A study comparing the effects of dual or triple combinations of HIV-1 reverse transcriptase inhibitors with respect to CD4 T cell counts

Introduction

The data for this report are from a randomized, double-blind, placebo-controlled study of AIDS patients with advanced immune suppression (i.e., CD4 counts $\leq$ 50 cell/mm^3). 1313 patients in AIDS Clinical Trial Group Study 193A (ACTG 193) were randomized to treatments with dual or triple combinations of HIV-1 reverse transcriptase inhibitors. In particular, patients were randomized to one of four daily regimens containing 600mg of zidovudine: zidovudine alternating monthly with 400mg didanosine (Placebo+DDI); zidovudine plus 2.25mg of zalcitabine (ZDV+DDI); zidovudine plus 400mg of didanosine (ZDV+DDC); or zidovudine plus 400mg of didanosine plus 400mg of nevirapine (ZDV+DDI+DDC). Measurements of CD4 counts were scheduled to be collected at baseline and at 8-week intervals during 40 weeks of follow-up. However, the CD4 cell count data are unbalanced among subjects due to mistimed measurements and missing data that resulted from skipped visits and dropout. Although Dr. Henry et.al have compared the survival benefit of four treatments in this trial [1], the change of CD4 cell counts among different therapies has not been thoroughly investigated yet. The objectives in the present study were to identify the trajectories of CD4 cell counts and to compare the effects of dual or triple combinations of HIV-1 reverse transcriptase inhibitors with respect to CD4 cell counts. We hypothesized 1) that the association between time and rates of change in CD4 counts significantly depends on treatments; 2) that a combination of triple inhibitors leads to higher CD4 counts when compared with dual combinations. To test these hypotheses, the primary outcome was CD4 counts and the predictors include time, treatments and other necessary factors.

Methods

Statistical analyses were performed using SAS for Windows software (version 9.3; SAS Institute, NC). CD4 cell counts were log-transformed to better meet model assumptions (e.g., normality and homogeneity of variance). Characteristics of study participants were expressed as mean and SD for continuous variables and as percentages for categorical variables. Since subjects came in fairly close to the prescribed dates, a new class variable for time was defined as following below: time=0: 0-4 weeks; time=8: 5-12 weeks; time=16: 13-20 weeks; time=24, 21-28 weeks; time=32: 27-36 weeks; time=40: 37-40 weeks. Non-paramedic regression models (PROC LOESS) were first used to indicate the change trend of log-transformed CD4 counts by time and treatments. Linear mixed models (PROC MIXED) were then used to address two objectives of interest. Besides adjustment for age and gender, these models account for random effect between subjects and the correlation within patients over time. The data were analyzed using time as a continuous

(week) versus time as a class variable (time). When time was analyzed as a continuous variable, models with higher order terms (i.e., quadratic, cubic, quartic) in addition to potential knots with splines were considered to best fit the data. Moreover, several combinations of random effects (random intercept, slope) for subjects and error covariance structures were examined and compared using the Akaike Information Criterion (AIC) and visual inspection of the model fit. Of note, maximum likelihood estimation (Method=ML) was used during model exploration. The final best model was fit using restricted maximum likelihood estimation (Method=REML) for all reported analyses. For all analyses, significance tests were two-sided with a significance level of 0.05.

Results

Table 1 shows characteristics of study participants in the AIDS Clinical Trial Group Study 193A (ACTG 193). 1299 were included in these analyses. The clinical characteristics of study participants are presented in Table 1. The subjects in four treatment groups had similar distributions in sex and ages. The overall drop-out rates increased eventually to 80% at the end of trial. However, there were no significant differences in drop-out rates among four treatment groups. The mean of log-transformed CD4 cell counts by treatments were also summarized in table 1.

Table 1. Characteristics of study participants by treatment groups

	Placebo+DDI (N=320)	ZDV+DDI (N=322)	ZDV+DDC (N=327)	ZDV+DDI+DDC (N=330)	Total (N=1299)
Male Sex	286(89.38%)	280(86.96%)	283(86.54%)	289(87.58%)	1138(87.61%)
Age (years)	37.83(8.60)	37.73(7.92)	37.47(8.10)	37.89(8.26)	37.73(8.16)
LogCD4 count					
0 week	2.96(0.82)	2.95(0.93)	2.91(0.95)	2.84(0.96)	2.91(0.92)
8 week	2.81(1.01)	2.94(1.08)	3.08(1.18)	3.15(1.17)	3.00(1.12)
16 week	2.81(0.96)	2.83(1.05)	2.96(1.19)	3.24(1.20)	2.96(1.12)
24 week	2.57(0.93)	2.60(1.11)	2.78(1.15)	2.99(1.17)	2.74(1.11)
32 week	2.56(0.91)	2.67(1.03)	2.81(1.19)	2.96(1.25)	2.75(1.12)
40 week	2.31(1.12)	2.39(1.27)	2.78(1.13)	2.90(1.17)	2.60(1.20)

Data are mean (SD) values or number (%) as indicated.

Figure 1 displays graphically the change of log-transformed CD4 counts by treatments. Scatterplots and the trend lines derived from non-parametric regression present different change patterns for log-transformed CD4 counts among four treatment groups.

The results of mixed model exploration were summarized in Appendix 1-4 (Page 6-8). The models using time as a continuous variable had lower AIC than models with time as a class predictor. Among the tested models, the best overall fit was a quartic model with a spatial error covariance structure along with random intercept and random time effects. Although the model with spline terms present lowest AIC, it was not finally chosen since the predicted trends did not well match the scatterplot, especially at the end of trial (Appendix 4, page 8).

Figure 1. Change of Log-transformed CD4 counts by 4 treatments

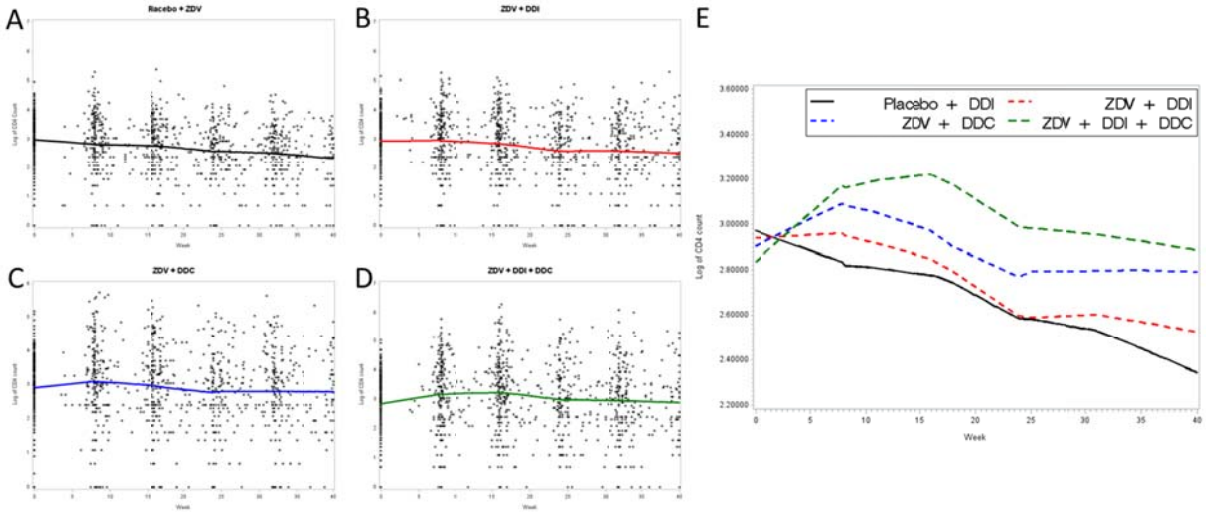


Figure 1. Scatter plot of log-transformed CD4 counts by treatments. The lines are non-parametric regression lines.

Table 2. Results of linear mixed models for time and treatment predicting logCD4 counts.

Predictors	β	SEM	P
Age (/1 year)	0.009861	0.002978	<.0001
Gender			
Feale	0.08953	0.07356	
Male	Reference	NA	NA
Treatment			
Treat1	0.1409	0.07143	0.0487
Treat2	0.1019	0.07136	0.1536
Treat3	0.06623	0.07109	0.3517
Treat4	Reference	NA	NA
Time			
Week	0.1019	0.0181	<.0001
Week^2	-0.00843	0.002204	0.0001
Week^3	0.000245	0.000089	0.0059
Week^4	-2.49E-06	1.14E-06	0.0294
Interaction*			
Week*treat1	-0.1138	0.02584	<.0001
Week*treat2	-0.0609	0.02588	0.0187
Week*treat3	-0.0595	0.02601	0.0223
Week*treat4	Reference	NA	NA
Week^2*treat1	0.008245	0.003152	0.009
Week^2 *treat2	0.003151	0.003151	0.3175
Week^2*treat3	0.004744	0.003175	0.1353
Week^2*treat4	Reference	NA	NA
Week^3*treat1	-0.00025	0.000128	0.0545
Week^3*treat2	-0.00008	0.000127	0.5367
Week^3*treat3	-0.00017	0.000129	0.1922
Week^3*treat4	Reference	NA	NA
Week^4*treat1	2.53E-06	1.65E-06	0.1243
Week^4*treat2	7.79E-07	1.64E-06	0.6348
Week^4*treat3	2.08E-06	1.66E-06	0.2104
Week^4*treat4	Reference	NA	NA

Table 2 shows the results of linear mixed models regression and figure 2 displays graphically the estimated differing trajectories of log-transformed CD4 counts among four treatment groups. The weekly rate of CD4 T cell count change in AIDS patients with advanced immune suppression significantly depended on treatments (P<0.0001). For those AIDS patients who received placebo treatment, CD4 T cells continued to decrease along the time. For those AIDS patients who were under dual or triple drug treatment, their CD4 T cells increased in the first few weeks and then drop in the following periods.

Table 3 summarizes the predicted changes of log-transformed CD4 count from baseline among four treatment groups. Specially, after 8 weeks of treatment, the log-transformed CD4 count decreases by 0.11 (95% CI: -0.21 to 0) for patients under treatment with placebo plus DDI, while it increase by 0.07 (95% CI: -0.04 to 0.17), 0.14 (95% CI: 0.04, 0.25), 0.39

(95% CI: 0.29, 0.49) for the other three treatments, respectively. The increase of log-transformed CD4 in first 8 weeks for triple drug treatment is significantly higher than any of dual drug treatments (treatment 4 vs. treatment 2, P=0.02; treatment 4 vs. treatment 3, P=0.04). After 16 week treatment, the logCD4 start falling down for all treatment groups. However, only patients under the triple drug treatment have significantly higher logCD4 count than the baseline (P<0.0001). At the end of trial, there are no significant differences in the change of logCD4 count between triple drug treatment and either of dual drug therapies (both P>0.2).

Figure 2. Predicted change trend of log of CD4 counts by treatments

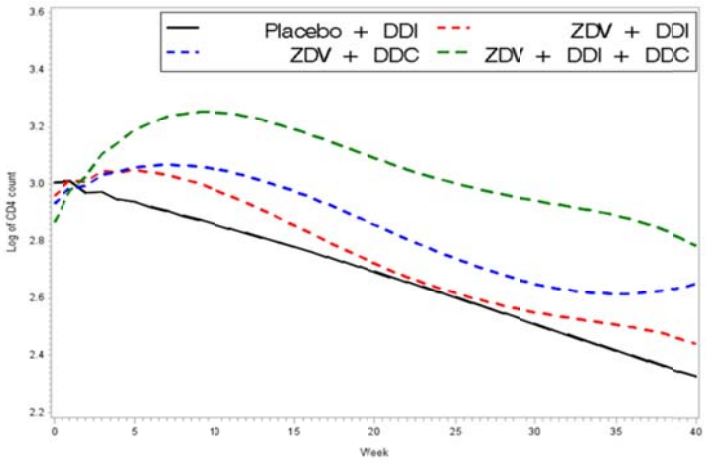


Table 3. Predicted change of logCD4 from baseline.

Weeks	Treatment (95% CI)			
	Placebo+DDI	ZDV+DDI	ZDV+DDC	ZDV+DDI+DDC
8	-0.11 (-0.21, 0)	0.07 (-0.04, 0.17)	0.14 (0.04, 0.25)	0.39 (0.29, 0.49)
16	-.24 (-0.34, -0.13)	-0.12 (-0.23, -0.02)	0.03 (-0.07, 0.13)	0.31 (0.22, 0.41)
24	-.038 (-0.48, -0.28)	-0.32 (-0.42, -0.22)	-0.17 (-0.27, -0.07)	0.16 (0.06, 0.26)
32	-0.53 (-0.65, -0.41)	-0.42 (-0.55, -0.30)	-0.30 (-0.42, -0.18)	0.06 (-0.06, 0.18)
40	-0.65 (-13.88, 0.87)	-0.52 (-0.72, -0.31)	-0.28 (-0.50, -0.06)	*

*Estimation was not shown due to big variability.

Conclusion

In this study, we found that the weekly rate of logCD4 change in advanced AIDS patients significantly depended on treatments and that the trajectories of log-transformed CD4 counts among dual or triple drug treatments were not linear while it was approximately linear for placebo control. Our study also revealed that the CD4 counts in patients with triple drug treatment were significantly higher than the ones under dual drug treatments. However, no significant differences were observed among dual drug and triple drug treatments after 40 weeks treatment. Thus, we conclude that the triple combination of ZDV plus DDI plus DDC has beneficial effect in increasing CD4 cells, at least for a short term, as compared to dual combinations and control. This might partially interpret one of previous findings that triple inhibitor treatment enables to prolong life [1].

At the end, we need to point out some limitations in this study. One limitation was high drop-out rate, especially at 40 week, which might affect the accuracy of our conclusion. Another limitation was that patients often had mistimed measurement. Moreover, the scheduled 8-week interval also raise concerns since it might be too long to catch the dynamic change of CD4 counts along the time. Given these above limitations and concerns, more cautions should be taken to interpret the results. More extensive studies might be needed to confirm our findings.

Reference:

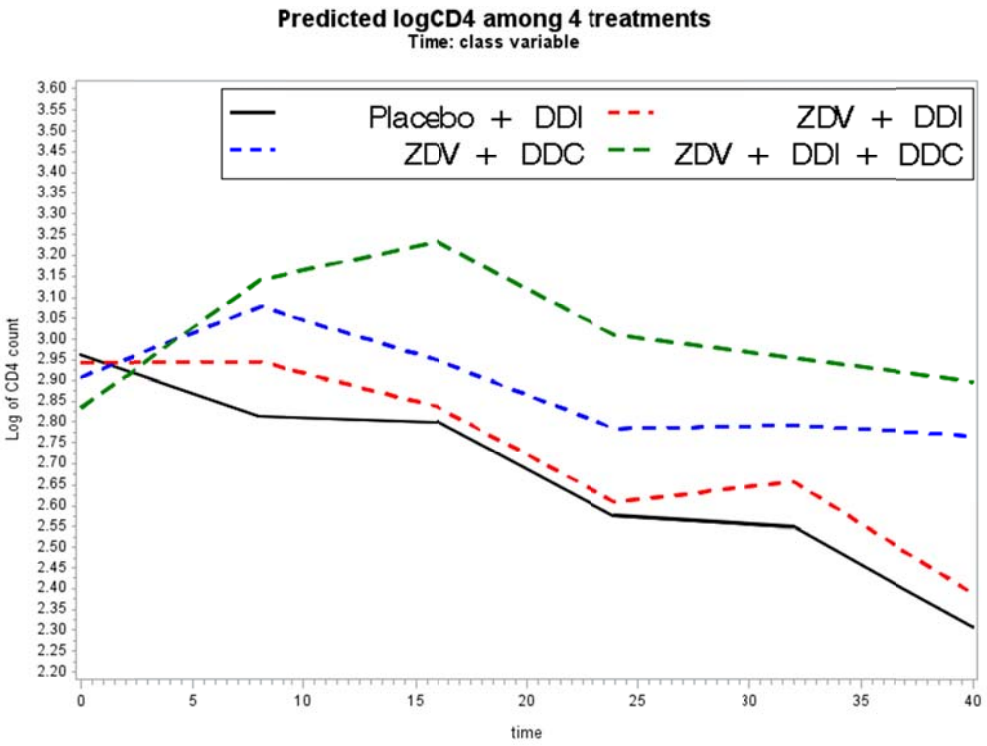
1. Henry, K., Erice, A., Tierney, C., Balfour, H.H. Jr, Fischl, M.A., Kmack, A., Liou, S.H., Kenton, A., Hirsch, M.S., Phair, J., Martinez, A. and Kahn J.O. for the AIDS Clinical Trial Group 193A Study Team (1998). A randomized, controlled, double-blind study comparing the survival benefit of four different reverse transcriptase inhibitor therapies (three-drug, two-drug,and alternating drug) for the treatment of advanced AIDS. Journal of Acquired Immune Deficiency Syndromes and Human Retrovirology, 19, 339-349.

Statistical Appendixes:

Appendix 1. Model exploring using time as a class variable

No.	Model (time as a class variable)	AIC (Method=ml)
1	VC for R (default setting in SAS)	14909
2	CS for R	12093.8
3	AR(1)for R	12285.5
4	UN for R	WARNING: Unable to make hessian positive definite
5	Banded UN, UN(1) for R	14858.4
6	Random intercept, AR(1) for R	**12032.3**

Appendix 2. Model fit using time as a class variable

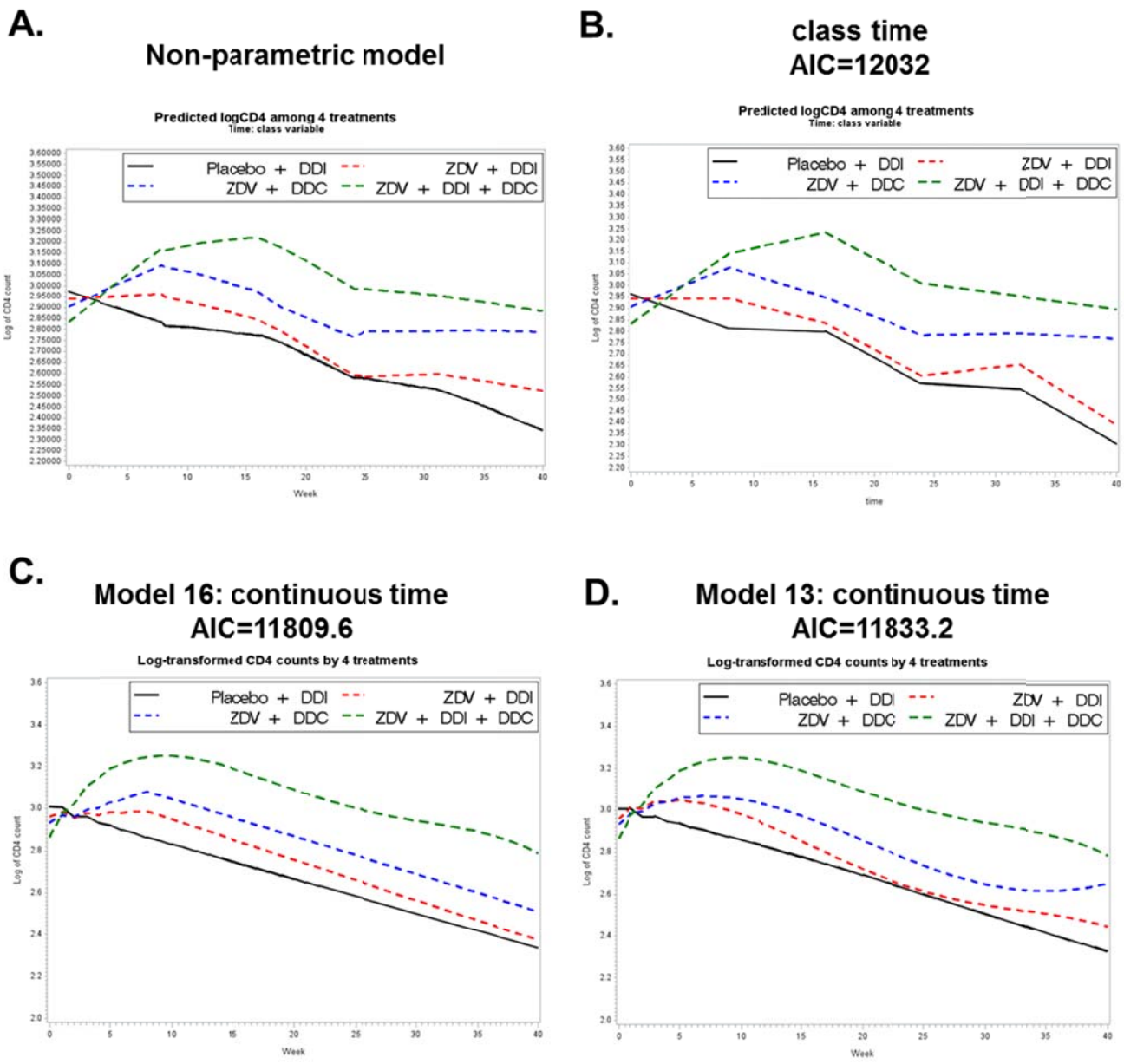


Appendix 3. Model exploring using time as a continuous variable

No.	Model (time as a continuous variable)	AIC (method=ml)
1	Linear; Random intercept, AR(1)for R	12120.3
2	Quadratic ; Random intercept, AR(1)for R	12052.7
3	Cubic; Random intercept, AR(1)for R	12019.2
4	Quartic; Random intercept, AR(1)for R	12021.5
5	Linear; Random intercept and slope, VC for G, AR(1)for R	12058.4
6	Quadratic ; Random intercept and slope, VC for G, AR(1)for R	11979.5
7	Cubic ; Random intercept and slope, VC for G, AR(1)for R	11943.8
8	Quartic; Random intercept and slope, VC for G, AR(1)for R	11946.5
9	Linear; Random intercept and slope, UN for G, AR(1)for R	12043.5
10	Quadratic ; Random intercept and slope, UN for G, AR(1)for R	11966.7
11	Cubic ; Random intercept and slope, UN for G, AR(1)for R	11931.4
12	Quartic; Random intercept and slope, VC for G, AR(1)for R	11934.2
13	Quartic; Random intercept and slope, UN for G, SP(pow)for R	**11833.2** **(note: expected mean match the observed one)***
14	Linear +spline term (`max (0, (week-8))`)* Random intercept and slope, UN for G, AR(1)for R	11828.7
15	Quadratic +spline term (`max (0, (week-8))`), Random intercept and slope, UN for G, AR(1)for R	11834.3
16	Linear + spline term for treatment 1-3 Quartic for treatment 4	**10809.6** (note: lowest AIC, but expected mean did not well match the observed one

*overall best fit model.

Appendix 4. Comparing models fit



Notes: Model 13 was chosen as final model rather than model 16 for the following reasons: 1). The predicted trend in model 13 better matches the one shown in scatter plot; 2). The model 13 is simpler than model 16; 3). All treatments were treated equally in model 13 during regression.

Appendix 5.

SAS ouput with final model including estimation and contrast

Dimensions	
Covariance Parameters	8
Columns in X	28
Columns in Z Per Subject	3
Subjects	1313
Max Obs Per Subject	41

Number of Observations	
Number of Observations Read	5200
Number of Observations Used	5040
Number of Observations Not Used	160

Convergence criteria met.

Covariance Parameter Estimates		
Cov Parm	**Subject**	**Estimate**
UN(1,1)	**ID**	0.5432
UN(2,1)	**ID**	0.01560
UN(2,2)	**ID**	0.003069
UN(3,1)	**ID**	-0.01877
UN(3,2)	**ID**	-0.00325
UN(3,3)	**ID**	0.003800
SP(POW)	**ID**	-0.6370
Residual		0.2918

Fit Statistics	
-2 Res Log Likelihood	12096.3
AIC (smaller is better)	12112.3
AICC (smaller is better)	12112.4

Fit Statistics	
BIC (smaller is better)	12153.8

Null Model Likelihood Ratio Test		
DF	**Chi-Square**	**Pr > ChiSq**
7	3080.26	<.0001

Solution for Fixed Effects

Effect	Treatment	Gender	Estimate	Standard Error	DF	t Value	Pr > |t|
Intercept			2.4507	0.1248	1308	19.64	<.0001
Treatment	**1**		0.1409	0.07143	1493	1.97	0.0487
Treatment	**2**		0.1019	0.07136	1493	1.43	0.1536
Treatment	**3**		0.06623	0.07109	1493	0.93	0.3517
Treatment	**4**		0	.	.	.	.
Age			0.009861	0.002978	1493	3.31	0.0010
Gender		**0**	0.08953	0.07356	1493	1.22	0.2237
Gender		**1**	0	.	.	.	.
Week			0.1019	0.01810	1183	5.63	<.0001
Week*Week			-0.00843	0.002204	1493	-3.82	0.0001
Week*Week*Week			0.000245	0.000089	1493	2.76	0.0059
Week*Week*Week*Week			-2.49E-6	1.141E-6	1493	-2.18	0.0294
Week*Treatment	**1**		-0.1138	0.02584	1493	-4.40	<.0001
Week*Treatment	**2**		-0.06090	0.02588	1493	-2.35	0.0187
Week*Treatment	**3**		-0.05950	0.02601	1493	-2.29	0.0223
Week*Treatment	**4**		0	.	.	.	.
Week*Week*Treatment	**1**		0.008245	0.003152	1493	2.62	0.0090
Week*Week*Treatment	**2**		0.003151	0.003151	1493	1.00	0.3175
Week*Week*Treatment	**3**		0.004744	0.003175	1493	1.49	0.1353
Week*Week*Treatment	**4**		0	.	.	.	.
Week*Week*Week*Treat	**1**		-0.00025	0.000128	1493	-1.92	0.0545
Week*Week*Week*Treat	**2**		-0.00008	0.000127	1493	-0.62	0.5367
Week*Week*Week*Treat	**3**		-0.00017	0.000129	1493	-1.30	0.1922

Solution for Fixed Effects

Effect	Treatment	Gender	Estimate	Standard Error	DF	t Value	Pr > |t|
Week*Week*Week*Treat	4		0	.	.	.	.
Wee*Wee*Wee*Wee*Trea	1		2.53E-6	1.645E-6	1493	1.54	0.1243
Wee*Wee*Wee*Wee*Trea	2		7.792E-7	1.64E-6	1493	0.48	0.6348
Wee*Wee*Wee*Wee*Trea	3		2.078E-6	1.658E-6	1493	1.25	0.2104
Wee*Wee*Wee*Wee*Trea	4		0	.	.	.	.

Type 3 Tests of Fixed Effects

Effect	Num DF	Den DF	F Value	Pr > F
Treatment	3	1493	1.41	0.2390
Age	1	1493	10.96	0.0010
Gender	1	1493	1.48	0.2237
Week	1	1183	22.11	<.0001
Week*Week	1	1493	15.25	<.0001
Week*Week*Week	1	1493	7.20	0.0074
Week*Week*Week*Week	1	1493	4.75	0.0294
Week*Treatment	3	1493	6.48	0.0002
Week*Week*Treatment	3	1493	2.36	0.0695
Week*Week*Week*Treat	3	1493	1.39	0.2439
Wee*Wee*Wee*Wee*Trea	3	1493	1.00	0.3937

Estimates

Label	Estimate	Standard Error	DF	t Value	Pr > |t|	Alpha	Lower	Upper
Treat1: 8 week vs 0 week	-0.1068	0.05351	1493	-1.99	0.0462	0.05	-0.2117	-0.00179
Treat2: 8 week vs 0 week	0.06837	0.05376	1493	1.27	0.2037	0.05	-0.03708	0.1738
Treat3: 8 week vs 0 week	0.1413	0.05368	1493	2.63	0.0086	0.05	0.03596	0.2466
Treat1: 16 week vs 0 week	-0.2351	0.05156	1493	-4.56	<.0001	0.05	-0.3362	-0.1339
Treat2: 16 week vs	-0.1248	0.05143	1493	-2.43	0.0154	0.05	-0.2257	-0.02390

Estimates

Label	Estimate	Standard Error	DF	t Value	Pr > |t|	Alpha	Lower	Upper
0 week								
Treat3: 16 week vs 0 week	0.02606	0.05078	1493	0.51	0.6079	0.05	-0.07356	0.1257
Treat1: 24 week vs 0 week	-0.3796	0.05249	1493	-7.23	<.0001	0.05	-0.4826	-0.2766
Treat2: 24 week vs 0 week	-0.3197	0.05272	1493	-6.06	<.0001	0.05	-0.4231	-0.2163
Treat3: 24 week vs 0 week	-0.1677	0.05189	1493	-3.23	0.0013	0.05	-0.2695	-0.06588
Treat1: 32 week vs 0 week	-0.5308	0.06152	1493	-8.63	<.0001	0.05	-0.6515	-0.4101
Treat2: 32 week vs 0 week	-0.4246	0.06235	1493	-6.81	<.0001	0.05	-0.5469	-0.3023
Treat3: 32 week vs 0 week	-0.3023	0.06132	1493	-4.93	<.0001	0.05	-0.4226	-0.1820
Treat1: 40 week vs 0 week	-6.5033	3.7582	1493	-1.73	0.0838	0.05	-13.8753	0.8687
Treat2: 40 week vs 0 week	-0.5157	0.1047	1493	-4.92	<.0001	0.05	-0.7211	-0.3103
Treat3: 40 week vs 0 week	-0.2804	0.1132	1493	-2.48	0.0134	0.05	-0.5024	-0.05833

Estimates

Label	Estimate	Standard Error	DF	t Value	Pr > |t|	Alpha	Lower	Upper
Treat4: 8 week vs 0 week	0.3910	0.05250	1493	7.45	<.0001	0.05	0.2880	0.4940
Treat4: 16 week vs 0 week	0.3143	0.05035	1493	6.24	<.0001	0.05	0.2156	0.4131
Treat4: 24 week vs 0 week	0.1566	0.05157	1493	3.04	0.0024	0.05	0.05543	0.2577
Treat4: 32 week vs 0 week	0.05988	0.05993	1493	1.00	0.3179	0.05	-0.05767	0.1774
Treat4: 40 week vs	5.7500	3.7643	1493	1.53	0.1268	0.05	-1.6338	13.1338

Estimates

Label	Estimate	Standard Error	DF	t Value	Pr > |t|	Alpha	Lower	Upper
0 week								

Contrasts

Label	Num DF	Den DF	F Value	Pr > F
8 week: Treat 4 Vs 2	1	1493	5.61	0.0180
8 week: Treat 4 Vs 3	1	1493	3.89	0.0488
40 week: Treat 4 Vs 2	1	1493	0.43	0.5120
40 week: Treat 4 Vs 3	1	1493	1.64	0.2000

Appendix 6: SAS codes:

```
*************************************************************;
*Created by: Yonghua Zhuang
*Created on: DEC 8, 2013
*Purpose: Project for Longitudinal Data Analysis.
*************************************************************;
data CD4;
infile "c:\SAS\CD4.txt" firstobs=2;
input ID Treatment Age  Gender  Week logCD4;
run;
data baseline postbase;
set CD4;
if week =0
then output baseline;
else output postbase;
run;
data baseline1;
set baseline;
rename logCD4=baseline;
run;
data CD4b;
merge CD4 (in=inp) baseline1 (in=inb);
by id;
percentage= logCD4/baseline*100;
run;
Proc univariate data=CD4b;
var logcd4 week;
run;
******Create a new class variable for time********;
Data CD4C;
Set CD4b;
If week <= 4 then time =0;
else if week > 4 and week <= 12 then time = 8;
else if week > 12 and week <= 20 then time = 16;
else if week > 20 and week <= 28 then time = 24;
else if week > 28 and week <= 36 then time = 32;
else time=40;
run;
proc means data = CD4C;
where week=0;
var age logCD4;
run;
proc means data = CD4C;
where week=0;
var age logCD4;
class treatment;
run;
Proc freq data=CD4C;
where week=0;
tables Gender*treatment;
run;
******check drop-out rate********;
Proc freq data=CD4C;
tables time*treatment;
run;
******Non-parametric regression to identify trend********;
proc loess data=CD4b;
where treatment=1;
model LogCD4=week  /smooth=0.4;
```

```
  ods output OutputStatistics=logout1;
  run;
proc sort data=logout1;
  by  week;
run;
title 'Placebo + ZDV';
axis1 order =(0 to 40 by 5);
axis2 order=(0 to 7 by 1) label=(r=0 a=90);
symbol1 c = black i=none v =star h=0.8;
symbol2 c=black i=join v=none h=0.8 line=1 WIDTH=3;
proc gplot data=logout1;
  format DepVar f4.0 income f8.0;
  plot DepVar*week=1 Pred*week=2 /overlay haxis=axis1 vaxis=axis2 hminor=0
vminor=0;
  label Week='Week';
  label DepVar='Log of CD4 Count';
run;
proc loess data=CD4b;
where treatment=2;
model LogCD4=week  /smooth=0.4;
  ods output OutputStatistics=logout2;
  run;
proc sort data=logout2;
  by  week;
run;
title 'ZDV + DDI';
axis1 order =(0 to 40 by 5);
axis2 order=(0 to 7 by 1) label=(r=0 a=90);
symbol1 c = black i=none v =star h=0.8;
symbol2 c=red i=join v=none h=0.8 line=1 WIDTH=3;
proc gplot data=logout2;
  format DepVar f4.0 income f8.0;
  plot DepVar*week=1 Pred*week=2 /overlay haxis=axis1 vaxis=axis2 hminor=0
vminor=0;
  label Week='Week';
  label DepVar='Log of CD4 count';
run;
proc loess data=CD4b;
where treatment=3;
model LogCD4=week  /smooth=0.4;
  ods output OutputStatistics=logout3;
  run;
proc sort data=logout3;
  by  week;
run;
title 'ZDV + DDC';
axis1 order =(0 to 40 by 5);
axis2 order=(0 to 6.5 by 1) label=(r=0 a=90);
symbol1 c = black i=none v =star h=0.8;
symbol2 c=blue i=join v=none h=0.8 line=1 WIDTH=3;
proc gplot data=logout3;
  format DepVar f4.0 income f8.0;
  plot DepVar*week=1 Pred*week=2 /overlay haxis=axis1 vaxis=axis2 hminor=0
vminor=0;
  label Week='Week';
  label DepVar='Log of CD4 count';
run;
proc loess data=CD4b;
where treatment=4;
model LogCD4=week  /smooth=0.4;
  ods output OutputStatistics=logout4;
```

```
  run;
proc sort data=logout4;
  by  week;
run;
title 'ZDV + DDI + DDC';
axis1 order =(0 to 40 by 5);
axis2 order=(0 to 7 by 1) label=(r=0 a=90);
symbol1 c = black i=none v =star h=0.8;
symbol2 c=green i=join v=none h=0.8 line=1 WIDTH=3;
proc gplot data=logout4;
  format DepVar f4.0 income f8.0;
  plot DepVar*week=1 Pred*week=2 /overlay haxis=axis1 vaxis=axis2 hminor=0
vminor=0;
  label Week='Week';
  label DepVar='Log of CD4 count';
run;
Data logout11;
set logout1;
Treatment=1;
run;
Data logout21;
set logout2;
Treatment=2;
run;
Data logout31;
set logout3;
Treatment=3;
run;
Data logout41;
set logout4;
Treatment=4;
run;
data logout;
merge logout11 logout21 logout31 logout41;
by treatment;
run;
Proc print data=logout (obs=100);
run;
title 'Log-transformed CD4 counts by 4 treatments';
axis1 order =(0 to 40 by 5);
axis2 order=(2.2 to 3.6 by 0.2) label=(a=90);
symbol1 c=black i=join v=none h=0.8 line=1 WIDTH=2;
symbol2 c=red i=join v=none h=0.8 line=2 WIDTH=2;
symbol3 c=blue i=join v=none h=0.8 line=2 WIDTH=2;
symbol4 c=green i=join v=none h=0.8 line=3 WIDTH=2;
legend label=none value=(h=2 font=swiss 'Placebo + DDI'
'ZDV + DDI' 'ZDV + DDC' 'ZDV + DDI + DDC')
position=(top right inside) mode=share cborder=black;
proc gplot data=logout;
  plot  Pred*week=treatment /overlay haxis=axis1 vaxis=axis2 legend = legend1;
  label Week='Week';
  label Pred='Log of CD4 count';
run;

****mixed regresion with class variable****;
proc mixed data=CD4C method=ml;
Class ID Treatment Gender time;
Model logCD4 = treatment age gender time time*treatment  / solution;
Repeated /subject=id  r rcorr;
Run;
proc mixed data=CD4C method=ml;
```

```
Class ID Treatment Gender time;
Model logCD4 = treatment age gender time time*treatment  / solution;
Repeated /subject=id type=CS r rcorr;
Run;
proc mixed data=CD4C method=ml;
Class ID Treatment Gender time;
Model logCD4 = treatment age gender time time*treatment  / solution;
Repeated /subject=id type=AR(1) r rcorr;
Run;
proc mixed data=CD4C method=ml;
Class ID Treatment Gender time;
Model logCD4 = treatment age gender time time*treatment  / solution;
Repeated /subject=id type=SP(pow)(time) r rcorr;
Run;
proc mixed data=CD4C;
Class ID Treatment Gender time;
Model logCD4 = treatment age gender time time*treatment  / solution;
Repeated /subject=id type=TOEP r rcorr;
Run;
proc mixed data=CD4C method=ml;
Class ID Treatment Gender time;
Model logCD4 = treatment age gender time time*treatment  / solution;
Repeated /subject=id type=UN r rcorr;
Run;
proc mixed data=CD4C method=ml;
Class ID Treatment Gender time;
Model logCD4 = treatment age gender time time*treatment  / solution;
Repeated /subject=id type=UN(1) r rcorr;
Run;
proc mixed data=CD4C method=ml;
Class ID Treatment Gender time;
Model logCD4 = treatment age gender time time*treatment  / solution;
Random intercept  / subject =ID ;
Repeated /subject=id type=CS r rcorr;
Run;
proc mixed data=CD4C method=ml;
Class ID Treatment Gender time;
Model logCD4 = treatment age gender time time*treatment  / solution;
Random intercept  / subject =ID ;
Repeated /subject=id type=AR(1) r rcorr;
Run;
proc mixed data=CD4C;
Class ID Treatment Gender time;
Model logCD4 = treatment age gender time time*treatment  / solution;
Random intercept  / subject =ID ;
Repeated /subject=id type=UN r rcorr;
Run;
proc mixed data=CD4C;
Class ID Treatment Gender time;
Model logCD4 = treatment age gender time time*treatment  / solution;
Random intercept  / subject =ID ;
Repeated /subject=id type=AR(1) r rcorr;
Contrast 'Test difference between treat 3 and treat 4 over time'
      time*treatment 0 0 0 0 0 0       0 0 0 0 0 0       1 -1 0  0 0    0   -1
1 0   0 0 0,
      time*treatment 0 0 0 0 0 0       0 0 0 0 0 0       1 0 -1  0 0    0   -1
0 1   0 0 0,
      time*treatment 0 0 0 0 0 0       0 0 0 0 0 0       1 0  0 -1 0    0   -1
0 0   1 0 0,
      time*treatment 0 0 0 0 0 0       0 0 0 0 0 0       1 0  0 0 -1 0   -1 0 0
      0 1 0,
```

```
      time*treatment 0 0 0 0 0 0       0 0 0 0 0 0       1 0  0 0 0 -1   -1 0 0
      0 0 1;
Contrast 'Test difference between treat 2 and treat 4 over time'
            time*treatment 0 0 0 0 0 0      1 -1 0   0 0    0   0 0 0 0 0 0  -1
1 0   0 0 0,
            time*treatment 0 0 0 0 0 0      1 0 -1   0 0    0   0 0 0 0 0 0  -1
0 1   0 0 0,
            time*treatment 0 0 0 0 0 0      1 0  0 -1 0     0   0 0 0 0 0 0  -1
0 0   1 0 0,
            time*treatment 0 0 0 0 0 0      1 0  0 0 -1  0   0 0 0 0 0 0  -1 0
0     0 1 0,
            time*treatment 0 0 0 0 0 0      1 0  0 0 0  -1    0 0 0 0 0 0  -1 0
0     0 0 1;
Estimate '8 week-BL, treat 4 vs. treat 1'
      time*treatment 1 -1 0 0 0 0     0 0 0 0 0 0       0 0 0   0 0    0   -1
1 0   0 0 0 /cl;
Estimate '8 week-BL, treat 4 vs. treat 2'
      time*treatment 0 0 0 0 0 0      1 -1 0 0 0 0      0 0 0   0 0    0   -1
1 0   0 0 0 /cl;
Estimate '8 week-BL, treat 4 vs. treat 3'
      time*treatment 0 0 0 0 0 0      0 0 0 0 0 0       1 -1 0  0 0    0   -1
1 0   0 0 0 /cl;
Run;
proc mixed data=CD4C;
Class ID Treatment Gender time;
Model logCD4 = treatment age gender time time*treatment  / solution outp= pred;
Random intercept  / subject =ID ;
Repeated /subject=id type=AR(1) r rcorr;
lsmeans time;
Run;
proc mixed data=CD4C;
Class ID Treatment Gender time;
Model logCD4 = treatment age gender time time*treatment  / solution outp= pred;
Random intercept  / subject =ID ;
Repeated /subject=id type=CS r rcorr;
lsmeans treatment age gender time time*treatment;
contrast 'linear' time -5 -3 -1 1  3 5;
contrast 'quadartic' time 5 -1 -4 -4  -1 5;
contrast 'cubic' time -5 7 4 -4  -7 5;
contrast 'lxl'    time*treatment -5 -3 -1 1  3 5   5 3 1 -1 -3 -5  0 0 0 0 0 0
0 0 0 0 0 0,
                       time*treatment -5 -3 -1 1  3 5   0 0 0 0 0 0    5 3 1 -
1 -3 -5  0 0 0 0 0 0,
                       time*treatment -5 -3 -1 1  3 5   0 0 0 0 0 0    0 0 0 0
0 0    5 3 1 -1 -3 -5;
contrast 'qxq'    time*treatment 5 -1 -4 -4 -1 5  -5 1  4 4 1 -5   0 0 0 0 0 0
0 0 0 0 0 0,
                       time*treatment 5 -1 -4 -4 -1 5  0 0 0 0 0 0    -5 1  4
4 1 -5  0 0 0 0 0 0,
                       time*treatment 5 -1 -4 -4 -1 5  0 0 0 0 0 0   0 0 0 0 0
0   -5 1  4 4 1 -5;
Run;
proc sort data = pred;
by treatment time;
run;
proc summary data = pred;
by treatment time;
var pred;
output out = means (drop = _:) mean = mean ;
run;
Proc print data=means;
```

```
run;
title1 'Predicted logCD4 among 4 treatments';
title2 'Time: class variable';
axis1 order =(0 to 40 by 5);
axis2 order=(2.2 to 3.6 by 0.05) label=(a=90);
symbol1 c=black i=j v=none h=0.8 line=1 WIDTH=2;
symbol2 c=red i=j v=none h=0.8 line=2 WIDTH=2;
symbol3 c=blue i=j v=none h=0.8 line=2 WIDTH=2;
symbol4 c=green i=j v=none h=0.8 line=3 WIDTH=2;
legend label=none value=(h=2 font=swiss 'Placebo + DDI'
'ZDV + DDI' 'ZDV + DDC' 'ZDV + DDI + DDC')
position=(top right inside) mode=share cborder=black;
proc gplot data=means;
  plot  mean*time=treatment /overlay haxis=axis1 vaxis=axis2 legend = legend1;
  label Week='Week';
  label mean='Log of CD4 count';
run;
proc mixed data=CD4C;
Class ID Treatment Gender time;
Model logCD4 = treatment age gender time time*treatment  / solution outp= pred;
Random intercept  / subject =ID ;
Repeated /subject=id type=AR(1) r rcorr;
run;
proc mixed data=CD4C method=ml;
Class ID Treatment Gender time;
Model logCD4 = treatment age gender time time*treatment  / solution outp= pred;
Random intercept  / subject =ID ;
Repeated /subject=id type=AR(1) r rcorr;
run;
****mixed regresion: time as a continuous variable ****;
****Linear & random intercept****;
proc mixed data=CD4C method=ml;
Class ID Treatment Gender;
Model logCD4 = treatment age gender week week*treatment  / solution;
Random intercept /subject =ID ;
Repeated /subject=id  type=AR(1) r rcorr;
Run;
****Quardratic & random intercept ****;
proc mixed data=CD4C method=ml;
Class ID Treatment Gender;
Model logCD4 = treatment age gender week week*treatment week*week
week*week*treatment / solution;
Random intercept / subject =ID ;
Repeated /subject=id type=AR(1) r rcorr;
Run;
****Cubic & random intercept****;
proc mixed data=CD4C method=ml;
Class ID Treatment Gender;
Model logCD4 = treatment age gender week week*treatment week*week
week*week*treatment week*week*week  week*week*week*treatment / solution;
Random intercept / subject =ID ;
Repeated /subject=id type=AR(1) r rcorr;
Run;
****Quartic & random intercept****;
proc mixed data=CD4C method=ml;
Class ID Treatment Gender;
Model logCD4 = treatment age gender week week*treatment week*week
week*week*treatment week*week*week  week*week*week*treatment
week*week*week*week  week*week*week*week*treatment/ solution;
Random intercept / subject =ID ;
Repeated /subject=id type=AR(1) r rcorr;
```

```
Run;
****Linear, random intercept & slope****;
proc mixed data=CD4C method=ml;
Class ID Treatment Gender;
Model logCD4 = treatment age gender week week*treatment  / solution;
Random intercept week/subject =ID ;
Repeated /subject=id  type=AR(1) r rcorr;
Run;
****Quardratic & random intercept & slope ****;
proc mixed data=CD4C method=ml;
Class ID Treatment Gender;
Model logCD4 = treatment age gender week week*treatment week*week
week*week*treatment / solution;
Random intercept week/ subject =ID ;
Repeated /subject=id type=AR(1) r rcorr;
Run;
****Cubic & random intercept & slope****;
proc mixed data=CD4C method=ml;
Class ID Treatment Gender;
Model logCD4 = treatment age gender week week*treatment week*week
week*week*treatment week*week*week  week*week*week*treatment / solution;
Random intercept week/ subject =ID ;
Repeated /subject=id type=AR(1)  r rcorr;
Run;
****Quartic & random intercept & slope****;
proc mixed data=CD4C method=ml;
Class ID Treatment Gender;
Model logCD4 = treatment age gender week week*treatment week*week
week*week*treatment week*week*week  week*week*week*treatment
week*week*week*week  week*week*week*week*treatment/ solution;
Random intercept week/ subject =ID ;
Repeated /subject=id type=AR(1)  r rcorr;
Run;
****Linear, random intercept & slope with UN for G****;
proc mixed data=CD4C method=ml;
Class ID Treatment Gender;
Model logCD4 = treatment age gender week week*treatment  / solution;
Random intercept week/Type=UN subject =ID ;
Repeated /subject=id  type=AR(1) r rcorr;
Run;
****quardratic with different structure for G matrix****;
proc mixed data=CD4C method=ml;
Class ID Treatment Gender;
Model logCD4 = treatment age gender week week*treatment week*week
week*week*treatment / solution;
Random intercept  week / Type=UN subject =ID v g;
Repeated /subject=id type=AR(1) r rcorr;
Run;
proc mixed data=CD4C method=ml;
Class ID Treatment Gender;
Model logCD4 = treatment age gender week week*treatment week*week
week*week*treatment
week*week*week  week*week*week*treatment/ solution;
Random intercept  week / Type=UN subject =ID v g;
Repeated /subject=id type=AR(1) r rcorr;
Run;
proc mixed data=CD4C method=ml;
Class ID Treatment Gender;
Model logCD4 = treatment age gender week week*treatment week*week
week*week*treatment
week*week*week  week*week*week*treatment
```

```
week*week*week*week  week*week*week*week*treatment
/ solution;
Random intercept  week / Type=UN subject =ID v g;
Repeated /subject=id type=AR(1) r rcorr;
Run;
****quardratic with different structure for errors****;
proc mixed data=CD4C method=ml;
Class ID Treatment Gender;
Model logCD4 = treatment age gender week week*treatment week*week
week*week*treatment / solution;
Random intercept  week /type= UN subject =ID v g;
Repeated /subject=id  Type=UN r rcorr;
Run;
proc mixed data=CD4C method=ml;
Class ID Treatment Gender;
Model logCD4 = treatment age gender week week*treatment week*week
week*week*treatment / solution;
Random intercept  week /type= UN subject =ID v g;
Repeated /subject=id  Type=CS r rcorr;
Run;
proc mixed data=CD4C method=ml;
Class ID Treatment Gender;
Model logCD4 = treatment age gender week week*treatment week*week
week*week*treatment / solution;
Random intercept  week /type= UN subject =ID v g;
Repeated /subject=id  type=AR(1) r rcorr;
Run;
proc mixed data=CD4C method=ml;
Class ID Treatment Gender;
Model logCD4 = treatment age gender week week*treatment week*week
week*week*treatment / solution;
Random intercept  week /type= UN subject =ID v g;
Repeated /subject=id  type=sp(pow)(week) r rcorr;
Run;
****Mixed regression with spline terms******;
data CD4C;
set CD4C;
s1=max (0, (week-8));
s2=max (0, (week-16));
s3=max (0, (week-24));
run;
proc mixed data=CD4C method=ml;
Class ID Treatment Gender ;
Model logCD4 = treatment age gender week s1 week*treatment s1*treatment  /
solution;
Random intercept  week s1/type= UN subject =ID v g;
Repeated /subject=id  type=Ar(1) r rcorr;
Run;
proc mixed data=CD4C method=ml;
Class ID Treatment Gender ;
Model logCD4 = treatment age gender week s1 week*treatment s1*treatment  /
solution;
Random intercept  week /type= VC subject =ID v g;
Repeated /subject=id  type=Ar(1) r rcorr;
Run;
****Mixed regression with spline terms, quadratic ******;
proc mixed data=CD4C method=ml;
Class ID Treatment Gender ;
Model logCD4 = treatment age gender week s1 week*treatment s1*treatment
week*week s1*s1 s1*s1*treatment/ solution;
Random intercept  week s1/type= UN subject =ID v g;
```

```
Repeated /subject=id  type=Ar(1) r rcorr;
Run;
****Mixed regression with spline terms******;
proc mixed data=CD4C method=ml;
Class ID Treatment Gender ;
Model logCD4 = treatment age gender week s1 week*treatment s1*treatment  /
solution ;
Random intercept  week s1/type= UN subject =ID v g;
Repeated /subject=id  type=Ar(1) r rcorr;
Run;
data CD4d;
set CD4c;
if treatment=4 then treatment4=1;
else treatment4=0;
run;
proc mixed data=CD4C_new method=ml;
Class ID Treatment time Gender ;
Model logCD4 = treatment age gender time time*treatment / solution outp=
result2 ;
Random intercept week/ subject =ID v g;
Repeated /subject=id  type=sp(pow)(week) r rcorr;
run;
****Regression with 2 knots ******;
proc mixed data=CD4d;
Class ID Treatment Gender ;
Model logCD4 = treatment age gender week s1 week*treatment s1*treatment s2
s2*treatment/ solution outp= result;
Random intercept  week s1 s2/type=un subject =ID v g;
Repeated /subject=id  type=Ar(1) r rcorr;
Run;
***Predict value by mixed model and check model fit with visual
inspection**********;
***Assume  patients based on the baseline means of variable by
treatments**********;
data new;
 input ID Treatment Age  Gender  Week logCD4 ;
 datalines;
2001  1     37.83 0     0     2.98
2001  1     37.83 0     1     .
2001  1     37.83 0     2     .
2001  1     37.83 0     3     .
2001  1     37.83 0     4     .
2001  1     37.83 0     5     .
2001  1     37.83 0     6     .
2001  1     37.83 0     7     .
2001  1     37.83 0     8     .
2001  1     37.83 0     9     .
2001  1     37.83 0     10    .
2001  1     37.83 0     11    .
2001  1     37.83 0     12    .
2001  1     37.83 0     13    .
2001  1     37.83 0     14    .
2001  1     37.83 0     15    .
2001  1     37.83 0     16    .
2001  1     37.83 0     17    .
2001  1     37.83 0     18    .
2001  1     37.83 0     19    .
2001  1     37.83 0     20    .
2001  1     37.83 0     21    .
2001  1     37.83 0     22    .
2001  1     37.83 0     23    .
```

```
2001  1     37.83 0     24    .
2001  1     37.83 0     25    .
2001  1     37.83 0     26    .
2001  1     37.83 0     27    .
2001  1     37.83 0     28    .
2001  1     37.83 0     29    .
2001  1     37.83 0     30    .
2001  1     37.83 0     31    .
2001  1     37.83 0     32    .
2001  1     37.83 0     33    .
2001  1     37.83 0     34    .
2001  1     37.83 0     35    .
2001  1     37.83 0     36    .
2001  1     37.83 0     37    .
2001  1     37.83 0     38    .
2001  1     37.83 0     39    .
2001  1     37.83 0     40    .
2002  2     37.73 0     0     2.93
2002  2     37.83 0     1     .
2002  2     37.83 0     2     .
2002  2     37.83 0     3     .
2002  2     37.83 0     4     .
2002  2     37.83 0     5     .
2002  2     37.83 0     6     .
2002  2     37.83 0     7     .
2002  2     37.83 0     8     .
2002  2     37.83 0     9     .
2002  2     37.83 0     10    .
2002  2     37.83 0     11    .
2002  2     37.83 0     12    .
2002  2     37.83 0     13    .
2002  2     37.83 0     14    .
2002  2     37.83 0     15    .
2002  2     37.83 0     16    .
2002  2     37.83 0     17    .
2002  2     37.83 0     18    .
2002  2     37.83 0     19    .
2002  2     37.83 0     20    .
2002  2     37.83 0     21    .
2002  2     37.83 0     22    .
2002  2     37.83 0     23    .
2002  2     37.83 0     24    .
2002  2     37.83 0     25    .
2002  2     37.83 0     26    .
2002  2     37.83 0     27    .
2002  2     37.83 0     28    .
2002  2     37.83 0     29    .
2002  2     37.83 0     30    .
2002  2     37.83 0     31    .
2002  2     37.83 0     32    .
2002  2     37.83 0     33    .
2002  2     37.83 0     34    .
2002  2     37.83 0     35    .
2002  2     37.83 0     36    .
2002  2     37.83 0     37    .
2002  2     37.83 0     38    .
2002  2     37.83 0     39    .
2002  2     37.83 0     40    .
2003  3     37.47 0     0     2.91
2003  3     37.47 0     1     .
2003  3     37.47 0     2     .
```

```
2003  3     37.47 0     3     .
2003  3     37.47 0     4     .
2003  3     37.47 0     5     .
2003  3     37.47 0     6     .
2003  3     37.47 0     7     .
2003  3     37.47 0     8     .
2003  3     37.47 0     9     .
2003  3     37.47 0     10    .
2003  3     37.47 0     11    .
2003  3     37.47 0     12    .
2003  3     37.47 0     13    .
2003  3     37.47 0     14    .
2003  3     37.47 0     15    .
2003  3     37.47 0     16    .
2003  3     37.47 0     17    .
2003  3     37.47 0     18    .
2003  3     37.47 0     19    .
2003  3     37.47 0     20    .
2003  3     37.47 0     21    .
2003  3     37.47 0     22    .
2003  3     37.47 0     23    .
2003  3     37.47 0     24    .
2003  3     37.47 0     25    .
2003  3     37.47 0     26    .
2003  3     37.47 0     27    .
2003  3     37.47 0     28    .
2003  3     37.47 0     29    .
2003  3     37.47 0     30    .
2003  3     37.47 0     31    .
2003  3     37.47 0     32    .
2003  3     37.47 0     33    .
2003  3     37.47 0     34    .
2003  3     37.47 0     35    .
2003  3     37.47 0     36    .
2003  3     37.47 0     37    .
2003  3     37.47 0     38    .
2003  3     37.47 0     39    .
2003  3     37.47 0     40    .
2004  4     37.89 0     0     2.84
2004  4     37.89 0     1     .
2004  4     37.89 0     2     .
2004  4     37.89 0     3     .
2004  4     37.89 0     4     .
2004  4     37.89 0     5     .
2004  4     37.89 0     6     .
2004  4     37.89 0     7     .
2004  4     37.89 0     8     .
2004  4     37.89 0     9     .
2004  4     37.89 0     10    .
2004  4     37.89 0     11    .
2004  4     37.89 0     12    .
2004  4     37.89 0     13    .
2004  4     37.89 0     14    .
2004  4     37.89 0     15    .
2004  4     37.89 0     16    .
2004  4     37.89 0     17    .
2004  4     37.89 0     18    .
2004  4     37.89 0     19    .
2004  4     37.89 0     20    .
2004  4     37.89 0     21    .
2004  4     37.89 0     22    .
```

```
2004  4     37.89 0     23    .
2004  4     37.89 0     24    .
2004  4     37.89 0     25    .
2004  4     37.89 0     26    .
2004  4     37.89 0     27    .
2004  4     37.89 0     28    .
2004  4     37.89 0     29    .
2004  4     37.89 0     30    .
2004  4     37.89 0     31    .
2004  4     37.89 0     32    .
2004  4     37.89 0     33    .
2004  4     37.89 0     34    .
2004  4     37.89 0     35    .
2004  4     37.89 0     36    .
2004  4     37.89 0     37    .
2004  4     37.89 0     38    .
2004  4     37.89 0     39    .
2004  4     37.89 0     40    .;
 run;
data new;
set new;
s1=max (0, (week-8));
run;
data CD4C_new;
 set CD4C new;
 run;
*****Treat therapies sepearatly in regression*******;
Data CD4C_new1;
set CD4C_new;
If treatment=1 then treatment1=1;else treatment1=0;
If treatment=2 then treatment2=1;else treatment2=0;
If treatment=3 then treatment3=1; else treatment3=0;
If treatment=4 then treatment4=4; else treatment4=0;
run;
proc mixed data=CD4C_new1 method=ml;
Class ID Treatment Gender ;
Model logCD4 = treatment1 treatment2 treatment3 treatment4 age gender week
week*treatment1 week*treatment2 week*treatment3 week*treatment4
 s1*treatment2 s1*treatment3
week*week*treatment4  week*week*week*treatment4 week*week*week*week*treatment4
/ solution outp= result001 ;
Random intercept  week s1/type= UN subject =ID v g;
Repeated /subject=id  type=sp(pow)(week) r rcorr;
run;
***Predict value by the mixed model with lowest AIC **********;
Data pred001;
set result001;
if ID <2000 then pred=.;
time=week;
run;
title 'Log-transformed CD4 counts by 4 treatments';
axis1 order =(0 to 40 by 5);
axis2 order=(2 to 3.6 by 0.2) label=(a=90);
symbol1 c=black i=j v=none h=0.8 line=1 WIDTH=2;
symbol2 c=red i=j v=none h=0.8 line=2 WIDTH=2;
symbol3 c=blue i=j v=none h=0.8 line=2 WIDTH=2;
symbol4 c=green i=j v=none h=0.8 line=3 WIDTH=2;
legend label=none value=(h=2 font=swiss 'Placebo + DDI'
'ZDV + DDI' 'ZDV + DDC' 'ZDV + DDI + DDC')
position=(top right inside) mode=share cborder=black;
proc gplot data=pred001;
```

```
  plot  Pred*week=treatment /overlay haxis=axis1 vaxis=axis2 legend = legend1;
  label Week='Week';
  label Pred='Log of CD4 count';
run;
**********continue to explore models since model with lowest AIC does not match
well the trend shown on scatter plot********;
proc mixed data=CD4C_new1 method=ml;
Class ID Treatment Gender ;
Model logCD4 = treatment age gender
week week*week week*week*week  week*week*week*week
week*treatment week*week*treatment  week*week*week*treatment
week*week*week*week*treatment
/ solution;
Random intercept  week s1/type= UN subject =ID v g;
Repeated /subject=id  type=sp(pow)(week) r rcorr;
run;
proc mixed data=CD4C_new1;
Class ID Treatment Gender ;
Model logCD4 = treatment age gender
week week*week week*week*week  week*week*week*week
week*treatment week*week*treatment  week*week*week*treatment
week*week*week*week*treatment
/ solution outp= result002 ;
Random intercept  week s1/type= UN subject =ID v g;
Repeated /subject=id  type=sp(pow)(week) r rcorr;
run;
Data pred002;
set result002;
if ID <2000 then pred=.;
time=week;
run;
title 'Log-transformed CD4 counts by 4 treatments';
axis1 order =(0 to 40 by 5);
axis2 order=(2 to 3.6 by 0.2) label=(a=90);
symbol1 c=black i=j v=none h=0.8 line=1 WIDTH=2;
symbol2 c=red i=j v=none h=0.8 line=2 WIDTH=2;
symbol3 c=blue i=j v=none h=0.8 line=2 WIDTH=2;
symbol4 c=green i=j v=none h=0.8 line=3 WIDTH=2;
legend label=none value=(h=2 font=swiss 'Placebo + DDI'
'ZDV + DDI' 'ZDV + DDC' 'ZDV + DDI + DDC')
position=(top right inside) mode=share cborder=black;
proc gplot data=pred002;
  plot  Pred*week=treatment /overlay haxis=axis1 vaxis=axis2 legend = legend1;
  label Week='Week';
  label Pred='Log of CD4 count';
run;
title 'Predicted log-transformed CD4 counts by 4 treatments';
axis1 order =(0 to 40 by 5);
axis2 order=(2.2 to 3.6 by 0.2) label=(a=90);
symbol1 c=black i=j v=none h=0.8 line=1 WIDTH=2;
symbol2 c=red i=j v=none h=0.8 line=2 WIDTH=2;
symbol3 c=blue i=j v=none h=0.8 line=2 WIDTH=2;
symbol4 c=green i=j v=none h=0.8 line=3 WIDTH=2;
legend label=none value=(h=2 font=swiss 'Placebo + DDI'
'ZDV + DDI' 'ZDV + DDC' 'ZDV + DDI + DDC')
position=(top right inside) mode=share cborder=black;
proc gplot data=pred002;
  plot  Pred*week=treatment /overlay haxis=axis1 vaxis=axis2 legend = legend1;
  label Week='Week';
  label Pred='Log of CD4 count';
run;
```

```
**********The above model match well the trend shown in scatter plot********;
**********Estimate with overall best fit model********;
proc mixed data=CD4C_new1;
Class ID Treatment Gender ;
Model logCD4 = treatment age gender
week week*week week*week*week  week*week*week*week
week*treatment week*week*treatment  week*week*week*treatment
week*week*week*week*treatment
/ solution;
Random intercept  week s1/type= UN subject =ID v g;
Repeated /subject=id  type=sp(pow)(week) r rcorr;
ESTIMATE "Treat1: 8 week vs 0 week " week 8 week*week 64 week*week*week 512
week*week*week*week 4096
week*treatment 8 0 0 0 week*week*treatment 64 0 0 0 week*week*week*treatment 512
0 0 0  week*week*week*week*treatment 4096 0 0 0 /cl;
ESTIMATE "Treat2: 8 week vs 0 week " week 8 week*week 64 week*week*week 512
week*week*week*week 4096
week*treatment 0 8 0 0 week*week*treatment 0 64  0 0 week*week*week*treatment 0
512  0 0  week*week*week*week*treatment 0 4096 0 0 /cl;
ESTIMATE "Treat3: 8 week vs 0 week" week 8 week*week 64 week*week*week 512
week*week*week*week 4096
week*treatment 0 0 8 0 week*week*treatment 0 0 64 0 week*week*week*treatment 0 0
512 0  week*week*week*week*treatment 0 0 4096 0 /cl;
ESTIMATE "Treat1: 16 week vs 0 week " week 16 week*week 256 week*week*week 4096
week*week*week*week 65536
week*treatment 16 0 0 0 week*week*treatment 256 0 0 0 week*week*week*treatment
4096 0 0 0  week*week*week*week*treatment 65536 0 0 0 /cl;
ESTIMATE "Treat2: 16 week vs 0 week " week 16 week*week 256 week*week*week 4096
week*week*week*week 65536
week*treatment 0 16 0 0 week*week*treatment 0 256  0 0 week*week*week*treatment
0 4096  0 0  week*week*week*week*treatment 0 65536 0 0 /cl;
ESTIMATE "Treat3: 16 week vs 0 week" week 16 week*week 256 week*week*week 4096
week*week*week*week 65536
week*treatment 0 0 16 0 week*week*treatment 0 0 256 0 week*week*week*treatment 0
0 4096 0  week*week*week*week*treatment 0 0 65536 0 /cl;
ESTIMATE "Treat1: 24 week vs 0 week " week 24 week*week 576 week*week*week 13824
week*week*week*week 331776
week*treatment 24 0 0 0 week*week*treatment 576 0 0 0 week*week*week*treatment
13824 0 0 0  week*week*week*week*treatment 331776 0 0 0 /cl;
ESTIMATE "Treat2: 24 week vs 0 week " week 24 week*week 576 week*week*week 13824
week*week*week*week 331776
week*treatment 0 24 0 0 week*week*treatment 0 576  0 0 week*week*week*treatment
0 13824 0 0  week*week*week*week*treatment 0 331776 0 0 /cl;
ESTIMATE "Treat3: 24 week vs 0 week" week 24 week*week 576 week*week*week 13824
week*week*week*week 331776
week*treatment 0 0 24 0 week*week*treatment 0 0 576 0 week*week*week*treatment 0
0 13824 0  week*week*week*week*treatment 0 0 331776 0 /cl;
ESTIMATE "Treat1: 32 week vs 0 week " week 32 week*week 1024 week*week*week
32768 week*week*week*week 1048576
week*treatment 32 0 0 0 week*week*treatment 1024 0 0 0 week*week*week*treatment
32768 0 0 0  week*week*week*week*treatment 1048576 0 0 0 /cl;
ESTIMATE "Treat2: 32 week vs 0 week " week 32 week*week 1024 week*week*week
32768 week*week*week*week 1048576
week*treatment 0 32 0 0 week*week*treatment 0 1024  0 0 week*week*week*treatment
0 32768 0 0  week*week*week*week*treatment 0 1048576 0 0 /cl;
ESTIMATE "Treat3: 32 week vs 0 week" week 32 week*week 1024 week*week*week 32768
week*week*week*week 1048576
week*treatment 0 0 32 0 week*week*treatment 0 0 1024 0 week*week*week*treatment
0 0 32768 0  week*week*week*week*treatment 0 0 1048576 0 /cl;
ESTIMATE "Treat1: 40 week vs 0 week " week 40 week*week 1600 week*week*week
64000 week*week*week*week 2560000
```

```
week*treatment 40 0 0 0 week*week*treatment 1600 0 0 0 week*week*week*treatment
64000 0 0 0  week*week*week*week*treatment 256000 0 0 0 /cl;
ESTIMATE "Treat2: 40 week vs 0 week " week 40 week*week 1600 week*week*week
64000 week*week*week*week 2560000
week*treatment 0 40 0 0 week*week*treatment 0 1600  0 0 week*week*week*treatment
0 64000 0 0  week*week*week*week*treatment 0 2560000 0 0 /cl;
ESTIMATE "Treat3: 40 week vs 0 week" week 40 week*week 1600 week*week*week 64000
week*week*week*week 2560000
week*treatment 0 0 40 0 week*week*treatment 0 0 1600 0 week*week*week*treatment
0 0 64000 0  week*week*week*week*treatment 0 0 2560000 0 /cl;
run;
**********Since SAS could not estimate treatment 4 in the above model, the
reference group as changed to treatment 1********;
Data CD4C_new2;
set CD4C_new1;
If treatment =1 then group=4;
If treatment =2 then group=3;
If treatment =3 then group=2;
If treatment =4 then group=1;
run;
proc mixed data=CD4C_new2;
Class ID group Gender ;
Model logCD4 = group age gender
week week*week week*week*week  week*week*week*week
week*group week*week*group  week*week*week*group  week*week*week*week*group
/ solution;
Random intercept  week s1/type= UN subject =ID v g;
Repeated /subject=id  type=sp(pow)(week) r rcorr;
ESTIMATE "Treat4: 8 week vs 0 week " week 8 week*week 64 week*week*week 512
week*week*week*week 4096
week*group 8 0 0 0 week*week*group 64 0 0 0 week*week*week*group 512 0 0 0
week*week*week*week*group 4096 0 0 0 /cl;
ESTIMATE "Treat4: 16 week vs 0 week " week 16 week*week 256 week*week*week 4096
week*week*week*week 65536
week*group 16 0 0 0 week*week*group 256 0 0 0 week*week*week*group 4096 0 0 0
week*week*week*week*group 65536 0 0 0 /cl;
ESTIMATE "Treat4: 24 week vs 0 week " week 24 week*week 576 week*week*week 13824
week*week*week*week 331776
week*group 24 0 0 0 week*week*group 576 0 0 0 week*week*week*group 13824 0 0 0
week*week*week*week*group 331776 0 0 0 /cl;
ESTIMATE "Treat4: 32 week vs 0 week " week 32 week*week 1024 week*week*week
32768 week*week*week*week 1048576
week*group 32 0 0 0 week*week*group 1024 0 0 0 week*week*week*group 32768 0 0 0
week*week*week*week*group 1048576 0 0 0 /cl;
ESTIMATE "Treat4: 40 week vs 0 week " week 40 week*week 1600 week*week*week
64000 week*week*week*week 2560000
week*group 40 0 0 0 week*week*group 1600 0 0 0 week*week*week*group 64000 0 0 0
week*week*week*week*group 256000 0 0 0 /cl;
Contrast "8 week: Treat 4 Vs 2" group -1 0 1 0
week*group -8 0 8  0 week*week*group -64 0 64 0 week*week*week*group -512  0 512
0  week*week*week*week*group -4096 0 4096 0;
Contrast "8 week: Treat 4 Vs 3" group -1 1 0 0
week*group -8 8  0 0 week*week*group -64  64 0 0 week*week*week*group -512 512 0
0  week*week*week*week*group -4096  4096 0 0;
Contrast "40 week: Treat 4 Vs 2" group -1 0 1 0
week*group -40 0 40  0 week*week*group -1600 0 1600 0 week*week*week*group -6400
0 6400 0  week*week*week*week*group -256000 0 256000 0;
Contrast "40 week: Treat 4 Vs 3" group -1 1 0 0
week*group -40 40  0 0 week*week*group -1600 1600 0 0 week*week*week*group -6400
6400 0 0  week*week*week*week*group -256000  256000 0 0;
run;
```