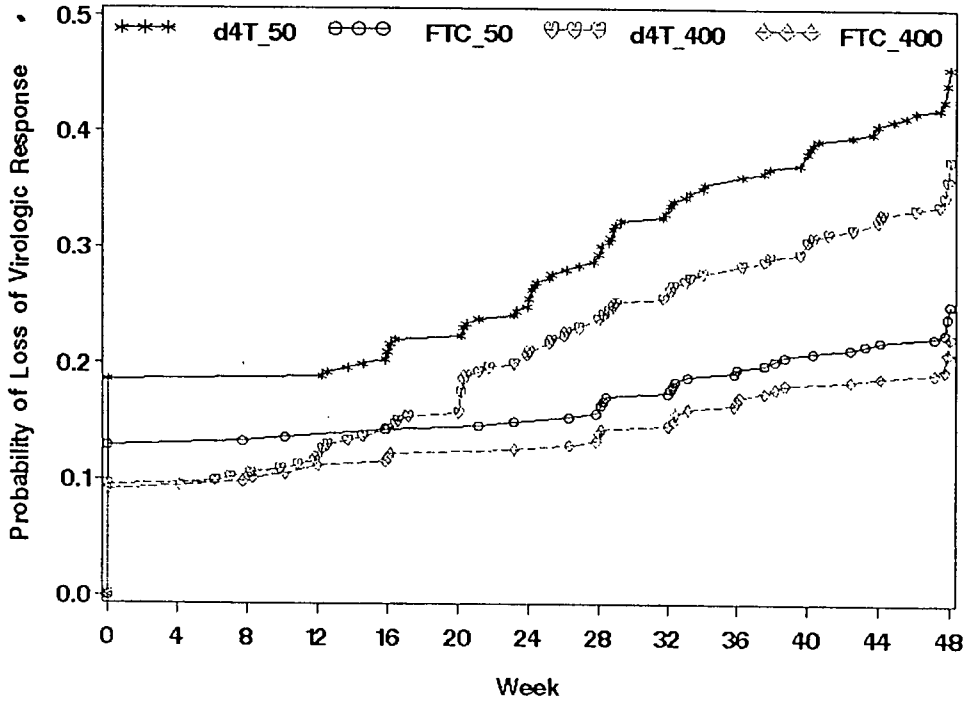


Figure 5: FTC301A: Probability of Loss of Virologic Response by Treatment Arm and LOQ

Table 11 shows treatment difference in LOVR and 95% CI at Week 48 by randomization stratum and LOQ. For LOQ=50 copies/mL, the stratum-adjusted difference between treatment arms (d4T-FTC) was -19.6% with a stratum-adjusted 95% confidence interval of −27.1% to −12.1. For LOQ=400 copies/mL, the stratum-adjusted difference between treatment arms (d4T-FTC) was -14.3% with a stratum-adjusted 95% confidence interval of −21.4% to −7.2. In both cases, the p-values <0.0001, by the t-test.

Table 11: Summary of Treatment Difference in Virologic Response by Randomization Stratum[a]

Endpoint						95% CI	
	N_{FTC}	N_{3TC}	P_{FTC}(%)	P_{3TC}(%)	$P_{FTC-3TC}$(%)	lower	upper
LOQ=400 copies/mL	**286**	**285**	**81.2**	**66.9**	**14.3**	**7.2**	**21.4**
NA & HIV RNA <=100 k	72	71	79.2	64.8	14.4	-0.3	29.1
EU & HIV RNA <=100 k	31	31	77.4	80.6	-3.2	-23.5	17.0
SA & HIV RNA <=100 k	56	60	87.5	78.3	9.2	-4.6	22.9
NA & HIV RNA >100 k	53	51	69.8	51.0	18.8	0.0	37.6
EU & HIV RNA >100 k	31	30	83.9	63.3	20.5	-1.5	42.6
SA & HIV RNA >100 k	33	32	90.9	68.8	22.2	2.7	41.6
NA & FTC301 Rollover	6	6	83.3	50.0	33.3	-20.0	86.7
SA & FTC301 Rollover	4	4	100.0	75.0	25.0	-20.8	70.8
LOQ=50 copies/mL	**286**	**285**	**78.1**	**58.4**	**19.6**	**12.1**	**27.1**
NA & HIV RNA <=100 k	72	71	75.0	60.6	14.4	-0.9	29.7
EU & HIV RNA <=100 k	31	31	77.4	71.0	6.5	-15.3	28.2
SA & HIV RNA <=100 k	56	60	85.7	70.0	15.7	0.5	30.9
NA & HIV RNA >100 k	53	51	66.0	39.2	26.8	7.6	46.0
EU & HIV RNA >100 k	31	30	83.9	53.3	30.5	7.3	53.8
SA & HIV RNA >100 k	33	32	84.8	59.4	25.5	3.7	47.2
NA & FTC301 Rollover	6	6	83.3	50.0	33.3	-20.0	86.7
SA & FTC301 Rollover	4	4	75.0	50.0	25.0	-42.1	92.1

a. Based on TLOVR algorithm.

3.2.3.3 Sensitivity Analysis: Percentage of Subjects with HIV RNA ≤ LOQ

Using HIV-1 RNA data, this reviewer obtained proportions of HIV RNA ≤ 50 copies/mL at Week 48 of 56.7% in the d4T treatment arm and 73.4% in the FTC treatment arm, respectively. In this calculation, those with no HIV-1 RNA data at Week 48 were considered as failure: 91 in the d4T treatment arm and 59 in the FTC treatment arm, respectively. When there were two HIV RNA measurements (ten cases), the first on was chosen for calculation. The response rates at Week 48 for HIV RNA ≤ 400 copies/mL were 65.6% in the d4T treatment arm and 78.3% in the FTC treatment arm, respectively.

3.2.3.4 Mean Change from Baseline in Plasma HIV RNA (log_{10} copies/mL)

HIV RNA data were generated for subjects with at least one dose of study drugs. The baseline HIV RNA values were those at day 1 or the one closest to day 1 if HIV RNA at day 1 is missing. Data were grouped by screening HIV RNA randomization strata, denoted by Hrna for HIV RNA > 100,000 copies/mL and Lrna for HIV RNA ≤ 100,000 copies/mL, and treatment arms d4T and FTC respectively. Twenty subjects who were rollover from Study 301 were assigned to one of the four strata according to their baseline HIV RNA ≤ 5 log_{10} or > 5 log_{10}.

The mean baseline HIV RNA was similar between treatment arms, i.e., 5.31 log_{10} for the d4T-Hrna and 5.36 log_{10} for the FTC-Hrna arm; 4.45 log_{10} for the d4T-Lrna and 4.44 log_{10} for the FTC-Lrna arm. At Week 48, HIV RNA data were available in 82% of the FTC-Lrna and 83% of FTC-Hrna strata, and in 74% of the d4T-Lrna and 61% of the d4T-Hrna strata.

Figure 6 shows the mean change from baseline in plasma HIV RNA (log_{10} copies/mL) for d4T-Hrna, d4T-Lrna, FTC-Hrna and FTC-Lrna groups.

For the Lrna groups, the mean plasma HIV RNA had a sharp drop of about 2.2 log_{10} at Week 4, and this decline continued in a slower pace until Week 12 and then level off. The mean differences between subjects in the FTC and d4T treatment arms were less than 0.1 log_{10}, indicating there were similar effect on HIV RNA suppression.

For the Hrna groups, the mean plasma HIV RNA had a sharp drop at Week 4 to about 2.4-2.5 log_{10} and this decline continued in a slower pace beyond Week 16. At Week 24, the mean decline reached 3.3 log_{10} for the d4T treatment arm and 3.5 log_{10} for the FTC treatment arm, respectively. The mean differences between subjects in the FTC and d4T treatment arms were between 0.2-0.37 log_{10}, indicating subjects in Hrna group had better effect on HIV RNA suppression. Comparing the change from baseline HIV RNA between the two treatment arms by the Wilcoxon tests, the statistical significance was reached at Weeks 24, 28 and 40, $p<0.05$.

3.2.3.5 Time-Averaged Difference Change from Baseline in log_{10} HIV RNA

This reviewer conducted three types of TAD analyses at different time intervals: through Week 24, 36 and 48. A visit window was defined from initiation of therapy (Day 1) to the scheduled visits +/- 14 days. An overall TAD was a weighted one adjusted by randomization strata for all subjects in the treated population. Calculation methods were defined as:

- Last TAD Carry Forward (LTadCF);
- Baseline Value Carry Forward (BVCF); and
- Last Observation Carry forward (LOCF).

Table 11 illustrates the TAD results in terms of plasma HIV RNA. A positive TAD estimate favors the FTC treatment arm. Overall, the $TAD_{D4T\text{-}FTC}$ estimate and the standard error depend on the method of calculation. For a given time interval, a greater variation of $TAD_{D4T\text{-}FTC}$ estimate is associated with the BVCF method.

By the BVCF method, the estimated $TAD_{D4T\text{-}FTC}$ through Week 24 was 0.08, 95% CI (-0.06,0.21), demonstrating that the d4T and FTC treatment arms had a similar effect on HIV RNA suppression over 24 weeks. These estimates were analogous with the LTadCF and LOCF. The estimated $TAD_{D4T\text{-}FTC}$ through Week 48 by the BVCF was 0.24, 95% CI (0.07,0.41), indicating that the FTC treatment arm had statistically significant better effect on HIV RNA suppression over 48 weeks, $p<0.05$, by the Wald t-test.

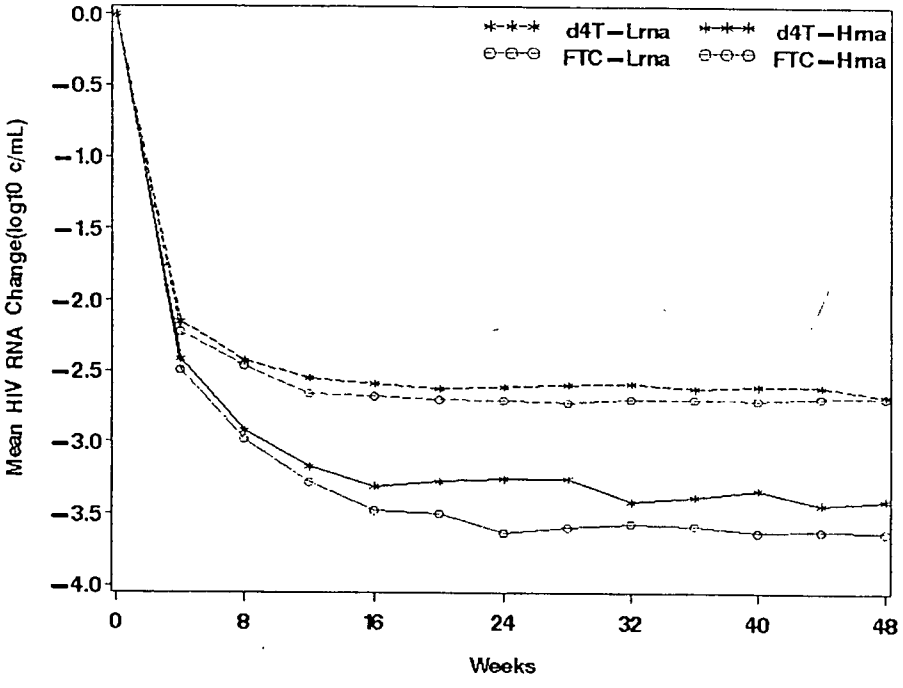


Figure 6: FTC301A: Mean Change from Baseline in Plasma HIV RNA (log_{10} copies/mL) by Treatment Arm and Randomization Strata

For randomization strata ≥ 100,000 copies/mL, majority of the estimated TAD_i (I=1,3,5,7) values are positive. Conversely, TAD_i (I=2,4,6,8) values are predominately negative. The absolute $TAD_{D4T-FTC}$ values are all less than 0.05 with the upper limits of 95% CI of the $TAD_{D4T-FTC}$ adjusting for randomization strata are all less than 0.1, supporting the similar effect between the FTC and the d4T treatment arms on HIV RNA suppression during 48 weeks of treatment.

Table 12: Time-Average Difference in HIV RNA Change From Baseline Adjusted by Randomization

				95% CI	
		$Tad_{d4T-FTC}$	se	lower	upper
LTadCF (n=564)	Week 24	0.092	0.056	-0.017	0.201
	Week 36	0.137	0.062	0.016	0.257
	Week 48	0.162	0.065	0.035	0.289
BVCF (n=571)	Week 24	0.079	0.069	-0.056	0.214
	Week 36	0.158	0.078	0.005	0.312
	Week 48	0.239	0.085	0.073	0.405
LOCF (n=571)	Week 24	0.085	0.061	-0.034	0.204
	Week 36	0.121	0.067	-0.010	0.251
	Week 48	0.155	0.070	0.017	0.293

3.2.3.6 Mean Change from Baseline in CD4+ Cell Count

At Week 48 time window, CD4+ cell count and CD4% data were available in 81% of the FTC-Lrna, in 69% of FTC-Hrna strata, in 75% of the d4T-Lrna, and in 57% of the d4T-Hrna strata. At baseline, the mean CD4+ cell count was similar between treatment arms: 281 for the d4T-Hrna and 264 for the FTC-Hrna arm; 358 for the d4T-Lrna and 346 for the FTC-Lrna arm. Likewise, the mean CD4% was similar between treatment arms: 17% and 16% for the d4T-Hrna and the FTC-Hrna arms; 22% and 20% for the d4T-Lrna and the FTC-Lrna arms, respectively.

Figure 7 shows the mean change from baseline in CD4+ cell count (cells/mm^3). The mean change from baseline in CD4+ cell count increased in the entire study period except for FTC-Lrna subgroup.

- At Week 48, the mean change from baseline in CD4+ cell count reached 149 (cells/mm^3) for d4T-Hrna, 193 FTC-Hrna, 129 for d4T-Lrna and 133 for FTC-Lrna groups, respectively.

- For Hrna strata, subjects in the FTC treatment arm had greater increase in mean CD4+ cell count than those in the d4T treatment arm at Weeks 12, 24, 36 and 48. By the Wilcoxon test, the significant differences between treatment arms were reached at Week 36 (p=0.0155) and at Week 48 (p=0.0245).

- For Lrna strata, subjects in the FTC treatment arm had greater increase in mean CD4+ cell count than those in the d4T treatment arm at Weeks 12, 24, 36 and 48. By the Wilcoxon test, the significant differences between treatment arms were reached at Week 24 (p=0.0127) and at Week 36 (p=0.0220).

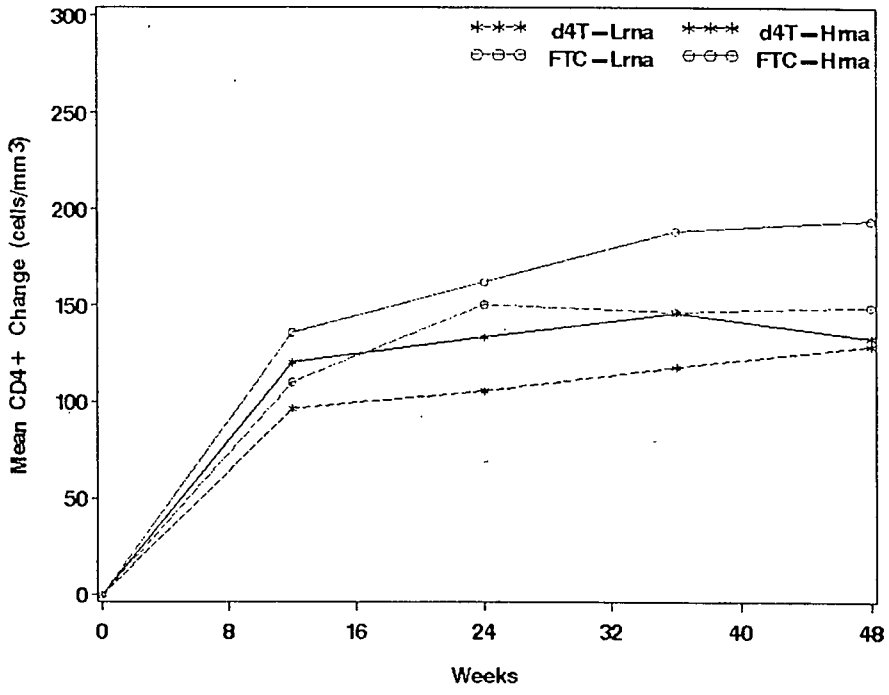


Figure 7: FTC301A: Mean Change from Baseline in CD4+ Cell Count (cells/mm^3) by Treatment Arm and Randomization Strata

3.2.3.7 Mean Change from Baseline in CD4%

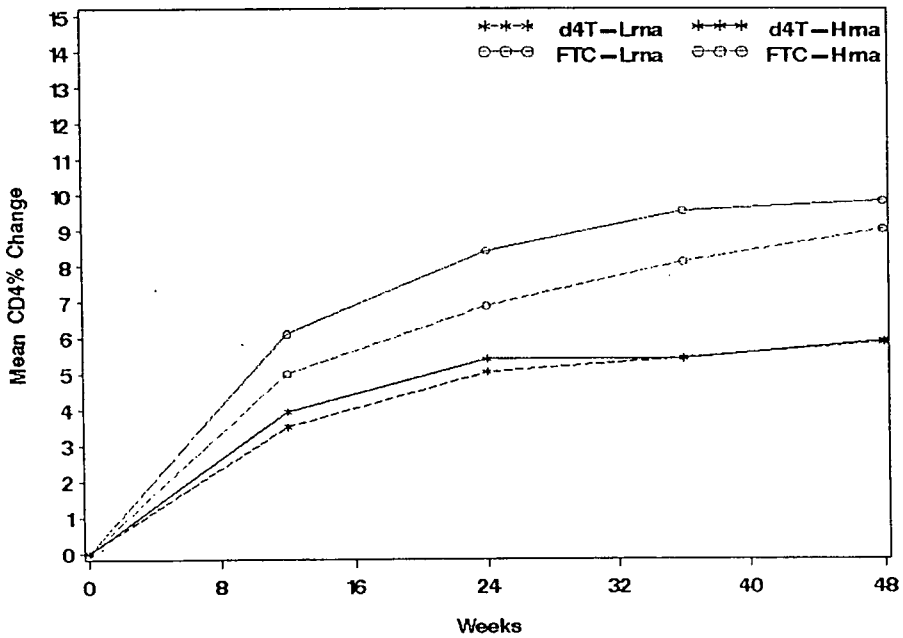


Figure 8: FTC301A: Mean Change from Baseline in CD4%

Figure 8 shows the mean change from baseline in CD4%. The mean change from baseline in CD4% increased in the entire study period to 9-10% at Week 48 for the two FTC subgroups. For the d4T subgroups, the mean change from baseline in CD4% increased to 6% at Week 24 and then level off.

- For Hrna strata, subjects in the FTC treatment arm had statistically significant greater increase in mean CD4% from baseline than those in the d4T treatment arm at Weeks 12, 24, 36 and 48, $p<0.001$, by the Wilcoxon test. At Week 48, the mean change from baseline in CD4% reached 6% for d4T-Hrna and 10% for the FTC-Hrna.

- For Lrna strata, subjects in the FTC treatment arm had statistically significant greater increase in mean CD4% than those in the d4T treatment arm at Weeks 12, 24, 36 and 48, $p<0.01$, by the Wilcoxon test. At Week 48, the mean change from baseline in CD4% reached 6% for d4T-Hrna and 9% for the FTC-Hrna.

3.2.3.8 Time-Averaged Difference Change from Baseline in CD4+ Cell Count

This reviewer applied three methods; like those for TAD analyses for HIV RNA to obtain TAD(D4T-FTC) change from baseline in CD4+ cell count and CD4% through Weeks 24, 36 and 48, using (1) Last TAD Carry Forward (LTadCF); (2) Last Observation Carry forward (LOCF); and (3) Baseline Value Carry Forward (BVCF).

Table 12 shows TAD by randomization strata and treatment arms using observed CD4+ cell data, i.e., last TAD value carry forward (LTadCF) where subjects with only baseline CD4+ cell count were excluded. The findings are as follows.

- It appears that the mean CD4+ cell count measured by TAD show increasing trend over time for each randomization stratum. Variations in TAD temporal trend among different strata and treatment arm were observed.

- For Stratum 1-6 with reasonable sample sizes, the mean TAD estimates through Week 48 were 63-121 (cells/mm^3) for subjects in the d4T treatment arm, and 87 to 126 for subjects in the FTC treatment arm. The estimated $TAD_{d4T\text{-}FTC}$ for randomization strata 1, 3, 4 and 6 were all negative, indicating that the subjects in the FTC treatment arm had greater increase from baseline CD4+ cell count than those in the d4T treatment arm. Conversely, for subjects in randomization stratum 2, the estimated $TAD_{d4T\text{-}FTC}$ values were all positive, indicating that subjects in the d4T treatment arm may be doing better.

- Stratum 7 (n=12) and Stratum 9 (n=8) had relatively smaller sample sizes. Therefore, the results should have minimal impact on the adjusted TAD.

Table 13 shows $TAD_{D4T\text{-}FTC}$ change from baseline CD4+ cell count adjusting for randomization strata including screening plasma HIV-1 RNA and geographical region.

- The $TAD_{D4T\text{-}FTC}$ estimates adjusting for randomization were all negative and decreased over time, indicating that subjects in the FTC treatment arm had increased TAD change from baseline CD4+ cell count than those in the d4T treatment arm.

- Except for Week 24 by the BVCF method, the upper limit of 95% CI was all negative, demonstrating that subject in the FTC treatment arm had statistically significant greater increase in CD4+ cell count through Weeks 24, 36 and 48, compared to those in the d4T treatment arm, $p<0.05$, by the Wald t-test.

- The results by three methods of computing TAD supported that the subjects in the FTC treatment arm had an extra 30-32 cells/mm^3 increase from baseline than those in the d4T treatment arm through 48 weeks of therapy.

Table 13: Time-Average Difference Change From Baseline CD4+ Cell Count by Randomization Strata§

Strata	n	d4T mean	se	n	FTC Mean	se	tad	se(tad)	weight
				Through Week 24					
1	69	49.44	11.01	68	95.81	9.10	-46.37	14.28	34.25
2	30	79.59	16.08	30	67.82	13.82	11.77	21.20	15.00
3	55	48.23	14.16	52	64.61	16.63	-16.39	21.84	26.73
4	46	46.75	18.03	51	89.68	11.65	-42.93	21.46	24.19
5	30	80.58	18.29	31	74.73	27.15	5.85	32.74	15.25
6	32	56.94	22.01	30	92.28	11.40	-35.33	24.79	15.48
7	6	138.98	51.93	6	31.34	41.35	107.64	66.38	3.00
9	4	115.00	60.74	4	126.29	72.00	-11.29	94.20	2.00
				Through Week 36					
1	69	59.34	12.49	68	116.41	10.06	-57.07	16.04	34.25
2	30	103.35	18.02	30	90.08	13.07	13.27	22.26	15.00
3	60	48.44	13.58	53	74.48	17.60	-26.04	22.23	28.14
4	47	56.18	19.87	51	109.16	12.50	-52.98	23.48	24.46
5	30	99.19	18.13	31	99.83	29.76	-0.64	34.85	15.25
6	32	75.44	23.24	31	103.95	14.65	-28.51	27.47	15.75
7	6	139.10	52.42	6	43.33	49.48	95.77	72.09	3.00
9	4	125.25	56.98	4	123.70	65.91	1.54	87.12	2.00
				Through Week 48					
1	69	62.70	13.39	68	126.14	9.99	-63.43	16.70	34.25
2	30	121.13	19.00	30	104.34	13.53	16.78	23.33	15.00
3	60	63.20	13.73	54	87.26	16.96	-24.06	21.82	28.42
4	47	65.78	18.93	51	120.73	13.39	-54.95	23.18	24.46
5	30	109.08	18.48	31	116.81	28.83	-7.73	34.24	15.25
6	32	81.98	22.95	31	117.62	15.73	-35.64	27.82	15.75
7	6	133.88	55.75	6	58.99	54.61	74.89	78.04	3.00
9	4	132.30	52.76	4	124.11	59.45	8.19	79.49	2.00

Table 14: Time-Average Difference Change From Baseline CD4+ Cell Count Adjusting For Randomization

	n	%	$Tad_{d4T-FTC}$	se	95% CI lower	95% CI upper
			LTadCF			
Week 24	544	95.27	-22.41	8.78	-39.61	-5.21
Week 36	552	96.67	-28.67	9.41	-47.11	-10.24
Week 48	553	96.85	-31.76	9.44	-50.26	-13.25
			BVCF			
Week 24	542	94.92	-13.11	6.72	-26.28	0.06
Week 36	567	99.30	-20.92	8.54	-37.65	-4.18
Week 48	570	99.82	-29.87	8.82	-47.15	-12.59
			LOCF			
Week 24	569	99.65	-21.50	8.93	-39.00	-3.99
Week 36	571	100.00	-25.42	9.26	-43.57	-7.27
Week 48	571	100.00	-28.75	8.41	-47.20	-10.29

3.2.3.9 Time-Average Difference Change from Baseline CD4%

Similar to those in CD4+ cell count, the estimated TAD_{D4T} and TAD_{FTC} in CD4% increase longitudinally.

Table13 lists the estimate of $TAD_{D4T-FTC}$ change from baseline CD4% and 95% CI adjusting for screening plasma HIV-1 RNA and geographical region stratum through Weeks 24, 36 and 48.

- The estimates of $TAD_{D4T-FTC}$ (CD4%) adjusting for randomization strata were all negative and decreased over time, indicating that subjects in the FTC treatment arm had greater increased TAD change from baseline CD4% than those in the d4T treatment arm.

- The overall estimate of $TAD_{D4T-FTC}$ change from baseline CD4% through Week 48 was about –2.5% regardless of methods, and the standard error of those estimates was very similar also.

- The 95% confidence upper limits were all less than zero, indicating that subjects in the FTC treatment arm had statistically significant greater CD4% increase from baseline than those in the d4T treatment arm, $p< 0.05$, by the Wald test.

Table 15: Time-Average Difference in CD4% Change From Baseline Adjusted by Randomization

				95% CI	
		$Tad_{d4T-FTC}$	se	lower	upper
LTadCF (n=564)	Week 24	-1.867	0.394	-2.639	-1.095
	Week 36	-2.182	0.388	-2.943	-1.421
	Week 48	-2.507	0.378	-3.248	-1.766
BVCF (n=571)	Week 24	-2.120	0.404	-2.912	-1.327
	Week 36	-2.298	0.396	-3.074	-1.522
	Week 48	-2.519	0.392	-3.288	-1.751
LOCF (n=571)	Week 24	-1.459	0.310	-2.066	-0.851
	Week 36	-1.935	0.385	-2.690	-1.180
	Week 48	-2.472	0.393	-3.243	-1.700

3.3 Evaluation of Safety

The evaluation of safety has not conducted by this reviewer. Please refer to medical reviewer's evaluations.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Study FTC303

Subgroup analyses were conducted examining associations between gender, race and age subgroups, and the TLOVR. Additionally, subgroup and sensitivity analyses were performed to examine the following five risk factors in predicting of longitudinal virologic failure:

- Randomization stratum and baseline plasma HIV RNA stratum;
- Previous Combivir use;
- Previous mono or dual ART with 3TC;
- History of HIV-1 related CDC defined Class B or C events; and
- Duration of ART with 3TC prior to entry.

Comparisons of longitudinal Kaplan-Meier TLOVR curves in subgroups of these variables were performed using the entire TLOVR dataset Week 48 and beyond base on LOQ=400 copies/mL. Log-rank test was used to test the difference in TLOVR K-M curves between designated subgroup. In the subgroup analysis, differences in K-M curves were compared among subgroups of a factor X_i and treatment ($X_i \times Trt$, i=1,...,8). If a significant result was observed, then a K-M analysis, stratified by subgroup of a factor X_{ij} or treatment Trt_k, was carried out. The effect of randomization stratum and risk factor was also examined when the sample sizes of subgroup were sufficiently large. Subjects in a subgroup A with a significant lower LOVR than subjects in subgroup B means that subjects in subgroup A had greater virologic response than those in subgroup B.

Note subjects in randomization strata 3 & 4 of the study FTC303 were combined into HIV RNA $\geq$ 50 copies/mL regardless of treatment with NNRTI or PI, since there were 8 subjects with the NNRTI treatment: 6 in the FTC-containing arm and 2 in the 3TC-containing arm.

4.1.1 Gender

Significant gender and treatment differences in LOVR were observed when comparing LOVR among gender x treatment arm subgroups, p=0.0168, by the log-rank test.

- Stratified by gender, there were significant treatment differences in LOVR among female subjects. Female subjects in the 3TC treatment arm had better virologic response than those in the FTC treatment arm, p=0.0366. No significant treatment difference was observed in the male subjects.

- Stratified by treatment arm, in the FTC treatment arm, male subjects had better virologic response than female subjects, p=0.0085. No gender difference was significantly different in the 3TC treatment arm.

- No further analysis by randomization stratum was performed due to small sample sizes in the female population.

It was observed that one third of female participants (21/63) discontinued from study due to adverse events, virologic failure, protocol violation, non-compliance, and other reasons. This was much higher than those in the male subjects (19.4%), p=0.0123, by the Chi-square test. Among female subjects, 15 (34.1%) in the FTC treatment arm including 3 developed adverse events, and 6 (31.6%) in the 3TC treatment arm discontinued from study early. These may explain why the K-M curves indicated significant differences between male and female, between FTC and 3TC in the female population.

It was noted that the PK properties of emtricitabine were similar in male and female patients. In addition, study FTC303 was not designed to investigate gender difference in virologic response. Female subjects consisted of 14.3% of the ITT population: 44 in the FTC treatment arm and 19 in the 3TC treatment arm. Therefore, interpretation of these finding should be limited and cautious.

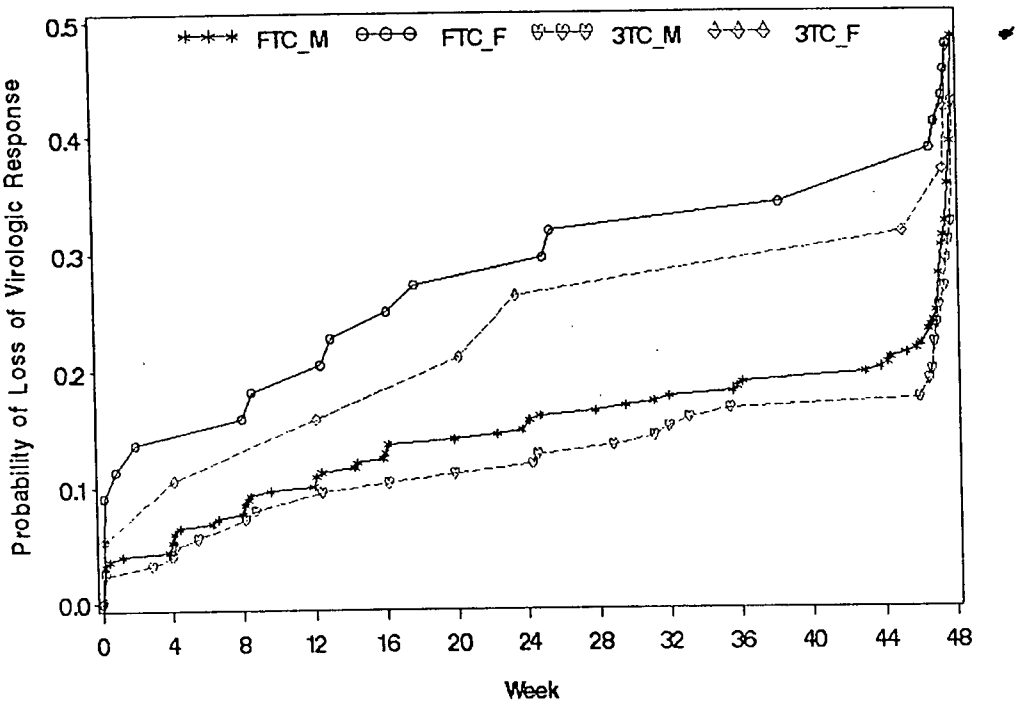


Figure 9: FTC303: K-M TLOVR by Gender and Treatment Arm

4.1.2 Age

To examining the association between age and TLOVR, a median age of 41 was chosen to categorize a subject as younger (≤42) or older (>42).

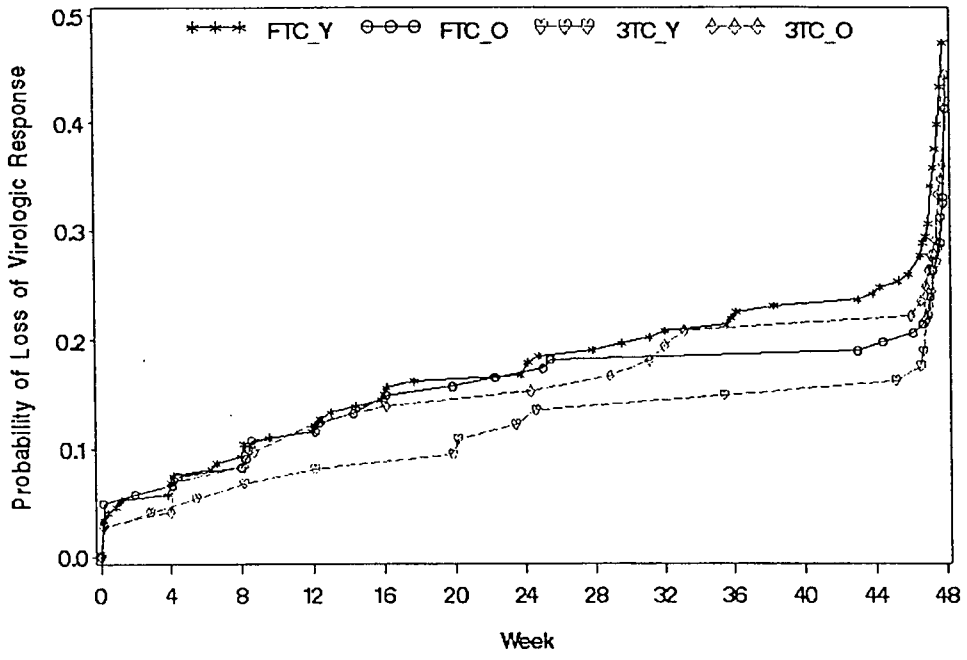
Overall, increased age was associated with LOVR, p=0.0028 comparing four age x treatment subgroups. Also, there were complex qualitative interactions between age, randomization stratum, and treatment arm. Younger subjects with ages ≤ 42 in the 3TC treatment arm were doing better in LOVR than those in the FTC treatment arm, p=0.0044. No treatment difference was found for the older subjects. Stratified by randomization stratum and treatment arm, age was associated with LOVR, p=0.0064, 0.4431 and 0.0764 by the Log-rank test for subjects in randomization strata 1, 2 and (3,4) respectively.

The upper plot in Figure 10 shows probability of LOVR by age and treatment arm for subjects in the entire ITT population, where younger subjects in 3TC treatment arm showed a significantly better virologic response than those in the FTC treatment arm. The bottom plot in Figure 9 shows those for subjects with HIV RNA ≤50 copies/mL treated with PI, i.e.

in randomization stratum 1, where older subjects in 3TC treatment arm showed a significant better virologic response than those in the FTC treatment arm.

4.1.3 Race

Subjects in three ethnic original White, Black and Hispanic consisted of 98% ITT study population, and were used for comparisons. Overall, there were no significant treatment differences in LOVR by race groups, p=0.7433, log-rank test. No further stratifications of treatment arm and race were needed. The randomization stratum-specific analyses were not performed due to small sample sizes in Black or Hispanic subgroups of the 3TC treatment arm in stratum 2, 3 and 4.



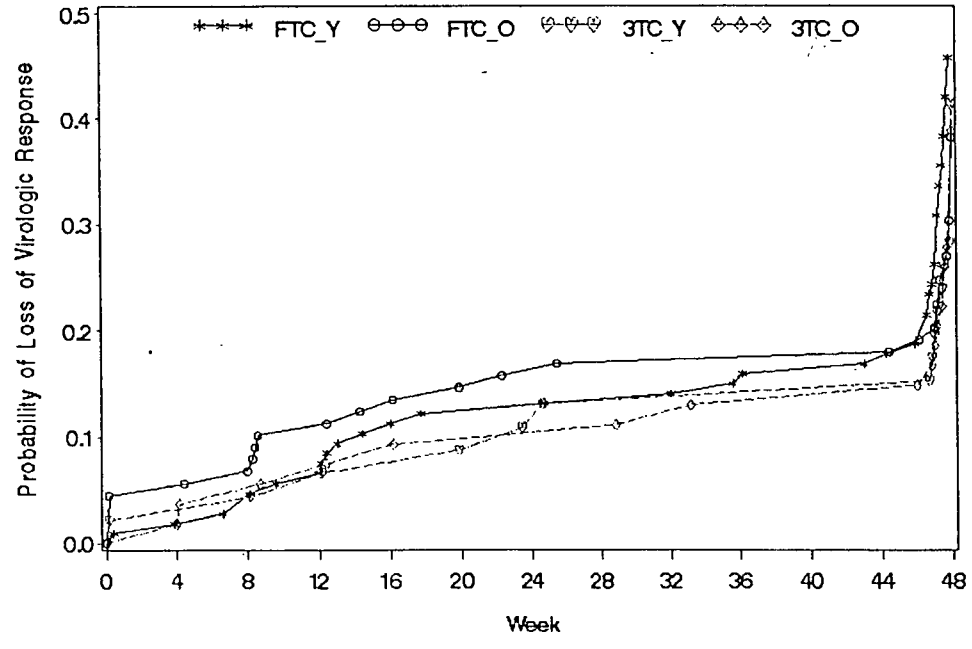


Figure 10: FTC303: K-M TLOVR by Age and Treatment Arm Overall and in Randomization Stratum 1

4.1.4 Randomization Stratum and Baseline Plasma HIV RNA

The randomization strata (1, 2, 3& 4) consisted of 67.3%, 19.1%, and 14.6% of treated subjects. It appeared the subjects with the screening plasma HIV RNA ≤ 50 copies/mL were doing significantly better than those with the screening plasma HIV RNA > 50 copies/mL, p=0.0226 by the log-rank test. The LOVR K-M curves by randomization stratum and treatment arm were presented in the top part of Figure 11.

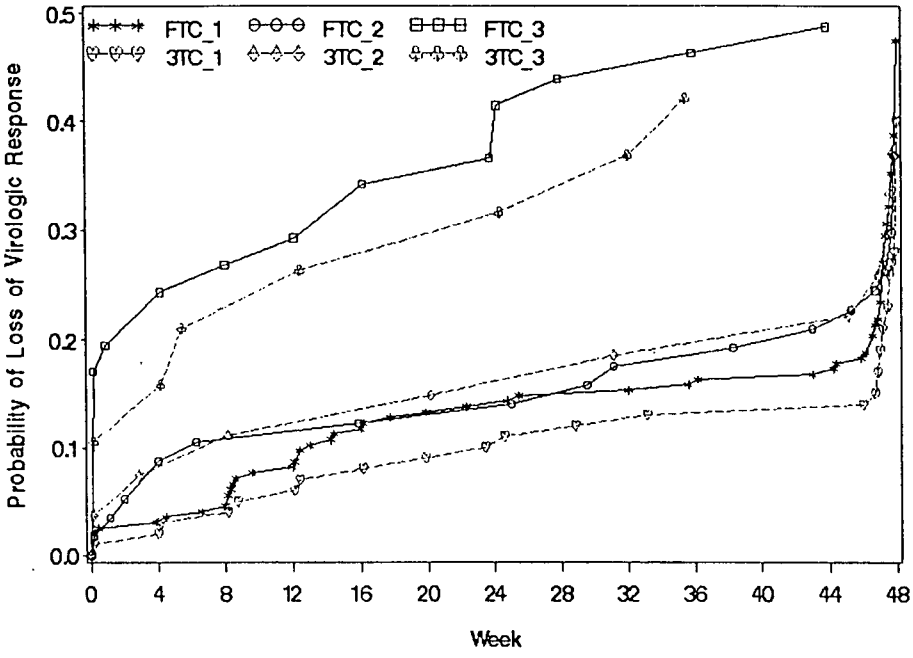
- Stratified by treatment arm, subjects in strata 1 & 2 of the 3TC treatment arm had better virologic response than those in strata 3 & 4, p=0.0018. No significant differences in LOVR were identified in the FTC treatment arm.

- For each randomization stratum, no treatment difference was identified.

The plasma HIV RNA pair at screening and at baseline was slightly different. At baseline, 12.5% of TREATED population had plasma HIV RNA >50 copies/mL: 40 (14%) of the subjects in the FTC treatment arm and 15 (10%) of the subjects in the 3TC treatment arm. A significant association of LOVR and baseline HIV RNA below or above 50 copies/mL was obtained, p=0.0002. The corresponding LOVR K-M curves were presented in the bottom of Figure 10.

- Subjects with a baseline plasma HIV RNA > 50 copies/mL had a greater probability of LOVR for both the FTC (p=0.0192) and 3TC treatment arm (p=0.0001).

- Stratified by baseline plasma HIV RNA (>50 or not), no treatment difference was identified.



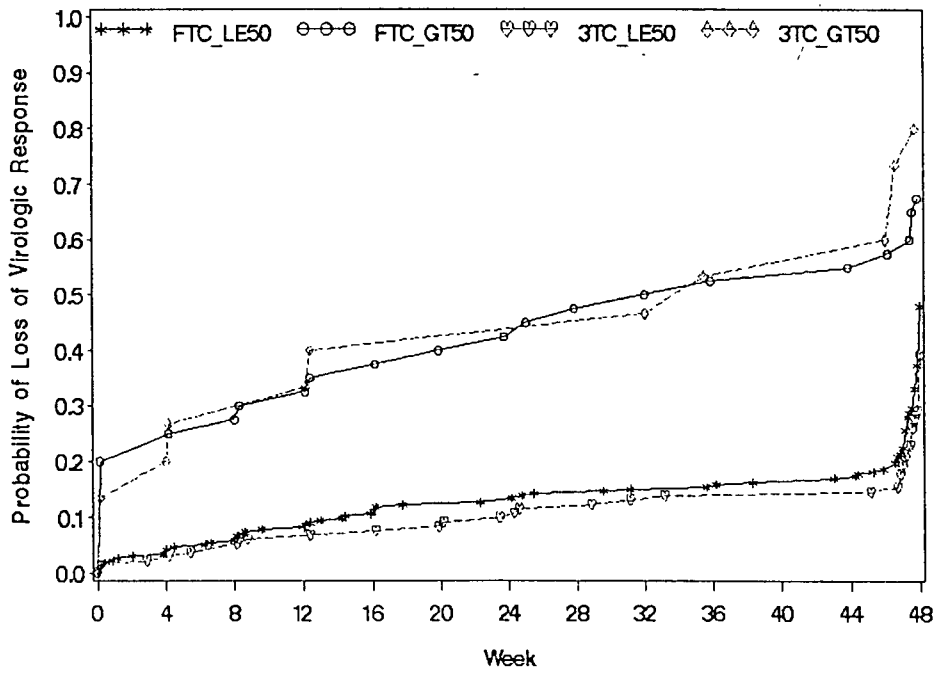
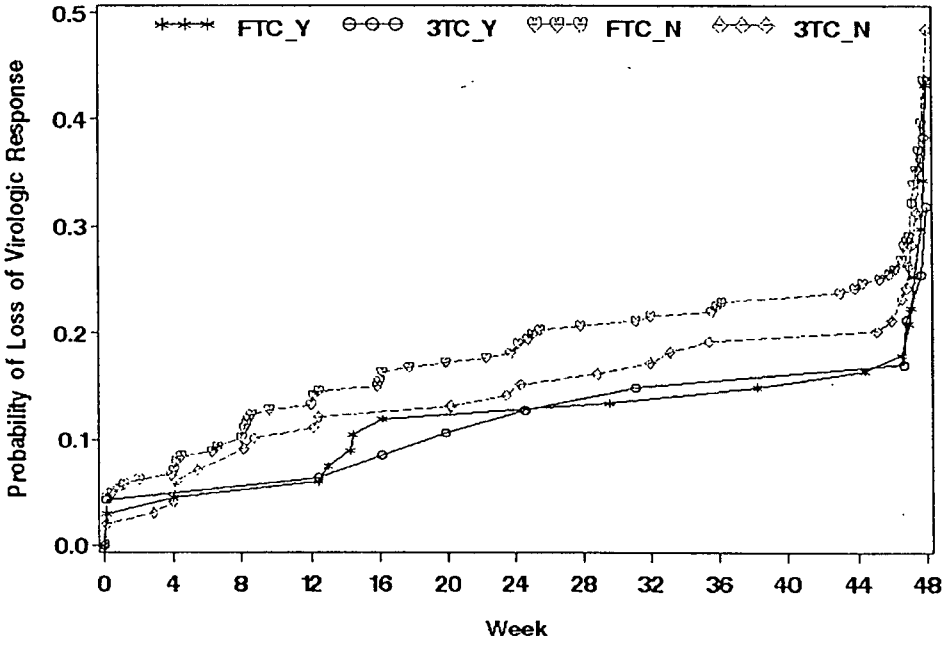


Figure 11: FTC303: K-M TLOVR by Randomization Stratum and Baseline Plasma HIV-1 RNA

4.1.5 Previous Combivir Use

Prior to entry, 75(25.5%) subjects in the FTC treatment arm had 3TC+ZDV (combivir) treatment, much lower than 52(35.6%) in the 3TC treatment arm, p=0.0276, by the Chi-square test. The comparisons of four K-M curves by previous combivir use and treatment arm showed a significant difference, p=0.0002, by the log-rank test. The top plot in Figure 12 shows K-M curves by previous combivir use and treatment arm for the entire treated population. The bottom plot in Figure 12 shows K-M curves by previous combivir use and treatment arm for subjects in randomization stratum=1.

- In both the FTC or the 3TC arm, the subjects with previous combivir use had better virologic responses than those without previous combivir use, p<0.01, logrank test.
- Stratified by randomization stratum, the only significant difference in probability of LOVR was found for subjects with HIV RNA ≤50 copies/mL and previously treated with PI (stratum=1). Subjects with a history of ZDV treatment in both treatment arms had better virologic response than those without previous ZDV treatment.
- Note the applicant reported a total number of 115 subjects with a history of combivir treatment prior to entry.



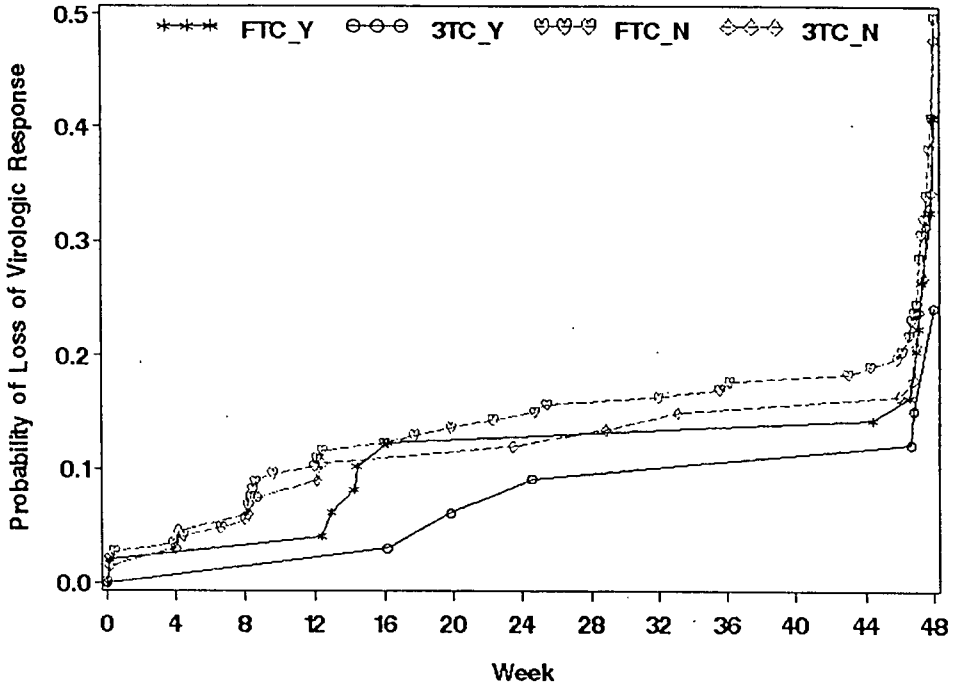


Figure 12: FTC303: K-M TLOVR by Previous Combivir Use and Treatment Arm

4.1.6 History of Mono or Dual ART with 3TC

Prior to entry, 117 (39.8%) subjects in the FTC treatment arm and 58 (39.7%) in the 3TC treatment arm had mono or dual ART with 3TC. Although the applicant identified that a history of mono or dual ART with 3TC was associated with an increased risk of virologic failure, the K-M analysis stratified by treatment arm and history of mono or dual ART with 3TC did not support their finding (p=0.2). Figure 13 shows the overall K-M curves by treatment arm and previous mono or dual ART with 3TC.

A non-significant qualitative treatment interaction was observed for both subgroups of mono, denoted by _LE2 or dual ART with 3TC, denoted by _GT2. Among subjects with previous mono Art with 3TC, subjects in the FTC arm had better virologic response than those in the 3TC arm. Among subjects with previous dual Art with 3TC, subjects in the 3TC arm had better virologic response than those in the FTC arm.

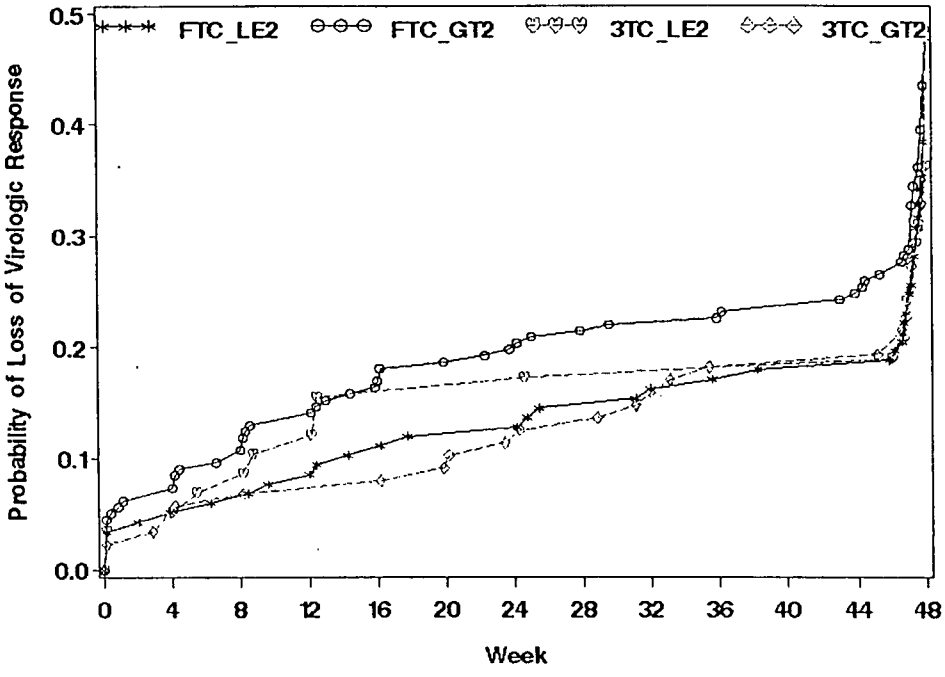


Figure 13: FTC303: K-M TLOVR by History of Mono or Dual ART with 3TC Treatment

4.1.7 History of HIV-1 Related-Event

Prior to entry, 151 (51%) of the subjects in the FTC treatment arm and 65 (45%) of the subjects in the 3TC treatment arm had a history of HIV-1 related CDC defined Class B or C events. Figure 14 shows the probability of LOVR by history of Class B or C events and treatment arm. The probability of LOVR was greatest in subjects with a history of CDC Class B or C events, denoted by FTC_YES and 3TC_YES in Figure 13, followed by subjects without B/C events, denoted by FTC_NO and 3TC_NO.

- Overall, no significant difference in LOVR was found amongst the four subgroups (p=0.29). Therefore, no further stratification of treatment arm and history of CDC Class B or C events was necessary.

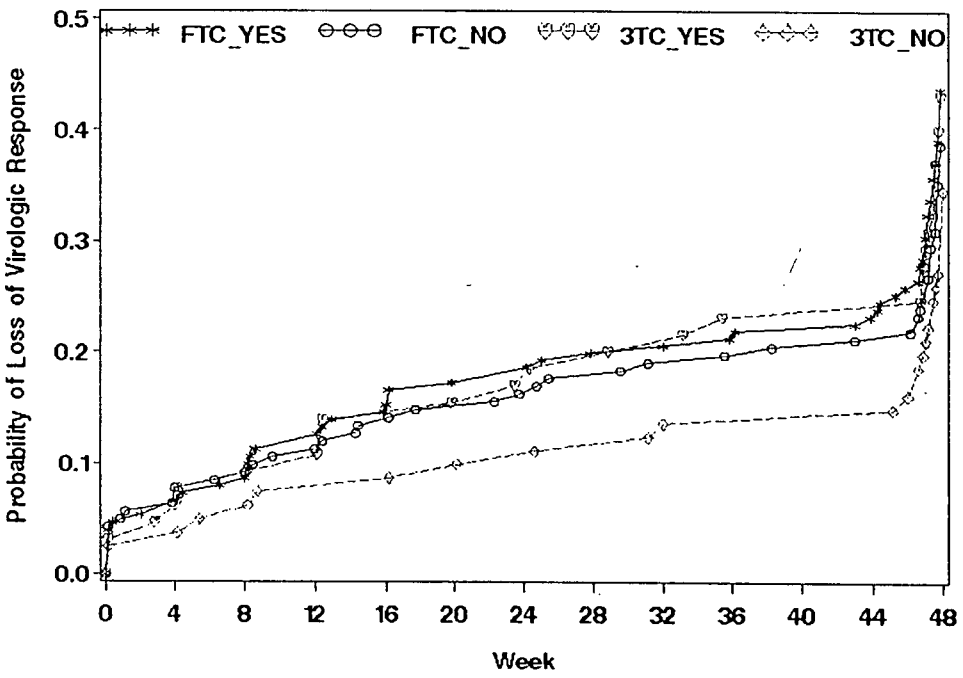


Figure 14: FTC303: K-M TLOVR by History of HIV Related Event and Treatment Arm

4.1.8 Duration of ART Prior to Entry

- Prior to entry, the median duration of ART (29.5 months) in the FTC treatment arm was statistically significantly greater than that (23.6 months) in the 3TC treatment arm, p=0.0228 by the Wilcoxon test. When categorizing subjects by the median duration of ART 27.65 months, 46.6% in the FTC treatment arm and 57.0% in the 3TC treatment arm, had duration of ART greater than the overall median duration. The K-M analysis did not show significant associations between the duration of ART prior to entry and probability of LOVR (p=0.43). A sensitivity analysis that categorizes subjects by ART duration of <24, 24-<48, ≥48 months supported this negative finding (p=0.56). In these analyses, treatment arm was controlled.

4.1.9 Summary

Table 16 summarizes the results of comparing K-M curves among subgroups of concern. The second column lists p-value by the log-rank test comparing subgroups of a factor X_i and treatment (X_i ×Trt, i=1,...,8). If a significant result was obtained in Column 2 ($p<0.05$), then the K-M analysis stratified by subgroup of a factor X_{ij} or treatment Trt_k (Column 3-5) and those by randomization stratum (Column 6-8) were proceeded when sample sizes were sufficiently large.

The comparisons of K-M curves were based on TLOVR through Week 48 and beyond. The length of study period would influence the significance of the associations. For example, if the TLOVR dataset was cut off at Week 48, the significance of the K-M curves among gender * treatment arm subgroups reduced to 0.0661. Likewise, the K-M for the Age (older or younger) * treatment arm, previous Combivir use (Yes, No) * treatment arm were no longer significant. However, the significant level of comparisons of randomization stratum and treatment six subgroups changed from 0,0226 to <0.0001, and the comparison of difference among randomization strata for FTC arm became significant ($p<0.0001$) from non-significant. Similar findings were obtained when this reviewer fit proportional hazard COX models.

Table 16: Study FTC303: Summary of Factors Associated with Virologic Failure[§]

Factor X_i	$X_i \times Trt$	P-value for comparison of K-M Curves X_{ij} or Trt_k			Randomization Stratum		
		Subgroup	P-value	favoring	Stratum	P-value	favoring
Gender	0.0168	Female	0.0366	3TC			
		Male	NS				
		FTC	0.0085	Male			
		3TC	NS				
Age	0.0028	Younger	0.0044	3TC	1	0.0064	3TC/Y
		Older	NS		2	NS	
		FTC	0.0016	Younger	3,4	NS	
		3TC	NS				
Race	NS						
Randomization Stratum	0.0226	S1	NS				
		S2	NS				
		S3&4	NS				
		FTC	NS				
		3TC	0.0018	S1 & S2			
Previous Combivir Use	0.0002	FTC	0.0087	Yes	1	0.0003	3TC/Yes
		3TC	0.0005	Yes	2	NS	
		Yes	NS		3,4	NS	
		No	NS				
Previous Mono/Dual ART with 3TC	NS						
History of HIV-1 related event	NS						
Duration of previous ART	NS						

§. TLOVR dataset through Week 48 and beyond based on LOQ=400 copies/mL.

4.2 Study FTC301A

- Similar to Study FTC303, subgroup analyses were conducted examining associations between gender, race, age, screening plasma HIV-1 RNA, history of HIV-1 related event, and tolerability of combination treatment, and TLOVR longitudinally. Comparisons of longitudinal Kaplan-Meier TLOVR curves in subgroups of these variables were performed using the entire TLOVR dataset Week 48 and beyond base on LOQ=400 copies/mL, and the log-rank test was used to test the difference in TLOVR K-M curves between designated subgroup.

  In subgroup analysis, differences in K-M curves were first compared among subgroups of a factor X_i and treatment ($X_i \times Trt$, i=1,...,6). If a significant result was observed, then a K-M analysis stratified by the jth subgroup of a factor X_i or treatment Trt_k, (k=1,2) was carried out. The effect of randomization stratum and risk factor was also examined when the sample sizes of subgroup were not too small. Subjects in a subgroup A with a significant lower LOVR than subjects in a subgroup B means that subjects in the subgroup A had greater virologic response than those in the subgroup B.

4.2.1 Gender

Figure 15 shows LOVR by gender and treatment arm.

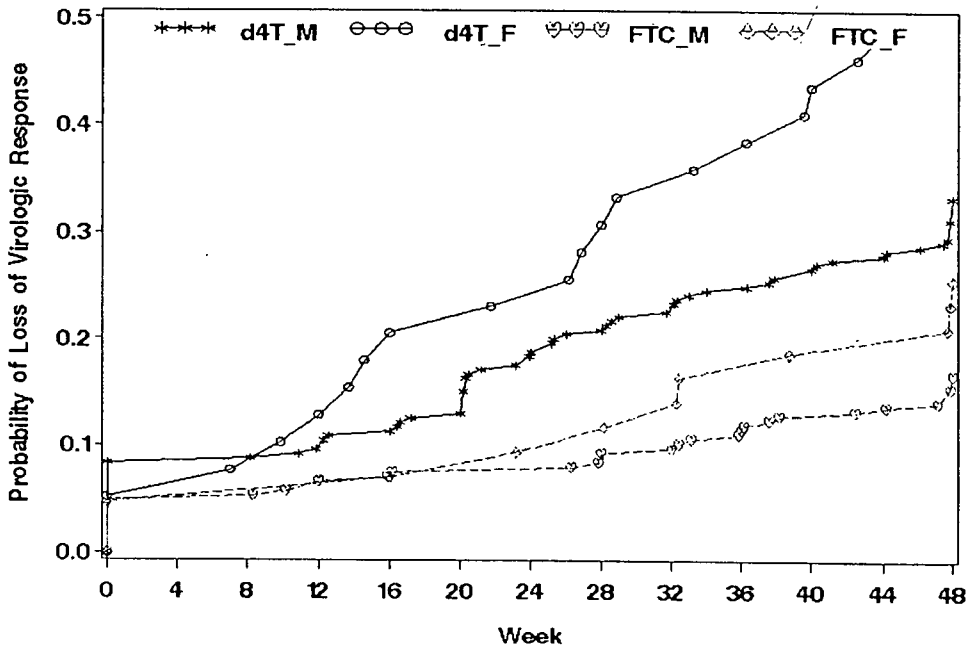


Figure 15: FTC301A: K-M TLOVR by Gender and Treatment Arm

Significant gender and treatment differences in LOVR were obtained comparing LOVR among four subgroups of gender and treatment arm, p=0.0042, by the log-rank test.

- Stratified by gender, there was significant treatment difference in LOVR among female subjects. Female subjects in the d4T treatment arm (d4T_F) had lower virologic response than those in the FTC treatment arm (FTC_F), p=0.0336. No significant treatment difference was observed in male subjects, i.e., d4T_M vs. FTC_M.

- Stratified by treatment arm, in the d4T treatment arm, male subjects had better virologic response than female subjects, p=0.0114. No gender difference was significantly different in the FTC treatment arm.

- In Study FTC301A, approximately 15% subjects were females. No further analysis by randomization stratum was performed due to small sample sizes in the female population.

4.2.2 Age

Figure 16 shows LOVR by age and treatment arm.

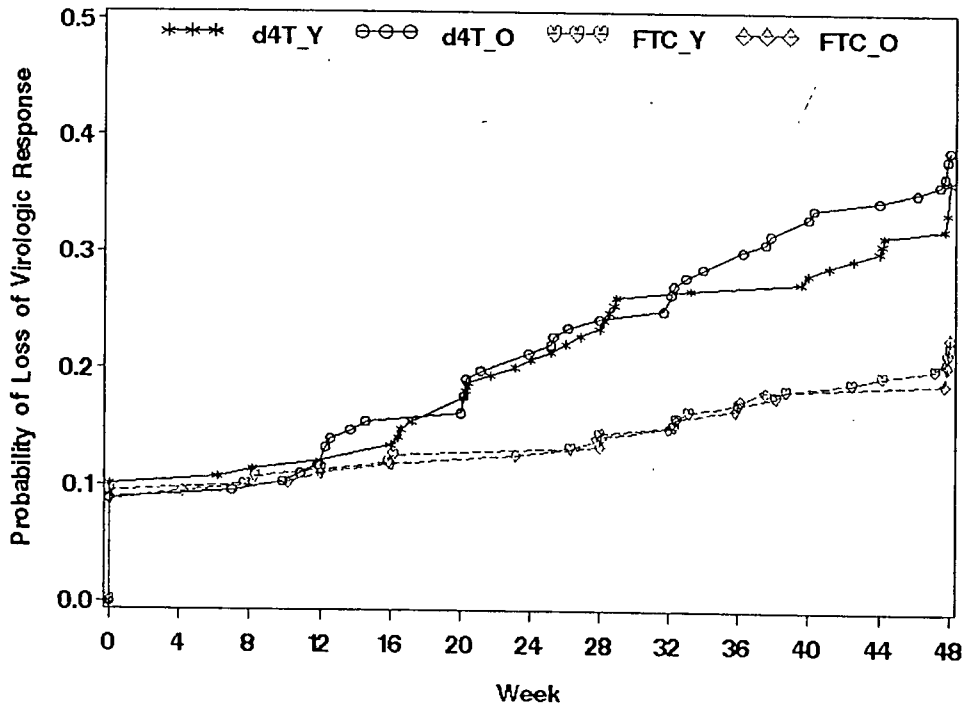


Figure 16: FTC301A: K-M TLOVR by Age and Treatment Arm

Significant age and treatment differences in LOVR were observed when comparing LOVR among four subgroups of age and treatment arm, p=0.0441 by the log-rank test.

- Stratified by age subgroup, subjects 35 years or older in the d4T treatment arm had worse virologic response or higher LOVR than the older subjects in the FTC treatment arm, p=0.0550 by the Log-rank test. No significant treatment effect in LOVR was observed among younger subjects with age < 35 years.

- Stratified by treatment arm, increased age was not statistically significantly associated with worse virologic response or higher LOVR.

- Further LOVR analysis by randomization stratum on subjects 35 years or older was performed. Results did not show significant treatment differences on LOVR between treatment arms. In addition, the screening HIV-1 RNA level was similar between these groups using the Wilcoxon test.

4.2.3 Race

White, black and Hispanic subjects consists 93.5% of the treated population, and were used for comparisons. Figure 17 shows six LOVR K-M curves.

Significant race and treatment differences in LOVR were observed, p=0.0003 by the log-rank test.

- Stratified by treatment arm, White subjects had the lowest LOVR, followed by Hispanic subjects, and Black subjects, p-value =0.0009 for subjects in the d4T treatment arm, and 0.1562 for subjects in the FTC treatment arm.

- Stratified by race, the only significant treatment difference was observed among Hispanic subjects. Hispanic subjects in the d4T treatment arm had greater LOVR than those in the FTC treatment arm, p=0.0018.

Further LOVR analysis by randomization stratum was performed. Significant findings are:

- Significant racial differences in LOVR were obtained among subjects with screening HIV RNA < 100k copies/mL in the d4T treatment arm, p=0.0044, which favors white subjects.

- Treatment differences in LOVR were obtained among Hispanic subjects with screening HIV RNA < 100k copies/mL, p=0.0058, which favors subjects in the FTC treatment arm.

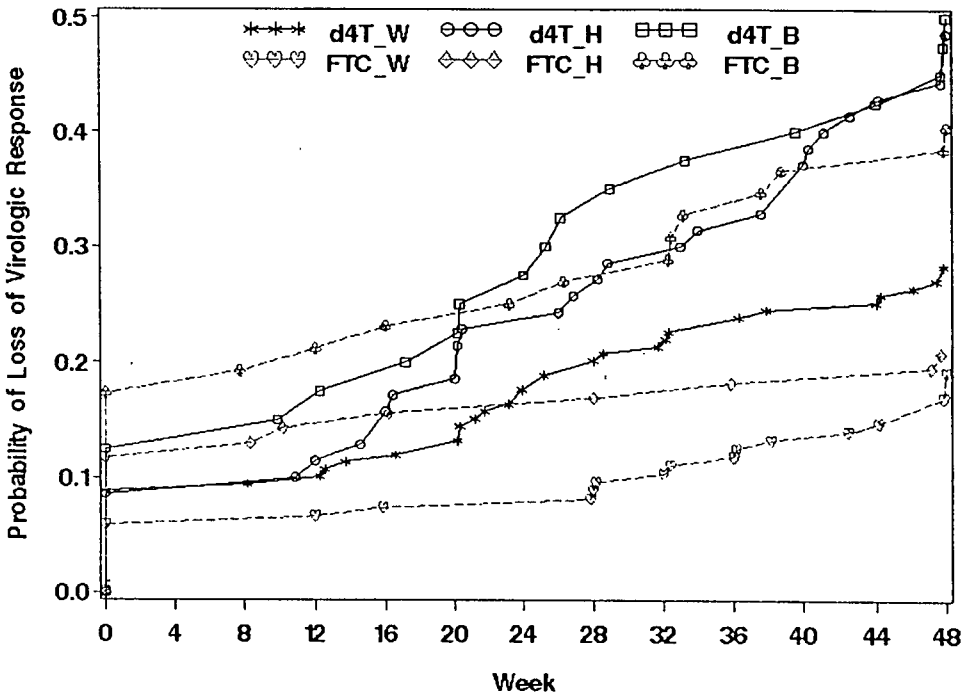


Figure 17: FTC301A: K-M TLOVR by Race and Treatment Arm

4.2.4 History of HIV-1 Related Event

Prior to entry, 54 subjects in d4T treatment arm and 65 subjects in FTC treatment arm had history of HIV-1 related event. Comparisons of LOVR K-M curves did not show any significant differences among subgroups of treatment arm and history of HIV-1 related event, p=0.0882, by the log-rank test.

4.2.5 Randomization Stratum

The randomization stratum was regrouped into plasma HIV RNA ≤ 100k copies/mL (lower) and HIV RNA > 100k copies/mL (higher) groups. The 24 subjects who were rollover from Study FTC301 had HIV RNA ≤ 100k copies/mL and were assigned to the lower HIV RNA group. The new group consists of 40% subjects in the lower and 60% in the higher HIV RNA groups.

Figure 18 shows four LOVR K-M curves.

- Significant screening plasma HIV RNA and treatment differences in LOVR were observed, $p<0.0001$ by the log-rank test.

  - Stratified by treatment arm, subjects with screening HIV-1 RNA ≤ 100k copies/mL had the lower LOVR than those with screening HIV-1 RNA > 100k copies/mL, p-value =0.0040 for subjects in the d4T treatment arm, and 0.0004 for subjects in the FTC treatment arm.

  - Stratified by screening plasma HIV RNA level, no significant treatment difference was observed: p=0.0728 for the comparison of LOVR between treatment arms in subjects with lower HIV RNA; and p=0.2153 for the comparison of LOVR between treatment arms in subjects with higher HIV RNA.

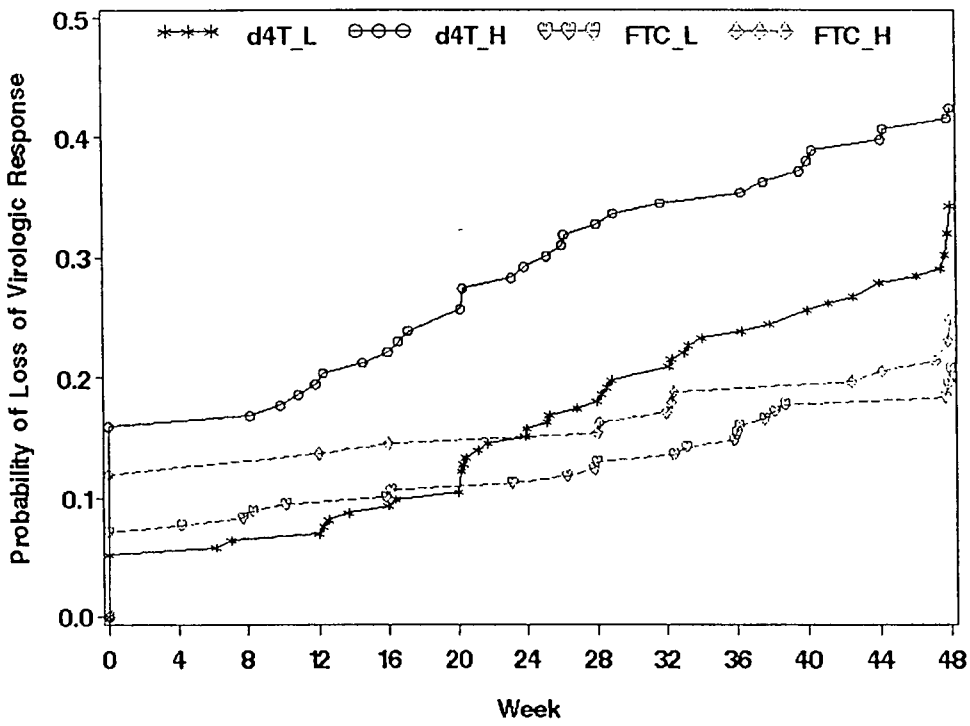


Figure 18: FTC301A: K-M TLOVR by Screening HIV RNA Stratum and Treatment Arm

4.2.6 Tolerability

It was hypothesized that the subjects with long term exposure of ART should have greater opportunity to develop drug resistance than those discontinued from study shortly after the initiation of treatment. Therefore, it is meaningful to see whether the subjects who can tolerate the ART in two treatment arms had similar efficacy results. In this study, 21 subjects, 16 in the FTC treatment arm and 7 in the d4T treatment arm with less than 8 weeks of study were excluded.

Significant screening plasma HIV RNA and treatment differences in LOVR were observed, $p<0.0001$ by the log-rank test. Figure 19 shows the K-M curves.

- Stratified by treatment arm, subjects with screening HIV-1 RNA ≤ 100k copies/mL had the lower LOVR than those with screening HIV-1 RNA > 100k copies/mL, p-value =0.0082 for subjects in the d4T treatment arm, and 0.0005 for subjects in the FTC treatment arm. These results were similar to those for the entire treated population.

- Stratified by screening plasma HIV RNA level, significant treatment difference was observed: p=0.0337 which favors the FTC treatment arm for the comparison of LOVR between treatment arms in subjects with lower screening HIV RNA; and p=0.1472 for the comparison of LOVR between treatment arms in subjects with screening HIV RNA >100k copies/mL. The significant levels increased comparing those with the entire treated population.

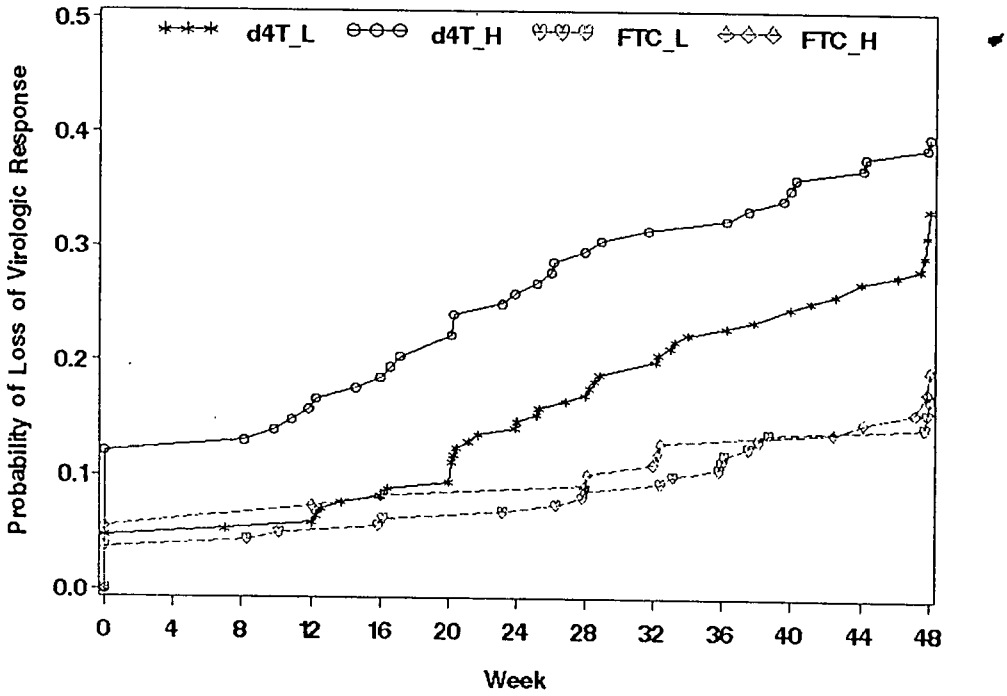


Figure 19: FTC301A: K-M TLOVR among Those with More Than 8 Weeks On Study by Screening HIV RNA Stratum and Treatment Arm

4.2.7 Summary

Table 17 summarizes the results of comparing K-M curves among subgroups of concern. The second column lists p-value by the log-rank test comparing subgroups of a factor X_i and treatment ($X_i \times Trt$, i=1,...,6). Significant results were obtained in all variables except for history of HIV-1 related event. Therefore, the K-M analysis stratified by subgroup of a factor X_{ij} or treatment Trt_k (Column 3-5). Age and race analyses by randomization stratum (Column 6-8) were proceeded because of the sample sizes in subgroups were sufficiently large.

Table 17: Study FTC301A: Summary of Factors Associated with Virologic Failure[§]

		P-value for comparison of K-M Curves					
Factor X_i	$X_i \times Trt$	X_{ij} or Trt_k			Randomization Stratum		
		Subgroup	P-value	Favoring	Stratum	P-value	Faoring
Gender	0.0042	Female	0.0336	FTC			
		Male	NS				
		FTC	NS				
		d4T	0.0114	Male			
Age	0.0441	Younger	NS		≤ 100k	NS	
		Older	0.0550	FTC	> 100k	NS	
		FTC	NS				
		d4T	NS				
Race	0.0003	White	NS				
		Hispanic	0.0018	FTC	≤ 100k	0.0129	W>H>B
		Black	NS		>100k	NS	
		FTC	NS		≤ 100k	0.0058	H-FTC
		d4T	0.0009	W>H>B	≤ 100k	NS	W
					≤ 100k	NS	B
Screening HIV RNA	<0.0001	≤ 100 k	NS				
		>100 k	NS				
		FTC	0.0004	≤ 100 k			
		d4T	0.0040	≤ 100 k			
History of HIV-1 related event	NS						
Tolerability	<0.0001	≤ 100 k	0.0337	FTC			
		>100 k	NS				
		FTC	0.0005	≤ 100 k			
		d4T	0.0082	≤ 100 k			

§. TLOVR dataset through Week 48 and beyond based on LOQ=400 copies/mL.

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

5.1.1 Study FTC303

Study FTC303 was a phase III, randomized, open-label, non-inferiority study of emtricitabine versus lamivudine in patients who were previously on a stable triple antiretroviral therapy (ART) containing lamivudine, stavudine, or zidovudine, and a protease inhibitor (PI) or non-nucleoside reverse transcriptase inhibitor (NNRTI) had HIV-1 RNA ≤ 400 copies/mL. Patients were randomized 1:2 to emtricitabine 200 mg q.d. +ZDV/d4T+ NNRTI/PI (FTC treatment arm), and lamivudine 150 mg bid +ZDV/d4T+ NNRTI/PI (3TC treatment arm). Patients were stratified based on plasma HIV-1 RNA levels and the background therapy. The primary objective was to establish the non-inferiority of antiviral activity between emtricitabine and lamivudine by comparing the proportion of randomized subjects at weeks 48 whose plasma HIV-1 RNA level remains at or below 400 copies/mL.

The analysis population is the treated population consisting of 294 subjects in the FTC treatment arm, and 146 subjects in the 3TC treatment arm. The two treatment arms in FTC303 were well balanced with respect to demographic variables and baseline characteristics, except for duration of ART prior to entry. The treated population was 86% male, 64% Caucasian, 21% Black and 13% Hispanic. The mean age was 42 years with the median age 41 and range 22-80 years. The mean baseline CD4+ cell counts was 527, with a median 488 and range 37-1909 cells/mm^3. The mean baseline HIV RNA was 1.8 $\log_{10}$ copies/mL with a median 1.7 and the range 1.7-4.0 $\log_{10}$ copies/mL. Overall, the median duration of prior antiretroviral therapy was 27.6 months: 29.5 months for the FTC arm and 23.9 months for the 3TC arm respectively. The completion rate was 78.6% with a mean duration of 42.6 weeks in the treated population and the proportion of completion was slightly lower in the FTC treatment arm.

5.1.1.1 Similarities and discrepancies in the efficacy of the two study arms

Sensitivity analyses of efficacy endpoints based on Time to Loss-of-Virologic Response (TLOVR) data were obtained according to the definition of Loss-of-Virologic Response (LOVR) by the DAVDP, and the results were summarized in 1 and 2 below. Comparisons of longitudinal Kaplan-Meier curves for TLOVR in subgroups of gender, age, ethnic and other risk factors were performed using the TLOVR dataset based on LOQ=400 copies/mL. The findings are listed in 4 and 5 below.

1. The proportion of subjects with HIV RNA below 400 copies/mL at Week 48 between the treatment arms was 75.5% in the FTC treatment arm and 80.8% in the 3TC treatment arm. The stratum-adjusted difference (FTC treatment arm - 3TC treatment arm) was –4.8% which favors the 3TC treatment arm with the lower 95% confidence limit of -12.8%, meaning the FTC arm is at most 12.8% worse than the 3TC arm with 95% confidence.

2. The proportion of subjects with HIV RNA below 50 copies/mL at Week 48 was 66.3% in the FTC treatment arm and 69.9% in the 3TC treatment arm, respectively. The stratum-adjusted difference (FTC treatment arm - 3TC treatment arm) was –3.6% which favors the 3TC treatment arm with the lower confidence limit of –11.7%.

3. Immunological responses measured by mean increase from baseline in CD4+ cell count and CD4% at Week 48 were numerically not very different in both treatment arms. The mean increase from baseline in CD4+ cell count was 29 cells/mm^3 in the FTC treatment arm and 61 cells/mm^3 in the 3TC treatment arm. The mean increase from baseline in CD4% was 1.6% in the 3TC treatment arm and 2.4% in the FTC treatment arm. The mean difference in CD4+ cell was 32 cells/mm^3 which favors the 3TC treatment arm p=0.047 by the Wilcoxon test, and the mean difference in CD4% was 0.8% which favors the FTC treatment arm with p=0.045 by the Wilcoxon test.

   - A significant qualitative interaction between treatment and randomization stratum was identified in CD4+ cell count. Subjects with screening HIV-1 RNA $\leq$ 50 copies/mL in the 3TC arm had greater CD4+ cell count increase than those in the FTC arm. However, this effect was reversed in the remaining subgroup of subjects where subjects in the FTC arm had less decrease in CD4+ cell count than those in the 3TC arm.

4. Comparisons of longitudinal Kaplan-Meier curves for TLOVR dataset with LOQ=400 copies/mL were conducted to investigate associations between LOVR and demographic factors such as gender, race and age, and to identify treatment differences in TLOVR. The results show that gender and age were significantly associated with TLOVR, and differences in K-M curves between subgroups were observed. No association between TLOVR and race ethnic groups was identified. Significance was measured by the log-rank test and significant findings ($p<0.05$) in the subgroups are as follows:

   - Female subjects in the 3TC treatment arm had maintained an undetected HIV-1 RNA better than those in the FTC treatment arm.

   - In the FTC treatment arm, male subjects had maintained an undetected HIV-1 RNA better than female subjects.

   - Younger subjects below 42 years in the 3TC treatment arm had maintained an undetected HIV-1 RNA better than those in the FTC treatment arm.

- In the FTC treatment arm, younger subjects below 42 years had maintained an undetected HIV-1 RNA better than older subjects.

- When stratifying by randomization stratum for age subgroups, the significance remained for Randomization Stratum 1 (not other strata) where subjects with screening HIV-1 RNA below 50 copies/mL and treated with PI.

5. Comparisons of longitudinal Kaplan-Meier curves for the TLOVR dataset with LOQ=400 copies/mL were conducted to investigate associations between LOVR and other risk factors such as randomization stratum, history of Combivir use, history of mono or dual ART with lamivudine, history of HIV-1 related event, and duration of previous ART, and to identify treatment differences in subgroups. The results show that randomization stratum and history of Combivir use were significantly associated with TLOVR, and significant differences in K-M curves between subgroups were observed. No association between TLOVR and other risk factors was identified. Significance was measured by the log-rank test and significant findings ($p<0.05$) in the subgroup analysis are listed below.

   - Subjects in the 3TC treatment arm with screening HIV RNA ≤ 50 copies/mL had maintained an undetected HIV-1 RNA better than those with screening HIV RNA between 50 and 400 copies/mL. In the FTC arm, no significant difference in K-M curves was identified between randomization strata.

   - Subjects treated with triple ART other than combivir (AZT+3TC) prior to entry of the study had maintained an undetected HIV-1 RNA better than those subjects previous treated with combivir.

   - When stratifying by randomization stratum for combivir use analysis, the significance remained for Randomization Stratum 1 (not other strata) where subjects with screening HIV-1 RNA below 50 copies/mL and treated with PI.

5.1.1.2 Efficacy contributed by emtricitabine in this study design is unclear

The stratum-adjusted difference (FTC treatment arm - 3TC treatment arm) in percentage of subjects with HIV RNA below 400 copies/mL was –4.8% with the lower 95% confidence limit of –12.8% adjusting for randomization stratum, which favors the 3TC treatment arm. Based on this result, this reviewer can not judge the efficacy contributed by emtricitabine in this triple-drug regimen. The reasons are as follows.

(1) Although a non-inferiority margin of –15% was specified in the sample size calculation, and the lower 95% CI limit of the primary endpoint was greater than this value, it was only appropriate for sample size calculation, not a criterion for non-inferiority judgement.

(2) One can not directly infer efficacy of emtricitabine based on the FTC303 study design.

Though the two treatment arms in Study 303 were numerically similar in efficacy in maintaining an undetectable HIV RNA and immunologic responses, the lamivudine contribution in a triple-drug regimen has not been well established. Therefore, the non-inferiority of emtricitabine contribution in this Study FTC303 can not be inferred directly without further analysis and assumptions.

5.1.1.3 Estimation of efficacy contributed by emtricitabine via statistical modeling

Statistical modeling was carried out to estimate efficacy of emtricitabline indirectly using information from a historical lamivudine study (035 in NDA 20-683) and the current Study FTC303. In NDA 20-685, the applicant was seeking the approval of indinavir sulfate. In Study 035, approximately 80% subjects in the indinavir +ZDV+3TC arm (n=40) and 39.2% subjects in indinavir arm (n=28) had plasma HIV-1 RNA below 500 copies/mL at Week 24. Note subjects in indinavir arm were ZDV-experienced (median exposure 30 months), protease-inhibitor- and lamivudine-naïve.

Assuming drug efficacy to be ε, then the efficacy of emtricitabine relative to placebo is

$$\varepsilon \text{ (FTC-Placebo)} = \varepsilon \text{ (FTC-3TC)} + \varepsilon \text{ (3TC-Placebo)} \qquad \text{(Eq.1)}$$

The estimate of ε (3TC-Placebo) from Study 035 may need to be discounted by a factor λ 1-λ, ($0 \le \lambda \le 1$), which reflects the uncertainty associated with using data from a historical trial, possible contribution of the ZDV, and dissimilarity of the Study FTC303 and Study 035.

Assuming a discount factor λ of 5%-30%, then the estimated efficacy by emtricitabine over placebo was between 25%-35% at Week 24, with the lower 95% CI limit ranging 1.3%-11.1%, meaning that emtricitabline is at least 1.3% better than placebo with 95% confidence even with a 30% discount of the results from Study 035.

Since Study 035 was a 24-week study, in order to use it for FTC303 Week 48 evaluation, additional assumptions were needed to bridge the virologic response (1-LOVR) at Week 24 and the virologic response at Week 48. Denoting the probability of 1-LOVR at time t is $P(\text{FTC-Placebo})_t$, we assume that the efficacy at Week 48 can be estimated:

$$P(\text{FTC-Placebo})_{48} = \kappa\, P(\text{FTC-Placebo})_{24} \qquad \text{(Eq.2)}$$

where κ is a ratio of the two probabilities.

Using the FTC303 TLOVR data, the ratio of 1-LOVR at Week 48 vs. that at Week 24 for the FTC arm is 0.59. Assuming that this ratio is similar for FTC-Placebo, then the effective size ε(FTC-Placebo) at Week 48 would be 15% to 21%. If this indirect method is valid, then one can infer that emtricitabine was efficacious over placebo with respect to the primary study endpoint. However, as the discount factor λ increases to greater than 30%, the efficacy contributed by lamivudine over placebo through Study 035 would be reduced

so that emtricitabine efficacy would not be better than the placebo.

5.1.2 Study FTC301A

Study FTC301A was a phase III, randomized, double-blind non-inferiority trial comparing emtricitabine to stavudine within a triple drug combination containing didanosine plus efavirenz in antiretroviral-drug naïve HIV-1 infected patients. The primary objective was to assess the safety and efficacy of emtricitabine versus stavudine. Patients were randomized 1:1 to emtricitabine 200 mg QD +stavudine placebo BID +didanosine (250 mg QD if <60kg, or otherwise 400 mg QD) +efavirenz (600 mg QD) (FTC treatment arm), and emtricitabine placebo QD +stavudine (30 mg BID if < 60kg, or otherwise 40 mg BID) +didanosine (250 mg QD if <60kg, or otherwise 400 mg QD) +efavirenz (600 mg QD) (d4T treatment arm). Patients were stratified based on plasma HIV-1 RNA levels and geographic regions.

The analysis population is the treated population consisting 286 subjects in the FTC treatment arm and 285 subjects in the d4T treatment arm. The two treatment arms in FTC301A were well balanced with respect to demographic variables and baseline characteristics. The treated population had a mean age of 36 years. 85% was male, was 52% Caucasian, 26% Hispanic and 16% Black, 45% from North America, 33% from South American, and 22% from European counties. The mean and median baseline CD4+ cell count were 318 and 288 cells/mm^3, respectively. The mean baseline HIV RNA was 4.8 in $\log_{10}$ copies/mL. The treated population included 57% subjects with screening HIV RNA between 5000 and 100,000 copies/mL, 40% with screening HIV RNA above 100,000 copies/mL and 3% previously treated under the FTC301-protocol. Prior to entry, 21% of the subjects in the treated population had history of HIV-1 related events. The overall completion rate was 77% and the proportion of completion was 11% higher in the FTC treatment arm.

5.1.2.1 FTC Treatment Arm Showed Significant Benefit on Primary Efficacy Endpoint

The Study FTC301A demonstrated statistically superiority of the proportion of subjects with HIV RNA below 50 copies/mL at Week 48: 78% in the FTC treatment arm and 59% in the d4T treatment arm. The stratum-adjusted difference (FTC treatment arm - d4T treatment arm) was 19.6% with the 95% CI of 12.1% to 27.1%, meaning the FTC arm is at least 12% better in achieving a virologic response than the d4T arm.

5.1.2.2 FTC Treatment Arm Showed Significant Benefit on Other Efficacy Endpoints

1. Superiority of the proportion of subjects with HIV RNA below 400 copies/mL at Week 48 was achieved: 81% in the FTC treatment arm and 67% in the d4T treatment arm. The stratum-adjusted difference (FTC treatment arm - d4T treatment arm) was 14%,

with the 95% CI of 7.2% to 21.4%.

2. Superiority of time-weighted average change (TAD) from baseline in plasma HIV RNA through Week 48 was achieved. The estimated difference (FTC-d4T) in TAD change from baseline in plasma HIV RNA through Week 48 adjusting for screening HIV RNA was 0.24 $\log_{10}$ copies/mL with a 95% confidence interval of (0.073,0.405) by the base value carry forward (BOCF) method, which significantly favors the FTC treatment arm, $p<0.05$.

3. Immunological responses at Week 48 were statistically significantly better for subjects in the FTC treatment arm than those in the d4T treatment arm. The mean increase from baseline in CD4+ cell count was 168 cells/mm^3 in the FTC treatment arm and 128 cells/mm^3 in the d4T treatment arm. The randomization stratum adjusted TAD difference (FTC-d4T) in CD4+ cell count through Week 48 by last value carry forward (LVCF) method was 29 cells/mm^3 with 95% CI of 10 to 47 cells/mm^3, $p<0.05$. The mean increase from baseline in CD4% was 5.8% in the d4T treatment arm and 9.3% in the FTC treatment arm. The randomization stratum adjusted TAD difference (FTC-d4T) in CD4% through Week 48 by the LVCF method was 2.5% with 95% CI of 1.7% to 3.2%, $p<0.05$. Both results showed the immunologic responses were significantly in favor of the FTC treatment arm.

4. Comparisons of longitudinal K-M curves for the TLOVR dataset with LOQ=400 copies/mL were conducted to investigate the associations between LOVR and subgroups of gender, race, age, randomization stratum, history of HIV-1 related event prior to entry and subjects who had higher tolerability. The results show significant differences in LOVR between subgroups of gender, race, age, randomization stratum and subjects who had higher tolerability. No association between LOVR and history of HIV-1 related event was observed. Significance was measured by the log-rank test and significant findings were based on $p<0.05$ in the subgroup comparisons. In the following, the main analysis was based on the comparison of K-M between treatment arms, where subjects in the FTC arm had significant better virologic response.

   - **Gender:** LOVR results among female subjects were consistent with the main analysis. However, in the male subgroups, no significant difference in K-M curves was observed between the two treatment arms. In the d4T treatment arm, male subjects had significant better virologic response than female subjects. No significant gender difference was observed in the FTC arm.

   - **Age:** LOVR results among subjects 35 years or younger were consistent with main analysis. However, no significant difference in K-M curves was observed between the two treatment arms for older subjects (>35 year). No significant difference in K-M curves was observed between older and younger subgroups in the FTC arm or in the d4T arm.

   - **Race:** LOVR results in Hispanic subjects consistent with main analysis. However,

in the White or Black subgroups, no significant difference in K-M curves was observed between the two treatment arms. In the d4T treatment arm, the virologic response was the best, followed by Hispanic subjects, and black subjects. Further analysis on subjects with screening HIV RNA ≤100k copies/mL confirmed this finding. No significant race difference was observed in the FTC arm.

- **Randomization Stratum:** In both treatment arms, subjects with screening HIV RNA ≤100k copies/mL had significant better virologic response than those with screening HIV RNA >100k copies/mL. No significant differences in K-M were observed between the two treatment arms for higher (>100k copies/mL) or lower (≤100k copies/mL) screening HIV RNA stratum respectively.

- **Tolerability:** Among subjects who had at least eight weeks on study, LOVR results were consistent to those results of 'Randomization Stratum' with one exception: for subjects with screening HIV RNA ≤ 100 k copies/mL, subjects in the FTC arm had significant better virologic response than those in the d4T arm.

5.2 Conclusions and Recommendations

Based on analyses of the Week 48 data and beyond, it is concluded:

1. In Study FTC301A, of the two treatment arms the FTC arm had significantly better virologic suppression and immunologic responses than the d4T arm ($p<0.001$).

2. In Study FTC303 the FTC and 3TC treatment arms were numerically similar in maintaining HIV RNA below assay limit and immunologic responses. However, superiority of FTC over placebo in maintaining HIV RNA below assay limit could not be established without strong assumptions on the 3TC's contribution in the control regimen. The reviewer used the indinavir study 035 to derive the 3TC's contribution in efficacy in a combination regimen. Because Study 035 is small, only when we assume that more than 70% of the 3TC effect observed in Study 035 was preserved we can indirectly prove that FTC is superior to placebo at significant level 0.05.

   - Since patients in FTC303 were already 3TC-experienced, it is unlikely that 3TC contribution in this population will be as large as the 3TC contribution in the 3TC-naïve population in the Study 035. The combination regimen used in the historical trial also differed from the combination in FTC303 study. Given these differences the 70% preservation rate may be too high. The 70% preservation rate is also higher than the more commonly used 50% preservation rate. Therefore, we can not firmly establish the superiority of FTC over placebo.

6. APPENDICES

6.1 Source Information Section 3.1.4 (Study 035 in NDA 20-685)

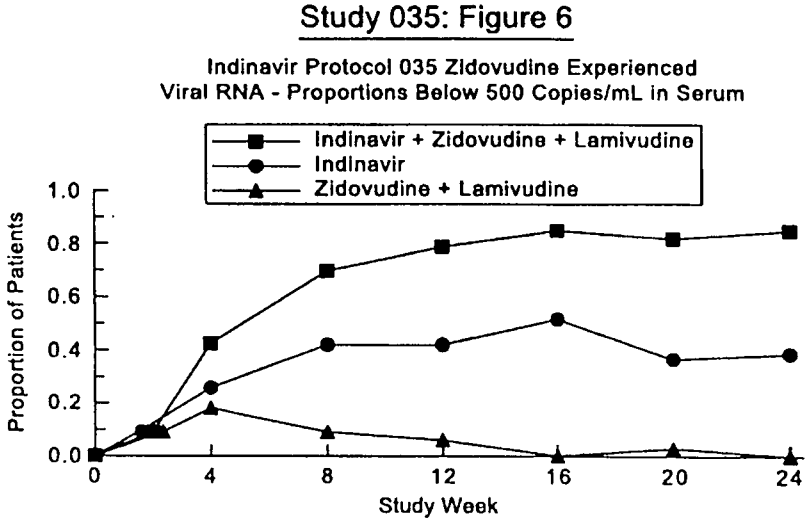


Figure 20: Study 035 in NDA 20-685: Proportion of Patients with Plasma HIV RNA Below 500 copies/mL at Week 24

Source: http://cdsode4serv/labels/default.asp

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Susan Zhou
7/2/03 01:13:57 PM
BIOMETRICS

Greg Soon
7/2/03 04:08:13 PM
BIOMETRICS