 459 | 2.7143700 | 0.000000000 | 6.623545517 | 0 |
| 428 | 9 | 2.2825200 | 0.000000000 | 1.629705681 | 0 |
| 429 | 150 | 2.1359300 | 0.000000000 | 2.582477755 | 0 |
| 430 | 1174 | 1.1166100 | 0.000000000 | 0.865845311 | 0 |
| 431 | 56 | 3.4375100 | 0.000000000 | 1.769336071 | 0 |
| 432 | 108 | 3.3067300 | 0.000000000 | 10.948665298 | 1 |
| 433 | 95 | 2.5972000 | 0.000000000 | 11.148528405 | 0 |
| 434 | 339 | 3.0099100 | 0.000000000 | 11.148528405 | 0 |
| 435 | 119 | 3.2549400 | 0.000000000 | 0.736481862 | 1 |
| 436 | 131 | 3.5618000 | 0.000000000 | 3.332648871 | 0 |
| 437 | 140 | 1.4277300 | 0.000000000 | 1.492813142 | 0 |
| 438 | 351 | 0.0000000 | 0.000000000 | 1.440793977 | 0 |
| 439 | 9 | 2.3773300 | 0.000000000 | 0.492813142 | 1 |
| 440 | 252 | 1.9168000 | 0.000000000 | 10.858316222 | 0 |
| 441 | 306 | 1.8980400 | 0.000000000 | 6.644763860 | 1 |
| 442 | 9 | 3.0093700 | 0.000000000 | 2.277891855 | 1 |
| 443 | 499 | 1.4488600 | 0.000000000 | 8.137577002 | 0 |
| 444 | 219 | 2.2976600 | 0.000000000 | 10.647501711 | 0 |
| 445 | 518 | 2.5289700 | 0.000000000 | 7.839151266 | 0 |
| 446 | 95 | 3.5295600 | 0.000000000 | 0.950034223 | 0 |
| 447 | 40 | 3.5740300 | 0.000000000 | 10.798083504 | 0 |
| 448 | 99 | 2.7834000 | 0.000000000 | 4.339493498 | 1 |

| | | | | | |
|---|---|---|---|---|---|
| 449 | 182 | 3.5127900 | 0.000000000 | 5.292950034 | 0 |
| 450 | 447 | 3.5740300 | 0.000000000 | 3.061601643 | 0 |
| 451 | 84 | 3.4975200 | 0.000000000 | 4.457905544 | 0 |
| 452 | 271 | 2.2673200 | 0.000000000 | 7.775496235 | 1 |
| 453 | 9 | 1.0119900 | 0.000000000 | 10.787132101 | 0 |
| 454 | 218 | 2.6224700 | 0.000000000 | 2.894592745 | 0 |
| 455 | 12 | 3.0411100 | 0.000000000 | 7.679671458 | 1 |
| 456 | 68 | 3.1845700 | 0.000000000 | 10.663928816 | 0 |
| 457 | 548 | 0.0000000 | 0.000000000 | 10.683093771 | 0 |
| 458 | 113 | 3.5328800 | 0.000000000 | 3.948665298 | 0 |
| 459 | 591 | 2.0835600 | 0.000000000 | 9.618754278 | 0 |
| 460 | 2 | 3.4170000 | 0.000000000 | 7.075290897 | 0 |
| 461 | 18 | 2.7531100 | 0.000000000 | 0.503764545 | 1 |
| 462 | 67 | 2.5801300 | 0.000000000 | 10.543463381 | 0 |
| 463 | 462 | 2.4493500 | 0.000000000 | 2.686516085 | 0 |
| 464 | 413 | 3.0808100 | 0.000000000 | 10.387405886 | 0 |
| 465 | 306 | 2.5179200 | 0.000000000 | 7.748802190 | 0 |
| 466 | 266 | 2.5750500 | 0.000000000 | 10.516084873 | 0 |
| 467 | 22 | 2.5964000 | 0.000000000 | 10.496919918 | 0 |
| 468 | 150 | 3.3344900 | 0.000000000 | 9.418206708 | 1 |
| 469 | 29 | 3.1536600 | 0.000000000 | 10.039698836 | 0 |
| 470 | 13 | 3.4885100 | 0.000000000 | 4.017111567 | 0 |
| 471 | 14 | 2.4983800 | 0.000000000 | 0.057494867 | 1 |
| 472 | 1005 | 0.0000000 | 0.000000000 | 8.958247775 | 0 |
| 473 | 165 | 3.0583900 | 0.000000000 | 2.538672142 | 0 |
| 474 | 72 | 2.2789500 | 0.000000000 | 10.968514716 | 0 |
| 475 | 356 | 1.5262700 | 0.000000000 | 8.062970568 | 0 |
| 476 | 234 | 2.6479600 | 0.000000000 | 1.000000000 | 0 |
| 477 | 32 | 3.5740300 | 0.000000000 | 0.646132786 | 0 |
| 478 | 265 | 1.7611000 | 0.000000000 | 0.885010267 | 0 |
| 479 | 89 | 2.4528200 | 0.000000000 | 7.225188227 | 0 |
| 480 | 155 | 2.9211000 | 0.000000000 | 0.501026694 | 1 |
| 481 | 366 | 2.5403000 | 0.000000000 | 3.794661191 | 0 |
| 482 | 313 | 2.5949400 | 0.000000000 | 5.639972621 | 1 |
| 483 | 103 | 2.5118800 | 0.000000000 | 5.971252567 | 0 |
| 484 | 5 | 3.3215500 | 0.000000000 | 3.075290897 | 0 |
| 485 | 5 | 3.0395200 | 0.000000000 | 4.054757016 | 0 |
| 486 | 552 | 1.0683700 | 0.000000000 | 2.798083504 | 0 |
| 487 | 5 | 2.6989700 | 0.000000000 | 3.173169062 | 0 |
| 488 | 13 | 3.4811900 | 0.000000000 | 3.104722793 | 0 |
| 489 | 569 | 2.2749800 | 0.000000000 | 2.685831622 | 0 |
| 490 | 275 | 2.7181900 | 0.000000000 | 2.718685832 | 0 |
| 491 | 631 | 2.4043900 | 0.000000000 | 4.191649555 | 0 |
| 492 | 63 | 3.5740300 | 0.000000000 | 2.579055441 | 0 |
| 493 | 679 | 2.2928900 | 0.000000000 | 2.064339493 | 0 |

| | | | | | |
|---|---|---|---|---|---|
| 494 | 630 | 0.0000000 | 0.000000000 | 2.242299795 | 0 |
| 495 | 387 | 2.6478700 | 0.000000000 | 2.154688569 | 0 |
| 496 | 322 | 2.4432600 | 0.000000000 | 2.154688569 | 0 |
| 497 | 5 | 3.3404400 | 0.000000000 | 2.020533881 | 0 |
| 498 | 542 | 2.7422800 | 0.000000000 | 2.028747433 | 0 |
| 499 | 39 | 3.5740300 | 0.000000000 | 1.848049281 | 0 |
| 500 | 98 | 3.5037900 | 0.000000000 | 1.837097878 | 0 |
| 501 | 973 | 2.0889300 | 0.000000000 | 1.812457221 | 0 |
| 502 | 145 | 2.6989700 | 0.000000000 | 3.230663929 | 0 |
| 503 | 183 | 1.5544900 | 0.000000000 | 1.661875428 | 0 |
| 504 | 638 | 2.9455500 | 0.000000000 | 1.763175907 | 0 |
| 505 | 337 | 2.4742200 | 0.000000000 | 1.618069815 | 0 |
| 506 | 46 | 3.0354300 | 0.000000000 | 1.645448323 | 0 |
| 507 | 417 | 2.6833700 | 0.000000000 | 0.525667351 | 0 |
| 508 | 33 | 3.2304500 | 0.000000000 | 1.284736482 | 0 |
| 509 | 169 | 2.7242800 | 0.000000000 | 1.533196441 | 0 |
| 510 | 65 | 2.6803400 | 0.000000000 | 1.552361396 | 0 |
| 511 | 715 | 2.3019400 | 0.000000000 | 1.396303901 | 0 |
| 512 | 683 | 1.9542400 | 0.000000000 | 1.549623546 | 0 |
| 513 | 354 | 2.2405500 | 0.000000000 | 1.429158111 | 0 |
| 514 | 133 | 2.0827900 | 0.000000000 | 1.379876797 | 0 |
| 515 | 839 | 0.6725600 | 0.000000000 | 1.000000000 | 0 |
| 516 | 202 | 2.2576800 | 0.000000000 | 1.278576318 | 0 |
| 517 | 54 | 3.5071800 | 0.000000000 | 1.352498289 | 0 |
| 518 | 278 | 2.1174200 | 0.000000000 | 1.215605749 | 0 |
| 519 | 79 | 2.8095600 | 0.000000000 | 1.399041752 | 0 |
| 520 | 366 | 2.6491200 | 0.000000000 | 0.947296372 | 0 |
| 521 | 60 | 2.9637900 | 0.000000000 | 1.368925394 | 0 |
| 522 | 289 | 2.5854600 | 0.000000000 | 1.232032854 | 0 |
| 523 | 144 | 2.9754300 | 0.000000000 | 0.610540726 | 0 |
| 524 | 313 | 2.5763400 | 0.000000000 | 0.824093087 | 1 |
| 525 | 494 | 1.1861100 | 0.000000000 | 1.084188912 | 0 |
| 526 | 418 | 2.6725600 | 0.000000000 | 1.205338809 | 0 |
| 527 | 25 | 2.6906400 | 0.000000000 | 1.316906229 | 0 |
| 528 | 212 | 2.7118100 | 0.000000000 | 1.152635181 | 0 |
| 529 | 408 | 1.6941200 | 0.000000000 | 0.947296372 | 0 |
| 530 | 561 | 2.3317100 | 0.000000000 | 0.744695414 | 0 |
| 531 | 754 | 2.0393500 | 0.000000000 | 1.199178645 | 0 |
| 532 | 209 | 2.5165400 | 0.000000000 | 1.032169747 | 0 |
| 533 | 72 | 2.2977600 | 0.000000000 | 1.051334702 | 0 |
| 534 | 960 | 1.5409500 | 0.000000000 | 0.492813142 | 0 |
| 535 | 24 | 3.1361900 | 0.000000000 | 1.097878166 | 0 |
| 536 | 412 | 1.9150600 | 0.000000000 | 0.955509925 | 0 |
| 537 | 202 | 1.5938400 | 0.000000000 | 1.051334702 | 0 |
| 538 | 209 | 3.3854300 | 0.000000000 | 0.988364134 | 0 |

| | | | | | |
|---|---|---|---|---|---|
| 539 | 426 | 2.2821700 | 0.000000000 | 0.977412731 | 0 |
| 540 | 324 | 1.4143000 | 0.000000000 | 0.900752909 | 0 |
| 541 | 336 | 1.9622000 | 0.000000000 | 0.958247775 | 0 |
| 542 | 621 | 2.8673100 | 0.000000000 | 0.793976728 | 0 |
| 543 | 603 | 0.9003700 | 0.000000000 | 0.758384668 | 0 |
| 544 | 196 | 3.5740300 | 0.000000000 | 0.791238877 | 0 |
| 545 | 461 | 2.9420100 | 0.000000000 | 0.829568789 | 0 |
| 546 | 380 | 1.9867700 | 0.000000000 | 0.878850103 | 0 |
| 547 | 253 | 3.4674700 | 0.000000000 | 0.914442163 | 0 |
| 548 | 374 | 1.6345300 | 0.000000000 | 0.783025325 | 0 |
| 549 | 307 | 1.9092100 | 0.000000000 | 0.372347707 | 0 |
| 550 | 840 | 2.6666000 | 0.000000000 | 0.783025325 | 0 |
| 551 | 5 | 2.1861100 | 0.000000000 | 0.610540726 | 0 |
| 552 | 1175 | 1.4970000 | 0.000000000 | 0.651608487 | 0 |
| 553 | 25 | 2.7993400 | 0.000000000 | 0.555783710 | 0 |
| 554 | 11 | 2.9138100 | 0.000000000 | 0.624229979 | 0 |
| 555 | 411 | 3.5072700 | 0.000000000 | 0.476386037 | 0 |
| 556 | 417 | 3.4741700 | 0.000000000 | 0.476386037 | 0 |
| 557 | 575 | 2.1748700 | 0.000000000 | 0.454483231 | 0 |

SAS (VERSION 9.2) CODE USED IN EXAMPLES

**NOTE: Before running the below SAS code the user must save the restricted quadratic spline macro (i.e., rqsmacro) in the same location as the SAS library name. To compare results from the restricted quadratic spline macro to Harrell's daspline macro, the user must download both the daspline and dshide macros from the referenced website and save these macros in the same location as the SAS library name. The user may also have to tailor graphing 'goptions' for their particular SAS version and computing system.**

```
*Automatically clearing the log and output windows;
dm log "clear;" continue; dm out "clear;" continue;

*Setting the following SAS options: page size "ps", line size "ls", turn-off date and start each run of output with page 1;
options ps=60 ls=90 nodate pageno=1;

*Specifying SAS libray name;
libname spline "C:\";

*Reading in UNC CFAR data on 557 male participants and calling temporary data file, 'a';
*Only first 5 records are displayed, however all 557 records must be included after the 'datalines' statement;
data a;
   input id cd4 log10rnac in out dead;
         label id="Participant ID";
         label cd4="CD4 cell count (cells/mm^3) at therapy initiation";
         label log10rnac="Centered HIV-1 viral load (log10 copies/ml) at therapy initiation";
         label in="Years since therapy initiation at start of follow up in years";
         label out="Years since therapy initiation at end of follow up in years";
         label dead="Indicator of death";
         datalines;
1 15 3.5740300 0.000000000 10.143737166 0
2 339 1.8286600 0.000000000 4.559206023 0
3 35 3.0345400 0.000000000 8.164271047 1
```

```
4 203 2.4417700 0.000000000 2.231348392 1
5 67 3.5355900 0.000000000 5.947296372 0
run;

*Printing contents of 'a' data;
proc contents data=a; run;

*Creating indicators for HIV-1 viral load and CD4 cell count;
data a;
	set a;
	highlog10rnac=0;
	if log10rnac>1 then highlog10rnac=1;

	log10rnac1i=0; log10rnac2i=0; log10rnac3i=0;
	if log10rnac>2.17487 and log10rnac<=2.61172 then log10rnac1i=1;
	if log10rnac>2.61172 and log10rnac<=3.20562 then log10rnac2i=1;
	if log10rnac>3.20562 then log10rnac3i=1;

	log10rnacd1i=0; log10rnacd2i=0; log10rnacd3i=0; log10rnacd4i=0;
	log10rnacd5i=0;		log10rnacd6i=0; log10rnacd7i=0;	log10rnacd8i=0;
	log10rnacd9i=0;
	if log10rnac>1.47712 and log10rnac<=1.98677 then log10rnacd1i=1;
	if log10rnac>1.98677 and log10rnac<=2.26732 then log10rnacd2i=1;
	if log10rnac>2.26732 and log10rnac<=2.46904 then log10rnacd3i=1;
	if log10rnac>2.46904 and log10rnac<=2.61172 then log10rnacd4i=1;
	if log10rnac>2.61172 and log10rnac<=2.78233 then log10rnacd5i=1;
	if log10rnac>2.78233 and log10rnac<=3.03952 then log10rnacd6i=1;
	if log10rnac>3.03952 and log10rnac<=3.34537 then log10rnacd7i=1;
	if log10rnac>3.34537 and log10rnac<=3.5618 then log10rnacd8i=1;
	if log10rnac>3.5618 then log10rnacd9i=1;
```

```
	cd4bin=0;
	if cd4<=350 then cd4bin=1;

	label highlog10rnac="Indicator of centered HIV-1 viral load (log10 copies/ml) at therapy initiation >1 ";

	label log10rnac1i="Indicator of centered HIV-1 viral load (log10 copies/ml) at therapy initiation from >2.17487 to 2.61172";
	label log10rnac2i="Indicator of centered HIV-1 viral load (log10 copies/ml) at therapy initiation from >2.61172 to 3.20562";
	label log10rnac3i="Indicator of centered HIV-1 viral load (log10 copies/ml) at therapy initiation from >3.20562 to 3.57403";

	label log10rnacd1i="Indicator of centered HIV-1 viral load (log10 copies/ml) at therapy initiation from >1.47712 to 1.98677";
	label log10rnacd2i="Indicator of centered HIV-1 viral load (log10 copies/ml) at therapy initiation from >1.98677 to 2.26732";
	label log10rnacd3i="Indicator of centered HIV-1 viral load (log10 copies/ml) at therapy initiation from >2.26732 to 2.46904";
	label log10rnacd4i="Indicator of centered HIV-1 viral load (log10 copies/ml) at therapy initiation from >2.46904 to 2.61172";
	label log10rnacd5i="Indicator of centered HIV-1 viral load (log10 copies/ml) at therapy initiation from >2.61172 to 2.78233";
	label log10rnacd6i="Indicator of centered HIV-1 viral load (log10 copies/ml) at therapy initiation from >2.78233 to 3.03952";
	label log10rnacd7i="Indicator of centered HIV-1 viral load (log10 copies/ml) at therapy initiation from >3.03952 to 3.34537";
	label log10rnacd8i="Indicator of centered HIV-1 viral load (log10 copies/ml) at therapy initiation from >3.34537 to 3.5618";
	label log10rnacd9i="Indicator of centered HIV-1 viral load (log10 copies/ml) at therapy initiation from >3.5618 to 3.57403";

	label cd4bin="Indicator of CD4 cell count (cells/mm^3) at therapy initiation <=350";
run;

data a;
	retain id cd4 cd4bin log10rnac highlog10rnac log10rnac1i log10rnac2i log10rnac3i log10rnacd1i log10rnacd2i log10rnacd3i
log10rnacd4i log10rnacd5i log10rnacd6i log10rnacd7i log10rnacd8i log10rnacd9i in out dead;
	set a;
	keep   id cd4 cd4bin log10rnac highlog10rnac log10rnac1i log10rnac2i log10rnac3i log10rnacd1i log10rnacd2i log10rnacd3i
log10rnacd4i log10rnacd5i log10rnacd6i log10rnacd7i log10rnacd8i log10rnacd9i in out dead;
run;

*Examine distribution of the data;
```

```
proc means data=a n min mean p25 median p75 max sum; var cd4 log10rnac in out;
proc freq data=a; tables cd4bin highlog10rnac log10rnac1i log10rnac2i log10rnac3i log10rnacd1i log10rnacd2i log10rnacd3i
log10rnacd4i log10rnacd5i log10rnacd6i log10rnacd7i log10rnacd8i log10rnacd9i dead;
run;

****************************************************************************************************
Example 1: Use of a spline when estimating the association between centered log10 HIV-1 viral load
centered at 2.3010 log10 copies/ml and hazard of death
****************************************************************************************************;
*Generating scatterplot of centered log10 HIV-1 viral load by CD4 count;
proc sort data=a; by cd4;
options nogstyle FONTRENDERING=HOST_PIXELS;
goptions reset=all;
filename grafout "C:\figure1.png";
goptions device=zpng target=png gsfname=grafout gsfmode=replace xmax=6 ymax=6 xpixels=3600 ypixels=3600;
axis1	color=black
		label=(angle=90 font=swiss h=2 justify=center "HIV-1, log10 copies/ml") w=2
		major=(h=1 w=2) minor=none value=(font=swiss h=2) order=(-1 to 4 by 1) offset=(0,0);
axis2	color=black
		label=(font=swiss h=2 justify=center "CD4, cells/mm^3") w=2
		major=(h=1 w=2) minor=none value=(font=swiss h=2) order=(0 to 1500 by 500) offset=(0,0);
symbol1 c=black l=1 w=3 h=.8 v=dot i=none;
proc gplot data=a;
	plot log10rnac*cd4/overlay vaxis=axis1 haxis=axis2 noframe nolegend; run; quit; run;

***Assumption of log-linear association between centered log10 HIV-1 viral load and hazard of death***;
*Fitting Cox model;
proc phreg data=a;
	model out*dead(0)= log10rnac /entry=in ties=efron rl;
	output out=xbeta (keep=xbeta xbetase log10rnac) xbeta=xbeta STDXBETA=xbetase; run;
proc sort data=xbeta; by log10rnac;
```

```
data log10rnacrhplot;
	set xbeta;
	xbetaul=xbeta+1.96*xbetase;
	xbetall=xbeta-1.96*xbetase;
	rh=exp(xbeta);
	rhul=exp(xbetaul);
	rhll=exp(xbetall);
proc means data=log10rnacrhplot min max; var rh rhul rhll log10rnac; run;
*Plotting relative hazard of death as a function of centered log10 HIV-1 viral load;
options nogstyle FONTRENDERING=HOST_PIXELS;
goptions reset=all;
filename grafout "C:\figure2a.png";
goptions device=zpng target=png gsfname=grafout gsfmode=replace xmax=6 ymax=6 xpixels=3600 ypixels=3600;
axis1	color=black logbase=e logstyle=expand interval=uneven order=(.1 .2 .5 1 2 5 10 100)
		label=(angle=90 font=swiss h=2 "Relative hazard of death") w=2
		major=(h=1 w=2) minor=none value=(font=swiss h=2 tick=1 '0.1' tick=2 '0.2' tick=3 '0.5' tick=4 '1.0' tick=5 '2.0' tick=6
'5.0' tick=7 '10.0' tick=8 '100.0') offset=(0,0);
axis2	color=black
		label=(font=swiss h=2 justify=center "HIV-1, log10 copies/ml") w=2
		major=(h=1 w=2) minor=none value=(font=swiss h=2) offset=(0,0);
symbol1 c=black l=1 w=3 h=.4 v=none i=join;
symbol2 c=black l=2 w=2 h=.4 v=none i=join;
symbol3 c=black l=2 w=2 h=.4 v=none i=join;
footnote move=(25,42) font=swiss color=black h=2 "AIC=655.91";
proc gplot data=log10rnacrhplot;
	plot (rh rhul rhll)*log10rnac/overlay vaxis=axis1 haxis=axis2 noframe nolegend; run; quit; run;
footnote " "; run;

***Using indicators corresponding to quartiles of centered log10 viral load with categories: >2.17487 to 2.61172,
>2.61172 to 3.20562, >3.20562 to 3.57403 log10 copies/ml to model association between centered log10 HIV-1 viral load
and hazard of death***;
```

```
*Fitting Cox model;
proc phreg data=a;
	model out*dead(0)= log10rnac1i log10rnac2i log10rnac3i /entry=in ties=efron rl;
	output out=xbeta (keep=xbeta xbetase log10rnac log10rnac1i log10rnac2i log10rnac3i) xbeta=xbeta STDXBETA=xbetase;
run;
proc sort data=xbeta; by log10rnac;
data log10rnacrhplot;
	set xbeta;
	xbetaul=xbeta+1.96*xbetase;
	xbetall=xbeta-1.96*xbetase;
	rh=exp(xbeta);
	rhul=exp(xbetaul);
	rhll=exp(xbetall);
proc means data=log10rnacrhplot min max; var rh rhul rhll log10rnac; run;
*Plotting relative hazard of death as a function of centered log10 HIV-1 viral load;
options nogstyle FONTRENDERING=HOST_PIXELS;
goptions reset=all;
filename grafout "C:\figure2b.png";
goptions device=zpng target=png gsfname=grafout gsfmode=replace xmax=6 ymax=6 xpixels=3600 ypixels=3600;
axis1	color=black logbase=e logstyle=expand interval=uneven order=(.1 .2 .5 1 2 5 10 100)
		label=(angle=90 font=swiss h=2 "Relative hazard of death") w=2
		major=(h=1 w=2) minor=none value=(font=swiss h=2 tick=1 '0.1' tick=2 '0.2' tick=3 '0.5' tick=4 '1.0' tick=5 '2.0' tick=6
'5.0' tick=7 '10.0' tick=8 '100.0') offset=(0,0);
axis2	color=black
		label=(font=swiss h=2 justify=center "HIV-1, log10 copies/ml") w=2
		major=(h=1 w=2) minor=none value=(font=swiss h=2) offset=(0,0);
symbol1 c=black l=1 w=3 h=.4 v=none i=stepjs;
symbol2 c=black l=2 w=2 h=.4 v=none i=stepjs;
symbol3 c=black l=2 w=2 h=.4 v=none i=stepjs;
footnote move=(25,42) font=swiss color=black h=2 "AIC=656.47";
proc gplot data=log10rnacrhplot;
```

```
	plot (rh rhul rhll)*log10rnac/overlay vaxis=axis1 haxis=axis2 noframe nolegend; run; quit; run;
footnote " "; run;

***Using restricted quadratic spline with 4 equal knots at the 20th, 40th, 60th, and 80th percentiles
based on the case distribution to model association between centered log10 HIV-1 viral load and hazard of death***;
*Running rqs macro;
%include "C:\rqsmacro.sas";
%rqspline(data=a,x=log10rnac,event=dead,k=4,equal=1,cases=1);
*Fitting Cox model;
proc phreg data=a;
	model out*dead(0)= log10rnac _log10rnac __log10rnac ___log10rnac /entry=in ties=efron rl;
	test_nonlinear: test _log10rnac, __log10rnac, ___log10rnac;
	output out=xbeta (keep=xbeta xbetase log10rnac) xbeta=xbeta STDXBETA=xbetase; run;
proc sort data=xbeta; by log10rnac;
data log10rnacrhplot;
	set xbeta;
	xbetaul=xbeta+1.96*xbetase;
	xbetall=xbeta-1.96*xbetase;
	rh=exp(xbeta);
	rhul=exp(xbetaul);
	rhll=exp(xbetall);
proc means data=log10rnacrhplot min max; var rh rhul rhll log10rnac; run;
*Plotting relative hazard of death as a function of centered log10 HIV-1 viral load;
options nogstyle FONTRENDERING=HOST_PIXELS;
goptions reset=all;
filename grafout "C:\figure2c.png";
goptions device=zpng target=png gsfname=grafout gsfmode=replace xmax=6 ymax=6 xpixels=3600 ypixels=3600;
axis1	color=black logbase=e logstyle=expand interval=uneven order=(.1 .2 .5 1 2 5 10 100)
		label=(angle=90 font=swiss h=2 "Relative hazard of death") w=2
		major=(h=1 w=2) minor=none value=(font=swiss h=2 tick=1 '0.1' tick=2 '0.2' tick=3 '0.5' tick=4 '1.0' tick=5 '2.0' tick=6
'5.0' tick=7 '10.0' tick=8 '100.0') offset=(0,0);
```

```
axis2   color=black
            label=(font=swiss h=2 justify=center "HIV-1, log10 copies/ml") w=2
            major=(h=1 w=2) minor=none value=(font=swiss h=2) offset=(0,0);
symbol1 c=black l=1 w=3 h=.4 v=none i=join;
symbol2 c=black l=2 w=2 h=.4 v=none i=join;
symbol3 c=black l=2 w=2 h=.4 v=none i=join;
footnote move=(25,42) font=swiss color=black h=2 "AIC=651.71";
proc gplot data=log10rnacrhplot;
    plot (rh rhul rhll)*log10rnac/overlay vaxis=axis1 haxis=axis2 noframe nolegend; run; quit; run;
footnote " "; run;

***Using restricted cubic spline with 5 equal knots at the 16th, 33rd, 50th, 67th, and 84th percentiles
based on the case distribution to model association between centered log10 HIV-1 viral load and hazard of death***;
*Running daspline macro;
%include "C:\dshide.sas";
%include "C:\daspline.sas";
%daspline(x=log10rnac,nk=5,knot1=2.26732 2.75311 2.92302 3.28978 3.53285,data=a);
data a; set a; &_log10rnac; run;
*Fitting Cox model;
proc phreg data=a;
    model out*dead(0)= log10rnac log10rnac1 log10rnac2 log10rnac3 /entry=in ties=efron rl;
    test_nonlinear: test log10rnac1, log10rnac2, log10rnac3;
    output out=xbeta (keep=xbeta xbetase log10rnac) xbeta=xbeta STDXBETA=xbetase; run;
proc sort data=xbeta; by log10rnac;
data log10rnacrhplot;
    set xbeta;
    xbetaul=xbeta+1.96*xbetase;
    xbetall=xbeta-1.96*xbetase;
    rh=exp(xbeta);
    rhul=exp(xbetaul);
    rhll=exp(xbetall);
```

```
proc means data=log10rnacrhplot min max; var rh rhul rhll log10rnac; run;
*Plotting relative hazard of death as a function of centered log10 HIV-1 viral load;
options nogstyle FONTRENDERING=HOST_PIXELS;
goptions reset=all;
filename grafout "C:\figure2d.png";
goptions device=zpng target=png gsfname=grafout gsfmode=replace xmax=6 ymax=6 xpixels=3600 ypixels=3600;
axis1   color=black logbase=e logstyle=expand interval=uneven order=(.1 .2 .5 1 2 5 10 100)
                label=(angle=90 font=swiss h=2 "Relative hazard of death") w=2
                major=(h=1 w=2) minor=none value=(font=swiss h=2 tick=1 '0.1' tick=2 '0.2' tick=3 '0.5' tick=4 '1.0' tick=5 '2.0' tick=6
'5.0' tick=7 '10.0' tick=8 '100.0') offset=(0,0);
axis2   color=black
                label=(font=swiss h=2 justify=center "HIV-1, log10 copies/ml") w=2
                major=(h=1 w=2) minor=none value=(font=swiss h=2) offset=(0,0);
symbol1 c=black l=1 w=3 h=.4 v=none i=join;
symbol2 c=black l=2 w=2 h=.4 v=none i=join;
symbol3 c=black l=2 w=2 h=.4 v=none i=join;
footnote move=(25,42) font=swiss color=black h=2 "AIC=652.67";
proc gplot data=log10rnacrhplot;
        plot (rh rhul rhll)*log10rnac/overlay vaxis=axis1 haxis=axis2 noframe nolegend; run; quit; run;
footnote " "; run;

*************************************************************************************************************
Example 2: Use of a spline when controlling for centered log10 HIV-1 viral load
(i.e., centered viral load > 1 log10 copies/ml) as a confounder of the association
between an indicator of CD4 <= 350 cells/mm^3 high at therapy initiation and hazard of death
*************************************************************************************************************;
*Unadjusted for centered log10 HIV-1 viral load;
proc phreg data=a;
        model out*dead(0)= cd4bin /entry=in ties=efron rl; run;
*Adjusted for centered log10 HIV-1 viral load using binary indicator for centered HIV-1 viral load >1 log10 copies/ml;
proc phreg data=a;
```

```
        model out*dead(0)= cd4bin highlog10rnac/entry=in ties=efron rl; run;
*Adjusted for centered log10 HIV-1 viral load using 9 indicators for centered log10 HIV-1 viral load categories:
>1.47712 to 1.98677, >1.98677 to 2.26732, >2.26732 to 2.46904, >2.46904 to 2.61172, >2.61172 to 2.78233,
>2.78233 to 3.03952,>3.03952 to 3.34537, >3.34537 to 3.5618, and >3.5618 to 3.57403 cells/mm^3;
proc phreg data=a;
        model out*dead(0)= cd4bin log10rnacd1i log10rnacd2i log10rnacd3i log10rnacd4i log10rnacd5i log10rnacd6i log10rnacd7i
log10rnacd8i log10rnacd9i /entry=in ties=efron rl; run;
*Adjusted for centered log10 HIV-1 viral load assuming log-linear association between centered log10 HIV-1 viral load;
*and hazard of death;
proc phreg data=a;
        model out*dead(0)= cd4bin log10rnac /entry=in ties=efron rl; run;
*Adjusted for centered log10 HIV-1 viral load using restricted quadratic spline with with 4 equal knots at
the 20th, 40th, 60th, and 80th percentiles based on the case distribution;
proc phreg data=a;
        model out*dead(0)= cd4bin log10rnac _log10rnac __log10rnac ___log10rnac /entry=in ties=efron rl;
run;
*Adjusted for centered log10 HIV-1 viral load using restricted cubic spline with with 5 equal knots at
the 16th, 33rd, 50th, 67th, and 84th percentiles based on the case distribution;
proc phreg data=a;
        model out*dead(0)= cd4bin log10rnac log10rnac1 log10rnac2 log10rnac3 /entry=in ties=efron rl;
run;
```

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