CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

207561Orig1s000

STATISTICAL REVIEW(S)

STATISTICAL REVIEW AND EVALUATION

NDA#:	207561 SDN 000
DRUG NAME:	Genvoya™ or Elvitegravir/Cobicistat/ Emtricitibine/Tenofovir Alafenamide FDC
INDICATION:	Treatment of HIV Infection
TYPE OF REVIEW:	Clinical
APPLICANT:	Gilead
DATES:	Nov. 5, 2014
REVIEW PRIORITY:	Priority
BIOMETRICS DIVISION:	Division of Biometrics IV
STATISTICAL REVIEWER:	Thomas Hammerstrom, (HFD-725)
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STATISTICAL REVIEW AND EVALUATION

NDA#: 207561

1. Executive Summary

The applicant has conducted five trials to test the efficacy of Tenofovir Alafenamide as part of the FDC (fixed dose combination) E/C/F/TAF (Elvitegravir/Cobicistat/Emtricitibine/Tenofovir Alafenamide) in the treatment of HIV-1 for patients over the age of 12 without prior failure on anti-retroviral treatment. These include three phase 3 trials, one phase 2 trial, and one small, uncontrolled, pediatric study.

The first three components are already approved drugs so the main issue in this NDA is the efficacy of TAF at 10 mg qd compared to Tenofovir Disoproxil Fumarate, TDF, at 300 mg qd. The comparator drug is all four trials is Stribild (STB) which is Elvitegravir/Cobicistat /Emtricitibine/Tenofovir Disoproxil Fumarate in an FDC. I.e. the only difference in the regimens is the switch of TDF to TAF.

Phase 3 trials 292-0104 and 292-0111 and phase 2 trial 292-0102 compared (E/C/F/TAF) to Stribild (Elvitegravir/Cobicistat /Emtricitibine/Tenofovir Disoproxil Fumarate, STB) in treatment naïve adults. Phase 3 trial 292-0109 was a switch trial in which adults who were visibly suppressed on STB were randomized to either switch to (E/C/F/TAF) or continue their successful STB regimen. Trial 292-0106 was a small (48 subjects), open label, single arm study on subjects 12 to 18. This trial is the only clinical efficacy study supplementing the PK/PD data in support of pediatric efficacy.

In three trials on previously untreated adults, the applicant demonstrated that once daily E/C/F/TAF was, with high statistical confidence, between 5% worse and 10% better than the control regimen of Stribild (=E/C/F/TDF) with respect to viral suppression at 48 weeks.

In all three of these trials, both regimens also showed improvements in CD4 counts from about 550 cells/ml to about 650-700. In the two large, phase 3 trials, the difference in change was, with high confidence, between 40 cells worse and 40 cells better for E/C/F/TAF. The smaller phase 2 trial had similar point estimates but wider confidence intervals for the difference.

In addition, in a trial in which virally suppressed adults on their first regimen (Stribild, Atripla, or Ritonavir-boosted

Atazanavir plus Truvada) were switched to E/C/F/TAF, patients maintained viral suppression at over 90% and maintained CD4 counts around 700 cells/ml in both regimens. With high confidence, E/C/F/TAF was between 4% worse and 2% better in percent with viral suppression and between 20 cells worse and 40 cells better in CD4 count.

Finally, a small uncontrolled trial in 12-18 year olds showed comparable efficacy to adults on the E/C/F/TAF arms in the four controlled trials. Further information on efficacy in adolescents is in the pharmacological review.

Overall, the applicant has provided adequate evidence to support the efficacy of E/C/F/TAF in the treatment of HIV-1 infected subjects over the age of 12 and without prior failure to an anti-retroviral treatment.

2. Introduction

2.1 Overview

The applicant submitted five trials in support of the efficacy of Tenofovir Alafenamide as part of multi-drug FDC regimen for the treatment of HIV-1. These trials include three phase 3 trials, one phase 2 trial, and one small, uncontrolled, pediatric study. They all test the efficacy of the fixed dose combination (FDC) of Elvitegravir/Cobicistat/Emtricitibine/Tenofovir Alafenamide (E/C/F/TAF) at 150/150/200/10 mg qd in HIV-1 infected patients. The first three components are already approved drugs so the main issue in this NDA is the efficacy of TAF at 10 mg qd compared to Tenofovir Disoproxil Fumarate, TDF, at 300 mg qd. The comparator drug is all four trials is Stribild (STB) which is Elvitegravir/Cobicistat /Emtricitibine/Tenofovir Disoproxil Fumarate in an FDC. I.e. the only difference in the regimens is the switch of TDF to TAF.

Phase 3 trials 292-0104 and 292-0111 and phase 2 trial 292-0102 compared (E/C/F/TAF) to Stribild (Elvitegravir/Cobicistat

/Emtricitibine/Tenofovir Disoproxil Fumarate, STB) in treatment naïve adults. Phase 3 trial 292-0109 was a switch trial in which adults who were visibly suppressed on STB were randomized to either switch to (E/C/F/TAF) or continue their successful STB regimen. Trial 292-0106 was a small (48 subjects), open label, single arm study on subjects 12 to 18. This trial is the only clinical efficacy study supplementing the PK/PD data in support of pediatric efficacy.

2.2 Data Sources

2.2.1 Objectives in Trials

The primary objective of the four trials was to establish the efficacy of Tenofovir Alafenamide as part of multi-drug FDC regimen for the treatment of HIV-1. The fixed dose combination (FDC) being tested was Elvitegravir/Cobicistat/Emtricitibine/Tenofovir Alafenamide (E/C/F/TAF) at 150/150/200/10 mg qd.

2.2.2 Summary of Study Design

Trials 0104 and 0111 were identically designed randomized, active control, double blind, double dummy, multicenter, international trials in treatment naïve subjects. Both intended to randomize 840 subjects in 1:1 ratio to (E/C/F/TAF) or STB. In both trials, the randomization was stratified by screening visit load (<= 100 K, 100-400 K, or >400 K copies/ml), screening CD4 count (<50, 50-200, or >=200 cells/µl), and region (US or non-US).

Both trials actually randomized 872 subjects. In trial 0104, there were 438 on (E/C/F/TAF) and 434 on STB. Subjects were enrolled in a total of 120 study sites: 82 in the US, 9 in Spain, 8 in Canada, 6 in Thailand, 5 in Australia, 3 in Switzerland, 2 in Austria, 2 in Belgium, 1 in Italy, 1 in Japan, and 1 in the UK.

In trial 0111, there were 435 subjects on (E/C/F/TAF) and 437 on STB. Subjects were enrolled in a total of 121 study sites: 82 in the US, 10 in the UK, 9 in France, 5 in Canada, 4 in Italy, 4 in Portugal, 2 in Mexico, 2 in the Netherlands, 2 in Sweden, and 1 in Dominican Republic.

Trial 0102 was also a randomized, active control, double blind, double dummy, multicenter trial in treatment naïve subjects. This

trial intended to randomize 150 subjects in 2:1 ratio to (E/C/F/TAF) or STB. The randomization was stratified by screening visit viral load (<= or > 100 K). They actually randomized 113 subjects to (E/C/F/TAF) and 58 to STB. Subjects were enrolled in a total of 37 study sites: 36 in the US and 1 in Puerto Rico.

This trial had an additional open label phase beyond the double blind phase that ended at the week 48 primary endpoint. Subjects who had been in a different Gilead trial (299-0102, not 292-0102), who were on darunavir (DRV) + cobicistat + emtricitibine/TDF (Truvada), and who had reached their week 48 time point while visibly suppressed were eligible to switch to E/C/F/TAF. This was open label and not randomized.

Trial 0109 was an open-label switch study in which subjects in from a predefined set of Gilead clinical studies and virologically suppressed on one of the four following FTC/TDF regimens:
1. EVG/COBI/FTC/TDF (Stribild; STB)
2. Efavirenz (EFV)/FTC/TDF (Atripla; ATR)
3. COBI-boosted Atazanavir (ATV/co) + FTC/TDF (Truvada; TVD)
4. Ritonavir (RTV)-boosted Atazanavir (ATV/r) + TVD

It was planned that 1500 subjects would be randomized in a 2:1 ratio to
1. Switch to E/C/F/TAF (n = 1000) or
2. Stay on preexisting FTC/TDF+3rd Agent regimen.
Randomization was stratified by prior treatment regimen. This was the only study with treatment-experienced subjects but, since it was a switch study with subjects virally suppressed on their current regimen, it did not include prior treatment failures.

This trial actually randomized 963 subjects to switch to (E/C/F/TAF) and 480 to remain on their current regimen. Subjects were enrolled in a total of 168 study sites: 91 in the US, 9 in Australia, 3 in Austria, 2 in Belgium, 4 in Brazil, 10 in Canada, 1 in Denmark, 1 in Dominican Republic, 8 in France, 10 in Germany, 4 in Italy, 1 in Mexico, 2 in the Netherlands, 2 in Portugal, 3 in Spain, 1 in Sweden, 3 in Switzerland, 5 in Thailand, 5 in the UK, and 3 in Puerto Rico.

At the time of the NDA submission, the trial was not completed so an interim analysis was conducted using only the subjects with 48 weeks of data. This interim analysis was not in the original protocol but because the reason for conducting the analysis was external to the study, the statistical validity of the analysis is not impaired.

Trial 0106 was a small (48 subjects), open label, single arm study on subjects 12 to 18. It was planned to follow subjects for 48 weeks but not all subjects had reached this time point at the time of NDA submission.

2.2.3 Patient Accounting and Baseline Characteristics

The two large phase 3 trials in treatment naïve subjects were 0104 and 0111. Trial 0104 randomized 872 subjects out of 1105 screened; trial 0111 randomized 872 subjects out of 1070 screened. The progress of the subjects is documented in table 2.2.3.1 A.

TABLE 2.2.3.1 A
SUBJECTS' DISPOSITION IN NAÏVE SUBJECTS, PHASE 3

	Trial 0104		Trial 0111	
	E/C/F/TAF	STB	E/C/F/TAF	STB
Randomized	438	434	435	437
Treated	435	432	431	435
Completed treatment	413	400	408	396
Discontinued treatment	22	32	23	39
AE	4	6	4	7
Death	0	0	1	2
LOE	0	2	2	1
LTFU	5	9	10	9
Other	13	15	6	20

The two trials were similar in their baseline demographic and illness characteristics. Subjects in trial 0104 had a median age of 34 years, were 85% male, were 15% Hispanic, and were 58% White and 20% Black. 93% were asymptomatic, 75% had visit load <100_k copies/ml. Median baseline HIV-1 RNA was 4.61 log copies/ml, median baseline CD4 count was 404. 75% identified homosexual activity as their risk factor, 24% heterosexual contact and .7% injectable drug use.

Subjects in trial 0111 had a median age of 34 years, were 85% male, were 24% Hispanic, and were 55% White and 30% Black. 90% were asymptomatic, 78% had visit load <100_k copies/ml. Median baseline HIV-1 RNA was 4.55 log copies/ml, median baseline CD4 count was 406. 74% identified homosexual activity as their risk factor, 26% heterosexual contact.

The phase 2 trial 0102 randomized 171 subjects out of 232 screened. The progress of the subjects is documented in table 2.2.3.1 B.

TABLE 2.2.3.1 B
SUBJECTS' DISPOSITION IN NAÏVE SUBJECTS, PHASE 2

	Trial 0102	
	E/C/F/TAF	STB
Randomized	113	58
Treated	112	58
Completed treatment	105	53
Discontinued treatment	7	5
AE	4	0
Death	0	0
LOE	0	1
LTFU	2	2
Other	1	2

Subjects in trial 0102 had a median age of 34 years, were 97% male, were 21% Hispanic, and were 67% White and 30% Black. 89% were asymptomatic, 79% had visit load <100_k copies/ml. Median baseline HIV-1 RNA was 4.55 log copies/ml, median baseline CD4 count was 391. 89% identified homosexual activity as their risk factor, 13% heterosexual contact, and 0.6% injection drug use. These figures are all similar to the results for the two phase 3 trials, except for the virtual absence of females.

The phase 3 switch trial 0109 randomized 1443 subjects out of 1559 screened. The progress of the subjects is documented in table 2.2.3.1 C.

TABLE 2.2.3.1 C
SUBJECTS' DISPOSITION IN SUBJECTS ON TREATMENT, PHASE 3

	Trial 0109	
	E/C/F/TAF	PREVIOUS THERAPY
Randomized	963	480
Treated	959	477
Continuing treatment	939	447
Discontinued treatment	20	30
AE	9	7
Death	2	0
LOE	1	0
LTFU	3	5
Other	5	18

Subjects in trial 0109 had a median age of 41 years, were 89% male, were 23% Hispanic, and were 67% White and 19% Black. 89% were asymptomatic, 79% had visit load <100_k copies/ml. Subjects are on a stable HIV-suppressive regimen so 98% had undetectable HIV-1 visit load; median baseline CD4 count was 669. 78% identified homosexual activity as their risk factor, 22% heterosexual contact, and 1% injection drug use. Because of their being currently on a successful therapy, these subjects have better HIV and CD4 readings at baseline than in the other three trials. They are also slightly older as would be expected. They are similar to the other trials in sex, race, and self-identified risk factors.

2.2.4 Summary of Methods of Assessment

2.2.4.1 Schedule of Measurements

The two large phase 3 trials (0104 and 0111) both measured HIV-1 RNA (by Ultrasensitive assay) and CD4 count at weeks 2, 4, 8, 12, 16, 24, and then every 12 weeks out to week 96. The phase 2 trial, 0102, had these measurements at weeks 2, 4, 8, 12, 16, 24, then every 8 weeks to week 48 and every 12 weeks thereafter. The phase 3 open-label switch study (0109) used the same schedule as trials 0104 and 0111.

2.2.4.2 Assessment of Treatment Effects

The primary endpoint in both phase 3 trials (0104 and 0111) and in trial 0102 was percent of subjects with undetectable HIV-1 visit load at week 48. The primary endpoints of undetectable visit load was at week 24 for phase 2 trial 0102 but undetectable at week 48 was also examined.

2.2.5 Summary of Statistical Analysis

In both phase 3 trials, the determination of efficacy was based on establishing clinical non-inferiority with a margin of 12%. Both trials had two interim analyses. At either of these, non-inferiority could be claimed if the 99.999% two-sided confidence interval for the difference in suppression rates had a lower bound greater than -12%. At the conclusion of the trial, non-inferiority could be claimed in the 95.002% two-sided confidence interval had a lower bound greater than -12%. These analyses were conducted after 420 subjects had reached week 12 and after all subjects had reached week 24.

The above confidence intervals were computed by the Cochran-Mantel-Haenszel method stratifying by the variables used in the randomization: screening visit load, screening CD4 count, and region.

In the phase 2 trial 0102, there was one interim analysis when all subjects had completed week 12. At the analysis phase, the stratifying variable was changed from screening HIV-1 RNA to baseline HIV-1 RNA. The FDA reviewer remarks that this should have no consequential difference.

2.2.6 Summary of Applicant's Results

2.2.6.1 Trials with Treatment Naïve Patients

The results for trial 0104 are given in tables 2.2.6 A and B. The first table gives the percent with snapshot visit suppression in the two arms at week 48, together with the E/C/F/TAF-STB difference and 95% confidence limits, computed adjusting for the weights in the different strata. Subjects discontinued or switched to other therapy are classified as failures. The second table gives a breakdown of the reasons for failure at week 48. Week 96 data are not yet available for this trial. At week 48, the primary conclusion of non-inferiority of E/C/F/TAF to STB is established.

TABLE 2.2.6 A
TRIAL 0104 HIV RNA RESULTS
OBSERVED HIV-1 RNA<50 C/ML

	E/C/F/TAF	STB	Adjusted Difference	95% Confidence Limits
Week_48	405/435=93%	399/432=92%	1.0%	-2.6%, 4.5%

TABLE 2.2.6 B
TRIAL 0104 HIV RNA RESULTS
SUPPRESSIONS AND FAILURES AT WEEK 48

	E/C/F/TAF	STB
N	435	432
Success	405 93%	399 92%
Missed Week 48		
but on drug	2 0.5%	2 0.5%
>50 by Week 48	12 2.8%	9 2.1%
New ART	1 0.2%	0 0%
Discontinued		
LOE	0 0%	2 0.5%
AE	4 0.9%	5 1.2%
Other	11 2.5%	15 3.5%

The results for trial 0111 are given in tables 2.2.6 C and D. The first table gives the percent with snapshot visit suppression in the two arms at week 48, together with the E/C/F/TAF-STB difference and 95% confidence limits, computed adjusting for the weights in the different strata. At week 48, the primary conclusion of non-inferiority of E/C/F/TAF to STB is confirmed.

TABLE 2.2.6 C
TRIAL 0111 HIV RNA RESULTS
OBSERVED HIV-1 RNA<50 C/ML

	E/C/F/TAF	STB	Adjusted Difference	95% Confidence Limits
Week_48	395/431=92%	385/435=89%	3.1%	-1.0%, 7.1%

TABLE 2.2.6 D
TRIAL 0111 HIV RNA RESULTS
SUPPRESSIONS AND FAILURES AT WEEK 48

	E/C/F/TAF	STB
N	431	435
Success	395 92%	385 89%
Missed Week 48		
but on drug	4 0.9%	1 0.2%
>50 by Week 48	16 2.8%	22 2.1%
New ART	0 0%	1 0.2%
Discontinued		
LOE	2 0.5%	1 0.2%
AE	4 0.9%	9 2.1%
Other	10 2.3%	16 3.7%

The results for phase 2 trial 0102 are given in tables 2.2.6 E and F. The first table gives the percent with snapshot visit suppression in the two arms at week 24 (the protocol specified primary endpoint) and at week 48 (the conventional endpoint for NDAs), together with the E/C/F/TAF-STB difference and 95% confidence limits, computed adjusting for the weights in the different strata. The reasons for failure are given only for week 48.

TABLE 2.2.6 E
TRIAL 0102 HIV RNA RESULTS
OBSERVED HIV-1 RNA<50 C/ML

	E/C/F/TAF	STB	Adjusted Difference	95% Confidence Limits
Week_24	99/112=88%	52/58=90%	-2.9%	-13.5%, 7.7%
Week_48	99/112=88%	51/58=88%	-1.0%	-12.1%, 10.0%

TABLE 2.2.6 F
TRIAL 0102 HIV RNA RESULTS
SUPPRESSIONS AND FAILURES AT WEEK 48

	E/C/F/TAF	STB
N	112	58
Success	99 88%	51 88%
>50 by Week 48	7 6.3%	5 8.6%
Discontinued		
LOE	0 0%	1 1.7%
AE	4 3.6%	0 0%
Other	2 1.8%	1 1.7%

The results for phase 3 switch trial 0109 are given in tables 2.2.6 G and H. The first table gives the percent with snapshot visit suppression in the two arms at week 24 (the protocol specified primary endpoint) and at week 48 (the conventional endpoint for NDAs), together with the E/C/F/TAF-STB difference and 95% confidence limits, computed adjusting for the weights in the different strata. The reasons for failure are given only for week 48.

TABLE 2.2.6 G
TRIAL 0109 HIV RNA RESULTS
OBSERVED HIV-1 RNA<50 C/ML

	E/C/F/TAF	Previous Regimen	Adjusted Difference	95% Confidence Limits
Week_48	764/799=96%	369/397=93%	2.7%	-0.3%, 5.6%

TABLE 2.2.6 F
TRIAL 0102 HIV RNA RESULTS
SUPPRESSIONS AND FAILURES AT WEEK 48

	E/C/F/TAF	STB
N	799	397
Success	764 96%	369 93%
Missed Week 48		
but on drug	13 1.6%	5 1.3%
>50 by Week 48	11 1.4%	20 5.0%
New ARV	2 0.3%	0 0%
Discontinued		
LOE	1 0.1%	0 0%
AE	8 1.0%	3 0.8%

2.2.7 Summary of Applicant's Conclusions

The applicant concluded that once daily E/C/F/TAF was clinically non-inferior to STB with respect to viral suppression at 48 weeks in HIV-1 infected, treatment naïve adults. This was confirmed to a statistically significant extent in two separate trials. Both regimens also showed comparable improvements in CD4 counts. This was further confirmed in a large phase 2 trial with similar subjects and control regimen.

The applicant also concluded that, for HIV-1 patients who were virally suppressed on Stribild, Atripla, or Ritonavir-boosted Atazanavir plus Truvada, switching to E/C/F/TAF resulted in clinically non-inferior viral suppression at 48 weeks after the switch. Again, CD4 counts were also comparable for 48 weeks after the switch.

3. Statistical Evaluation

3.1 Primary Efficacy Results

3.1.1 Replication of Applicant's Primary Results

The FDA reviewer has been able to reproduce the applicant's results nearly exactly. The overall conclusion of clinical and statistical non-inferiority are the same for both the FDA and the applicant's analyses.

TABLE 3.1.1 A
COMPARISON OF APPLICANT AND FDA ANALYSES

	E/C/F/TAF	STB	Adjusted Difference	95% Confidence Limits
0104_Week 48				
App	405/435=93%	399/432=92%	1.0%	-2.6%, 4.5%
FDA	406/435=93.3%	399/432=92.4%	1.0%	-2.5%, 4.4%
0111				
App	395/431=92%	385/435=89%	3.1%	-1.0%, 7.1%
FDA	390/431=90.5%	383/435=88.0%	2.4%	-1.7%, 6.6%
0102_Week_24				
App	99/112=88%	52/58=90%	-2.9%	-13.5%, 7.7%
FDA	97/112=86.6%	50/58=86.2%	0.4%	-10.5%, 11.3%
Week_48				
App	99/112=88%	51/58=88%	-1.0%	-12.1%, 10.0%
FDA	99/112=88.4%	49/58=84.5%	3.9%	-7.1%, 15.0%
0109_Week_48				
App	764/799=96%	369/397=93%	2.7%	-0.3%, 5.6%
FDA	760/799=95.1%	374/397=94.2%	0.9%	-1.8%, 3.7%

3.1.2 Reasons for Failure

Table 3.1 C gives the breakdown of successes and failures by reason in the four trials (0104, 0111, 0109, and 0102). (Here LOE=lack of efficacy, LFTU=lost to follow-up.) These results use the applicant's SAS datasets and are slightly discrepant from the tables in their printed report and reproduced in section 2.2.3 above.

TABLE 3.1 C
OUTCOMES ON VISTB SUPPRESSION WEEK 48

OUTCOME	REASON	TAF	CONTROL
TRIAL_0104			
SUCCESS		406	399
FAILED		29	33
	COMPLETE	9	7
	AE	3	4
	DEATH	1	1
	LOE	0	2
	LTFU	16	19
TRIAL_0111			
SUCCESS		390	383
FAILED		41	52
	COMPLETE	20	17
	AE	3	7
	DEATH	1	2
	LOE	2	1
	LTFU	15	25
TRIAL_0109			
SUCCESS		760	374
FAILED		39	23
TRIAL_0102			
SUCCESS		99	49
FAILED		13	9
	COMPLETE	5	4
	AE	4	0
	LOE	0	1
	LTFU	4	4

3.2 Time Course of Viral Load

The following graphs provide a brief summary of the comparative effects of E/C/F/TAF and the control on HIV levels over time in the four trials considered. For each trial, the first graph gives the point estimates and the 95% confidence intervals for the percent BLQ at each time point for the two arms; the second graph gives the point estimate and the 95% confidence interval for the difference between the E/C/F/TAF minus the STB arm in percent BLQ; the third graph gives the point estimates and the 95% confidence intervals for the observed log HIV levels; and the fourth graph gives the point estimate and the 95% confidence limits for the difference between the E/C/F/TAF minus the STB arm in observed log HIV RNA level.

One will notice that in every one of the four trials, there was heavy overlap between the TAF and STB (or, in trial 0109, pool of 5 controls), both with respect to percent BLQ and actual log HIV RNA levels. The lower confidence limit for the difference between TAF and control with respect to percent BLQ is consistently above -5% (except out late in the trial, week 60 or later, where the sample size is small). With respect to log HIV RNA, the lower confidence limit is closer to -.5 than to -.1 consistently, except for the smaller trial 0102 and the late weeks (60 and beyond) for the other trials. In addition, the point estimates for the differences are consistently close to zero. Finally, the point estimates for percent BLQ on TAF are in the mid 90%'s to high 80%'s with fairly narrow limits. Collectively, these graphs provide ample support for the contention of clinical non-inferiority.

Trial 104 results:

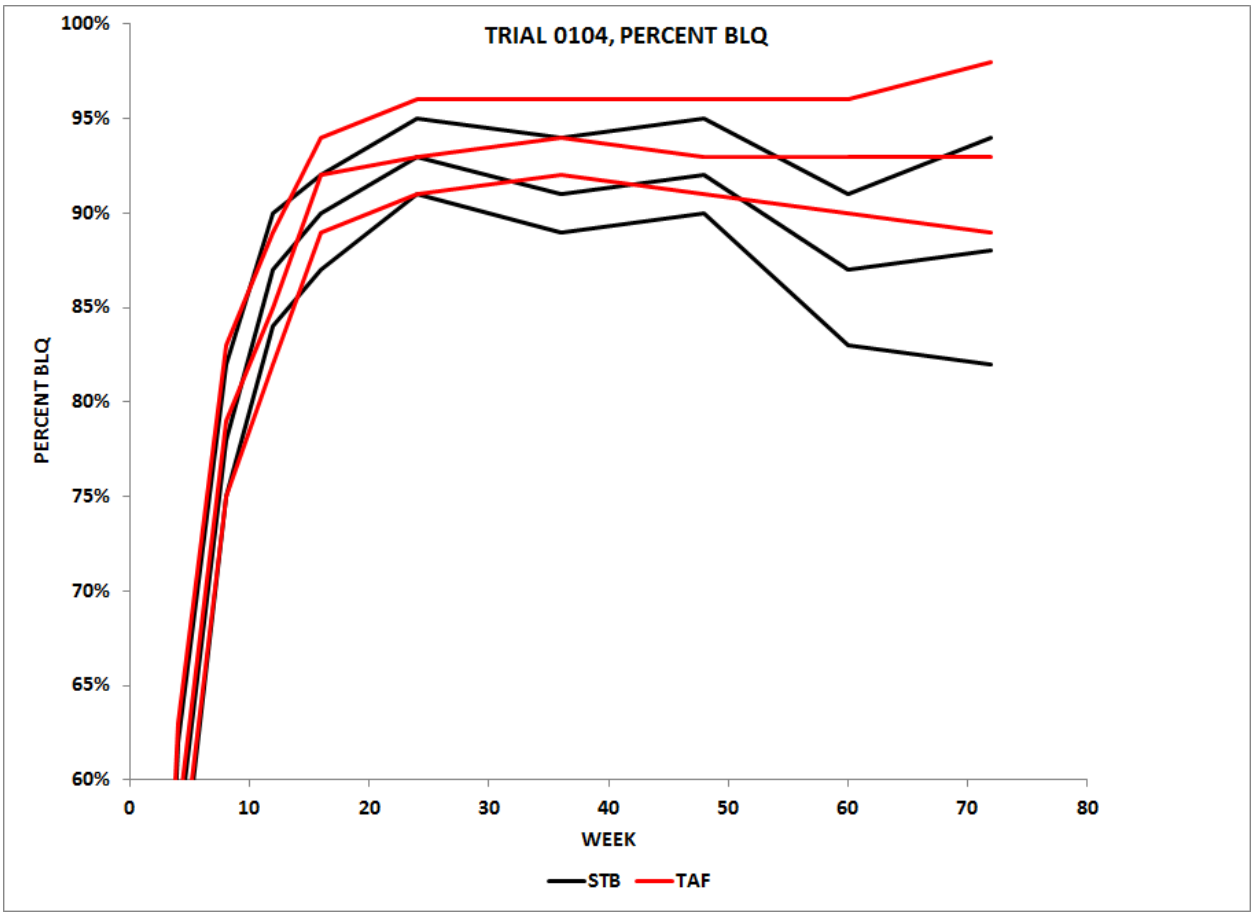


Figure 3.2 A

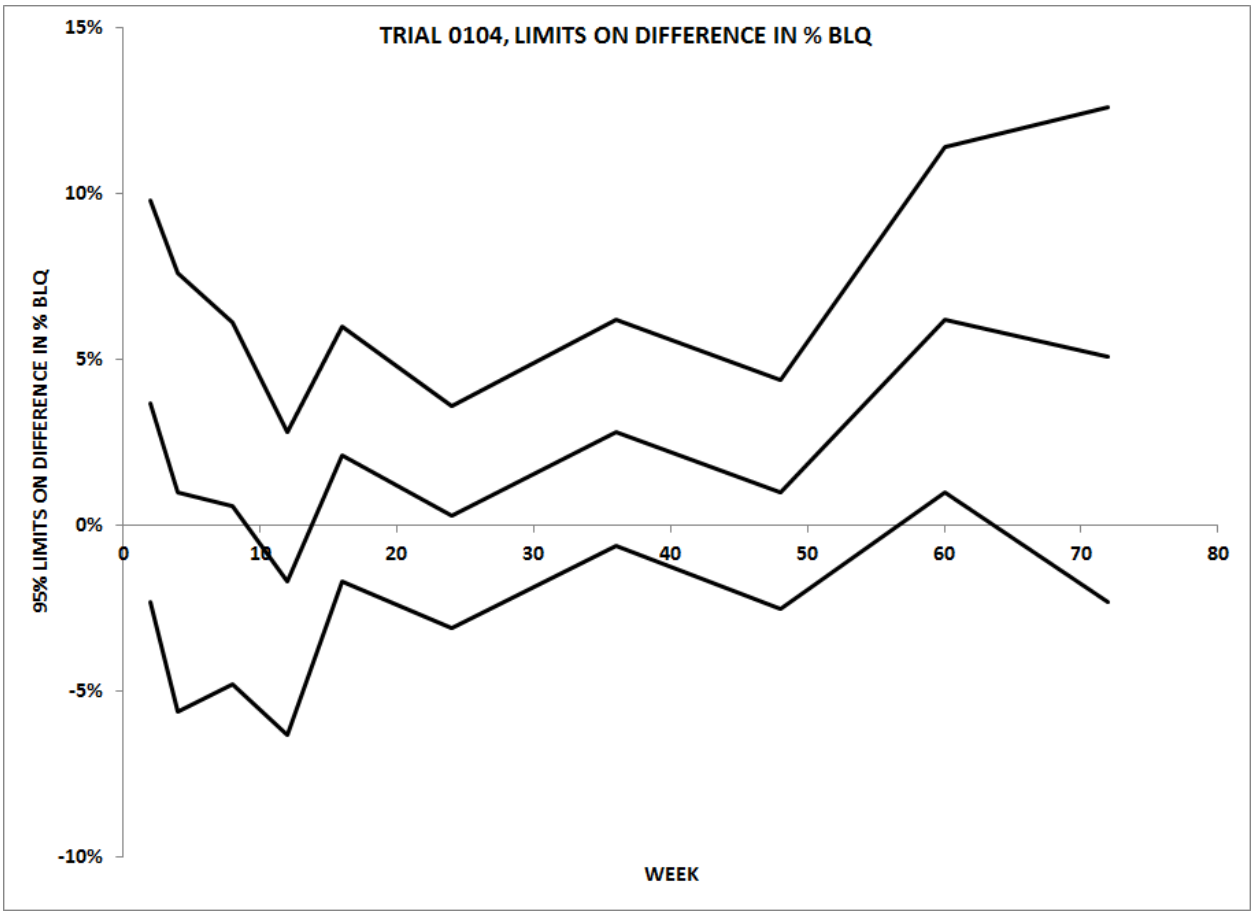


Figure 3.2 B

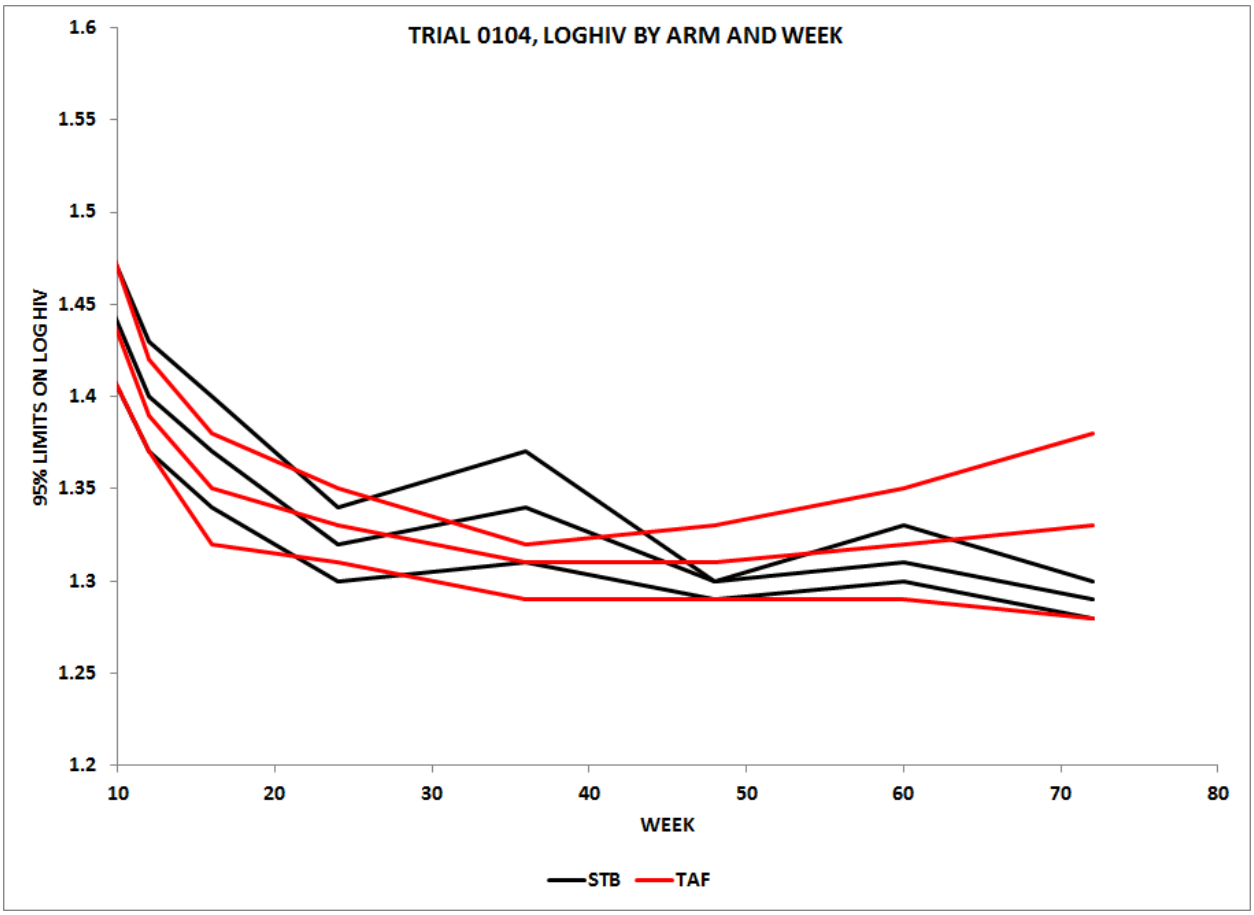


Figure 3.2 C

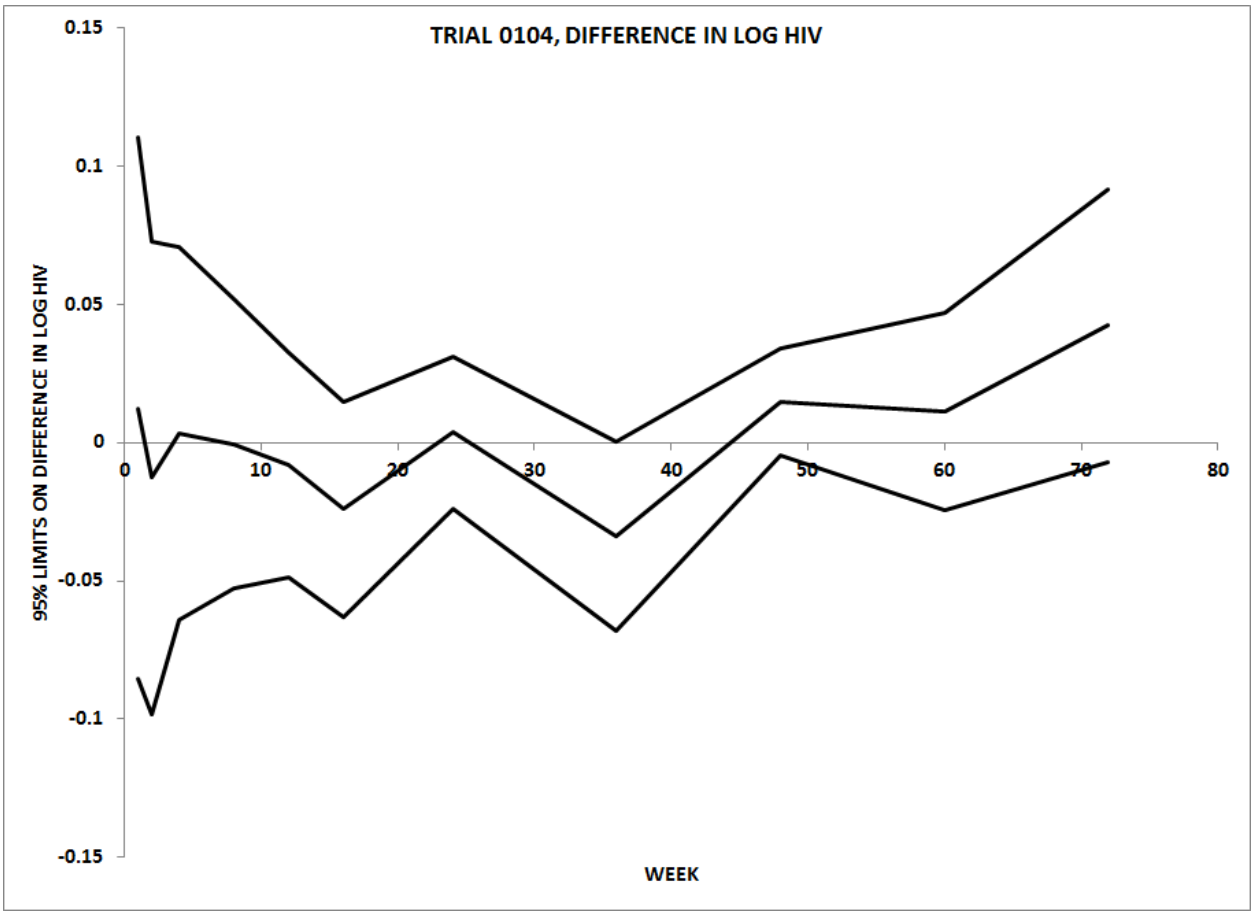


Figure 3.2 D

Trial 111 results:

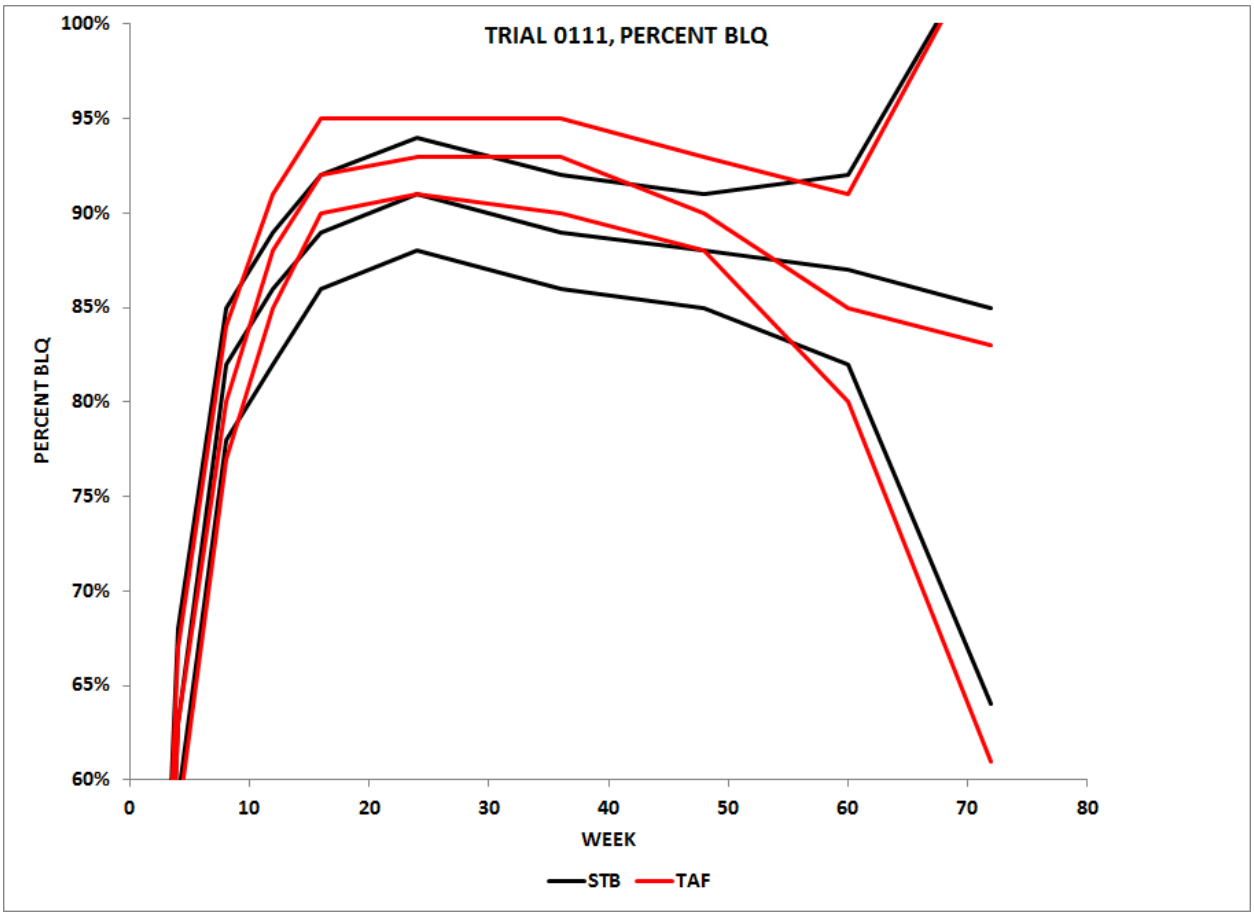


Figure 3.2 E

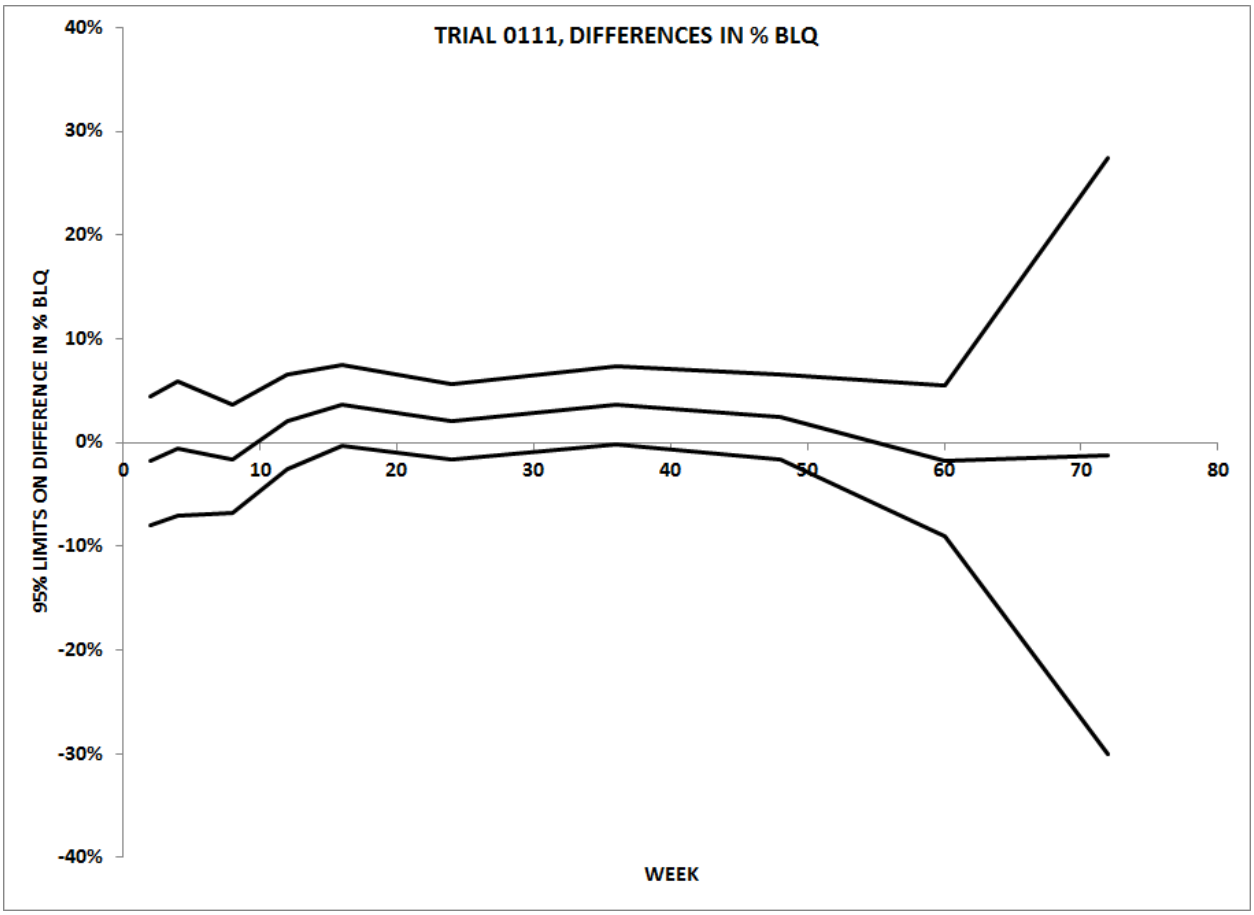

TRIAL 0111, DIFFERENCES IN % BLQ
95% LIMITS ON DIFFERENCE IN % BLQ
40%
30%
20%
10%
0%
-10%
-20%
-30%
-40%
0
10
20
30
40
50
60
70
80
WEEK

Figure 3.2 F

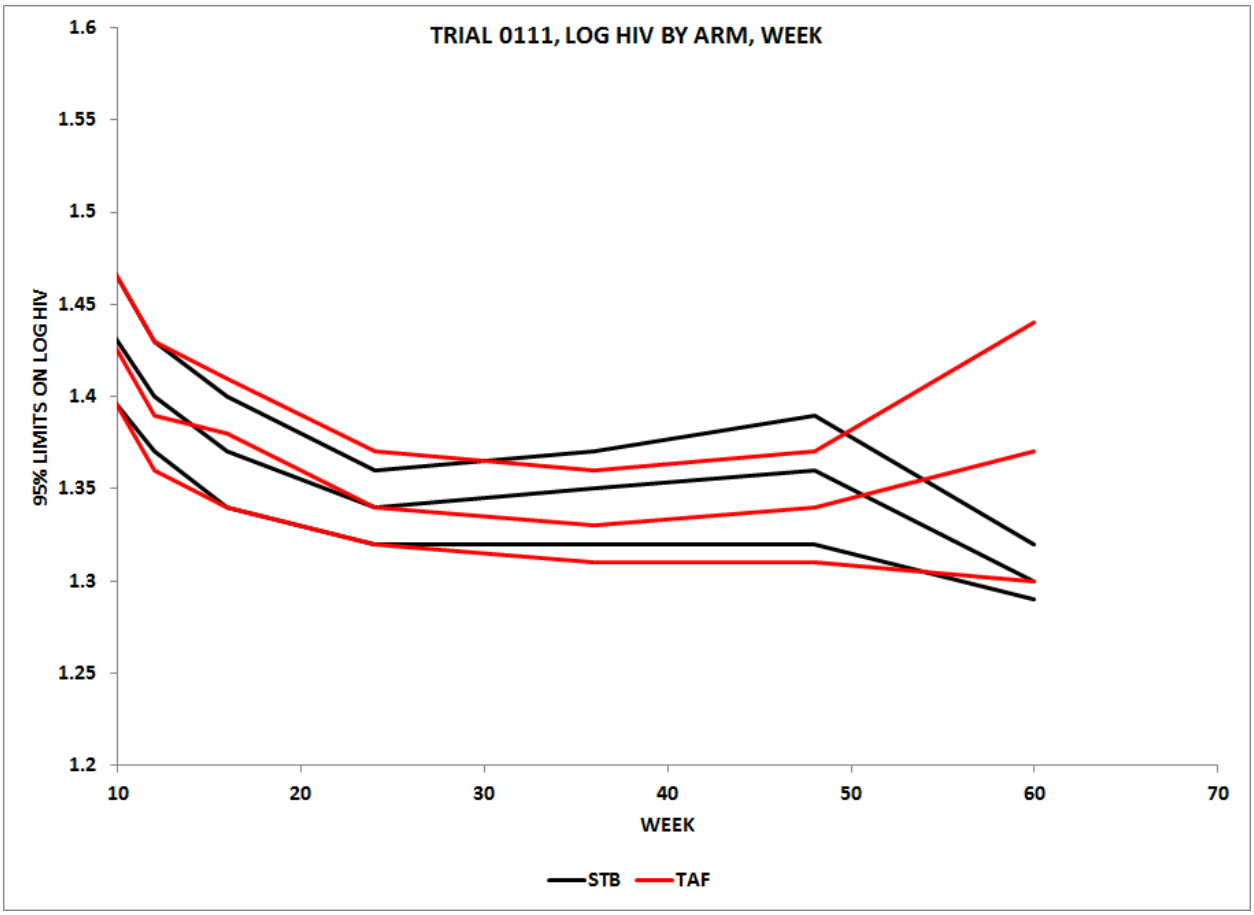


Figure 3.2 G

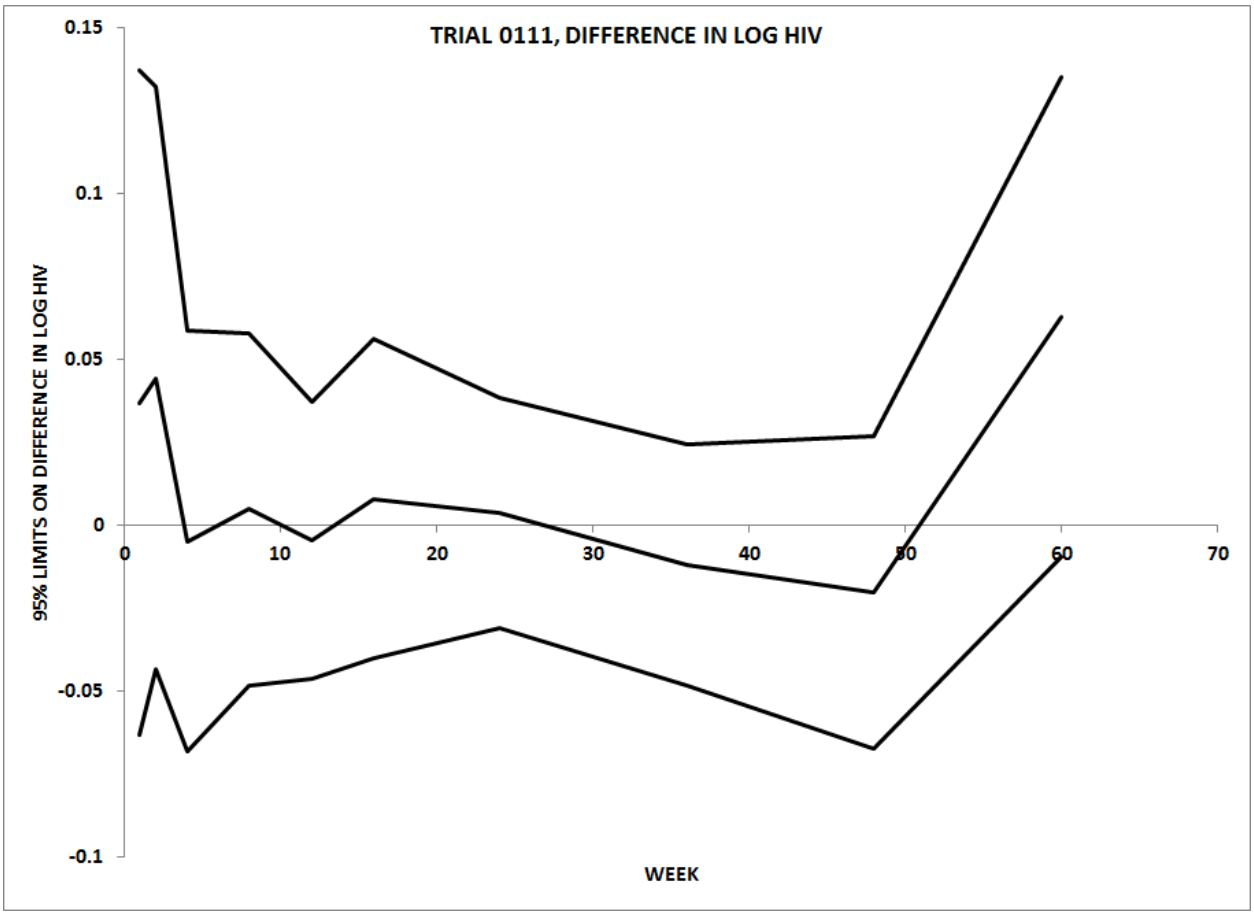


Figure 3.2 H

Trial 102 results:

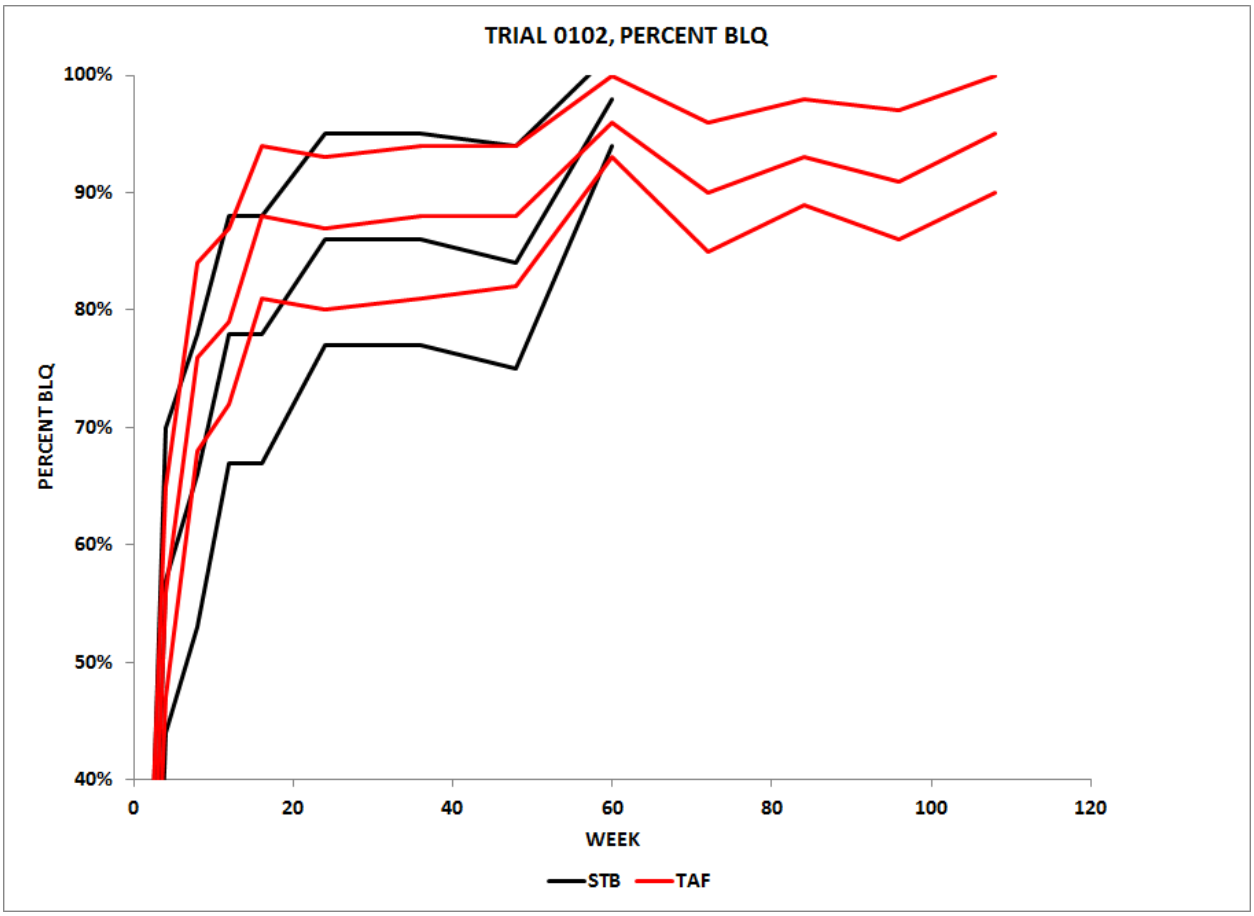


Figure 3.2 I

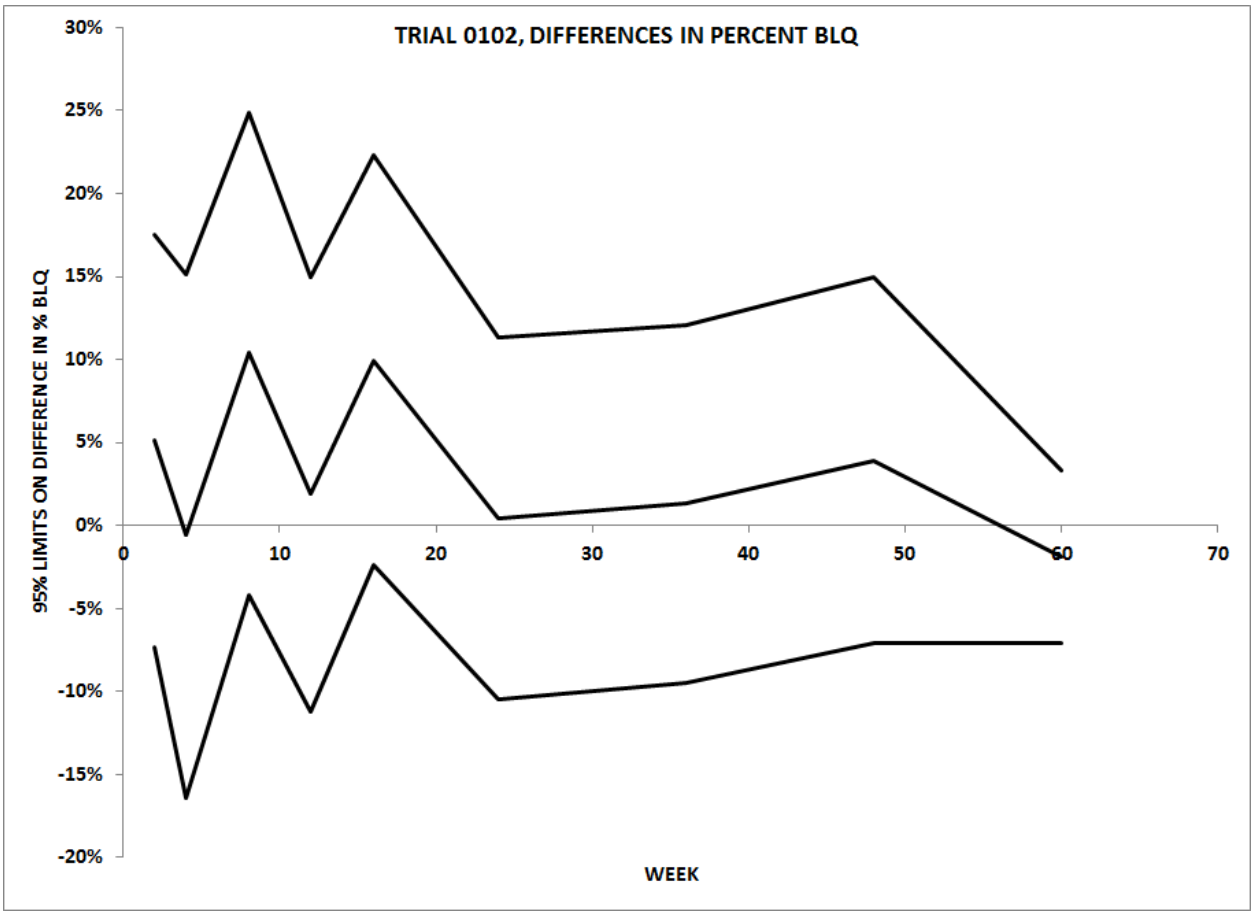


Figure 3.2 J

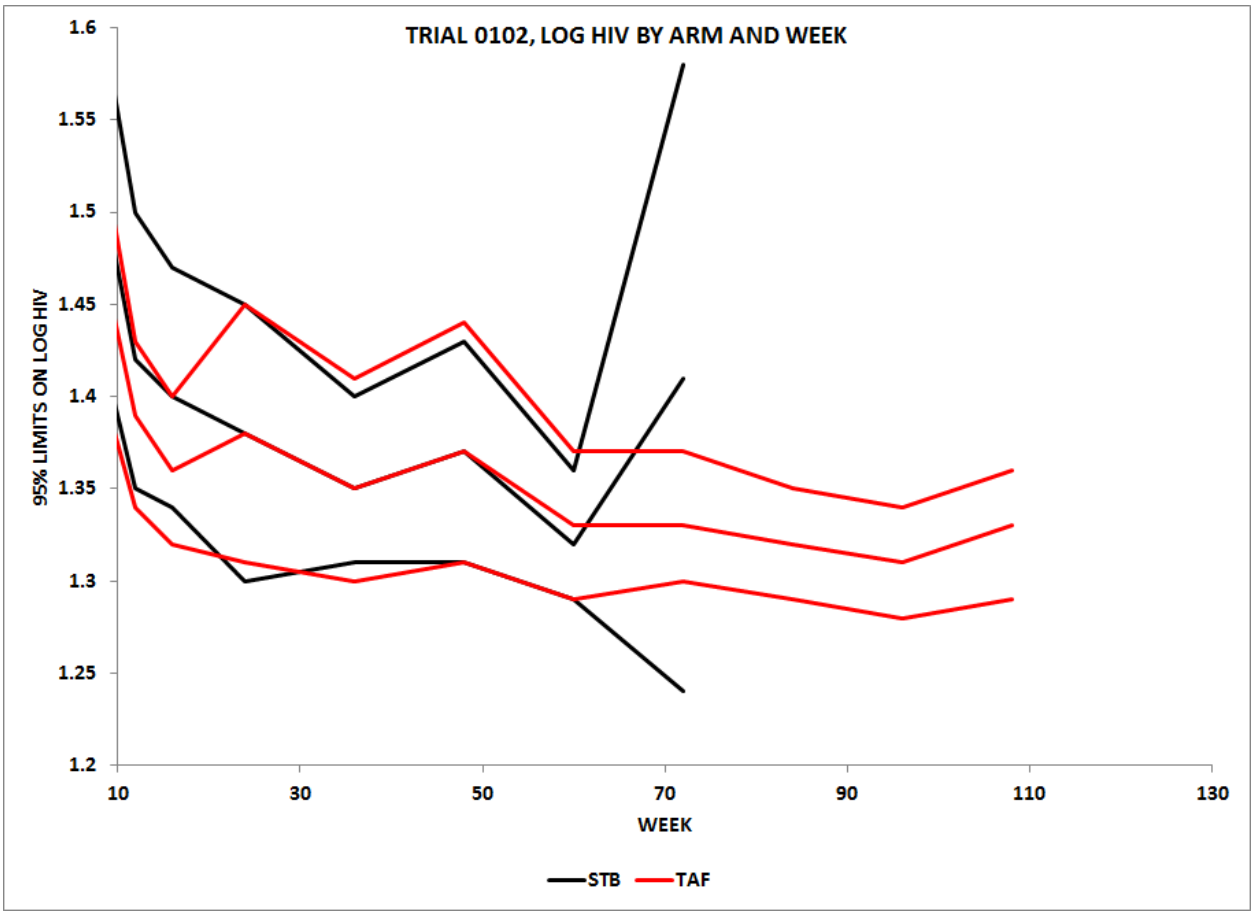


Figure 3.2 K

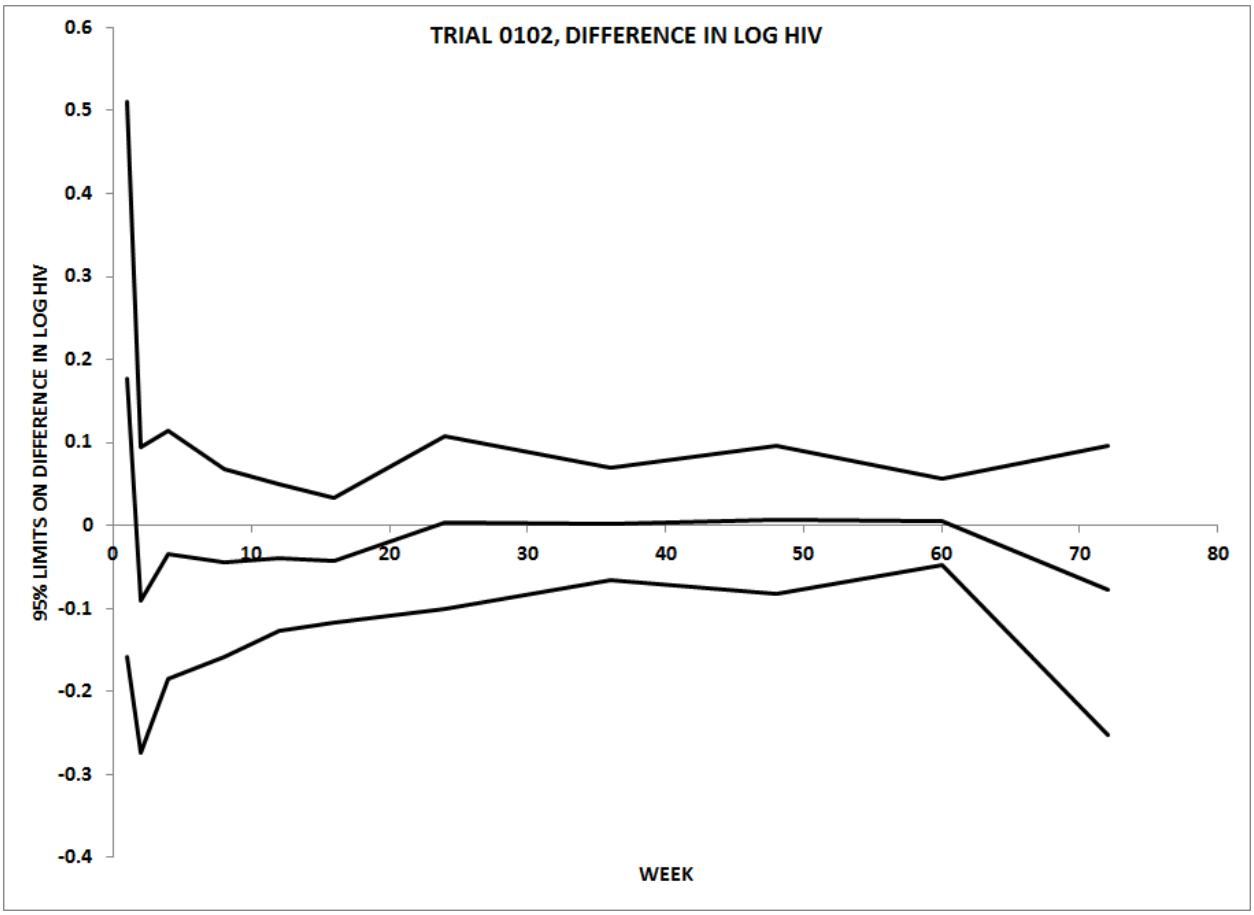


Figure 3.2 L

Trial 109 results: This trial had 5 arms instead of just a single control. Here there are two extra graphs. This first one gives the point estimates of the percent BLQ for all five arms. The 95% confidence limits are omitted because they would overly clutter the graph and would be too wide for the control arms which each have many fewer subjects than the TAF arm. It will be seen, even without the confidence intervals that there is no dramatic difference among the control arms.

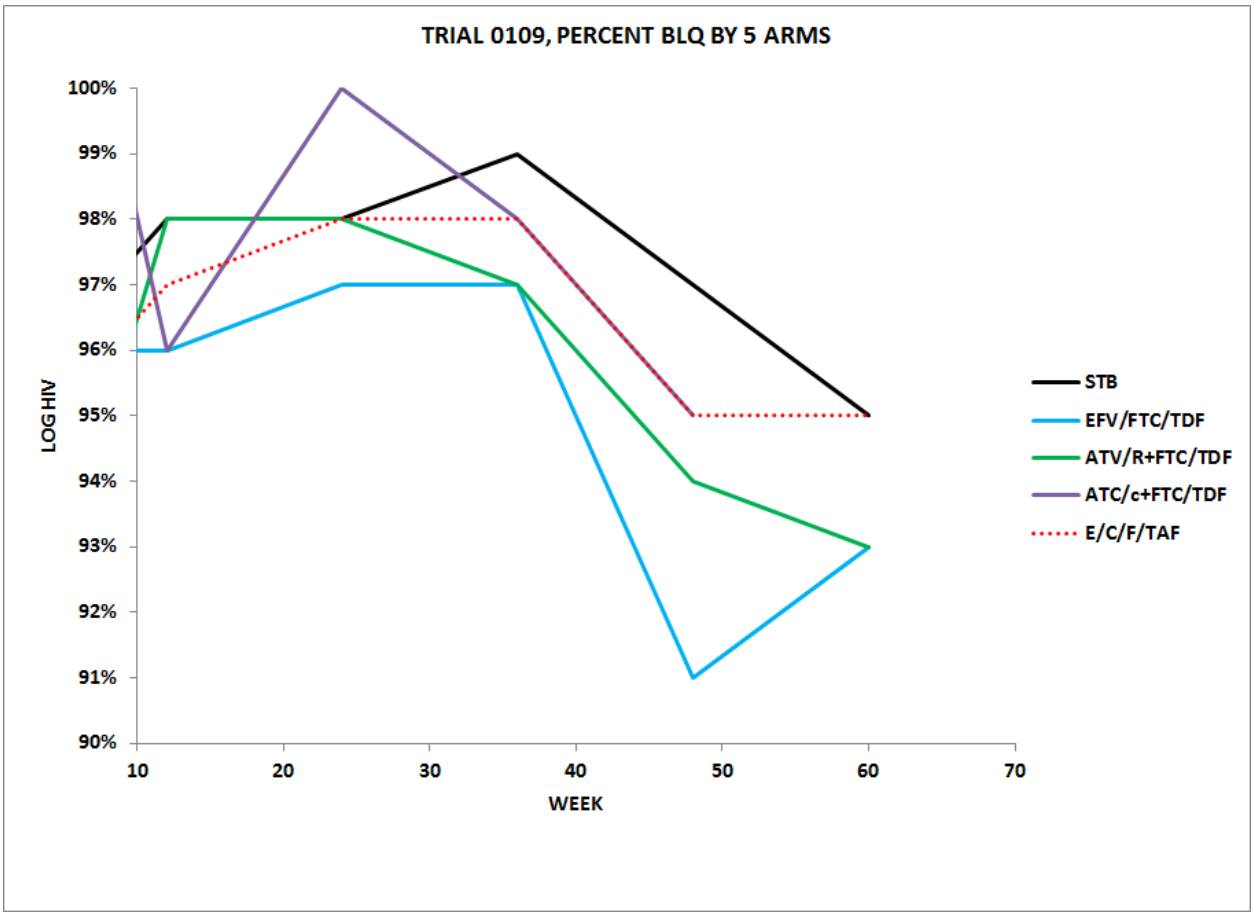


Figure 3.2 M

The second and third graphs compare the percent BLQ for the TAF with the four control arms pooled into one: point estimates and 95% confidence intervals for TAF and pooled control are given here, poet estimates and 95% confidence intervals for the difference between TAF minus pooled control are in the immediately following graph.

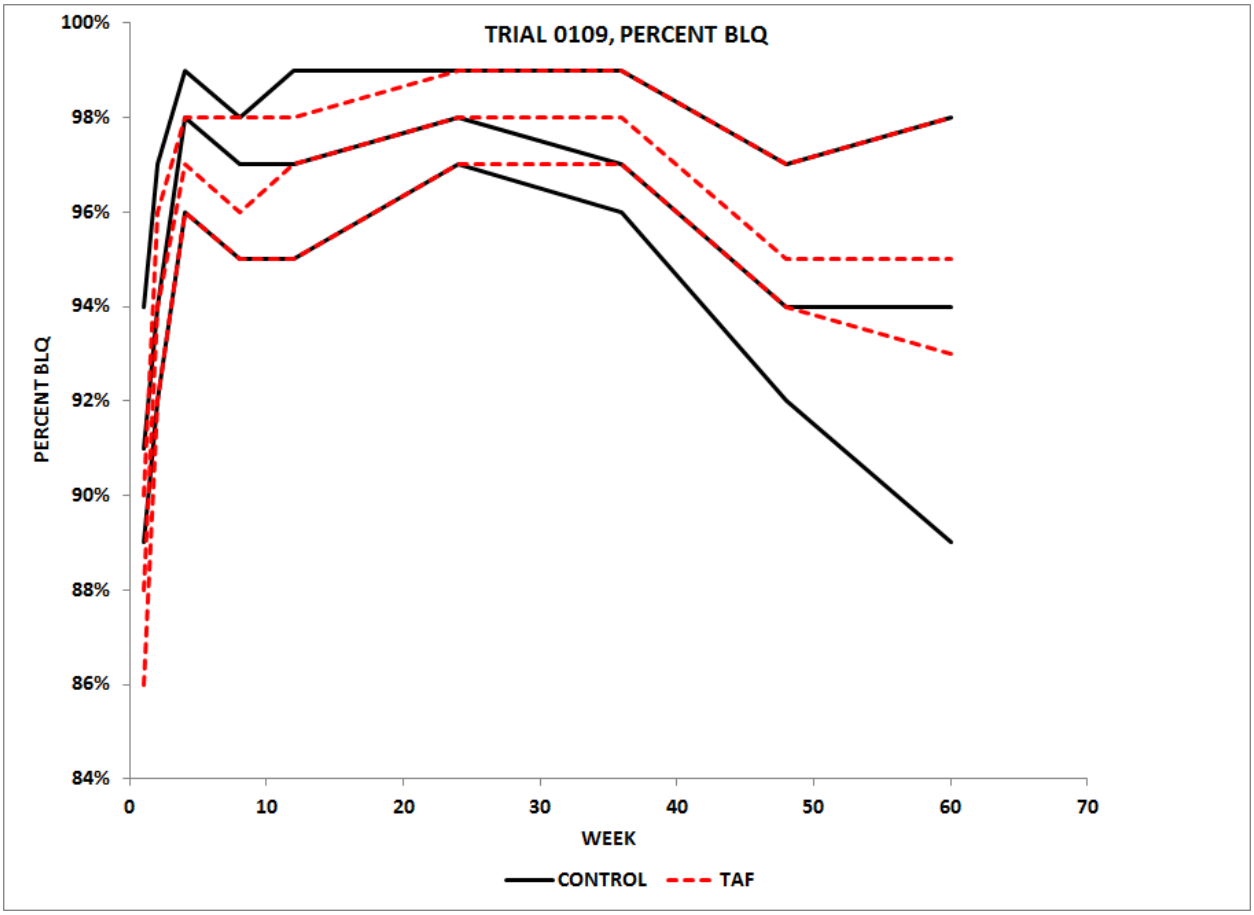


Figure 3.2 N

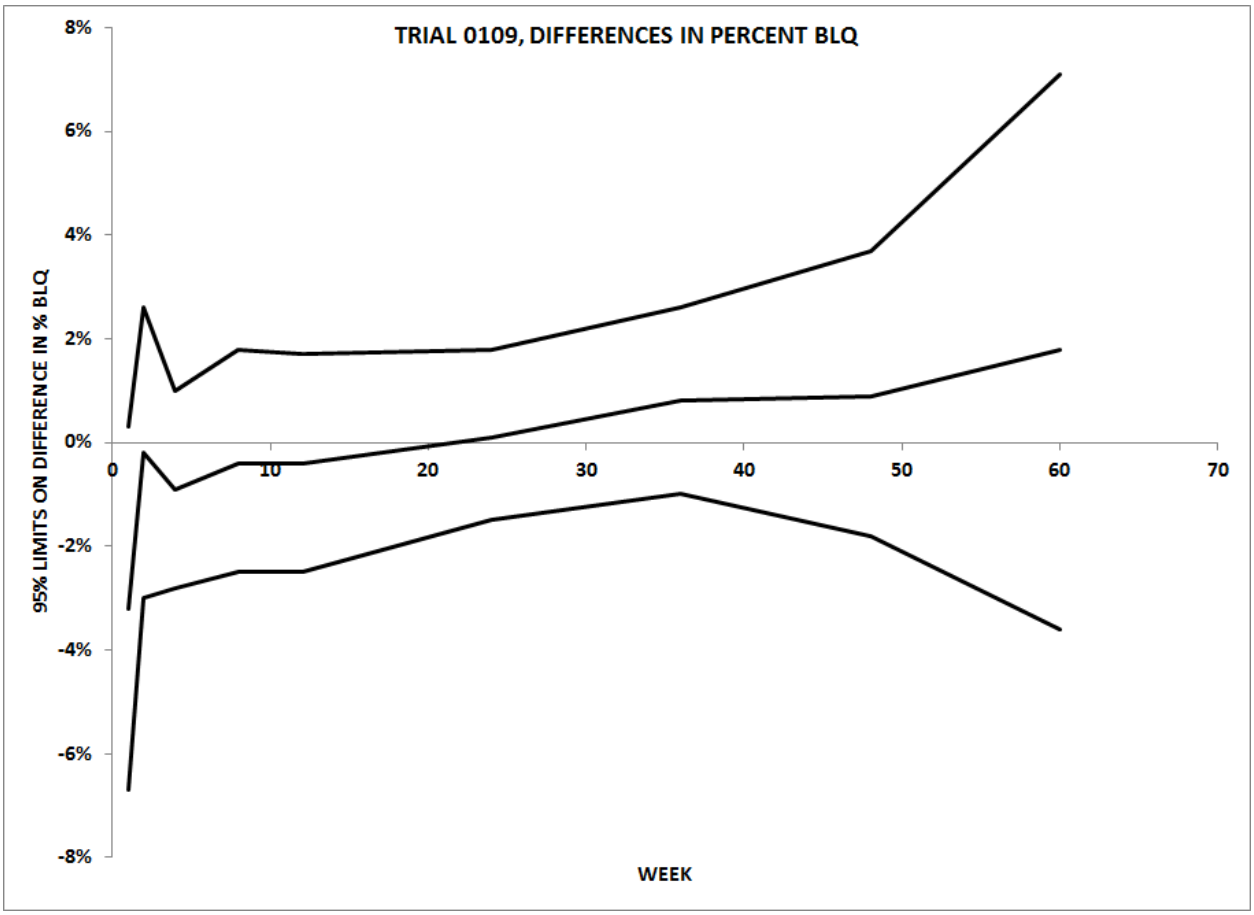


Figure 3.2 O

This graph gives the point estimates (without the cluttering confidence intervals) for all five arms with respect to observed log HIV RNA. As above, one will notice that there is no conspicuous difference among the control arms.

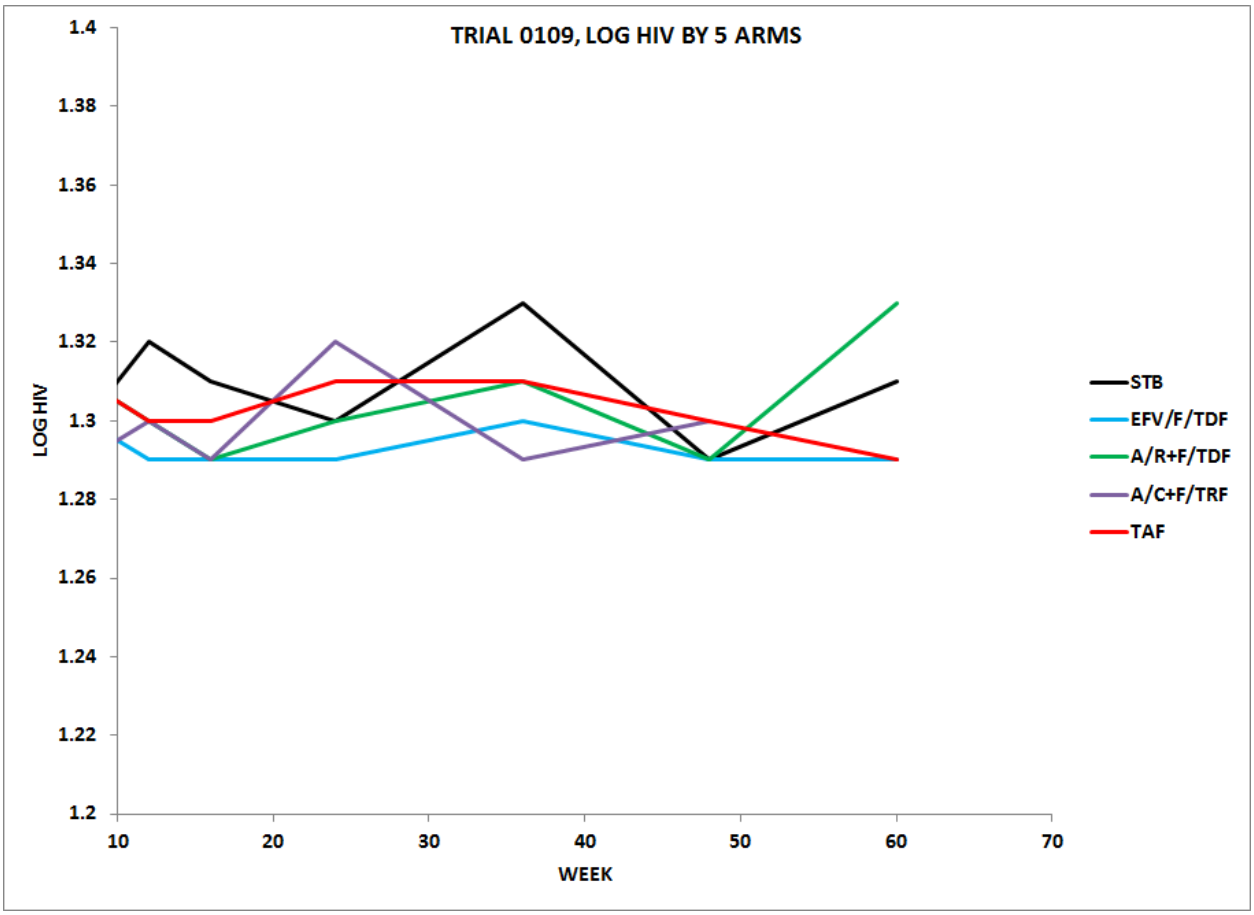


Figure 3.2 P

The last two graphs give the point estimates and 95% confidence intervals for the TAF and pooled control arms with respect to log HIV RNA levels and for the difference in log HIV RNA for TAF minus pooled control.

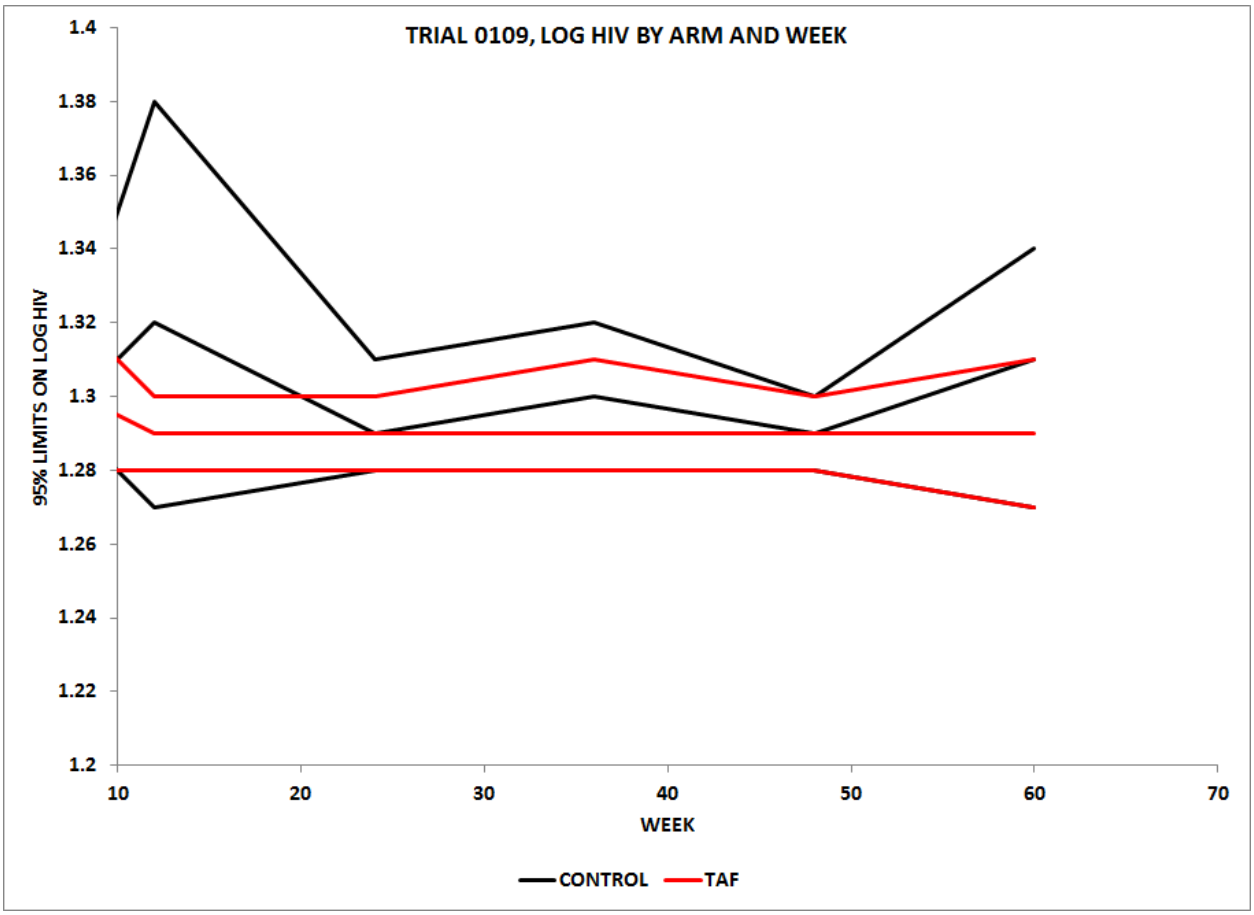


Figure 3.2 Q

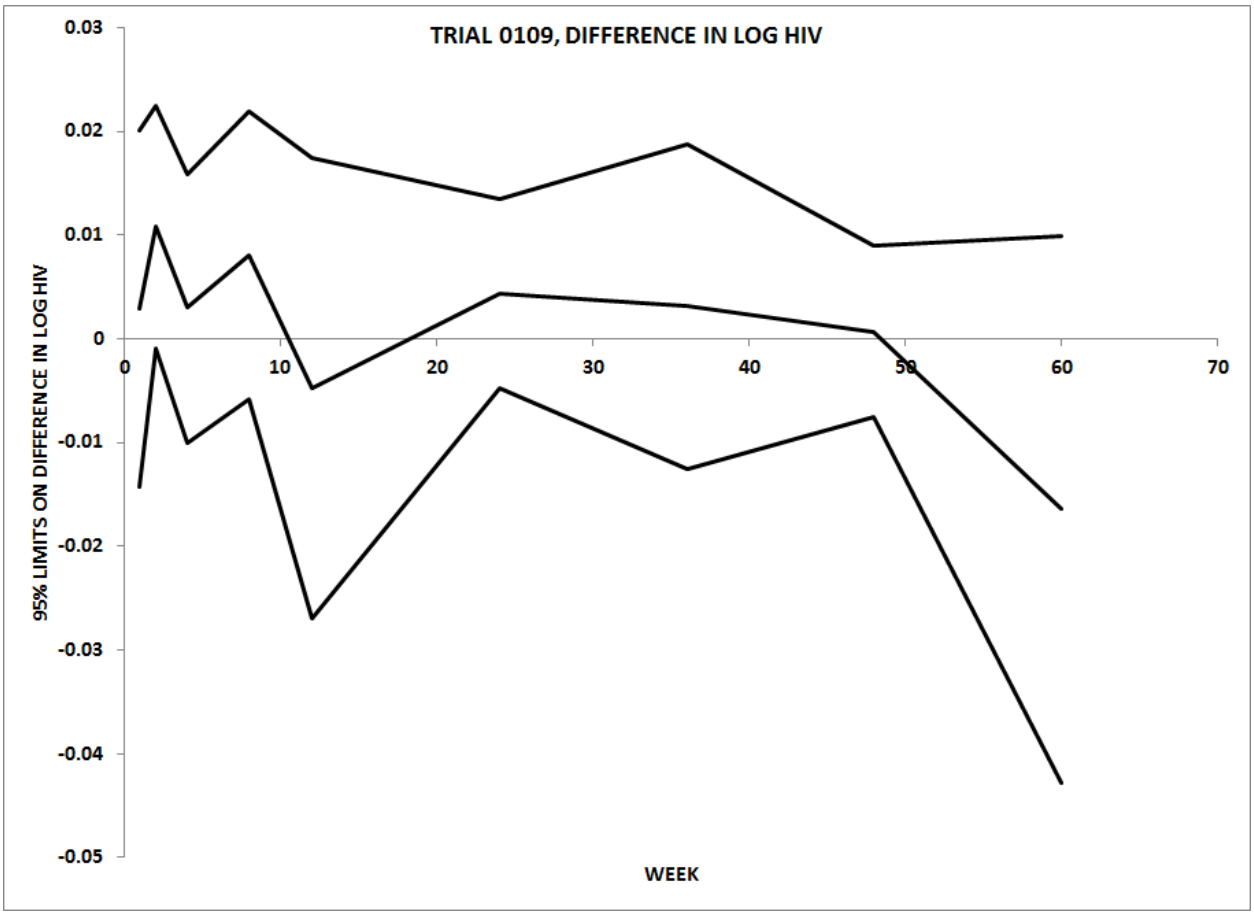


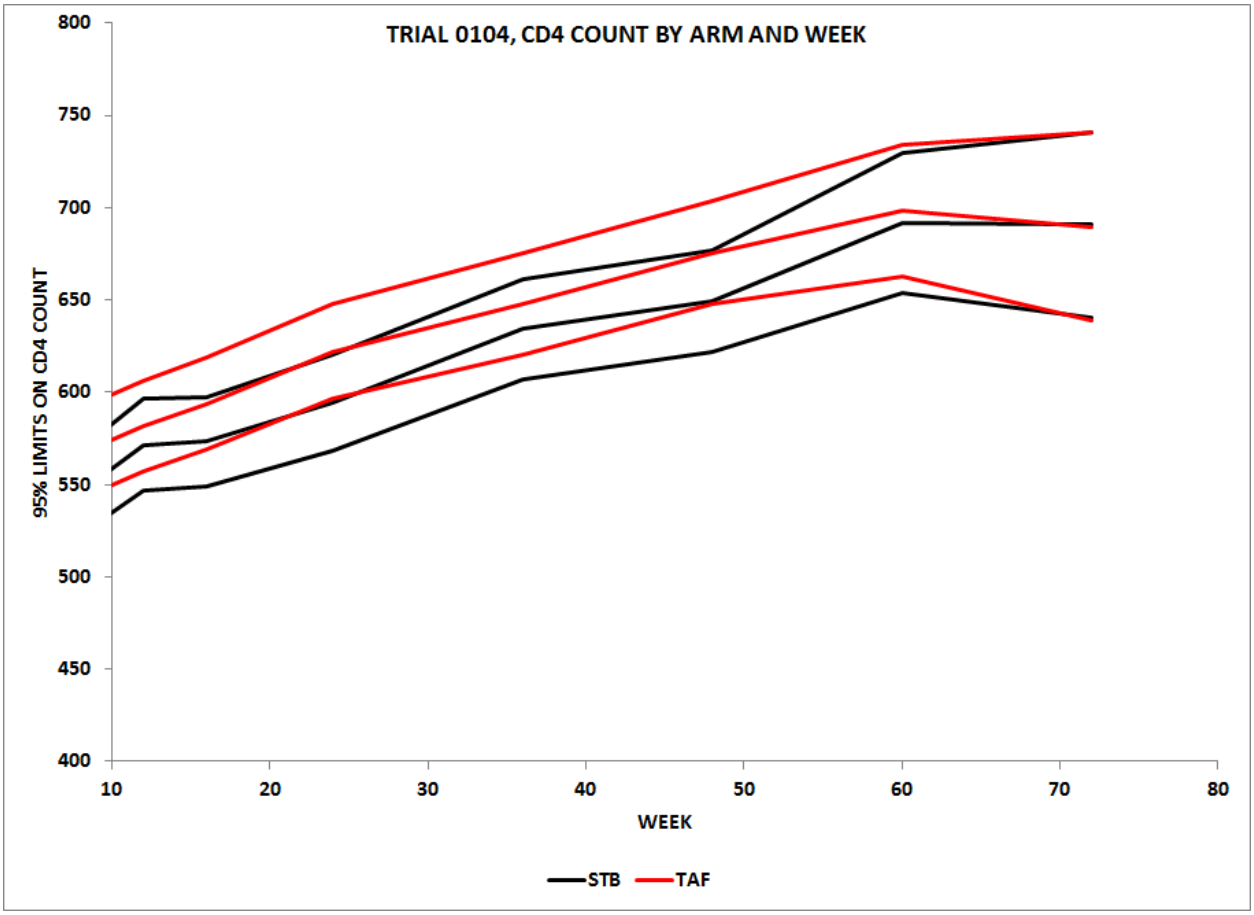
Figure 3.2 R

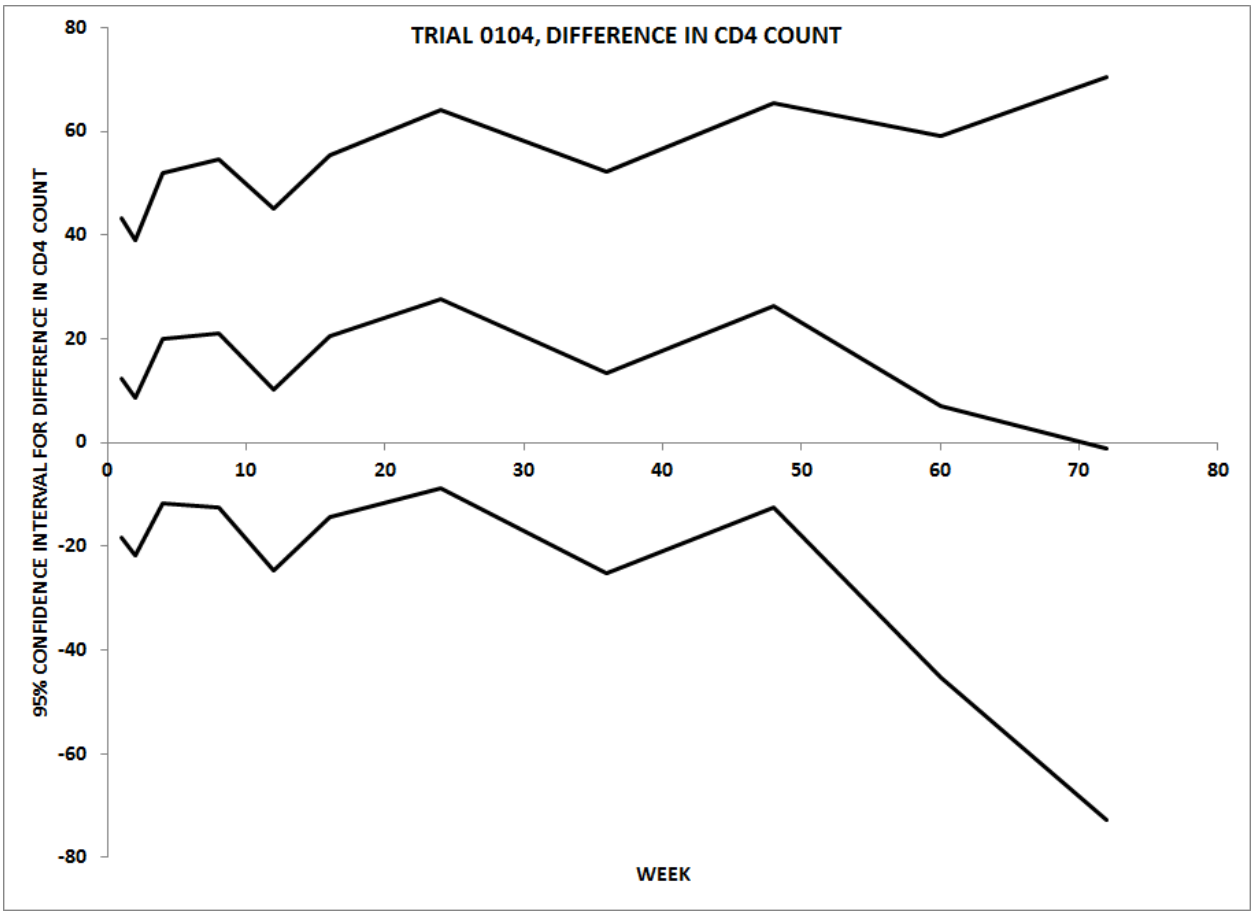
3.3 Change in CD4 Count

The following graphs are intended to show that the pattern of change in CD4 count reflects the above demonstrated change in log HIV. For each trial, there are two graphs. The first one shows the point estimates and 95% confidence limits for the CD4 count at each time point on each arm; the second shows the point estimate and the 95% confidence limit for the difference in CD4 count between TAF minus control.

One will notice that trial 0104, 0111, and 0102 all look similar in that both arms increase CD4 count from about 550 cells to about 650 cells. For the two large phase 3 trials (0104 and 0111), the uncertainty in the difference between the two arms stays mostly between +40 and -40; for the smaller phase 2 trial (0102), the uncertainty is between +60 and -60. There is less improvement over time in trial 0109, which started with a higher baseline of about 700 cells. Overall, the graphs support the conclusion of clinical non-inferiority conveyed from the HIV RNA observations.

Trial 0104 results: Both arms increase CD4 count from about 550 cells to about 650 cells





Trial 0111 results: Both arms increase CD4 count from about 550 cells to about 650 cells

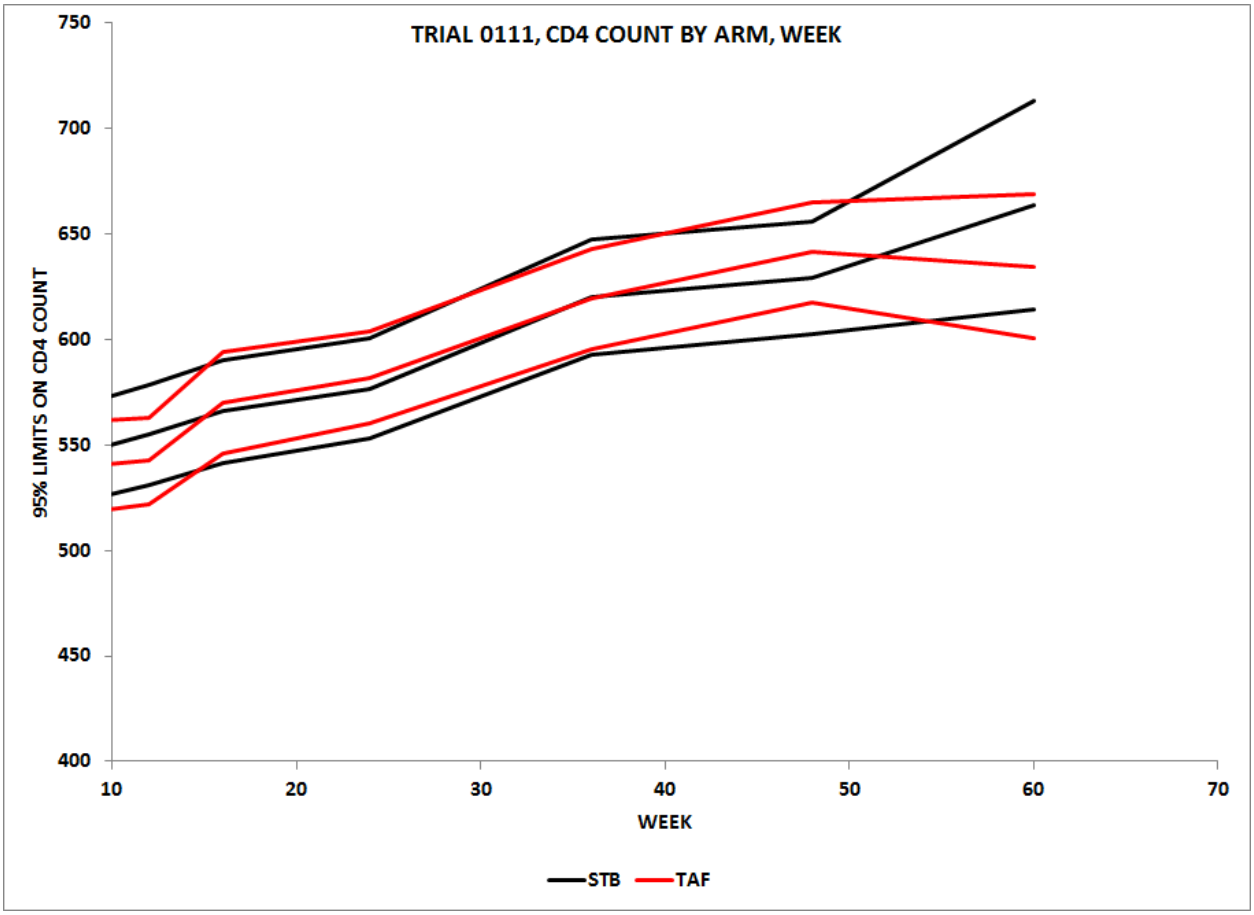


Figure 3.3 A

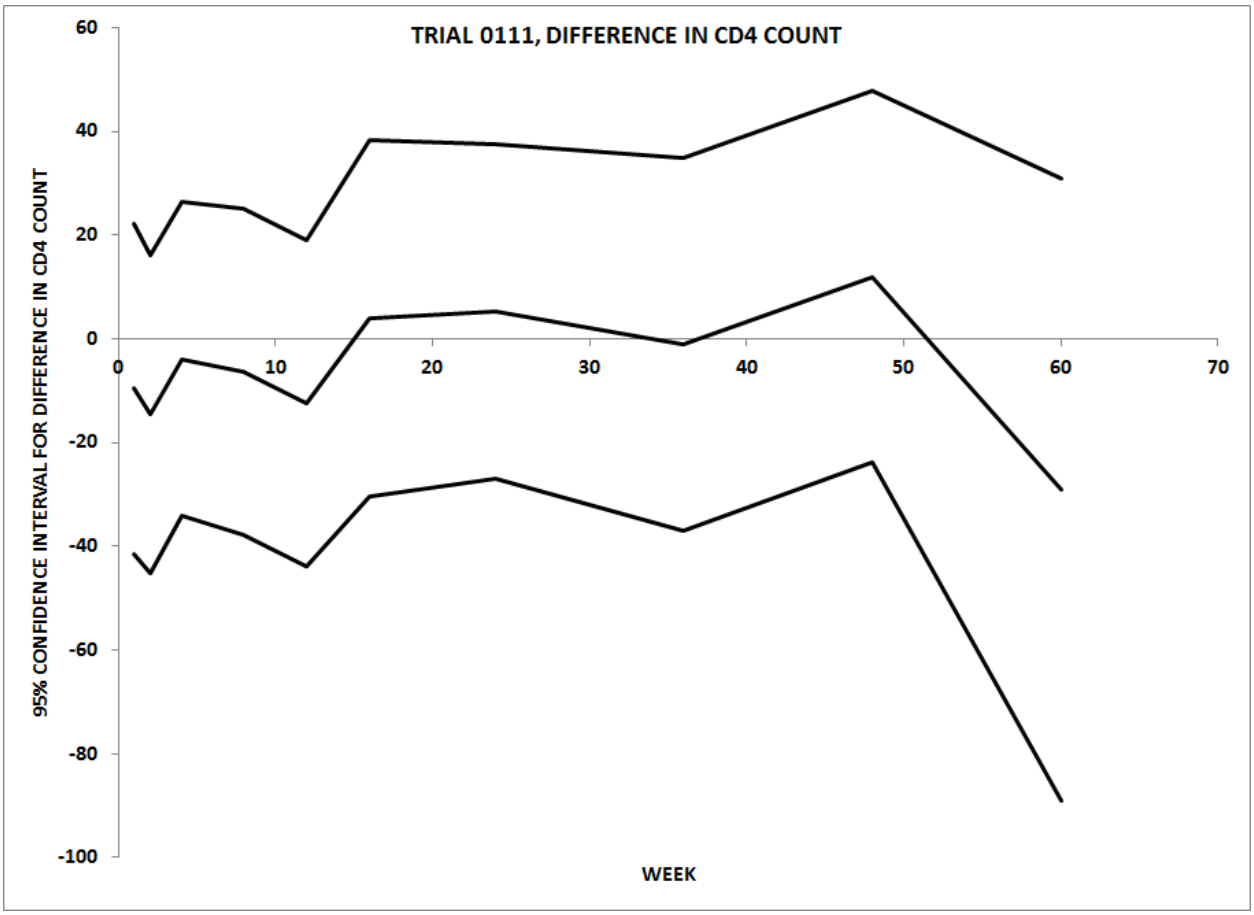


Figure 3.3 B

Trial 0102 results: Both arms increase CD4 count from about 550 cells to about 650 cells

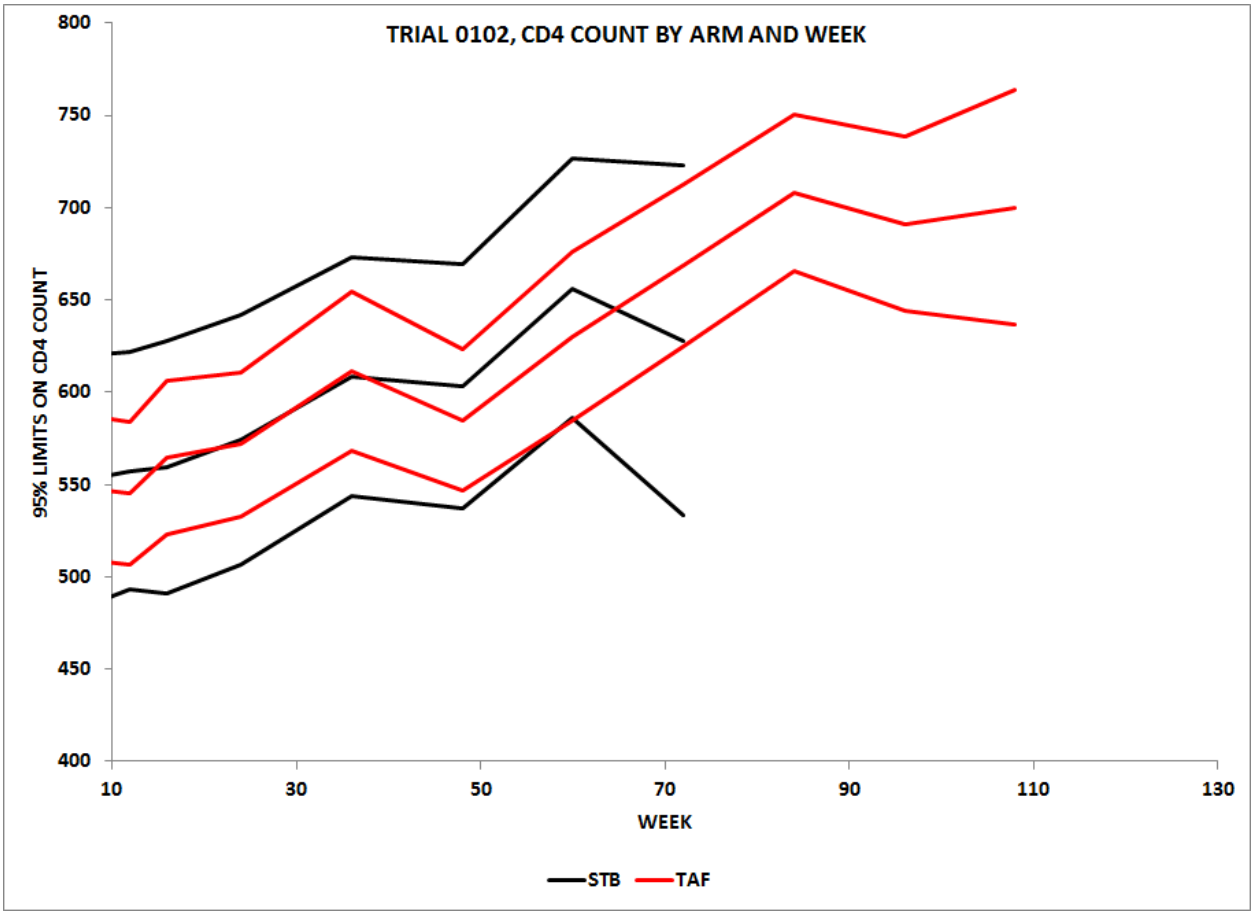


Figure 3.3 C

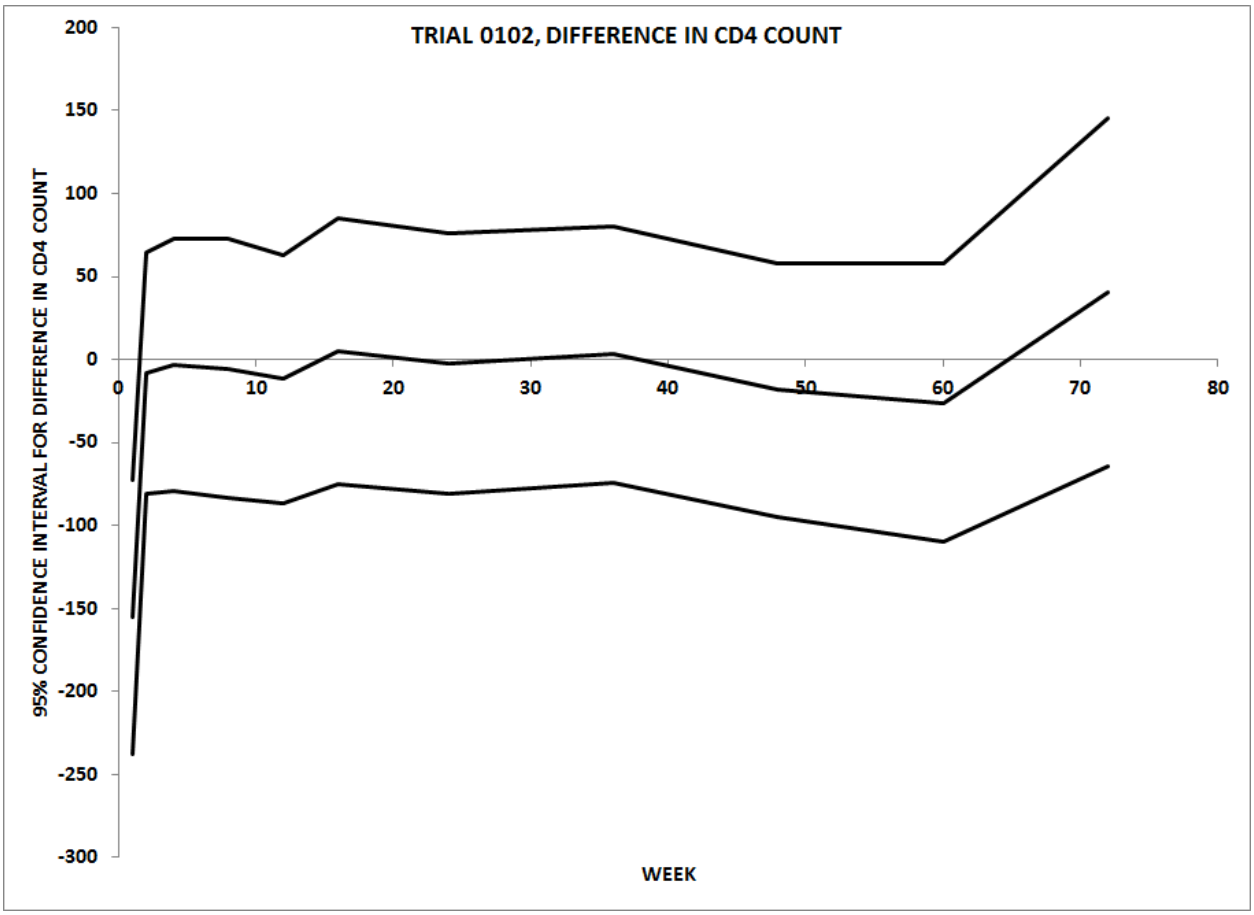


Figure 3.3 D

As was the case in the previous section with HIV RNA levels, there are three graphs for trial 0109. The first gives the point estimates, without the cluttering confidence intervals, for the five arms individually. In this trial, CD4 levels tend to stay flat in 700-750 cell range for all arms, except for the late, and more uncertain, week 60 data.

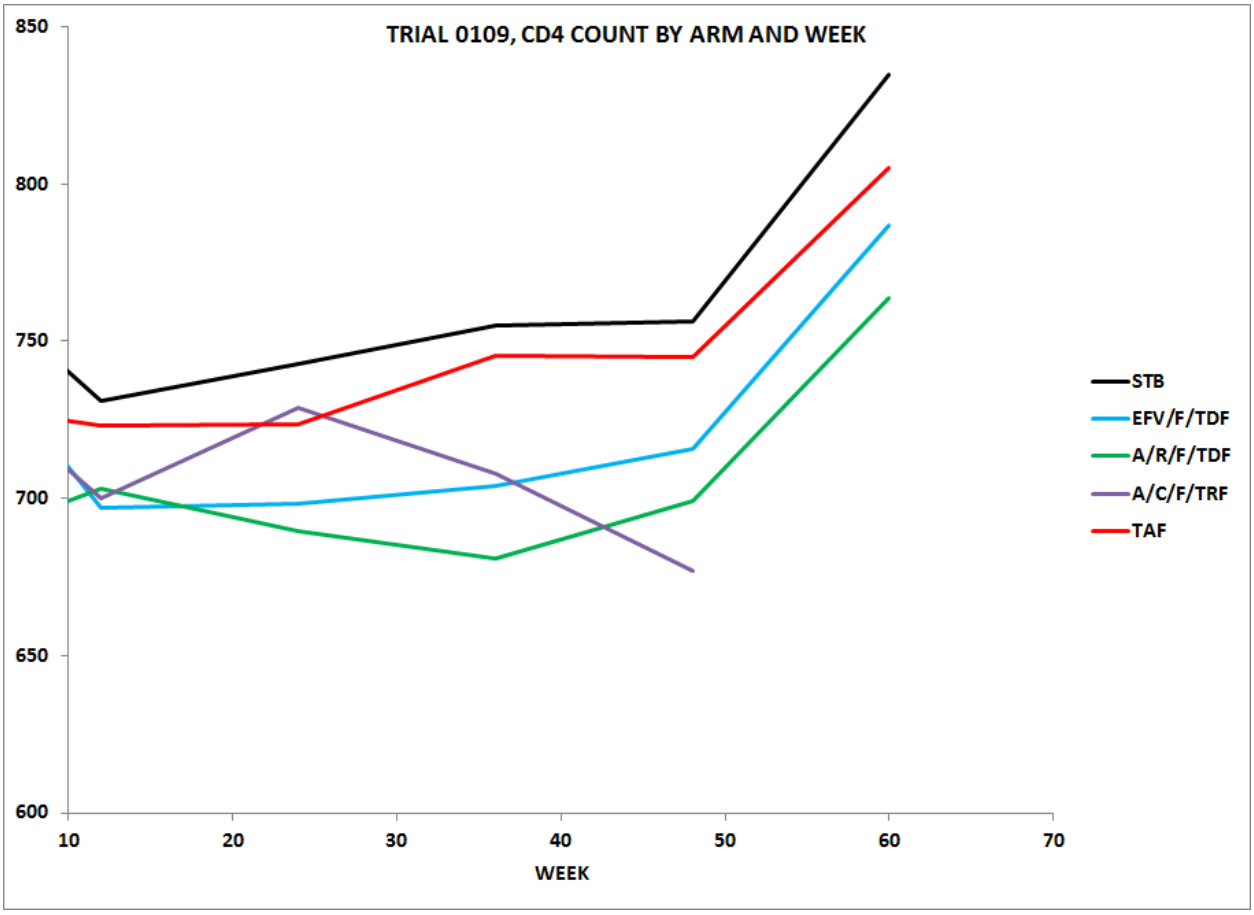


Figure 3.3 E

The second and third graphs give point estimates and 95% confidence intervals comparing TAF to the pooled control arm. In these graphs, one sees a slight 20 cell improvement in the TAF compared to the control by week 48, although the lower confidence bound for the difference remains below zero, leaving one uncertain as to whether the apparent improvement is just happenstance.

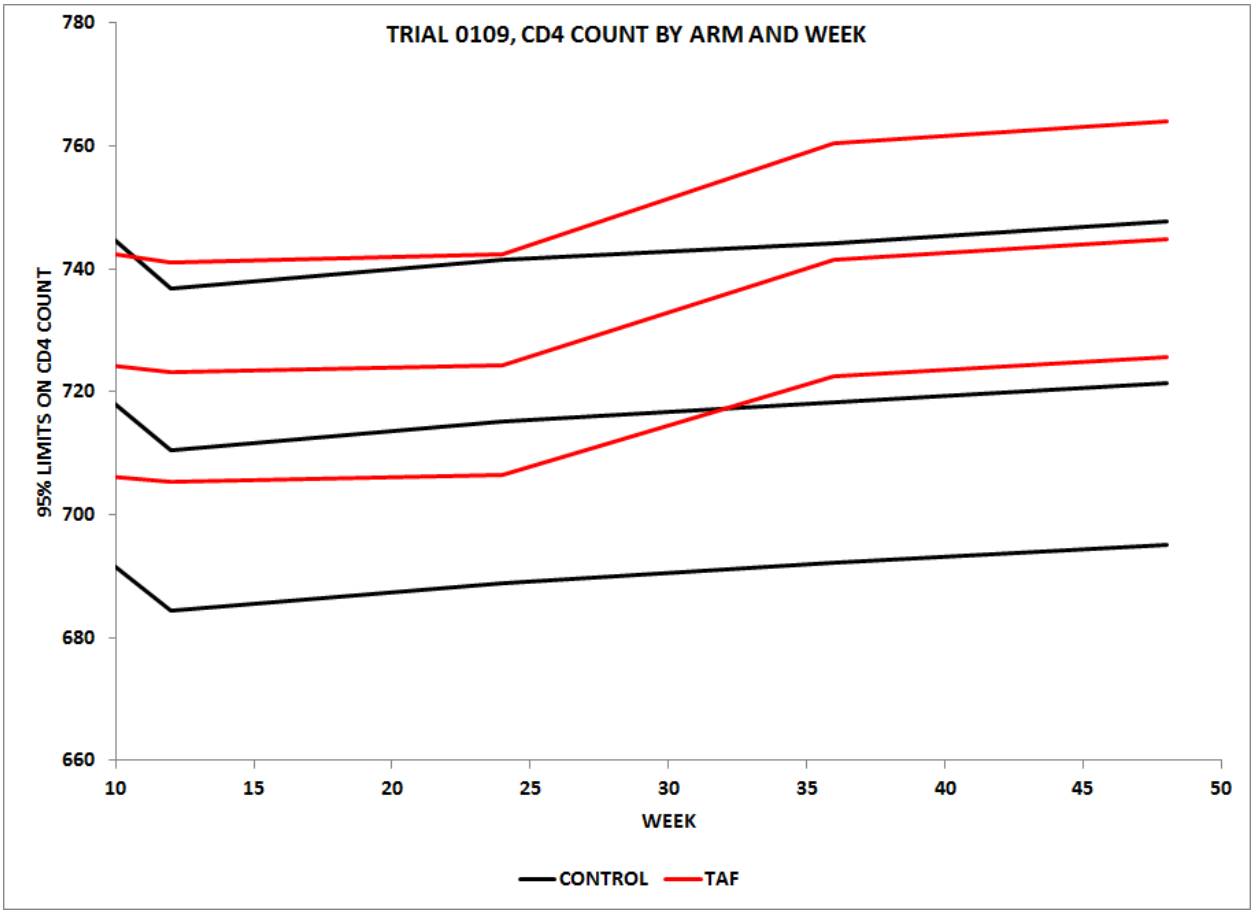


Figure 3.3 F

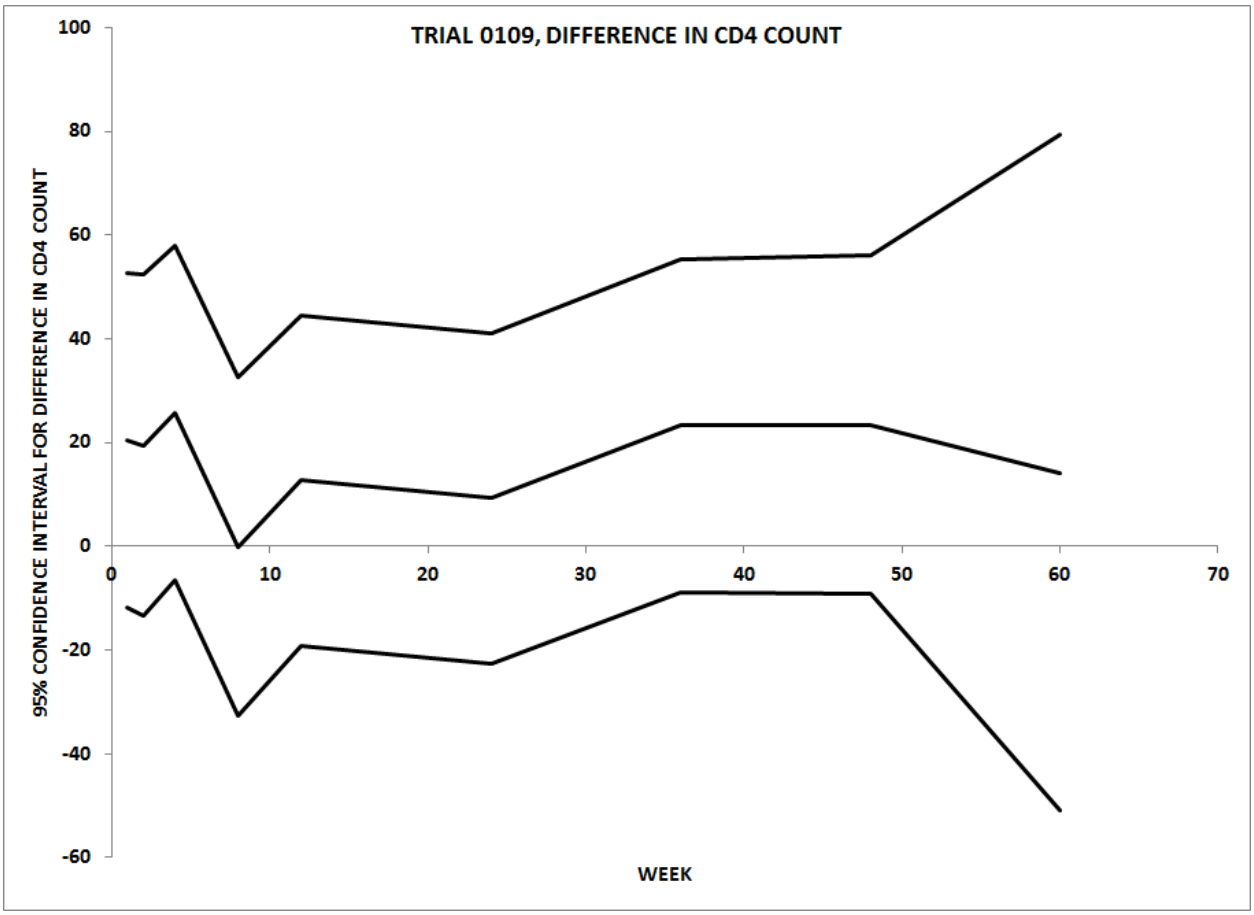


Figure 3.3 G

3.4 Time to Loss of Viral Response in Trial 0109

Because all subjects in trial 0109 were suppressed at the initiation of the trial, there was interest in comparing the pooled control and E/C/F/TAF arms with respect to the time to loss of viral response. This was defined as time to the earlier of two consecutive measurements with HIV>50 or to the time of the first measurement with HIV>50 if that measurement were the last HIV measurement on trial. (The assay is known to give occasional spurious readings so one measurement with HIV>50 is not considered a loss of viral response if it is preceded and succeeded by measurements with HIV<=50.) Table 3.5 gives the number and percent of subjects with observed loss of viral response by arm.

TABLE 3.4

NUMBER AND PERCENT OF SUBJECTS WITH OBSERVED LOSS OF RESPONSE

TRT	FAIL	PERCENT
STB	2/135	1.4815%
EFV/FTC/TDF	2/119	1.6807%
ATV/R+FTC/TDF	1/88	1.1364%
ATC/c+FTC/TDF	3/55	5.4545%
POOLED CONTROL	8/397	2.0151%
E/C/F/TAF	24/799	3.0038%

The following graphs give the Kaplan-Meier curves for time to loss of viral response, pooling all four control arms together, and for the 95% upper and lower confidence bounds on the difference in percent who have experienced viral failure. Subjects without observed loss of viral response are censored at their last measurement.

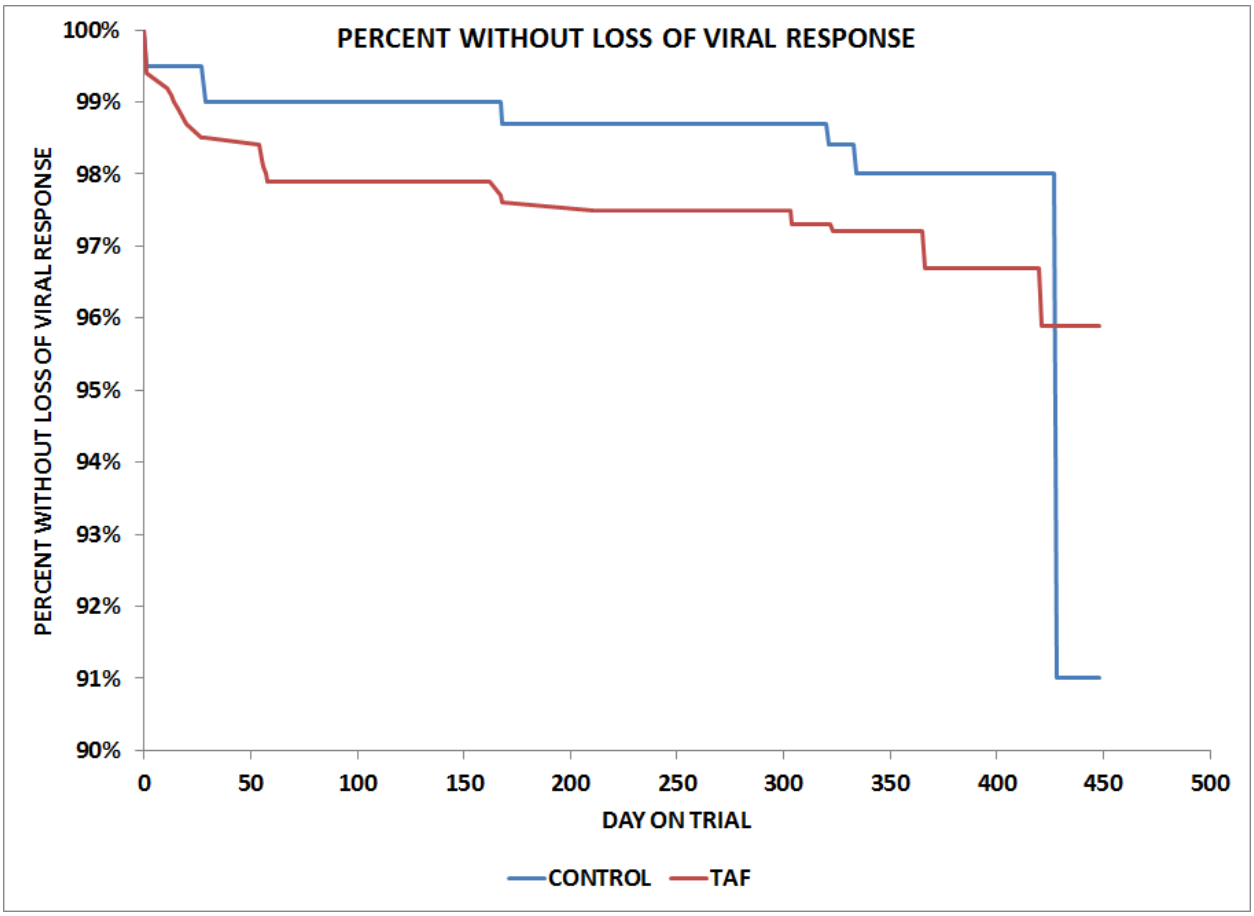

PERCENT WITHOUT LOSS OF VIRAL RESPONSE
100%
99%
98%
97%
96%
95%
94%
93%
92%
91%
90%
PERCENT WITHOUT LOSS OF VIRAL RESPONSE
0
50
100
150
200
250
300
350
400
450
500
DAY ON TRIAL
CONTROL
TAF

Figure 3.4 A

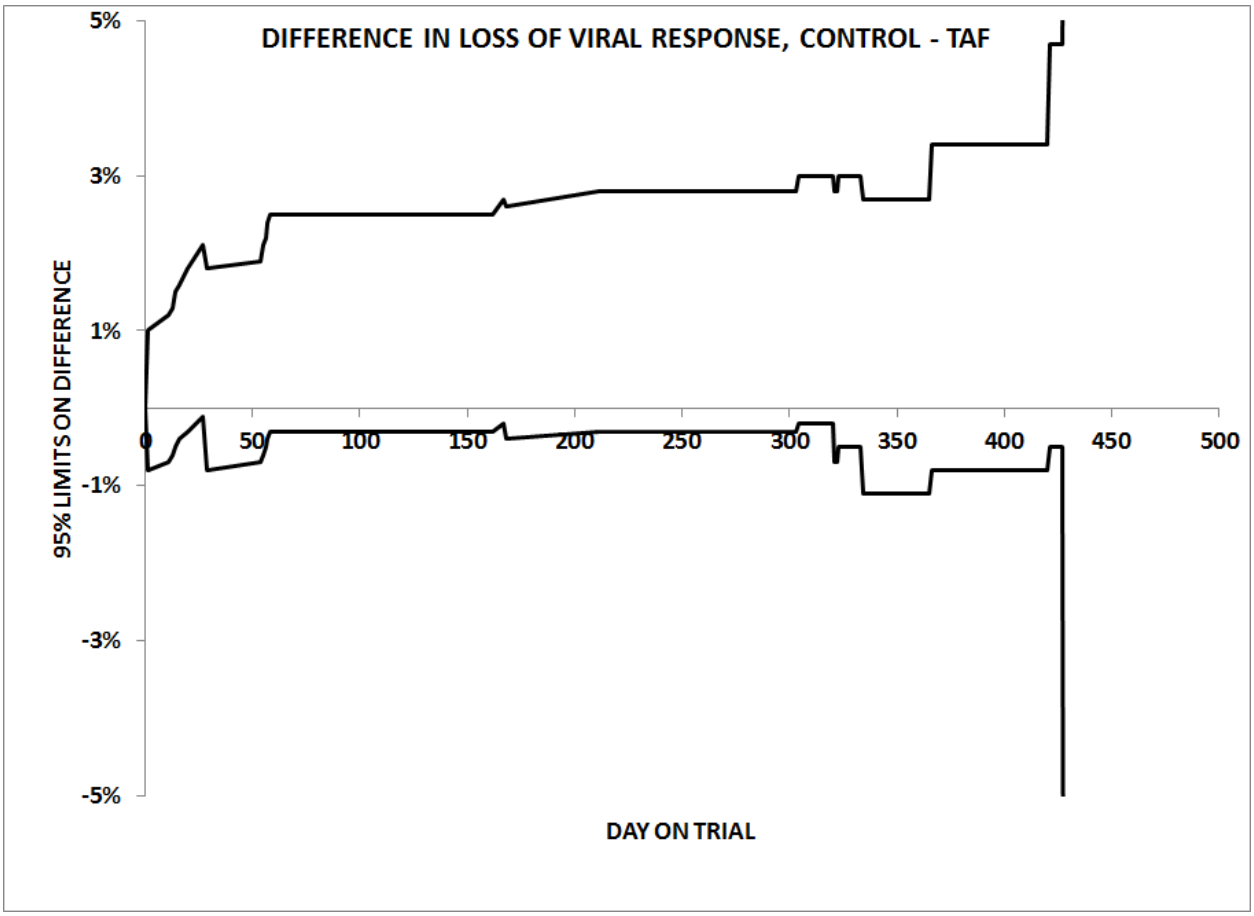

DIFFERENCE IN LOSS OF VIRAL RESPONSE, CONTROL - TAF
95% LIMITS ON DIFFERENCE
5%
3%
1%
-1%
-3%
-5%
0
50
100
150
200
250
300
350
400
450
500
DAY ON TRIAL

Figure 3.4 B

The Wilcoxon chi-square statistic for an effect of treatment on time to loss of viral response was 1.19 with a p-value of .257; the corresponding log rank test was 1.16 with a p-value of .281. The tests, as might be expected, agree. Neither the Kaplan-Meier confidence intervals nor the log rank and Wilcoxon tests give any reason to question the conclusion of clinical equivalence with respect to viral suppression.

3.5 Pediatric Study Results

The applicant also submitted one small (48 subjects), open label, single arm study, trial 0106, on subjects 12 to 18. Since this is the only pediatric efficacy data, a brief examination of this small, uncontrolled study is warranted.

Table 3.5 A gives the percent BLQ, mean log HIV RNA, CD4 count, and sample size for each week of the trial. (There are slightly different numbers of subjects with HIV RNA and CD4 data.)

TABLES 3.5 A
PEDIATRIC STUDY 0106
%BLQ, LOG HIV RNA, CD4 COUNT, SAMPLE SIZE

WEEK	BLQ	LOGHIV	N_HIV	CD4	N_CD4
1	4.2%	3.41342	48	468.89	47
2	28.9%	2.06276	45	570.61	46
4	58.1%	1.6831	43	578.59	41
8	80.6%	1.48946	31	630.56	32
12	85.2%	1.41609	27	600.48	27
16	87.0%	1.53433	23	548.17	23
24	95.7%	1.40685	23	638.65	23
36	94.4%	1.52724	18	630.78	23

The percent BLQ for week 36, the last week with more than one observation, is high and the CD$ count has gone up from about 470 to about 630.

The adult and pediatric trials are separate trials but in the absence of a pediatric control, it may be useful to compare the results of the adult trials (E/C/F/TAF arms) to the results in pediatric trial 0106. These are observational, non-randomized comparisons but they still give some opportunity for judging whether the pediatric results are close to the adult results.

The following graph (figure 3.5 A) compares the plots of log HIV for the 48 subjects in trial 0106 with the plots for the first 48 subjects, ordered by subject id number, in trial 0104. The time, on the x-axis, is on the log scale to make the early decline from baseline to below detection more visible. The overall impression of this graph is that there is no particular difference between the results in the double blind adult trial, 0104, and the single arm pediatric trial, 0106.

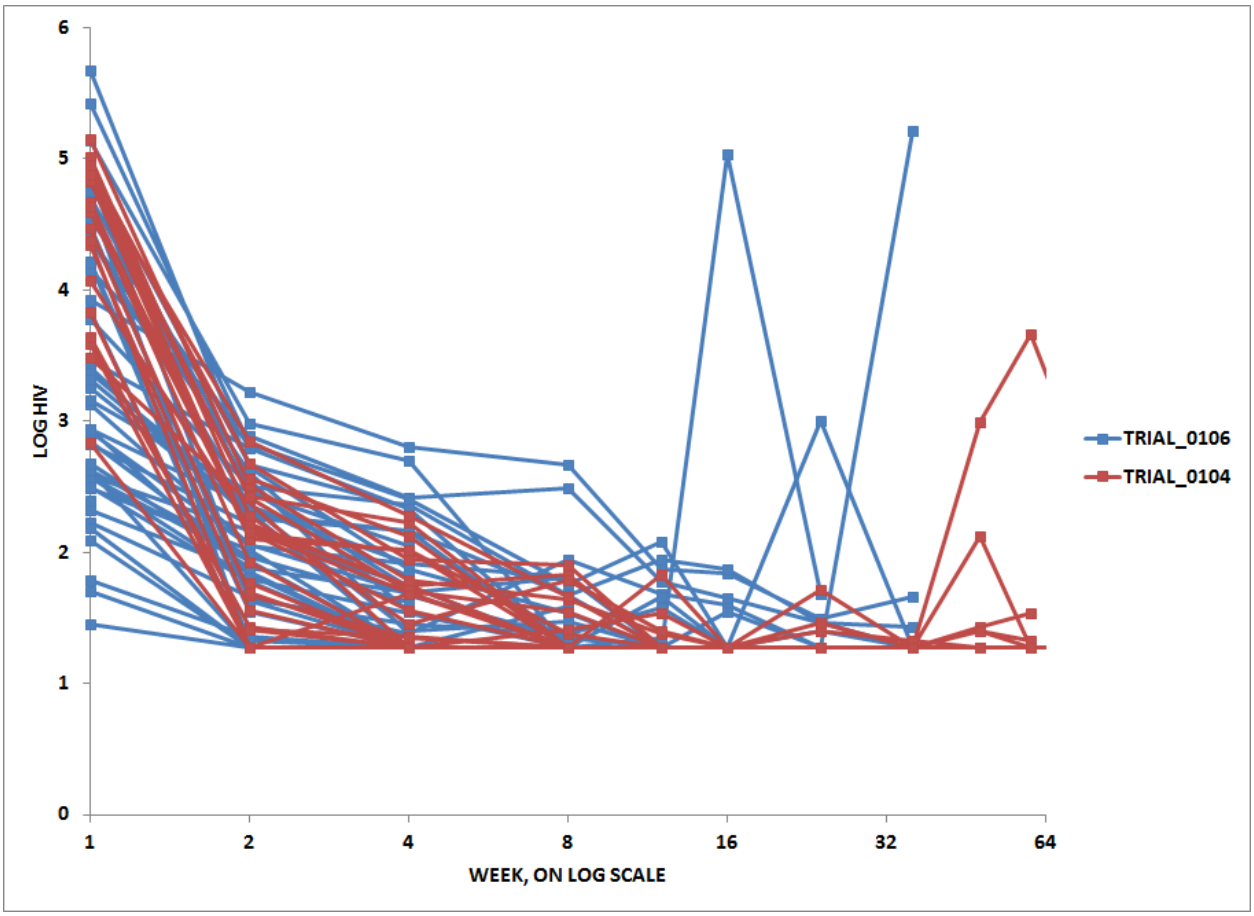


Figure 3.5 A

Figures 3.5 B-D give, successively, b)the point and 95% confidence limits for the percent BLQ by week, for the pediatric trial 0106, and the pooled E/C/F/TAF arms for the four adult studies; c)the point estimates for percent BLQ by week for all five E/C/F/TAF arms across the studies, and d)the point estimate for the difference in percent BLQ between the pediatric study minus the four pooled adult studies. It is worth re-iterating that this latter is a purely observational, non-randomized comparison.

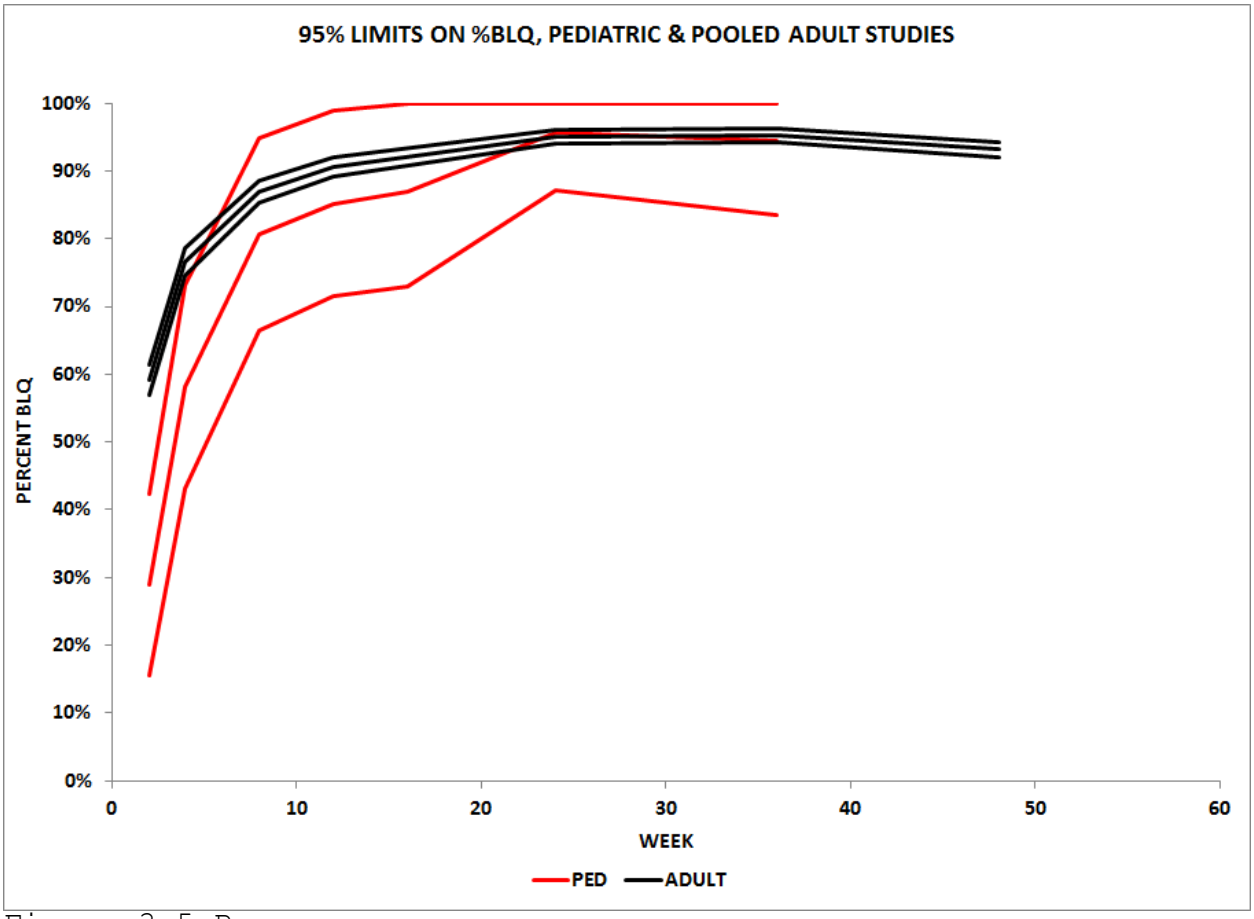


Figure 3.5 B

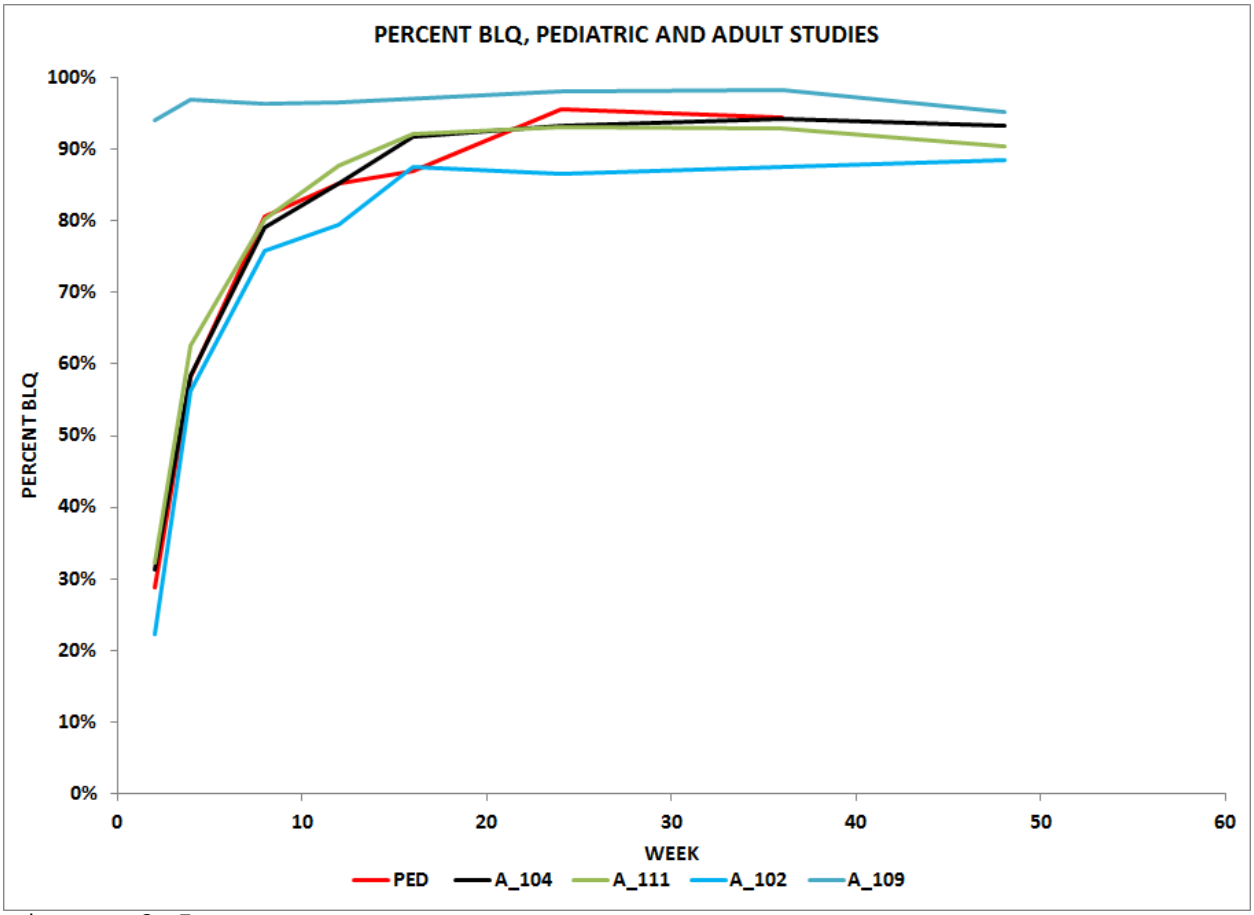

PERCENT BLQ, PEDIATRIC AND ADULT STUDIES
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
PERCENT BLQ
0
10
20
30
40
50
60
WEEK
PED
A_104
A_111
A_102
A_109

Figure 3.5 C

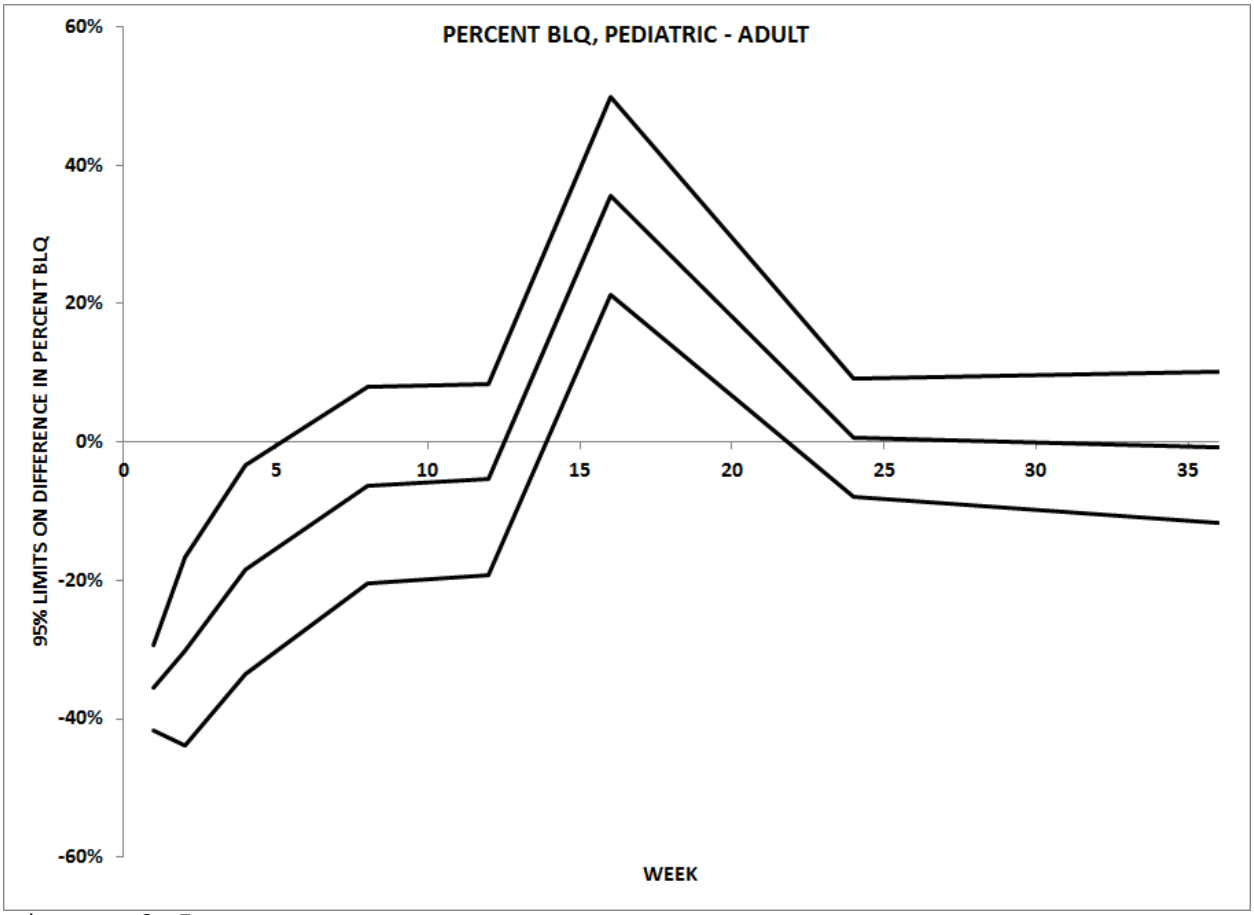


Figure 3.5 D

The confidence intervals for the pooled adult studies, all large, are much narrower than for the small pediatric study (figure 3.5 B) but the pediatric results are more or less in the middle of the adult results (figures 3.5 B and C). The difference is estimated to be essentially zero by the later weeks of the study (figure 3.5 D) with the wide limits being just a result of the small pediatric sample size.

Figures 3.5 E-G give, successively, b)the point and 95% confidence limits for the mean log HIV RNA by week, for the pediatric trial 0106, and the pooled E/C/F/TAF arms for the four adult studies; c)the point estimates for mean log HIV RNA by week for all five E/C/F/TAF arms across the studies, and d)the point estimate for the difference in mean log HIV RNA between the pediatric study minus the four pooled adult studies.

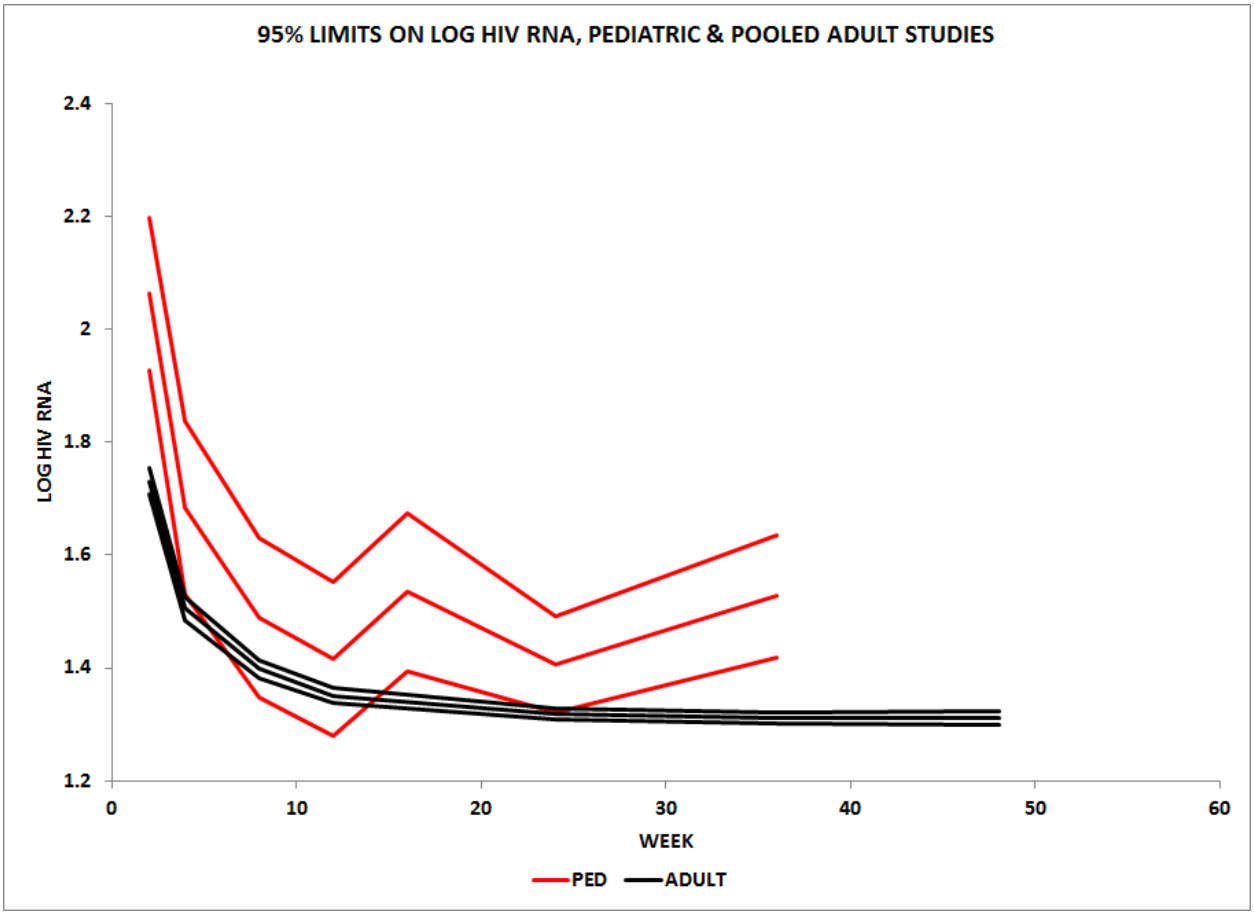


Figure 3.5 E

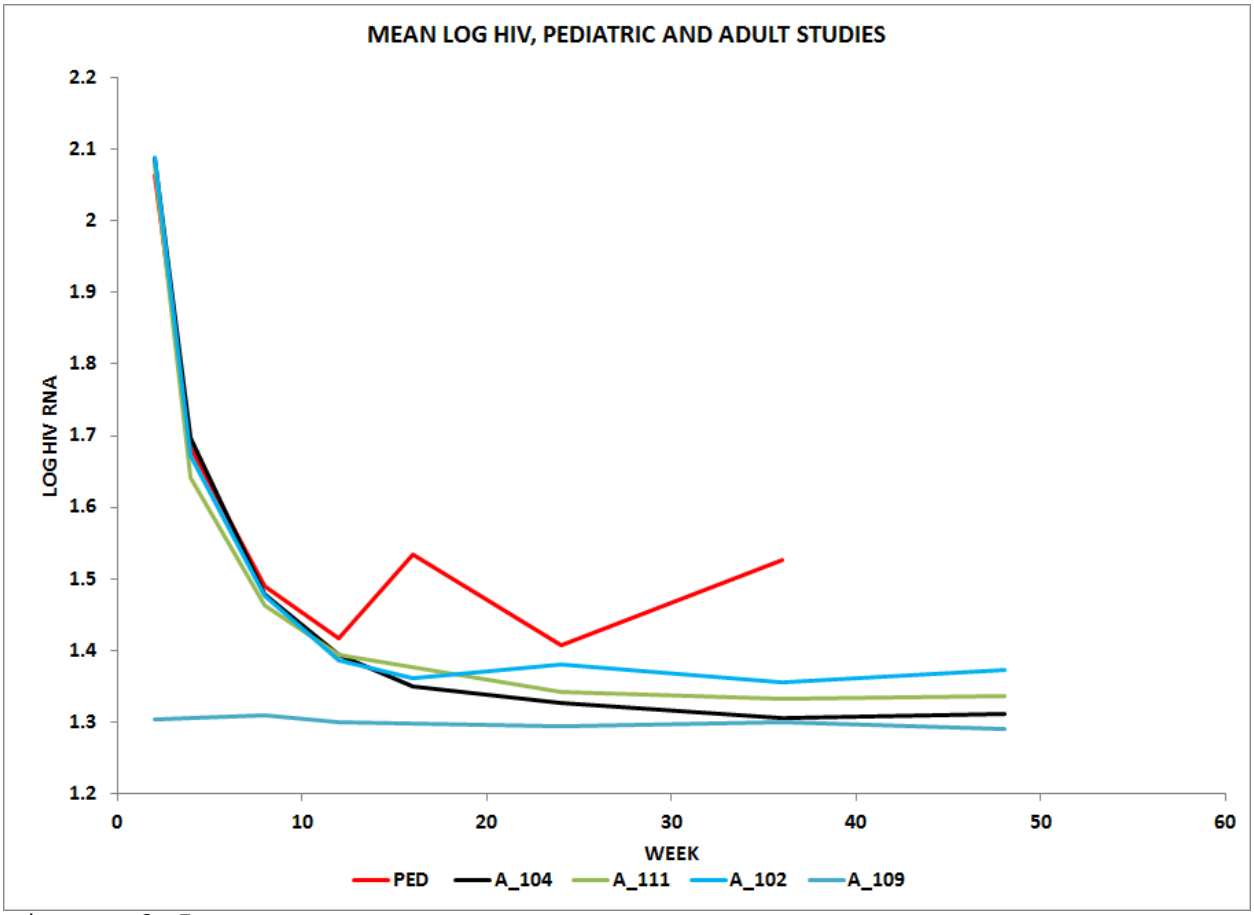


Figure 3.5 F

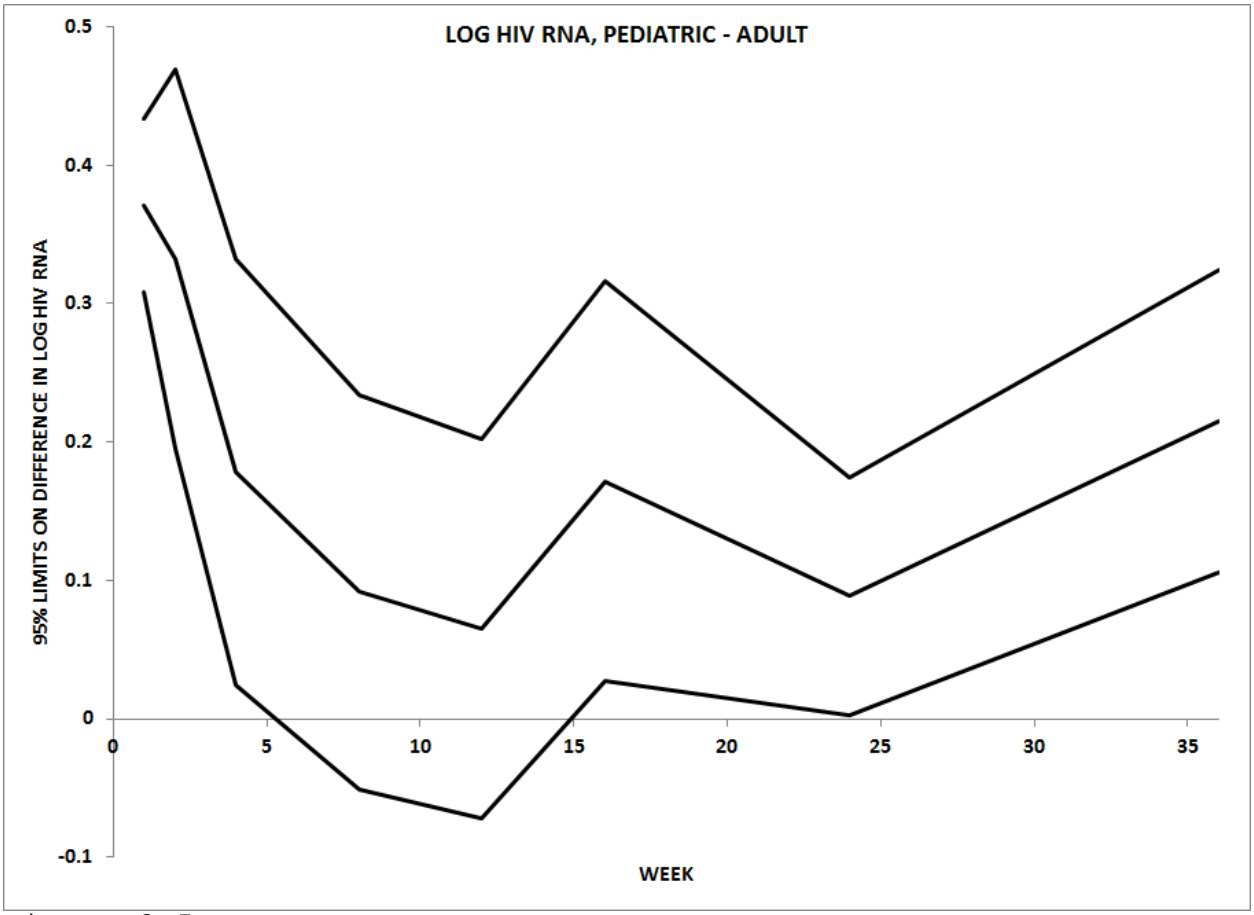


Figure 3.5 G

The log HIV RNA is a little bit worse for the pediatric subjects than for the adults but this occurs because the assay reports values below 50 for the adult studies. Remember that log(50) is 1.69 so even the apparently higher pediatric levels are still below 50 and the apparent difference may be nothing but an artifact of overly precise reporting of viral loads that are actually BLQ.

An overall conclusion is that trial 0106 is supportive of a pediatric indication.

4. Results in Special Populations

There was little evidence of interactions between treatment and any interesting covariates.

4.1 Gender, Race, and Age

The following tables give the results of analyzing the primary endpoints of all seven trials by age, sex, race and the stratum variable used at randomization. For each trial, the tables give the mean difference in the estimated parameter, the lower and upper 95% confidence intervals for the difference, the mean values in the DTG and control arms, and the p-value for testing homogeneity across the sub-groups under consideration. The analyses in this section are all conducted by simple normal approximation without using the protocol specified Mantel-Haenszel weighting based on the randomization strata.

TABLE 4.1 A

TRIAL_0104_%BLQ

	MEAN DIFF	95% LIMITS LOWER	UPPER	TAF	STB	PVALU
ALL	1.0%	-2.5%	4.4%	406/435=93.3%	399/432=92.4%	
AGEQ						
<=27	10.4%	3.1%	17.7%	121/125=96.8%	89/103=86.4%	0.023
27-34	-1.5%	-7.7%	4.7%	109/117=93.2%	106/112=94.6%	
34-42	-1.9%	-9.4%	5.7%	91/100=91.0%	91/98=92.9%	
>42	-3.6%	-10.5%	3.4%	85/93=91.4%	113/119=95.0%	
OLD						
<65	1.0%	-2.4%	4.5%	404/433=93.3%	393/426=92.3%	
>=65	0.0%	0.0%	0.0%	2/2=100%	6/6=100%	
SEX						
F	1.5%	-7.1%	10.1%	67/71=94.4%	52/56=92.9%	0.87
M	0.8%	-2.9%	4.6%	339/364=93.1%	347/376=92.3%	
RACE						
ASIAN	2.2%	-3.4%	7.9%	79/81=97.5%	81/85=95.3%	0.47
BLACK	8.2%	-2.9%	19.4%	82/94=87.2%	64/81=79.0%	
OTHER	0.0%	0.0%	0.0%	10/10=100%	11/11=100%	
WHITE	-1.3%	-5.2%	2.6%	235/250=94.0%	243/255=95.3%	
ETHNIC						
Hispanic	-2.6%	-11.5%	6.2%	55/60=91.7%	66/70=94.3%	0.39
Not	1.6%	-2.1%	5.3%	351/375=93.6%	333/362=92.0%	

TABLE 4.1 A

TRIAL_0111_%BLQ

	MEAN DIFF	95% LIMITS LOWER	UPPER	TAF	STB	PVALU
ALL	2.4%	-1.7%	6.6%	390/431=90.5%	383/435=88.0%	
AGEQ						
<=27	6.5%	-3.1%	16.1%	115/133=86.5%	84/105=80.0%	0.12
27-34	3.7%	-3.4%	10.9%	94/100=94.0%	102/113=90.3%	
34-43	-5.8%	-13.6%	1.9%	90/102=88.2%	95/101=94.1%	
>43	6.9%	-0.5%	14.3%	91/96=94.8%	102/116=87.9%	
OLD						
<65	2.5%	-1.6%	6.7%	389/430=90.5%	379/431=87.9%	
>=65	0.0%	0.0%	0.0%	1/1=100%	4/4=100%	
SEX						
F	12.1%	1.8%	22.3%	59/62=95.2%	59/71=83.1%	0.059
M	0.7%	-3.8%	5.2%	331/369=89.7%	324/364=89.0%	
RACE						
ASIAN	3.8%	-21.0%	28.5%	17/20=85.0%	13/16=81.3%	0.99
BLACK	3.5%	-4.5%	11.6%	115/129=89.1%	113/132=85.6%	
OTHER	2.7%	-8.3%	13.7%	44/47=93.6%	40/44=90.9%	
WHITE	1.8%	-3.6%	7.1%	214/235=91.1%	217/243=89.3%	
ETHNIC						
Hispanic	-1.0%	-9.2%	7.1%	96/107=89.7%	88/97=90.7%	0.68
Not	3.5%	-1.3%	8.3%	294/324=90.7%	294/337=87.2%	

TABLE 4.1 A

TRIAL_0109_%BLQ

	MEAN DIFF	95% LIMITS LOWER	UPPER	TAF	CONTROL	PVALU
ALL	0.9%	-1.8%	3.7%	760/799=95.1%	374/397=94.2%	
AGEQ						
<=33	0.3%	-4.4%	5.0%	204/213=95.8%	106/111=95.5%	0.66
33-41	3.2%	-2.8%	9.1%	202/211=95.7%	87/94=92.6%	
41-48	1.9%	-3.8%	7.6%	173/181=95.6%	89/95=93.7%	
>48	-1.5%	-7.2%	4.1%	181/194=93.3%	92/97=94.8%	
OLD						
<65	0.9%	-1.9%	3.7%	750/789=95.1%	369/392=94.1%	1
>=65	0.0%	0.0%	0.0%	10/10=100%	5/5=100%	
SEX						
F	-1.0%	-10.1%	8.1%	73/78=93.6%	35/37=94.6%	0.65
M	1.1%	-1.8%	4.0%	687/721=95.3%	339/360=94.2%	
RACE						
ASIAN	3.6%	-8.0%	15.3%	47/49=95.9%	24/26=92.3%	0.78
BLACK	1.8%	-4.7%	8.2%	149/158=94.3%	87/94=92.6%	
OTHER	-3.6%	-8.6%	1.3%	53/55=96.4%	16/16=100%	
WHITE	0.5%	-2.8%	3.8%	511/537=95.2%	247/261=94.6%	
ETHNIC						
Hispanic	2.6%	-2.8%	8.0%	202/206=98.1%	63/66=95.5%	0.28
Not	0.1%	-3.1%	3.3%	558/593=94.1%	311/331=94.0%	

TABLE 4.1 A

TRIAL_0102_%BLQ

	MEAN DIFF	95% LIMITS LOWER	UPPER	TAF	STB	PVALU
ALL	3.9%	-7.1%	15.0%	99/112=88.4%	49/58=84.5%	
AGEQ						
<=26	-12.5%	-30.5%	5.5%	26/32=81.3%	15/16=93.8%	0.16
26-34	12.5%	-16.5%	41.6%	28/31=90.3%	7/9=77.8%	
34-44	8.1%	-16.3%	32.6%	22/26=84.6%	13/17=76.5%	
>44	12.5%	-3.7%	28.7%	23/23=100%	14/16=87.5%	
OLD						
<65	3.8%	-7.3%	14.9%	98/111=88.3%	49/58=84.5%	1
>=65	.	.	.	1/1=100%	0/0=.	
SEX						
F	0.0%	0.0%	0.0%	4/4=100%	1/1=100%	1
M	3.8%	-7.5%	15.0%	95/108=88.0%	48/57=84.2%	
RACE						
ASIAN	50.0%	-19.3%	119.3%	3/3=100%	1/2=50.0%	0.47
BLACK	5.0%	-20.0%	30.0%	28/35=80.0%	12/16=75.0%	
WHITE	1.9%	-9.3%	13.1%	68/74=91.9%	36/40=90.0%	
ETHNIC						
Hispanic	9.1%	-7.9%	26.1%	25/25=100%	10/11=90.9%	0.16
Not	2.1%	-11.0%	15.2%	74/87=85.1%	39/47=83.0%	

4.2 Baseline HIV, CD4, HIV Status

The following tables give the results of analyzing the primary endpoints of all four trials by covariates reflecting baseline illness levels: baseline HIV level, baseline CD4 count, baseline HIV status , and also risk factor attributed to initial infection. The tables are laid out as in the previous section.

TABLE 4.1 A

TRIAL_0104_%BLQ

	MEAN DIFF	95% LIMITS LOWER	UPPER	TAF	STB	PVALU
BASELINE HV RNA						
<100_K	1.7%	-1.9%	5.3%	314/331=94.9%	313/336=93.2%	0.32
100-400_K	-4.2%	-14.5%	6.1%	68/79=86.1%	65/72=90.3%	
>400_K	8.5%	-6.8%	23.8%	24/25=96.0%	21/24=87.5%	
BASELINE CD4 COUNT						
<50	-3.3%	-35.9%	29.2%	8/10=80.0%	10/12=83.3%	0.87
50-200	-1.0%	-12.2%	10.1%	44/48=91.7%	38/41=92.7%	
>200	1.3%	-2.3%	4.9%	354/377=93.9%	351/379=92.6%	
HIV STATUS						
AIDS	8.9%	-23.3%	41.1%	8/9=88.9%	8/10=80.0%	0.79
Asymp.	0.4%	-3.1%	3.9%	375/402=93.3%	377/406=92.9%	
Symp.	9.0%	-10.1%	28.1%	22/23=95.7%	13/15=86.7%	
Unknown	0.0%	0.0%	0.0%	1/1=100%	1/1=100%	
RISK						
Hetero_Sex	1.6%	-5.8%	9.0%	90/96=93.8%	82/89=92.1%	0.28
Homo_Sex	-0.5%	-4.4%	3.4%	295/317=93.1%	305/326=93.6%	
Needle	50.0%	1.0%	99.0%	9/9=100%	2/4=50.0%	
Transfus	0.0%	0.0%	0.0%	1/1=100%	2/2=100%	
Vert_Trans	.	.	.	2/2=100%	0/0=.	
Unknown	17.3%	-15.0%	49.5%	9/10=90.0%	8/11=72.7%	

TABLE 4.1 A

TRIAL_0111_%BLQ

	MEAN DIFF	95% LIMITS LOWER	UPPER	TAF	STB	PVALU
BASELINE HV RNA						
<100_K	4.2%	-0.2%	8.7%	313/339=92.3%	296/336=88.1%	0.14
100-400_K	-1.3%	-12.5%	9.9%	58/68=85.3%	71/82=86.6%	
>400_K	-15.0%	-34.7%	4.8%	19/24=79.2%	16/17=94.1%	
BASELINE CD4 COUNT						
<50	-21.9%	-48.7%	4.9%	10/14=71.4%	14/15=93.3%	0.27
50-200	-0.7%	-15.5%	14.1%	34/40=85.0%	42/49=85.7%	
>200	3.6%	-0.7%	7.9%	345/376=91.8%	327/371=88.1%	
HIV STATUS						
AIDS	-6.5%	-29.9%	16.8%	17/21=81.0%	14/16=87.5%	0.84
Asymp.	3.1%	-1.2%	7.4%	344/378=91.0%	348/396=87.9%	
Symp.	0.0%	-17.0%	17.0%	27/30=90.0%	18/20=90.0%	
Unknown	0.0%	0.0%	0.0%	2/2=100%	3/3=100%	
RISK						
Hetero_Sex	2.4%	-6.6%	11.3%	82/91=90.1%	86/98=87.8%	0.59
Homo_Sex	1.3%	-3.4%	6.1%	291/323=90.1%	276/311=88.7%	
Needle	14.3%	-11.6%	40.2%	8/8=100%	6/7=85.7%	
Transfus	0.0%	0.0%	0.0%	1/1=100%	2/2=100%	
Unknown	23.5%	3.4%	43.7%	8/8=100%	13/17=76.5%	

TABLE 4.1 A

TRIAL_0109_%BLQ

	MEAN DIFF	95% LIMITS LOWER	UPPER	TAF	CONTROL	PVALU
BASELINE HV RNA						
<50	1.1%	-1.6%	3.8%	748/784=95.4%	365/387=94.3%	0.4
>50	-10.0%	-37.5%	17.5%	12/15=80.0%	9/10=90.0%	
BASELINE CD4 COUNT						
50-200	-50.0%	-119.3%	19.3%	1/2=50.0%	3/3=100%	0.045
200-350	2.0%	-11.1%	15.0%	44/47=93.6%	22/24=91.7%	
350-500	9.5%	0.6%	18.3%	112/115=97.4%	51/58=87.9%	
>500	-0.6%	-3.4%	2.3%	603/635=95.0%	298/312=95.5%	
RISK						
Hetero_Sex	2.9%	-5.4%	11.1%	129/138=93.5%	58/64=90.6%	0.66
Homo_Sex	0.5%	-2.4%	3.4%	605/634=95.4%	301/317=95.0%	
Needle	-12.5%	-35.4%	10.4%	7/8=87.5%	4/4=100%	
Transfus	0.0%	0.0%	0.0%	2/2=100%	2/2=100%	
Unknown	10.0%	-8.6%	28.6%	17/17=100%	9/10=90.0%	

TABLE 4.1 A

TRIAL_0102_%BLQ

	MEAN DIFF	95% LIMITS LOWER	UPPER	TAF	STB	PVALU
BASELINE HV RNA						
<100_K	6.8%	-5.1%	18.6%	86/93=92.5%	36/42=85.7%	0.36
100-400_K	-13.2%	-43.9%	17.5%	10/14=71.4%	11/13=84.6%	
>400_K	-6.7%	-75.1%	61.8%	3/5=60.0%	2/3=66.7%	
BASELINE CD4 COUNT						
<50	0.0%	0.0%	0.0%	2/2=100%	1/1=100%	0.83
50-200	-13.3%	-49.7%	23.1%	8/12=66.7%	8/10=80.0%	
200-350	5.8%	-19.1%	30.7%	27/32=84.4%	11/14=78.6%	
350-500	8.6%	-12.0%	29.2%	30/33=90.9%	14/17=82.4%	
>500	3.2%	-10.0%	16.4%	32/33=97.0%	15/16=93.8%	
HIV STATUS						
AIDS	-25.0%	-67.4%	17.4%	3/4=75.0%	1/1=100%	0.17
Asymp.	0.4%	-10.2%	11.1%	88/99=88.9%	46/52=88.5%	
Symp.	48.9%	1.3%	96.5%	8/9=88.9%	2/5=40.0%	

4.3 Baseline Concomitant Disease Covariates

The following tables give the results of analyzing the primary endpoints of three trials (0104, 0111, and 0102) by covariates relating to concomitant baseline diseases: cardiovascular disease, diabetes mellitus, hypertension, and hyperlipidemia.

TABLE 4.1 A

TRIAL_0104_%BLQ

	MEAN DIFF	95% LIMITS LOWER	UPPER	TAF	STB	PVALU
CARDIO-VASCULAR DISEASE						
N	1.1%	-2.4%	4.6%	400/429=93.2%	388/421=92.2%	1
Y	0.0%	0.0%	0.0%	6/6=100%	11/11=100%	
HYPERLIPIDEMIA						
N	0.5%	-3.2%	4.1%	366/393=93.1%	354/382=92.7%	0.42
Y	5.2%	-5.3%	15.8%	40/42=95.2%	45/50=90.0%	
HYPERTENSION						
N	1.5%	-2.1%	5.0%	359/381=94.2%	333/359=92.8%	0.36
Y	-3.4%	-14.6%	7.8%	47/54=87.0%	66/73=90.4%	
DIABETES MELLITUS						
N	1.1%	-2.4%	4.6%	396/424=93.4%	383/415=92.3%	0.67
Y	-3.2%	-23.5%	17.1%	10/11=90.9%	16/17=94.1%	

TABLE 4.1 A

TRIAL_0111_%BLQ

	MEAN DIFF	95% LIMITS LOWER	UPPER	TAF	STB	PVALU
CARDIO-VASCULAR DISEASE						
N	2.4%	-1.7%	6.6%	385/426=90.4%	380/432=88.0%	1
Y	0.0%	0.0%	0.0%	5/5=100%	3/3=100%	
HYPERLIPIDEMIA						
N	2.8%	-1.6%	7.2%	345/381=90.6%	338/385=87.8%	0.69
Y	0.0%	-11.8%	11.8%	45/50=90.0%	45/50=90.0%	
HYPERTENSION						
N	2.1%	-2.4%	6.5%	332/367=90.5%	320/362=88.4%	0.73
Y	4.3%	-6.3%	15.0%	58/64=90.6%	63/73=86.3%	
DIABETES MELLITUS						
N	2.1%	-2.2%	6.3%	376/417=90.2%	363/412=88.1%	0.22
Y	13.0%	-0.7%	26.8%	14/14=100%	20/23=87.0%	

TABLE 4.1 A

TRIAL_0102_%BLQ

	MEAN DIFF	95% LIMITS LOWER	UPPER	TAF	STB	PVALU
HYPERLIPIDEMIA						
N	3.9%	-8.4%	16.2%	84/97=86.6%	43/52=82.7%	
Y	0.0%	0.0%	0.0%	15/15=100%	6/6=100%	
HYPERTENSION						
N	7.1%	-4.8%	19.0%	88/98=89.8%	43/52=82.7%	0.11
Y	-21.4%	-42.9%	0.1%	11/14=78.6%	6/6=100%	
DIABETES MELLITUS						
N	3.6%	-7.7%	15.0%	94/107=87.9%	48/57=84.2%	
Y	0.0%	0.0%	0.0%	5/5=100%	1/1=100%	

4.4 Region, Site Covariates

The following tables give the results of analyzing the primary endpoints of three trials (0104, 0111, and 0109) by other covariates including country and site.

TABLE 4.1 A

TRIAL_0104_%BLQ

	MEAN DIFF	95% LIMITS LOWER	UPPER	TAF	STB	PVALU
SITEGRP						
Region_1	0.8%	-16.2%	17.9%	21/23=91.3%	19/21=90.5%	0.94
Region_2	-4.3%	-18.6%	9.9%	21/23=91.3%	22/23=95.7%	
Region_3	0.3%	-6.1%	6.7%	61/63=96.8%	56/58=96.6%	
Region_4	-4.8%	-13.8%	4.3%	39/42=92.9%	41/42=97.6%	
Region_5	5.3%	-1.8%	12.4%	32/32=100%	36/38=94.7%	
Region_6	5.1%	-7.5%	17.7%	33/35=94.3%	33/37=89.2%	
Region_7	-0.5%	-11.7%	10.7%	42/46=91.3%	45/49=91.8%	
Region_8	1.5%	-8.7%	11.6%	44/47=93.6%	47/51=92.2%	
Region_9	4.1%	-7.1%	15.4%	62/68=91.2%	47/54=87.0%	
Region_10	2.0%	-8.5%	12.5%	26/27=96.3%	33/35=94.3%	
Region_11	2.9%	-16.6%	22.4%	25/29=86.2%	20/24=83.3%	
REGION						
US	2.1%	-2.9%	7.1%	232/252=92.1%	225/250=90.0%	0.53
ex-US	-0.5%	-4.8%	3.8%	174/183=95.1%	174/182=95.6%	
COUNTRY						
AUS	2.8%	-19.2%	24.9%	17/19=89.5%	13/15=86.7%	0.99
AUT	0.0%	0.0%	0.0%	15/15=100%	8/8=100%	
BEL	0.0%	0.0%	0.0%	7/7=100%	7/7=100%	
CAN	-4.3%	-18.6%	9.9%	21/23=91.3%	22/23=95.7%	
CHE	16.7%	-4.4%	37.8%	6/6=100%	10/12=83.3%	
ESP	-4.8%	-13.8%	4.3%	39/42=92.9%	41/42=97.6%	
GBR	0.0%	0.0%	0.0%	1/1=100%	5/5=100%	
ITA	0.0%	0.0%	0.0%	3/3=100%	6/6=100%	
JPN	0.0%	0.0%	0.0%	4/4=100%	6/6=100%	
PRI	0.0%	0.0%	0.0%	2/2=100%	4/4=100%	
THA	0.3%	-6.1%	6.7%	61/63=96.8%	56/58=96.6%	
USA	2.2%	-2.9%	7.2%	230/250=92.0%	221/246=89.8%	

TABLE 4.1 A

TRIAL_0111_%BLQ

	MEAN DIFF	95% LIMITS LOWER	UPPER	TAF	STB	PVALU
SITEGRP						
Region_2	4.5%	-4.2%	13.2%	19/19=100%	21/22=95.5%	0.36
Region_5	1.5%	-8.8%	11.8%	75/86=87.2%	72/84=85.7%	
Region_6	7.2%	-4.2%	18.6%	38/40=95.0%	43/49=87.8%	
Region_7	10.2%	-0.2%	20.6%	80/88=90.9%	67/83=80.7%	
Region_8	-2.3%	-11.8%	7.2%	66/75=88.0%	84/93=90.3%	
Region_9	1.5%	-6.9%	9.8%	64/68=94.1%	63/68=92.6%	
Region_10	-15.2%	-27.4%	-2.9%	28/33=84.8%	15/15=100%	
Region_11	5.2%	-14.0%	24.4%	20/22=90.9%	18/21=85.7%	
REGION_						
US	2.1%	-3.0%	7.2%	253/280=90.4%	249/282=88.3%	0.81
ex-US	3.1%	-3.8%	10.1%	137/151=90.7%	134/153=87.6%	
COUNTRY						
CAN	4.5%	-4.2%	13.2%	19/19=100%	21/22=95.5%	0.62
DOM	11.0%	-2.3%	24.2%	29/30=96.7%	30/35=85.7%	
FRA	4.9%	-13.9%	23.6%	15/16=93.8%	16/18=88.9%	
GBR	1.7%	-13.2%	16.6%	23/25=92.0%	28/31=90.3%	
ITA	-2.5%	-47.7%	42.7%	6/10=60.0%	5/8=62.5%	
MEX	-4.2%	-26.7%	18.4%	14/16=87.5%	11/12=91.7%	
NLD	-25.0%	-75.0%	25.0%	3/6=50.0%	6/8=75.0%	
PRI	33.3%	-20.0%	86.7%	4/4=100%	2/3=66.7%	
PRT	0.0%	0.0%	0.0%	21/21=100%	16/16=100%	
SWE	54.2%	-3.9%	112.2%	7/8=87.5%	1/3=33.3%	
USA	1.7%	-3.4%	6.8%	249/276=90.2%	247/279=88.5%	

TABLE 4.1 A

TRIAL_0109_%BLQ

	MEAN DIFF	95% LIMITS LOWER	UPPER	TAF	CONTROL	PVALU
SITEGRP						
Region_1	-13.0%	-26.8%	0.7%	20/23=87.0%	12/12=100%	0.21
Region_2	1.2%	-10.9%	13.2%	45/48=93.8%	25/27=92.6%	
Region_3	0.0%	0.0%	0.0%	22/22=100%	12/12=100%	
Region_4	-1.8%	-23.7%	20.1%	33/47=70.2%	18/25=72.0%	
Region_5	1.2%	-3.5%	5.9%	159/163=97.5%	79/82=96.3%	
Region_6	5.0%	-0.5%	10.5%	145/145=100%	57/60=95.0%	
Region_7	-0.5%	-5.7%	4.7%	109/112=97.3%	45/46=97.8%	
Region_8	0.1%	-4.7%	4.9%	109/112=97.3%	70/72=97.2%	
Region_9	8.9%	-5.2%	23.0%	54/56=96.4%	21/24=87.5%	
Region_10	-4.5%	-14.5%	5.6%	64/71=90.1%	35/37=94.6%	
REGION_						
Ex-US	-1.2%	-9.7%	7.3%	143/164=87.2%	76/86=88.4%	0.34
US	1.3%	-1.2%	3.9%	617/635=97.2%	298/311=95.8%	
COUNTRY						
AUS	-13.0%	-26.8%	0.7%	20/23=87.0%	12/12=100%	0.48
AUT	-18.2%	-41.0%	4.6%	9/11=81.8%	2/2=100%	
BEL	-35.7%	-60.8%	-10.6%	9/14=64.3%	8/8=100%	
CAN	1.2%	-10.9%	13.2%	45/48=93.8%	25/27=92.6%	
DOM	0.0%	0.0%	0.0%	16/16=100%	8/8=100%	
ESP	0.0%	-98.0%	98.0%	1/2=50.0%	1/2=50.0%	
FRA	40.0%	-2.9%	82.9%	4/4=100%	3/5=60.0%	
GBR	-15.0%	-75.4%	45.4%	3/5=60.0%	3/4=75.0%	
ITA	45.0%	-6.1%	96.1%	7/10=70.0%	1/4=25.0%	
MEX	37.5%	-35.5%	110.5%	7/8=87.5%	1/2=50.0%	
PRI	0.0%	0.0%	0.0%	23/23=100%	10/10=100%	
THA	0.0%	0.0%	0.0%	22/22=100%	12/12=100%	
USA	1.4%	-1.3%	4.0%	594/612=97.1%	288/301=95.7%	

4.4 Forest Plots Summarizing Preceding Tables

The following graphs, figures 4.4 A-G give a visual view of the preceding tables, with forest plots giving the point estimates and 95% confidence intervals for the difference in percent BLQ, TAF minus control. Small subgroups with very wide confidence intervals are omitted. There are two graphs for each of trials 0104, 0111, and 0109 to avoid excessive clutter.

Figure 4.4 A

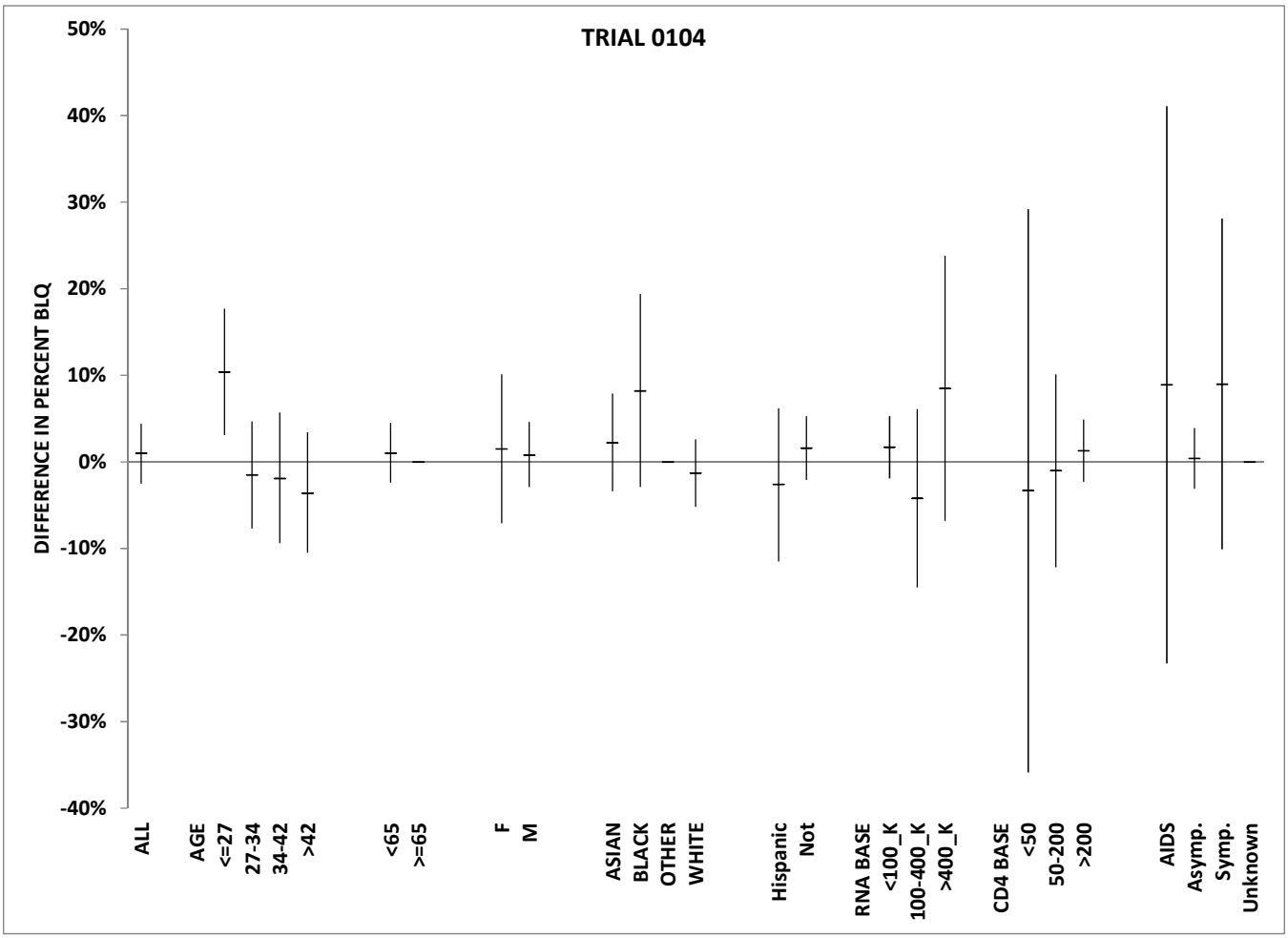

TRIAL 0104
DIFFERENCE IN PERCENT BLQ
50%
40%
30%
20%
10%
0%
-10%
-20%
-30%
-40%
ALL
AGE
<=27
27-34
34-42
>42
<65
>=65
F
M
ASIAN
BLACK
OTHER
WHITE
Hispanic
Not
RNA BASE
<100_K
100-400_K
>400_K
CD4 BASE
<50
50-200
>200
AIDS
Asymp.
Symp.
Unknown

Figure 4.4 B

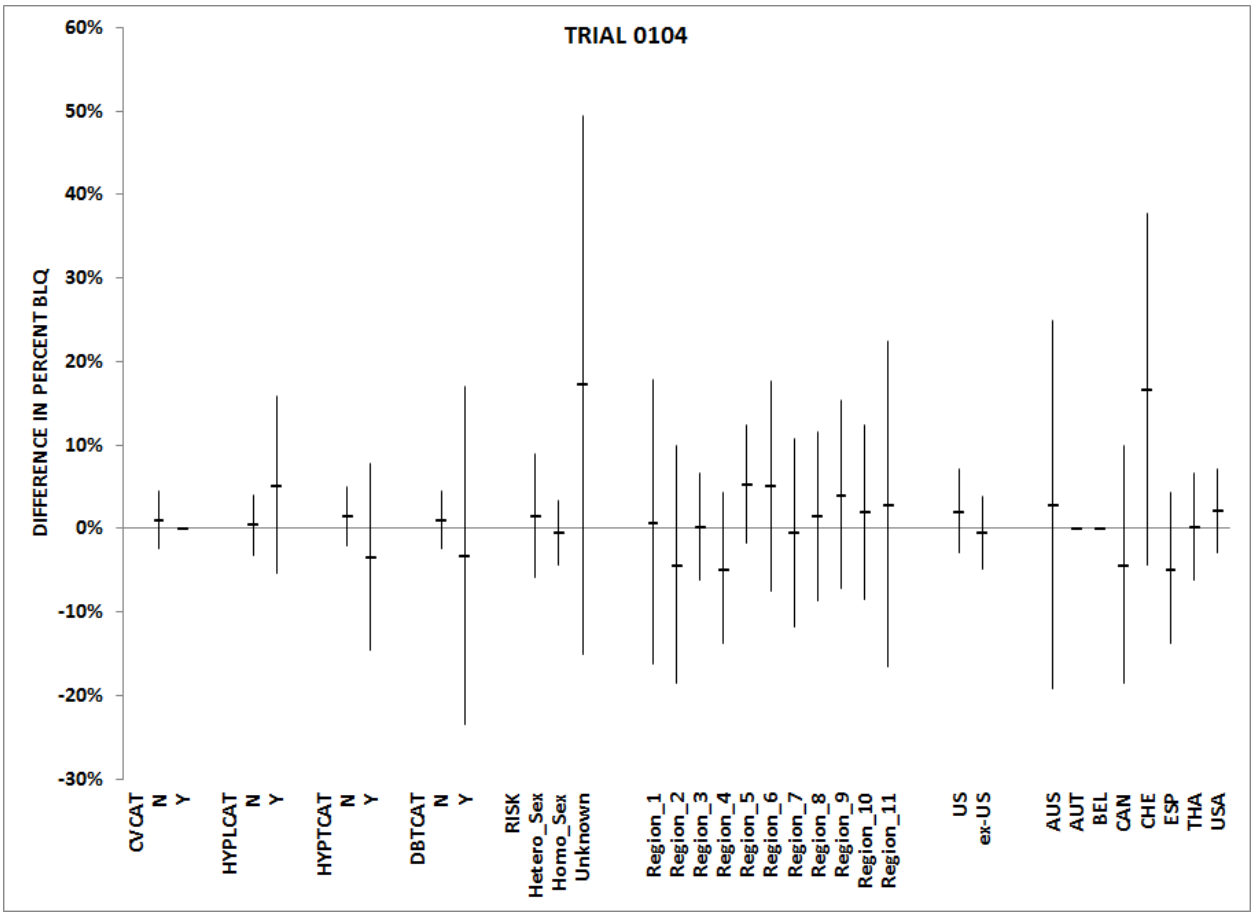

TRIAL 0104
DIFFERENCE IN PERCENT BLQ
60%
50%
40%
30%
20%
10%
0%
-10%
-20%
-30%
CVCAT
N
Y
HYPLCAT
N
Y
HYPTCAT
N
Y
DBTCAT
N
Y
RISK
Hetero_Sex
Homo_Sex
Unknown
Region_1
Region_2
Region_3
Region_4
Region_5
Region_6
Region_7
Region_8
Region_9
Region_10
Region_11
US
ex-US
AUS
AUT
BEL
CAN
CHE
ESP
THA
USA

Figure 4.4 C

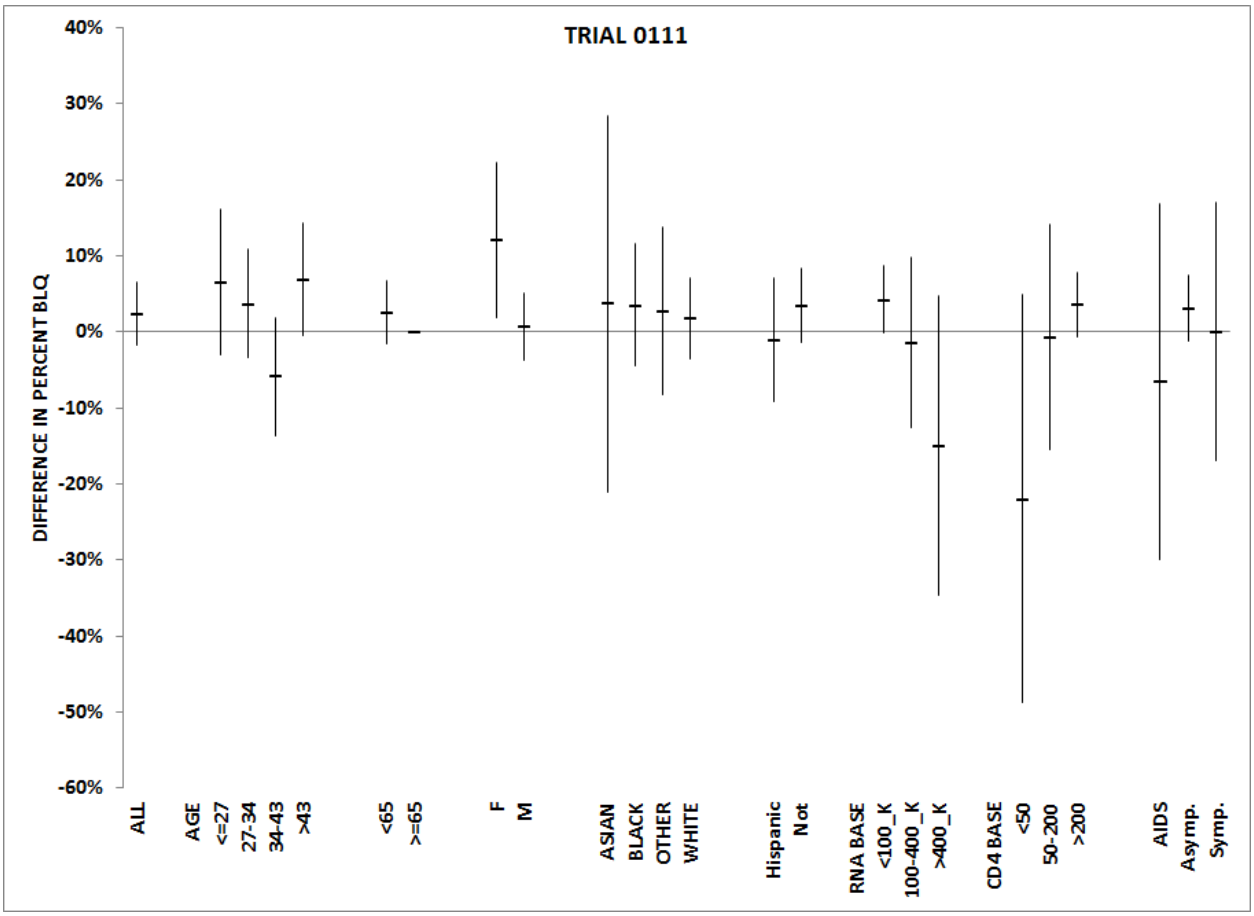

TRIAL 0111
DIFFERENCE IN PERCENT BLQ
40%
30%
20%
10%
0%
-10%
-20%
-30%
-40%
-50%
-60%
ALL
AGE
<=27
27-34
34-43
>43
<65
>=65
F
M
ASIAN
BLACK
OTHER
WHITE
Hispanic
Not
RNA BASE
<100_K
100-400_K
>400_K
CD4 BASE
<50
50-200
>200
AIDS
Asymp.
Symp.

Figure 4.4 D

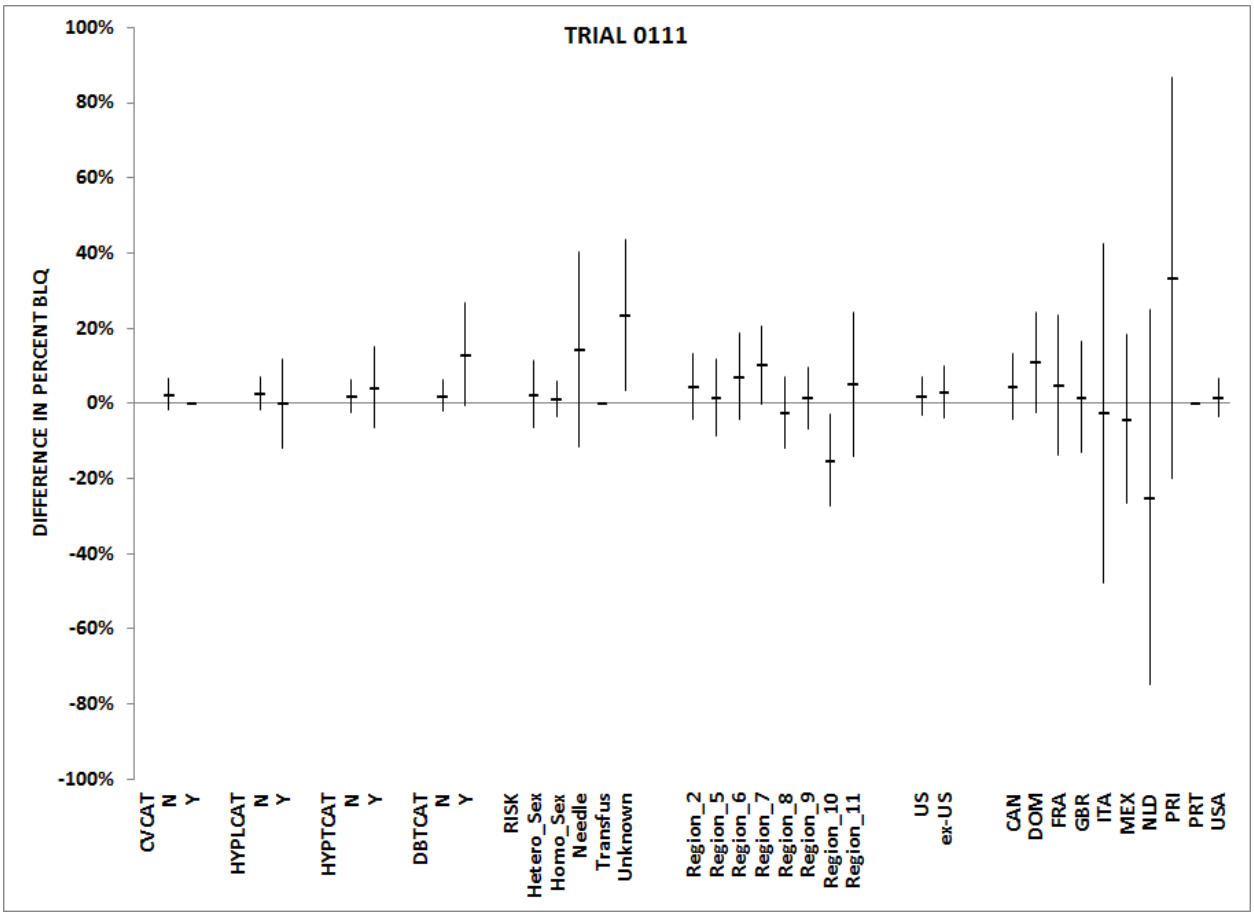

TRIAL 0111
DIFFERENCE IN PERCENT BLQ
100%
80%
60%
40%
20%
0%
-20%
-40%
-60%
-80%
-100%
CVCAT
N
Y
HYPLCAT
N
Y
HYPTCAT
N
Y
DBTCAT
N
Y
RISK
Hetero_Sex
Homo_Sex
Needle
Transfus
Unknown
Region_2
Region_5
Region_6
Region_7
Region_8
Region_9
Region_10
Region_11
US
ex-US
CAN
DOM
FRA
GBR
ITA
MEX
NLD
PRI
PRT
USA

Figure 4.4 E

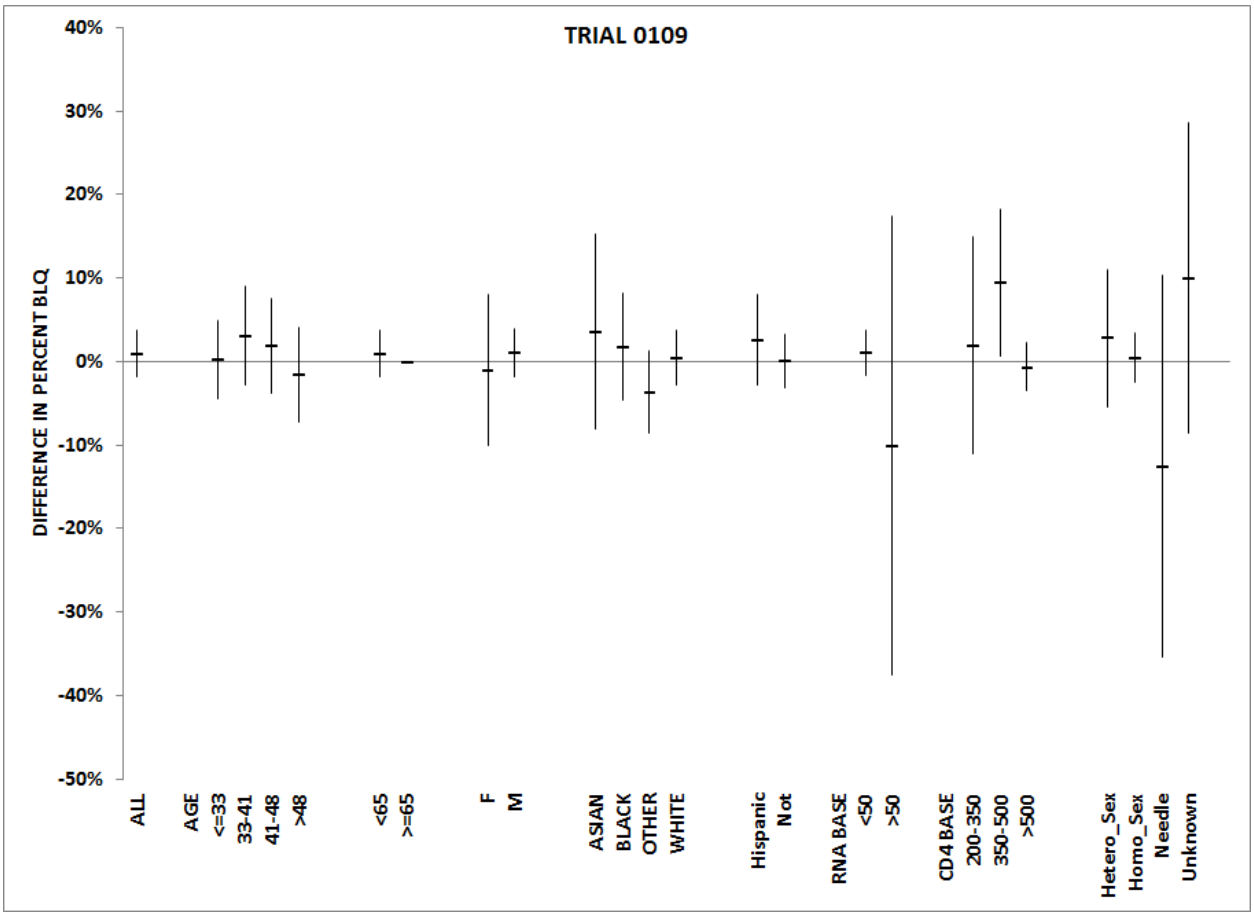

TRIAL 0109
DIFFERENCE IN PERCENT BLQ
40%
30%
20%
10%
0%
-10%
-20%
-30%
-40%
-50%
ALL
AGE
<=33
33-41
41-48
>48
<65
>=65
F
M
ASIAN
BLACK
OTHER
WHITE
Hispanic
Not
RNA BASE
<50
>50
CD4 BASE
200-350
350-500
>500
Hetero_Sex
Homo_Sex
Needle
Unknown

Figure 4.4 F

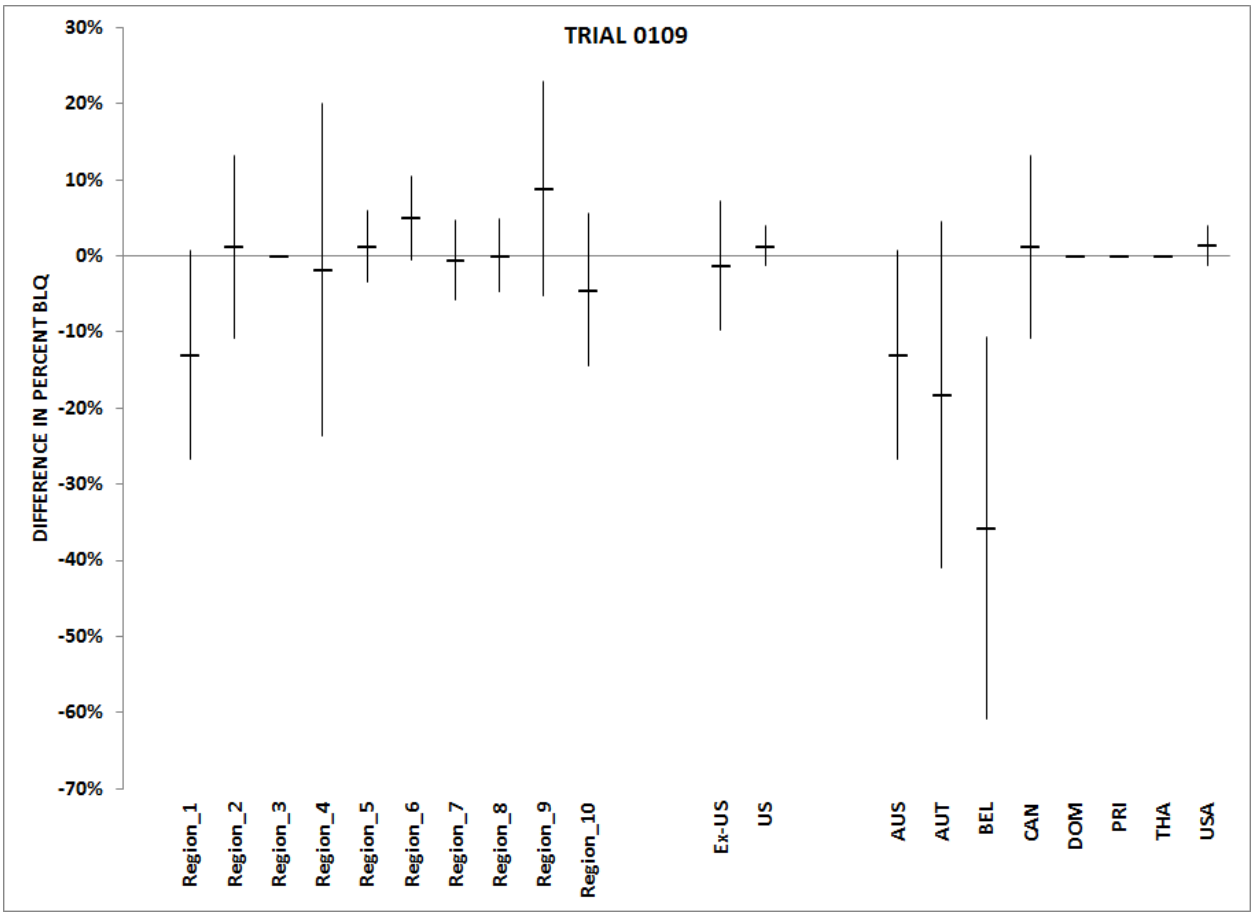
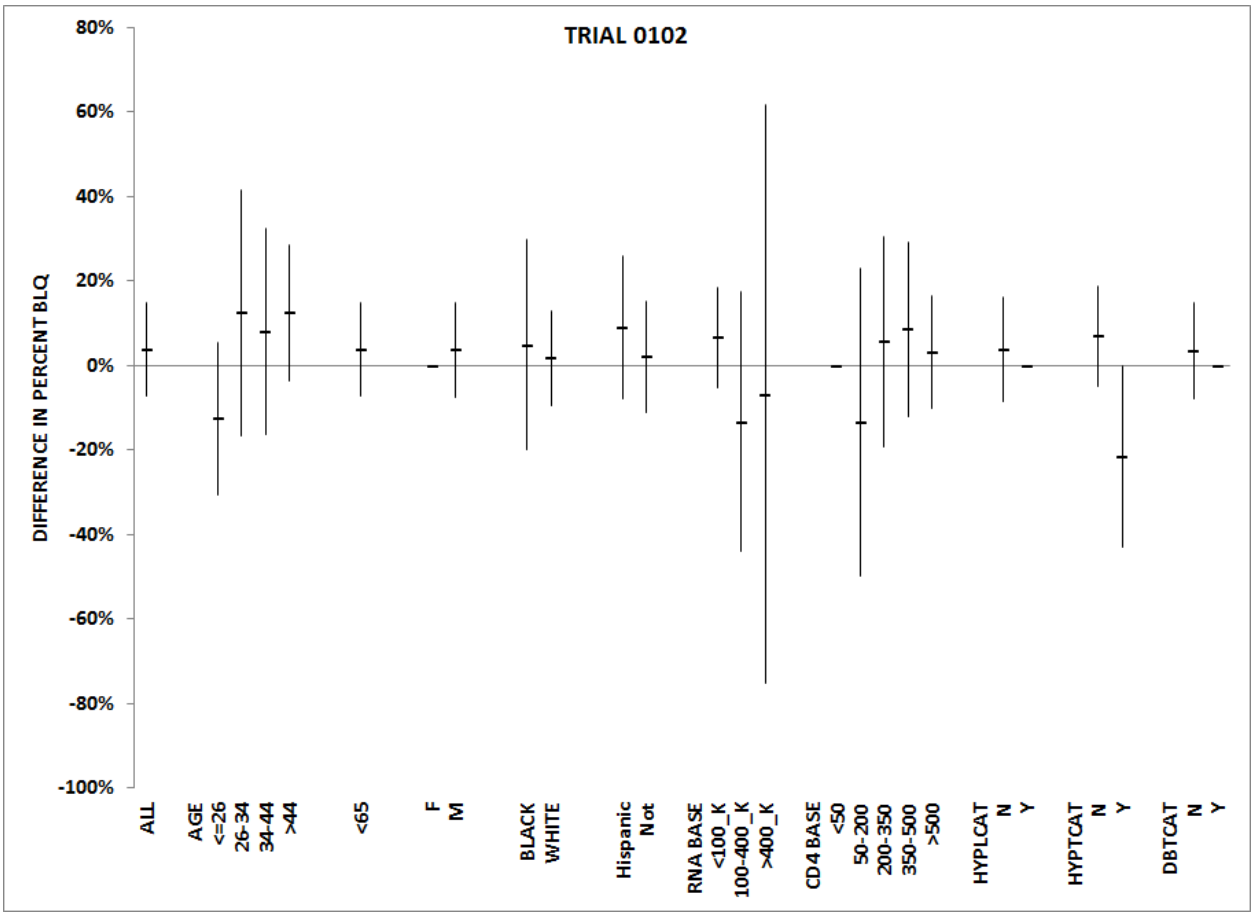

TRIAL 0109
DIFFERENCE IN PERCENT BLQ
30%
20%
10%
0%
-10%
-20%
-30%
-40%
-50%
-60%
-70%
Region_1
Region_2
Region_3
Region_4
Region_5
Region_6
Region_7
Region_8
Region_9
Region_10
Ex-US
US
AUS
AUT
BEL
CAN
DOM
PRI
THA
USA

Figure 4.4 G



Mostly, the confidence intervals in these forest plots cross the zero line, indicating that there is no statistically difference in the arms within that sub-group with respect to percent BLQ at week 48. Age <=27 in trial 0104, Females in trial 0111, Belgium in trial 0102, and CD4 count in the interval 350-500 seem to be the only violators. Nothing systematic appears and nothing seems label-worthy.

4.5 Exploratory Looks for Treatment-Covariate Interactions

The following graphs are intended to look for any suggestions of treatment-covariate interactions. By absence of interaction, this reviewer means that the difference between TAF and control is constant across all levels of the covariate. This reviewer does not count a change in the TAF response and a change in the control response as an interaction. One would obviously expect that both TAF and control would perform better in, say, subjects with lower baseline HIV load than in subjects with higher baseline HIV load. The question of interest is whether both regimens improve or worsen by comparable amounts as one goes from one covariate level to another.

The first four graphs, figures 4.5 A-D, give forest plots but sorted from smallest to largest difference in percent BLQ rather than, as above in figures 4.4 A-G, grouped by covariate. In these plots, absence of covariate-treatment interaction would be indicated by a nearly straight-line in the mean differences, going from lowest to highest. One should be looking for high or low levels of the mean difference that differ conspicuously from such a straight line.

Figure 4.5 A

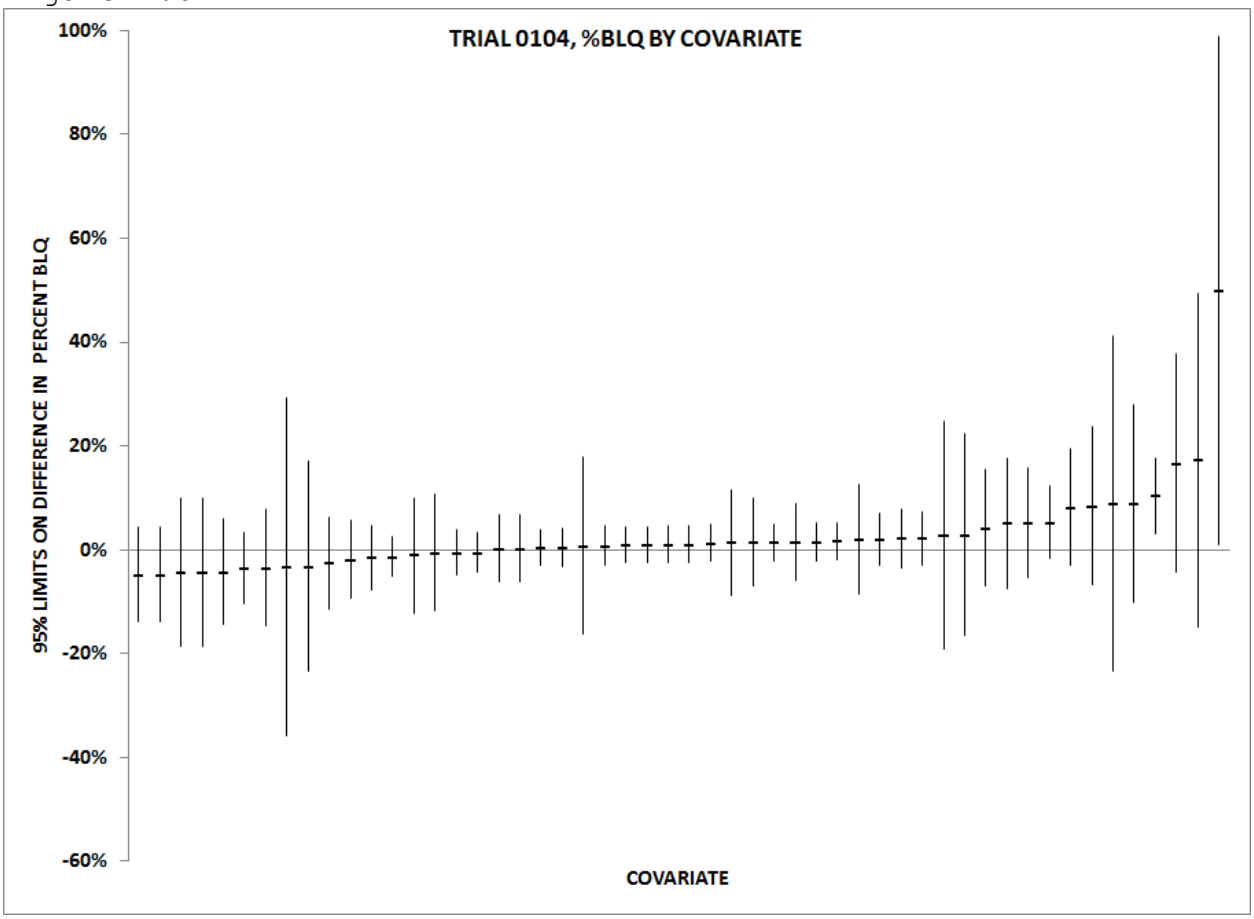

TRIAL 0104, %BLQ BY COVARIATE
100%
80%
60%
40%
20%
0%
-20%
-40%
-60%
95% LIMITS ON DIFFERENCE IN PERCENT BLQ
COVARIATE

Figure 4.5 B

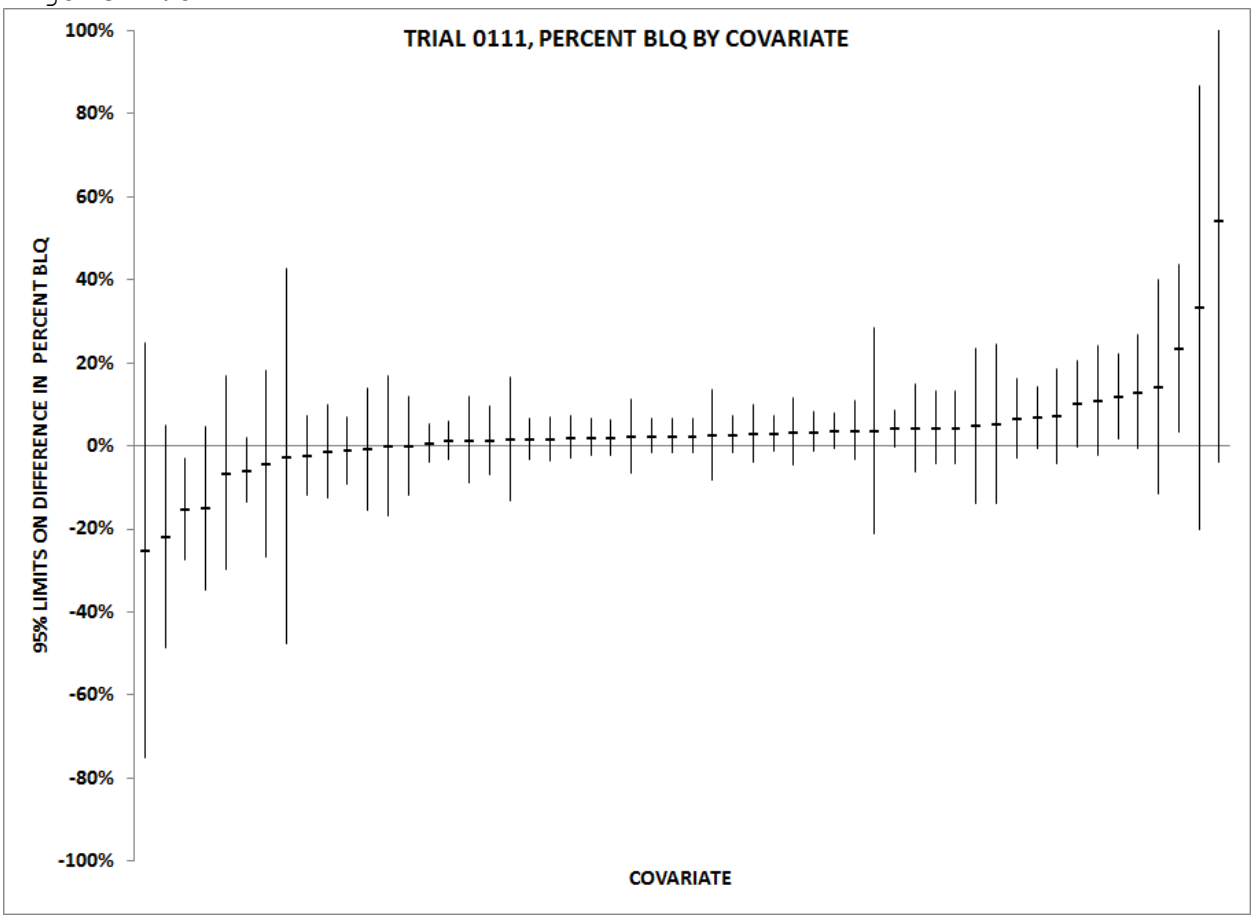

TRIAL 0111, PERCENT BLQ BY COVARIATE
100%
80%
60%
40%
20%
0%
-20%
-40%
-60%
-80%
-100%
95% LIMITS ON DIFFERENCE IN PERCENT BLQ
COVARIATE

Figure 4.5 C

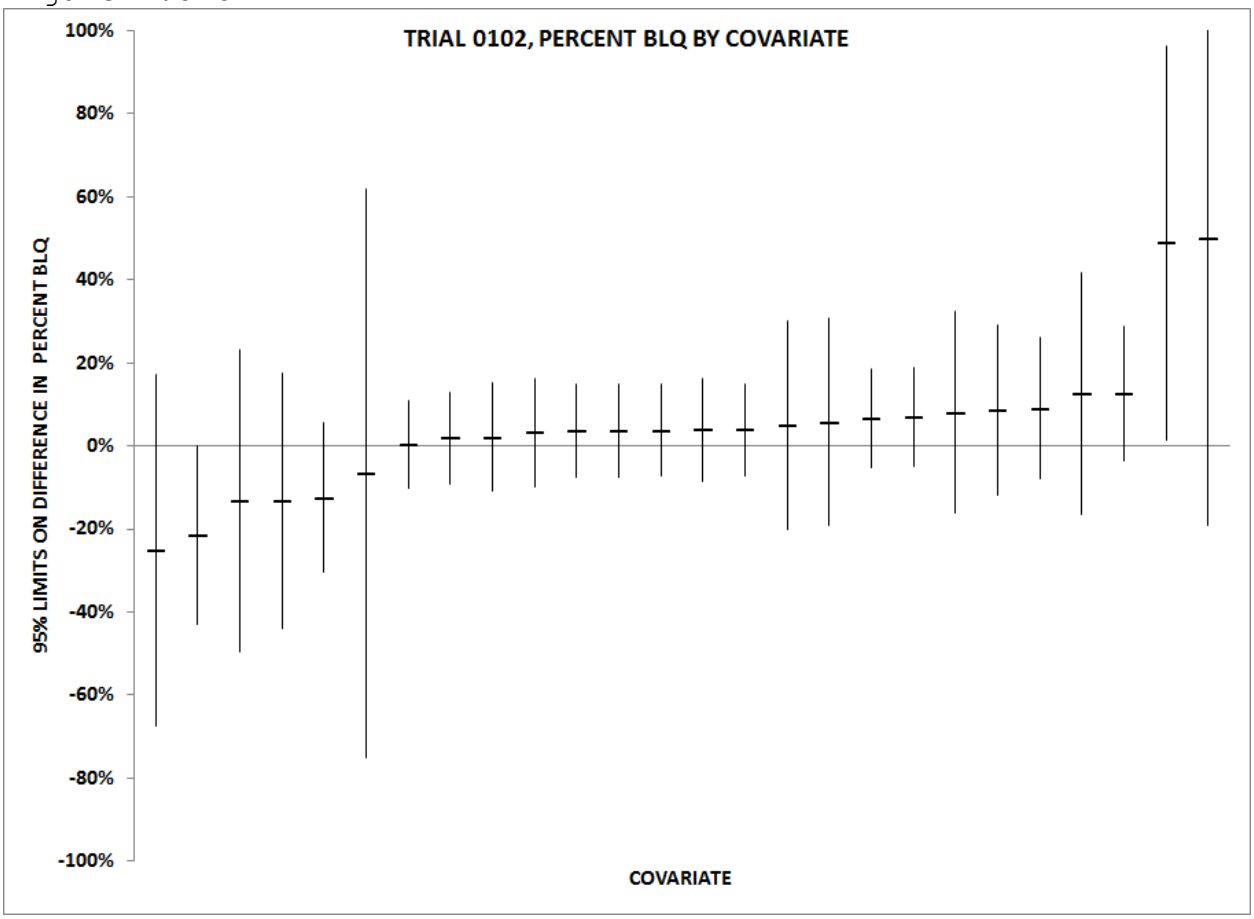
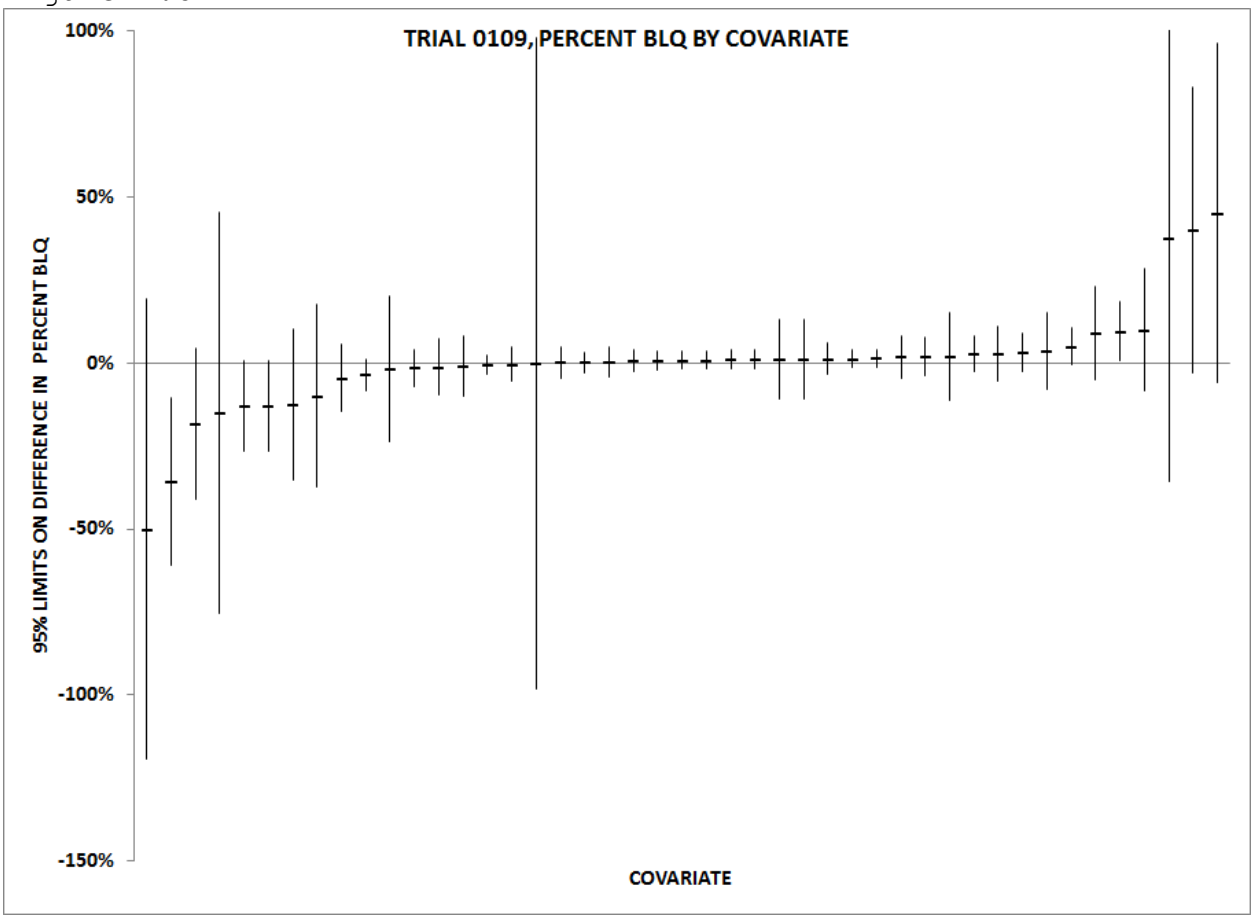


Figure 4.5 D


TRIAL 0109, PERCENT BLQ BY COVARIATE
100%
50%
0%
-50%
-100%
-150%
95% LIMITS ON DIFFERENCE IN PERCENT BLQ
COVARIATE

The next four graphs, figures 4.5 E-H, give an alternative exploration of possible covariate-treatment interactions. In these graphs, the pooled sample size in the covariate subgroup is on the x-axis, the difference in percent BLQ between the arms is on the y-axis. The red line marks the difference in percent BLQ for all subjects pooled, the red curves mark the expected upper and lower 95% intervals for the difference of two arms within a sub-group of the given sample size under the assumption that the true difference within that sub-group is the same as for the whole population. Black dots correspond to individual covariate sub-groups where the observed difference is either within or outside the expected 95% limits. There are a modest number of violators for the smaller sub-groups but none of the previous exploratory graphs suggested any interactions worthy of inclusion in the label.

Figure 4.5 E

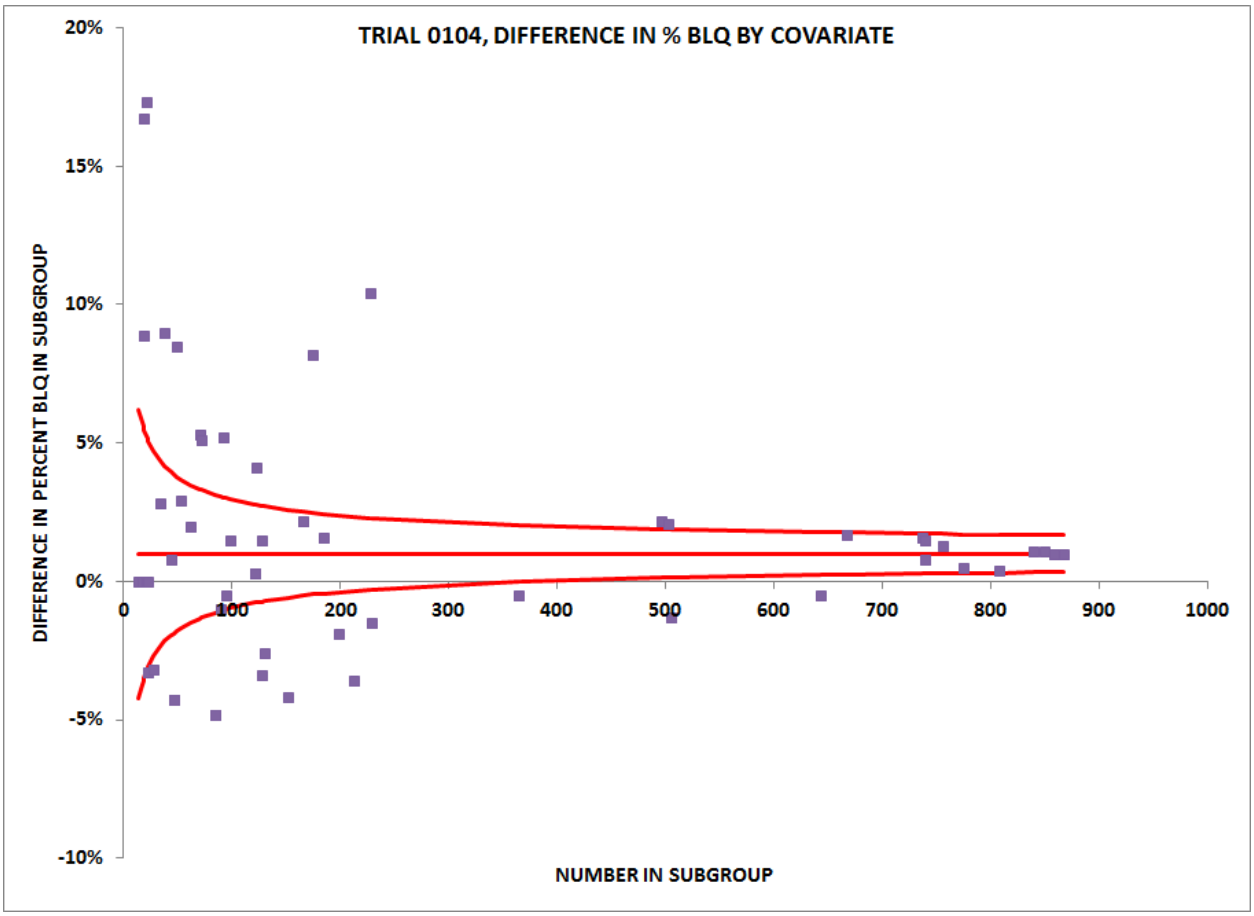


Figure 4.5 F

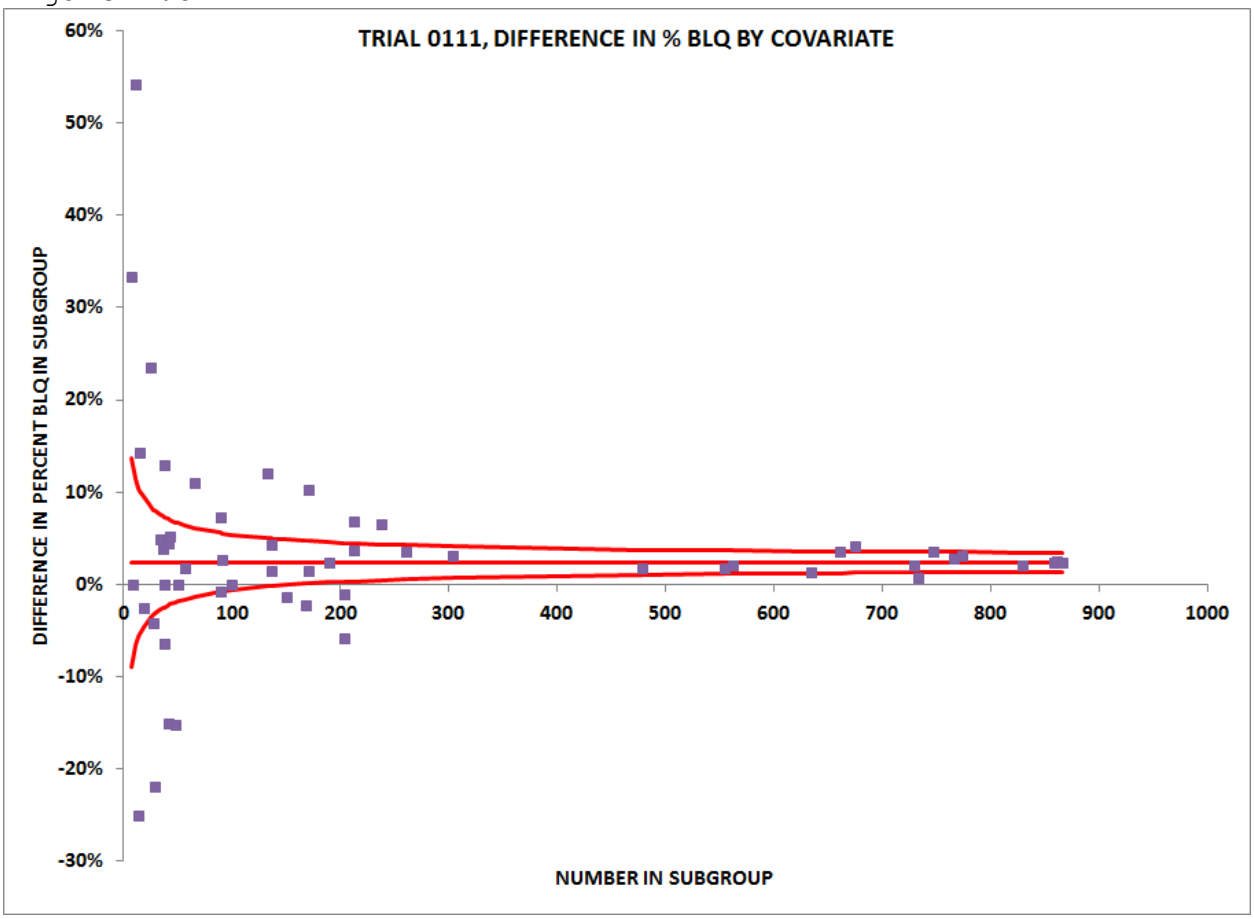

TRIAL 0111, DIFFERENCE IN % BLQ BY COVARIATE
DIFFERENCE IN PERCENT BLQ IN SUBGROUP
NUMBER IN SUBGROUP
60%
50%
40%
30%
20%
10%
0%
-10%
-20%
-30%
0
100
200
300
400
500
600
700
800
900
1000

Figure 4.5 G

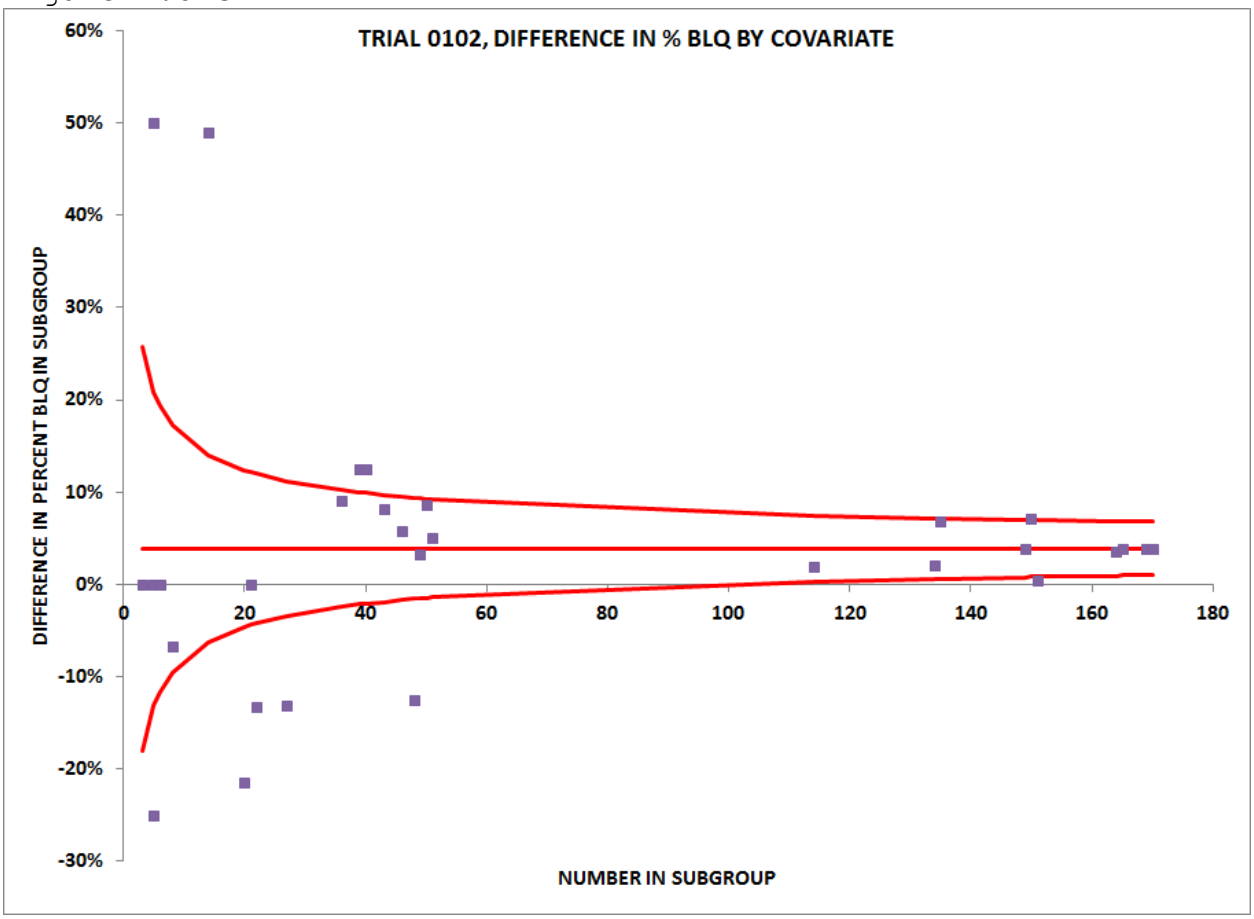
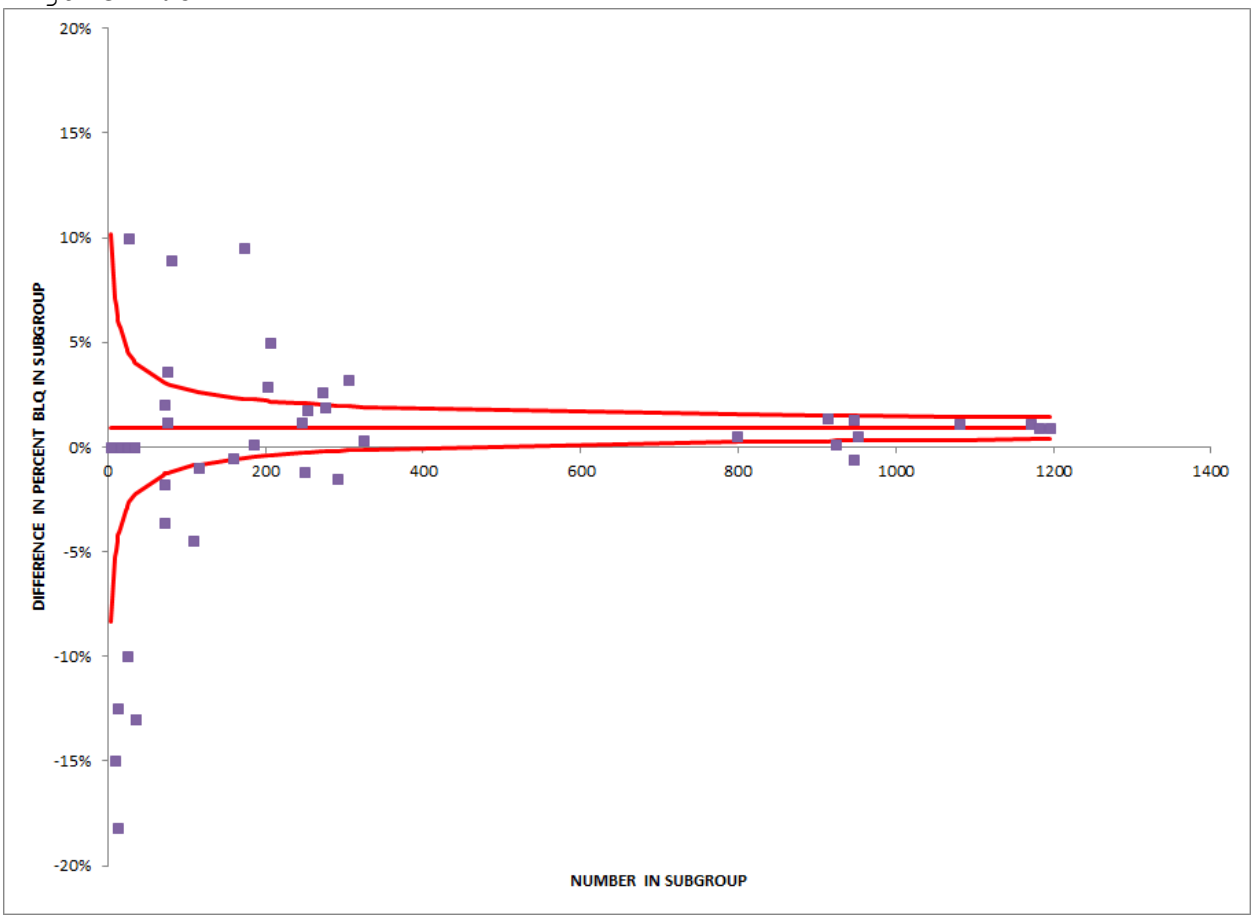


Figure 4.5 H



Overall, one can conclude that there are no sub-groups which merit special concern about efficacy results which are significantly different from the global findings. One word of caution with respect to this conclusion. None of the above analyses detail renally or hepatically impaired patients.

5. Summary and Conclusions:

The applicant has conducted five trials to test the efficacy of Tenofovir Alafenamide as part of the FDC E/C/F/TAF (Elvitegravir/Cobicistat/Emtricitibine/Tenofovir Alafenamide) in the treatment of HIV-1 for patients over the age of 12 without prior failure on anti-retroviral treatment.

In three trials on previously untreated adults, the applicant demonstrated that once daily E/C/F/TAF was, with high statistical confidence, between 5% worse and 10% better than the control regimen of Stribild (=E/C/F/TDF) with respect to viral suppression at 48 weeks.

In all three of these trials, both regimens also showed improvements in CD4 counts from about 550 cells/ml to about 650-700. In the two large, phase 3 trials, the difference in change was, with high confidence, between 40 cells worse and 40 cells better for E/C/F/TAF. The smaller phase 2 trial had similar point estimates but wider confidence intervals for the difference.

In addition, in a trial in which virally suppressed adults on their first regimen (Stribild, Atripla, or Ritonavir-boosted Atazanavir plus Truvada) were switched to E/C/F/TAF, patients maintained viral suppression at over 90% and maintained CD4 counts around 700 cells/ml in both regimens. With high confidence, E/C/F/TAF was between 4% worse and 2% better in percent with viral suppression and between 20 cells worse and 40 cells better in CD4 count.

Finally, a small uncontrolled trial in 12-18 year olds showed comparable efficacy to adults on the E/C/F/TAF arms in the four controlled trials. Further information on efficacy in adolescents is in the pharmacological review.

Overall, the applicant has provided adequate evidence to support the efficacy of E/C/F/TAF in the treatment of HIV-1 infected subjects over the age of 12 and without prior failure to an anti-retroviral treatment.

Thomas Hammerstrom, Ph.D.
Mathematical Statistician

Concur: Dr. Soon

cc:
Archival NDA #207-561
HFD-530
HFD-530/Dr. Birnkrant
HFD-530/Dr. Murray
HFD-530/Dr. Lewis
HFD-530/Dr. Tauber
HFD-530/Ms. Min
HFD-725/Dr. Hammerstrom
HFD-725/Dr. Soon
HFD-725/Dr. Lin
HFD-725/Dr. Price
HFD-725/Dr. Patrician

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/s/

THOMAS S HAMMERSTROM
07/08/2015

GUOXING SOON
07/09/2015

DIONNE L PRICE
07/10/2015
Concur with overall conclusion

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

NDA Number: 207561 **Applicant: Gilead** **Stamp Date: 11/05/2014**

Drug Name:Tenofovir Alafenamide **NDA/BLA Type: NDA**

On **initial** overview of the NDA/BLA application for RTF:

	Content Parameter	Yes	No	NA	Comments
1	Index is sufficient to locate necessary reports, tables, data, etc.	X			
2	ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)	X			
3	Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated (if applicable).	X			
4	Data sets in EDR are accessible and do they conform to applicable guidances (e.g., existence of define.pdf file for data sets).	X			

IS THE STATISTICAL SECTION OF THE APPLICATION FILEABLE? __Yes_____

If the NDA/BLA is not fileable from the statistical perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Content Parameter (possible review concerns for 74-day letter)	Yes	No	NA	Comment
Designs utilized are appropriate for the indications requested.	X			
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	X			
Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available.	X			
Appropriate references for novel statistical methodology (if present) are included.			X	
Safety data organized to permit analyses across clinical trials in the NDA/BLA.			X	
Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate.	X			

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

Thomas Hammerstrom	12/05/14
Reviewing Statistician	Date
Greg Soon	
Supervisor/Team Leader	Date

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/s/

THOMAS S HAMMERSTROM
12/05/2014

GUOXING SOON
01/14/2015