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APPLICATION NUMBER:

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STATISTICAL REVIEW(S)

STATISTICAL REVIEW AND EVALUATION

NDA#: 21752/S-001
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INDICATION: Prophylaxis of HIV Infection
APPLICANT: Gilead Pharmaceuticals, Inc.
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STATISTICAL REVIEW AND EVALUATION

NDA#: 21752

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1. Executive Summary

The applicant submitted two randomized, controlled, phase 3 clinical trials with truvada (=tenofovir+emtricitibine=TDF+FTC) or tenofovir alone for pre-exposure prophylaxis of HIV infections. One trial focused on prophylaxis in males having sex with males (MSM) while the other trial focused on prophylaxis in heterosexual contacts, with either gender being the infected partner. The former was conducted by NIH/DAIDS, the latter by the University of Washington.

These trials were not conducted by the applicant but by other parties. Both of the drugs used in these trials are already approved for HIV treatment and thus may be obtained by any licensed physician for use in trials. In addition to the included studies, the use of these drugs in humans has been evaluated in as a Phase 2 clinical study of TDF for HIV PrEP (pre-exposure prophylaxis) among initially uninfected MSM in the US (CDC 4323). A Phase 2 clinical study of TDF for HIV PrEP has also been conducted with women in West Africa (FHI PrEP Study). Finally, the CDC TDF2 study was conducted with young heterosexuals in Botswana, and the VOICE and FEM-PrEP studies were conducted in high-risk women in Africa.

Trial 288 (Iprex) enrolled males having sex with males (MSM) who were at high risk of HIV-1 infection. The objective of the trial was to compare the efficacy of truvada = TRV =(combination pill of emtricitibine(FTC) 200mg/tenofovir(TDF) 300mg) to placebo in preventing infection by HIV-1 during sex between men. Sample size in the trial was calculated to have an 80% power to reject the null hypothesis of risk reduction no more than 30% at the expected efficacy level. It is not clear whether failure to rule out a risk of no more than 30% would constitute failure to demonstrate adequate efficacy.

Trial 380 (Partners Prep) enrolled subjects who were not infected with HIV but were known to have HIV infected partners of the opposite sex. The infected partner could be of either sex. The objective of the trial was to determine the efficacies of either truvada = TRV or of TDF 300 mg relative to placebo in preventing transmission of HIV-1 during heterosexual intercourse

with an HIV-1 infected partner.

The analyses have demonstrated in two trials that truvada prophylaxis results in a risk reduction of 40-60% in males at risk of HIV infection. This efficacy is confirmed across sub-groups based on baseline and post-treatment covariates.

Analysis of subgroups show that although truvada is consistently superior to placebo, it is not perfect. Truvada in groups with elevated risk performs worse than truvada in groups with lower risk but is still superior to placebo in groups with elevated risk.

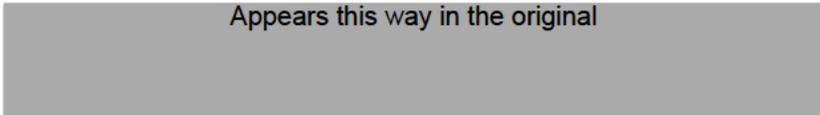
It is more problematic whether tenofovir alone is effective and whether oral truvada is effective in women. Both of these two questions were studied only in a single trial. That trial did show statistically significant reduction in risk with respect to both at risk males using tenofovir alone and at risk females using either tenofovir alone or truvada but there is no confirmatory trial. It is also of some concern that the applicant reports the existence a second trial in women, namely, FemPrep, but does not report even a summary of the results of this trial, much less sufficient data for the FDA to analyze the results.

On the other hand, with respect to FemPrep, the failure of the conductors of this trial to make their sites available to FDA inspection and their data to FDA review may serve to cast doubt on the reliability of any findings which may contradict efficacy. Nonetheless, the absence of a confirmatory trial, possibly combined with an unreviewed, uninspected negative trial renders it problematic to approve these two specific indications.

Neither trial was powered to answer questions about efficacy within subgroups. It would be useful to be able to determine whether truvada or tenofovir was or was not sufficiently beneficial in the lower risk sub-groups to justify the burden of those drugs' toxicity. There are suggestions that those with infected partner's with high CD4 count and those not practicing unprotected receptive anal intercourse receive minimal benefit. The FDA statistical reviewer wonders why these plausible results were not confirmed by related analyses: i.e. why are interactions

not apparent with partner's viral load or with number of anal sex acts?

Appears this way in the original



2. Introduction

2.1 Overview

The applicant submitted two randomized, controlled, phase 3 clinical trials with truvada (=tenofovir+emtricitibine=TDF+FTC) or tenofovir alone for pre-exposure prophylaxis of HIV infections. One trial focused on prophylaxis in males having sex with males (MSM) while the other trial focused on prophylaxis in heterosexual contacts, with either gender being the infected partner. The former was conducted by NIH/DAIDS, the latter by the University of Washington.

These trials were not conducted by the applicant but by other parties. Both of the drugs used in these trials are already approved for HIV treatment and thus may be obtained by any licensed physician for use in trials. In addition to the included studies, the use of these drugs in humans has been evaluated in as a Phase 2 clinical study of TDF for HIV PrEP (pre-exposure prophylaxis) among initially uninfected MSM in the US (CDC 4323). A Phase 2 clinical study of TDF for HIV PrEP has also been conducted with women in West Africa (FHI PrEP Study). Finally, the CDC TDF2 study was conducted with young heterosexuals in Botswana, and the VOICE and FEM-PrEP studies were conducted in high-risk women in Africa.

The CDC 4323 study was a randomized, placebo-controlled, double-blind, Phase 2 study of MSM in the US. This study was designed primarily to assess the safety, adherence, and acceptability of PrEP in subjects who used either TDF or placebo once-daily. The FEM-PrEP study was designed to evaluate the safety and efficacy of once-daily oral FTC/TDF compared with placebo as PrEP among high-risk African women. VOICE was a Phase 2b (proof of concept) study designed to evaluate both the safety and effectiveness of daily oral FTC/TDF or TDF, or daily use of TDF vaginal gel in preventing the sexual transmission of HIV in women. The FHI PrEP Study assessed the effectiveness and extended safety of once-daily TDF in high-risk HIV-negative women in countries suitable for introducing TDF as PrEP. The CDC TDF2 study evaluated the efficacy and safety of daily oral FTC/TDF compared with placebo in heterosexual Botswanan men and women who

were at high-risk for HIV infection. Finally, the Centre for the AIDS Programme of Research in South Africa (CAPRISA 004) study was a double-blind, randomized, placebo-controlled, Phase 2 study designed to evaluate 1% TDF vaginal gel in the prevention of HIV-1 infection in heterosexual women.

2.2 Data Sources

2.2.1 Objectives in Trials

2.2.1.1 Trial 288

Trial 288 (Iprex) enrolled males having sex with males (MSM) who were at high risk of HIV-1 infection. The objective of the trial was to compare the efficacy of truvada = TRV =(combination pill of emtricitibine(FTC) 200mg/tenofovir(TDF) 300mg) to placebo in preventing infection by HIV-1 during sex between men. Sample size in the trial was calculated to have an 80% power to reject the null hypothesis of risk reduction no more than 30% at the expected efficacy level. It is not clear whether failure to rule out a risk of no more than 30% would constitute failure to demonstrate adequate efficacy.

2.2.1.2 Trial 380

Trial 380 (Partners Prep) enrolled subjects who were not infected with HIV but were known to have HIV infected partners of the opposite sex. The infected partner could be of either sex. The objective of the trial was to determine the efficacies of either truvada = TRV or of TDF 300 mg relative to placebo in preventing transmission of HIV-1 during heterosexual intercourse with an HIV-1 infected partner.

All subjects were to be followed for 24 to 36 months in order to permit assessment of secondary objectives including 1) cofactors influencing infection rates, 2) long term adherence, 3) drug sharing between partners, and 4) modifications of behaviors influencing risk of transmission.

In this trial, there was provision for interim stopping for efficacy by the DSMB. These stopping rules used standard boundaries for testing against the null hypothesis that the reduction in risk was no more than 30%.

2.2.1.3 Fem-PrEP, FHI PrEP, VOICE, and CAPRISA Trials

The FEM-PrEP study was designed to evaluate the safety and efficacy of once-daily oral FTC/TDF compared with placebo as PrEP among high-risk African women. VOICE was a Phase 2b (proof of concept) study designed to evaluate both the safety and effectiveness of daily oral FTC/TDF or TDF, or daily use of TDF vaginal gel in preventing the sexual transmission of HIV in women. The FHI PrEP Study assessed the effectiveness and extended safety of once-daily TDF in high-risk HIV-negative women in countries suitable for introducing TDF as PrEP. The CDC TDF2 study evaluated the efficacy and safety of daily oral FTC/TDF compared with placebo in heterosexual Botswanan men and women who were at high-risk for HIV infection. Finally, the Centre for the AIDS Programme of Research in South Africa (CAPRISA 004) study was a double-blind, randomized, placebo-controlled, Phase 2 study designed to evaluate 1% TDF vaginal gel in the prevention of HIV-1 infection in heterosexual women.

None of these trials have been submitted as part of this application despite the fact that they were designed to address the question of efficacy of truvada and tenofovir in prophylaxis of at risk women.

All results in section 2 will be those of the applicant. Results generated by the FDA reviewer will be contained in section 3.

2.2.2 Summary of Study Design

2.2.2.1 Trial 288

Trial 288 was a phase 3, double-blind, placebo controlled, randomized two-arm, multicenter trial. Subjects were men having sex with men who were uninfected with HIV-1 at enrollment but who were at high risk of HIV infection defined as doing any of the following:

(1) did not use a condom during anal intercourse with an HIV-infected male partner or a male partner of unknown HIV-1 status in the previous 6 months; (2) had anal intercourse with > 3 male partners in the previous 6 months (> 5 partners per Protocol Version 3); (3) exchanged money, gifts, shelter, or drugs for anal sex with a male partner in the previous 6 months; (4) had sex with a male partner and was diagnosed with an STI in the previous 6 months or at screening; or (5) had sex with an HIV-infected male partner with whom condoms were not consistently used in the previous 6 months.

Subjects were enrolled at 11 sites in Peru, Ecuador, Brazil, Thailand, South Africa, and the US. Randomization was stratified by site. Enrollment lasted from July 10, 2007, to Dec. 17, 2009. The cutoff data for monitoring of HIV seroconversions was May 1, 2010.

At baseline and every visit subjects received counseling in HIV and STD infection risk reduction and, if necessary, treatment for other STI's, including syphilis, Chlamydia, and HSV2. Subjects also received counseling in the importance of adherence with the protocol for daily drug use and against sharing drugs.

2.2.2.2 Trial 380

Trial 380 was a phase 3, randomized, double blind, double dummy, placebo controlled, three arm trial enrolling subjects who were not infected with HIV but were known to have HIV infected partners of the opposite sex. The infected partner could be of either sex. The couples were required to be sexually active, defined as having vaginal intercourse ≥ 6 times in the previous 3

months, and to plan to stay in the relationship for the duration of the study.

Subjects were enrolled at four sites in Kenya and five sites in Uganda.

The uninfected subjects were randomized 1:1:1 to either truvada = TRV =(combination pill of emtricitibine(FTC) 200mg/tenofovir(TDF) 300mg) or TDF 300 mg or placebo once daily. All subjects took 2 tablets, either active or placebo TRV and either active or placebo TDF.

All subjects were to be followed for 24 to 36 months. Enrollment began on June 19, 2008 and the placebo arm was discontinued on July 10, 2011, at the recommendation of the DSMB. Despite the early stopping most subjects did receive 24 months of treatment.

At baseline and every visit subjects received counseling in HIV and STD infection risk reduction and, if necessary, treatment for other STI's, including syphilis, Chlamydia, and HSV2.

2.2.3 Patient Accounting and Baseline Characteristics

2.2.3.1 Trial 288

In trial 288, 2499 subjects were randomized, approximately 1250 to each of the two arms. Patient status is given in table 2.2.3.1 A.

TABLE 2.2.3.1 A
PATIENT STATUS, TRIAL 288 NAIVE

Arm	Placebo	TDF/FTC
Randomized	1248	1251
Follow Up	1225	1226
HIV+ Baseline	8	2
Modified ITT	1217	1224
Discontinued	147	162

20 placebo subjects and 22 truvada subjects discontinued due to AE. There were 4 deaths on placebo and 5 on truvada.

All subjects were born male although 29 reported their current gender identity as female. (The applicant does not report if these subjects had actual sex change operations or if the identity is just the way they perceive themselves.) Their mean age was 27 with a range of 18 to 67. Most of the subjects were enrolled in South America. Distribution of subjects by site is given in table 2.2.3.1 B.

TABLE 2.2.3.1 B
DISTRIBUTION OF SUBJECTS BY SITE

SITENAME		PLACEBO	TRUVADA
USA	Boston	43	41
	San_Francisco	70	69
SOUTH AFRICA	Cape_Town	39	42
THAILAND	Chiang_Mai	56	57
ECUADOR	Guayaquil	144	144
	Iquitos	227	227
PERU	Lima-INMENSA	244	247
	Lima-Impacta	217	214
BRAZIL	Rio-Praça_Onze	44	46
	Rio-FIOCRUZ	98	100
	Sao_Paulo	36	37

21% of subjects reported less than secondary education, 35% completed secondary education, 42% reported post secondary education. Subjects were 70% mixed, 17% white, and 9% black.

2.2.3.2 Trial 380

In trial 380, 7856 couples were screened and 4758 were randomized. A few randomized subjects were later found to be ineligible, either because both partners were infected at baseline or for other reasons. A few additional subjects had no return visits after treatment start. Patient status is given in table 2.2.3.2 A.

TABLE 2.2.3.2 A
PATIENT STATUS, TRIAL 380

Arm	TRV	TDF	Placebo
Randomized	1583	1589	1586
Ineligible	4	5	2
No Follow Up	8	7	10
Infected at Baseline	3	5	6
Modified ITT	1568	1572	1568
Retained			
6_Months	1553	1553	1559
12_Months	1379	1364	1378
18_Months	1070	1112	1083
24_Months	753	745	760
30_Months	296	294	301
36_Months	16	15	18

The uninfected partners were 61-64% male across the arms with a median age of 33-34 years. At least 78% of these subjects were earning an income. They had a median education of 7 years. Over 90% had not reported sex with an outside partner. At least 67% of the infected partners were earning an income and were similar to the uninfected partners with respect to education level and outside sex. Median duration of the partnerships was 7-7.1 years across arms.

Median baseline CD4 count among the infected partners was 491-499 and median baseline HIV RNA levels were 3.9 log copies per ml. The median couple had learned of the HIV infection only 0.4 to 0.5 years ago. 6-9% of infected and uninfected partners had a curable STI at baseline.

2.2.4 Summary of Methods of Assessment

2.2.4.1 Schedule of Measurements

In both trials uninfected subjects had rapid antigen test for HIV-1 infection every month, followed by an EIA test if the rapid antigen test was positive. In addition, a monthly structured interview and tablet count was used to assess adherence.

In trial 288, samples were collected for analysis of study drug concentrations in plasma and peripheral blood mononuclear cells. Plasma samples for possible assessments of FTC/TDF concentrations were collected from all subjects at baseline, every 12 weeks during the period of study drug administration, at the seroconversion visit, at the end-of-study visit, and at every post study-drug follow-up visit. PBMC samples for possible assessments of FTC/TDF concentration were collected from all subjects at baseline, every 24 weeks during the period of study drug administration, at the seroconversion visit, at the end-of-study visit, and at every post study-drug follow-up visit. At the end of the study, these drug levels were analyzed for all subjects who converted and for two matched uninfected controls, one from each arm.

In trial 380, a case-control sample of subjects had measurements of tenofovir in plasma. This sample consisted of 17 subjects who seroconverted on TDF and 12 of 13 subjects who seroconverted on FTC/TDF along with The cohort comparison included 100 randomly-selected non-converting subjects from each of the TDF and FTC/TDF arms. (One seroconverter in the FTC/TDF group did not have a sample available; this subject was found to have seroconverted to HIV-1 at the Month 23 visit and had not attended any other study visits since enrollment).

2.2.4.2 Assessment of Treatment Effects

In both trials, the primary efficacy variable was the time to seroconversion of the uninfected subject.

2.2.5 Summary of Statistical Analysis

For trials 288, the applicant does not specifically describe what test is used. The reported statistic appears to be based on the two by two contingency table of arm crossed with final HIV infection status. Time to infection is ignored in the primary analysis but the applicant does provide Kaplan-Meier curves to compare the infection rates in the two arms over time.

For trials 380, the primary analysis was a Cox proportional hazards regression with the analysis stratified by site. No baseline covariates were used in either the randomization or the analysis. Subjects who were lost to follow-up or died without seroconversion prior to their scheduled end visit were treated as non-informatively censored at the time of loss.

2.2.6 Summary of Applicant's Results

2.2.6.1 HIV-1 Incidence Rates Per Person-Year

Tables 2.2.6.1 A gives the results of the applicant's analysis on trial 288, counting seroconversions in the modified ITT set at the primary time point (which is not adequately described in the report, although it appears to have been planned to be the time at which 85 events had occurred), through the last dose of study drug, and through 8 weeks after the last dose of study drug. The p-values for testing superiority of truvada are all $<.05$ as indicated by 95% two-sided lower bounds for the relative rates all greater than zero.

TABLE 2.2.6.1 A
SEROCONVERSION RATES IN TRIAL 288

ARM	RATE	RELATIVE RATE	95% LIMITS
Primary Time Point			
Placebo	64/1217 = 5.26%		
Truvada	36/1224 = 2.94%	44%	(15%, 63%)
Last Study Drug			
Placebo	83/1217 = 6.82%		
Truvada	48/1224 = 3.92%	43%	(18%, 60%)
8 Weeks Post			
Placebo	85/1217 = 6.98%		
Truvada	52/1224 = 4.25%	39%	(14%, 57%)

In the applicant's analysis of trial 380, there were confirmed 82 seroconversions to HIV positive while on treatment. (Three seroconversions were ruled a false positive by the adjudication committee and 14 subjects were determined to have been HIV positive at baseline.) Table 2.2.6.1 B gives the hazard rates (in seroconversions per person-year exposure) together with 95% confidence limits on the rates and on the hazard ratios comparing the three treatment arms pairwise. (Ratios <1 indicate the test arm has lower seroconversion rate than placebo and that TRV has lower rate than TDF.) The table also gives the p-values for testing whether each of the test arms is more than 30% better than placebo against the null hypothesis that the test arm is no more than 30% better than placebo.

TABLE 2.2.6.1 B

SEROCONVERSIONS PER PERSON YEAR AND HAZARD RATIOS
TRIAL 380

ARM	TRV	TDF	PLACEBO
SUBJECTS	1576	1579	1578
SEROCONVERSIONS	13	17	52
PERSON-YEARS	2616	2604	2607
HAZARD RATES	.50%	.65%	1.99%
95% LIMITS	.27-.85%	.38-1.05%	1.49-2.62%
RATIO TO PLACEBO	.25	.33	
95% LIMITS ON RATIO	.13-.45	.19-.56	
P-VALUE	.0004	.0031	
RATIO TO TDF	.76		
95% LIMITS	.37-1.56		

In trial 288, the applicant also conducted two secondary analyses to see whether there was an interaction between adherence to study drug and relative risk. In the first such analysis, the applicant compared the relative risk in subjects with self reported adherence $\geq 50\%$ to the relative risk in the sub-group with adherence $\geq 90\%$. The results are given in table 2.2.6.1 C.

TABLE 2.2.6.1 C
RELATIVE RISK BY ADHERENCE, TRIAL 288

ADHERENCE RATE	INFECTION EVENTS		RISK
	PLACEBO	TRUVADA	RATIO
$\geq 50\%$	47	23	50%
$\geq 90\%$	30	8	73%

The second analysis to compare adherence with relative risk used the case-control subsample of actual drug levels in seroconverters and matched non-converting controls. Table 2.2.6.1D compares fraction of subjects with detectable drug among HIV seroconverters and non-converters in the truvada arm.

TABLE 2.2.6.1 D
DETECTABLE DRUG LEVELS, CONVERTERS AND CONTROLS, TRIAL 288

DRUG MEASUREMENT	FRACTION DETECTABLE	
	HIV+	HIV-
Intracellular FTC-TP	3/34	22/42
Intracellular TFV-DP	2/34	21/42

Plasma FTC	2/33	17/35
Plasma TFV	2/33	17/35

6 of the 17 (35%) seroconverters in the TDF arm and 3 out of 12 (25%) seroconverters in the truvada arm had detectable plasma tenofovir at the seroconversion visit. 363 out of 437 (83%) of samples from uninfected subjects in the TDF group and 375 out of 465 (80%) of samples from uninfected subjects in the TRV arm had detectable plasma tenofovir. One will notice that this does permit direct comparison: for the infected subjects, one has fraction of subjects with detectable plasma tenofovir while for the controls one has fraction of samples (multiple samples per subject). Nonetheless, the FDA statistical reviewer observes that one may infer that somewhere around 80% of control subjects had mostly samples with detectable plasma tenofovir. The applicant attempts to compute relative risk of seroconversion with detectable and undetectable plasma tenofovir levels but the FDA statistical reviewer must point out that one cannot compute relative risk with a case control sample. The correct parameter to compute is odds ratio but even this cannot be computed from the data provided due to the discrepancy between fraction of subjects and fraction of samples.

The applicant also reported higher efficacy in the subset of subjects reporting the high risk behavior of URAI (unprotected receptive anal intercourse). There was no statistically detectable change in efficacy with respect to circumcision, education, alcohol use, or age in trial 288.

In trial 380, the applicant conducted analyses on subgroups defined by gender, age, male circumcision, reported unprotected sex, country, and HIV viral load and CD4 count of the infected partner. Relative risks by subgroups are given in table 2.2.6.1E.

TABLE 2.2.6.1 E
RELATIVE RISKS BY SUBGROUPS, TRIAL 380

COVARIATE	TDF/PLACEBO	TRV/PLACEBO
Female	.13-.63	.16-.72
Male	.17-.80	.06-.46
Circumcised	.17-1.2	.06-.79
Not Circumcised	.08-1.0	.01-.68

Kenya	.14-.74	.13-.74
Uganda	.16-.68	.08-.48
Age 18-24	.08-1.01	.21-1.61
Age >=25	.18-.61	.07-.37
No Unprotected Sex	.25-.89	.12-.58
Unprotected Sex	.04-.44	.08-.58
Viral Load<50_K	.21-.76	.13-.58
Viral Load>=50_K	.08-.69	.08-.68
CD4 Count<350	.31-2.01	.12-1.26
CD4 Count>=350	.10-.44	.10-.44

In this table, the applicant considered that only the groups with infected partner having CD4 count <350 or CD4 count >=350 had convincingly different relative risks.

2.2.7. Summary of Applicant's Conclusions

The applicant concluded that in trial 288 that truvada prophylaxis among men having sex with men led to an estimated 39% reduction in risk with 95% confidence interval for the reduction in risk being 14% to 57%. They reported that although this was statistically significantly different from zero, it was not sufficient to rule out the null hypothesis that the risk reduction was only 30% or less. It is not completely clear whether the applicant considers the high confidence that truvada reduces risk combined with low confidence that truvada reduces risk by more than 30% constitutes evidence in favor or against approval.

The applicant also concluded in trial 380 that among serodiscordant heterosexual couples TDF and TRV prophylaxis reduced the risk of seroconversion by the HIV- partner by 67% and 75%, respectively. The two lower bounds on relative risk, 44% and 55%, were high enough to exclude, with statistical confidence, a risk reduction of 30% or lower. Thus either TDF or TRV prophylaxis provides a meaningful reduction in risk for serodiscordant heterosexual couples.

3. Statistical Evaluation

3.1 Evaluation of Efficacy

3.1.1 Basic Findings

The summary results of re-analysis of the applicant's computer files by the FDA statistical reviewer is given in table 3.1.1 A. This table gives the number of subjects exposed and the total person-years of exposure, the number of HIV infections, and the rate per person year for both trials and all arms. The second part of the table gives the hazard ratio of the three active arms to their respective placebos, together with 95% upper and lower confidence bounds. The relative risk reduction is $1 - \text{hazard ratio}$. The hazard ratio is the hazard rate of infection on active drug divided by hazard rate of infection on placebo with hazard rate for each arm being the number of infections divided by the total number of person-years on trial. (An alternative measure of difference between the arms is the odds ratio, which equals the odds of infection on active drug divided by odds of infection on placebo, computing using counts of infected and non-infected and ignoring person-years. Since subjects are exposed for an average of two years, odds of infection are about half the hazard rate.) Both hazard ratio and odds ratio have TRV or TDF rates in the numerator so values <1 indicate superiority for the active arm. In most analyses, the FDA reviewer used hazard ratios and risk reduction = $1 - \text{hazard ratio}$.

For trial 288, four different stopping rules are compared. Time on trial stops at the stopping date and HIV infections occurring after the stopping time are treated as not occurring. The stopping times are July 31, 2010 = the planned end of the trial; first visit after July 31, 2010 = expected last dose of dispensed drug, Nov 21, 2010 = planned end + 113 days \approx first visit after July, 31, 2010 for the last subject + 8 weeks ; and Feb 11, 2011 = day last database closure by the applicant.

TABLE 3.1.1 A
EFFICACY RESULTS IN BOTH TRIALS

ARM	INFECTIONS	PERSONS	PERSON_YRS	RATE PER YR
TRIAL 288				
July 31, 2010				
Placebo	76	1218	1940.9	3.916%
Truvada	45	1224	1949.7	2.308%
First Visit after July 31. 2010				
Placebo	83	1218	1986.4	4.178
Truvada	48	1224	1998.1	2.402
Nov 21, 2010				
Placebo	86	1218	2136.4	4.025%
Truvada	52	1224	2150.1	2.418%
Feb 15, 2011				
Placebo	87	1218	2225.9	3.909%
Truvada	54	1224	2241.0	2.410%
TRIAL 380				
Placebo	52	1578	2608.8	1.993%
TDF	17	1579	2605.4	0.652%
Truvada	13	1576	2618.2	0.497%

TABLE 3.1.1 B
EFFICACY RESULTS IN BOTH TRIALS

USING PERSONS

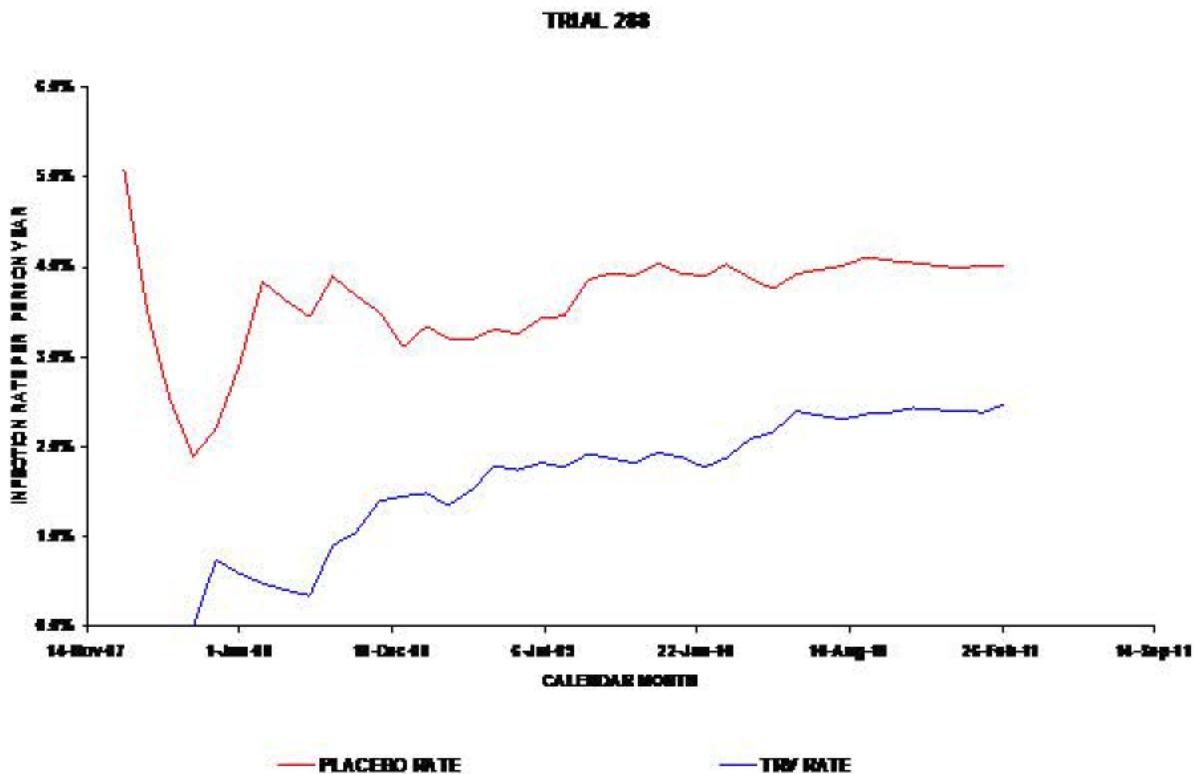
TRIAL, ARM	ODDS_RATIO	95% LOWER BOUND	95% UPPER BOUND
288, Truvada			
July 31, 2010	0.574	0.393	0.837
First Visit after July 31. 2010			
	0.558	0.388	0.804
Nov 21, 2010	0.584	0.410	0.832
Feb 15, 2011	0.600	0.423	0.851
380, TDF	0.319	0.184	0.555
380, TRV	0.244	0.132	0.45

USING PERSON YEARS

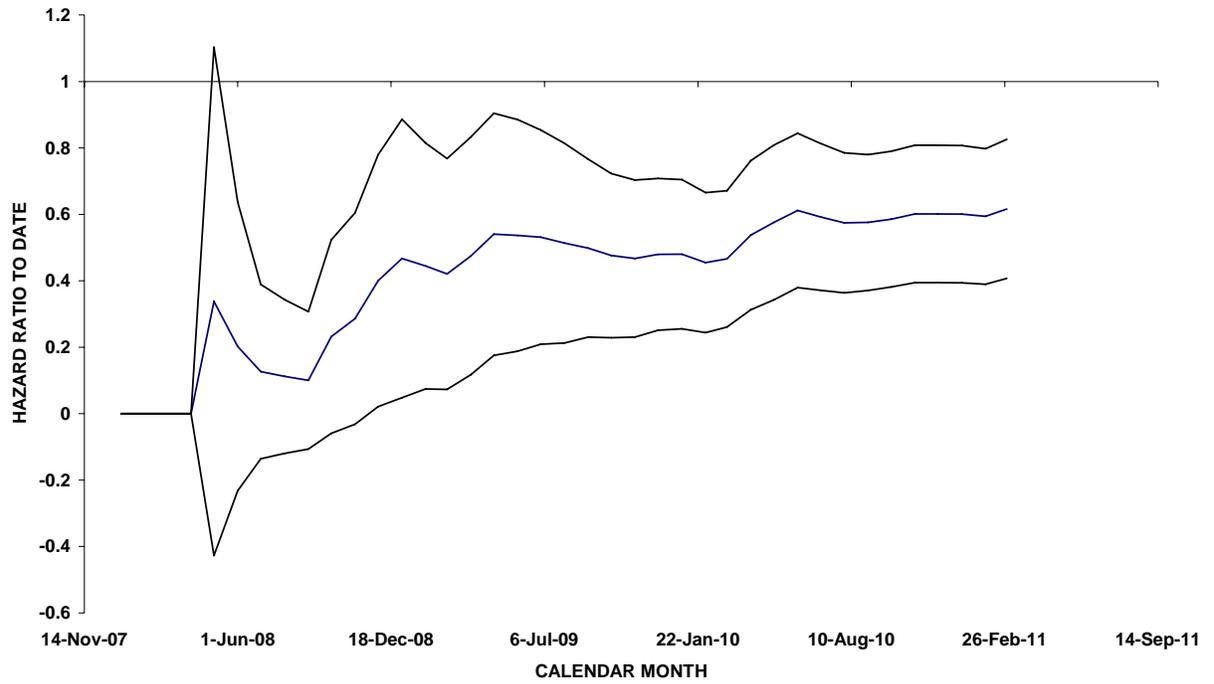
TRIAL, ARM	HAZ_RATIO	95% LOWER BOUND	95% UPPER BOUND
288, Truvada			
July 31, 2010	0.589	0.372	0.807
First Visit after July 31. 2010			
	0.575	0.371	0.779
Nov 21, 2010	0.601	0.394	0.808
Feb 15, 2011	0.617	0.407	0.826
380, TDF	0.327	0.148	0.507
380, TRV	0.249	0.098	0.400

One can see that, although these results are slightly discrepant from those reported by the applicant in section 2 above, the difference is small and the substantive conclusions are unchanged. First, truvada was statistically significantly superior to placebo in preventing HIV infection both in males having sex with males (trial 288) and in serodiscordant heterosexual couples (trial 380). Second, TDF was almost as effective as Truvada in heterosexual couples and was also statistically significantly superior to placebo. Third, with 95% confidence one could conclude that both TDF and Truvada reduced the risk of HIV infection by at least 55% ($1 - .45 = .55$) for Truvada and at least 44% for TDF in heterosexual couples. Fourth, one cannot rule out the possibility that the risk reduction for truvada is only 15% among males having sex with males.

As a further demonstration of the practical inconsequentiality of the particular of stopping rule in trial 288, the FDA reviewer computed the estimated infection rates and estimated ratios and 95% confidence limits assuming that data collection stopped at the first of each month from the first seroconversion to the database closure. The results are plotted below. (With respect to the 95% limits, they are nominal assuming only one look at the data and are not interim analysis stopping boundaries.)



HAZARD RATIO AND 95% INTERVALS



In what follows, the FDA reviewer will use the last visit after July 31 as the stopping date for trial 288. Also tables below will use the risk reduction, which is simply 1 minus the hazard ratio, since that is a familiar parameter.

One should note that, since only a few patients actually become infected, the ratio of number of infections is approximately equal to that ratio divided by any of the following: ratio of number of patients, ratio of number of non-infected patients, or ratio of person exposed. (The three possible quotients are called relative risk, odds ratio and hazard ratio using person years.) All three possible ratios in the denominator are nearly one and no practical difference in the conclusion obtains between any of the three methods. In other cases, where there is substantial number of events, the hazard ratio using person years is clearly statistically superior.

An alternative method of analysis is the Cox proportional hazards regression which fits a maximum likelihood estimate to the hazard ratio. This actually was the primary method specified in the protocol. The FDA statistical reviewer has used the hazard rate computed as events per person year as a demonstration that the conclusions of efficacy are robust to the method of analysis. There are some differences in the underlying assumptions about the process generating the data between the two methods. A more mathematically detailed discussion is given in the appendix.

Table 3.1.1 C gives the Cox regression results (point estimates and upper and lower 95% confidence bounds for the hazard ratio and p-value) for the three primary comparisons. As above, TRV in trial 288 and both TDF and TRV in trial 380 were statistically significantly superior to placebo. The estimates for the hazard ratio in the two methods are close. (Recall that risk reduction is 1 minus hazard ratio.)

TABLE 3.1.1 C
COX REGRESSION RESULTS, BOTH TRIALS

	HAZ_RAT	LOWER	UPPER	PVALUE
TRIAL_288	0.574	0.402	0.818	.001
TRIAL_380 TDF	0.326	0.189	0.564	<.0001
TRIAL_380 TRV	0.249	0.136	0.457	<.0001

There is one additional difference in the analyses in this review and the applicant's analyses. The FDA statistical reviewer recalculated the time until infection or censoring from the applicant's raw datasets. The recalculation used the date of initial visit from the demographic dataset (the only date in that dataset) as the start of time and the appropriate visit date from the HIV dataset as the stopping time. The appropriate visit was the last visit for subjects not seroconverting and either the date of the first positive HIV measurement or the date of the first inconclusive HIV measurement, provided that was followed at the next visit by a positive HIV measurement. This recalculation differed from the time to event used by the applicant in their analysis datasets for some patients but the two times to event were highly correlated, exactly the same in many cases, did not show a different pattern of deviation from the applicant's results in the different arms, and were very close to the applicant's numbers for total person years at risk.

3.1.2 Findings within Subgroups

The next several sections contain various sensitivity analyses intended to explore the effects of various covariates, some baseline and many post-randomization covariates, on the estimates of risk reduction due to truvada or TDF prophylaxis. It should be noted that adjustments on the basis of post-randomization covariates in a blinded, randomized trial violates the principles of ITT analysis. These results may be interesting but they should not be over-interpreted. Even adjustments on the basis of baseline covariates not used to stratify the randomization is quite problematic.

Several types of subgroups are interesting with respect to the refinements of the estimated benefit of truvada or TDF prophylaxis. In particular, these general categories are 1)compliance, 2)high risk behavior, 3)presence of other STI's, and 4)severity of HIV in the infected partner. The latter is relevant only to trial 380.

Tables 3.1.2 A-F give the infection rates and risk reductions of active drug to placebo, together with 95% confidence limits on the risk reduction in the covariate-defined subgroup. They also include the total number of HIV infections (INF) on all arms for each subgroup of the covariate. If INF is small, the results in that subgroup have too much uncertainty to be trustworthy. (The total of INF across all subgroups will not be constant because subjects for whom the covariate was not reported have been left out of these tables.) It should be noted that many of the covariates examined in this table are not baseline covariates but rather treatment emergent factors.

TABLE 3.1.2 A
RISK REDUCTION OF ACTIVE TO PLACEBO
BY COMPLIANCE

COMPLIANCE

RISK

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TRIAL_288	PLAC	TRV	REDUCTION	LOWER	UPPER	INF
<90%	4.806%	2.736%	0.431	0.108	0.754	51
>=90%	3.862%	2.225%	0.424	0.161	0.687	80
TRIAL_380	PLAC	TDF				
<90%	4.847%	0.738%	0.848	0.521	1.175	6
>=90%	1.876%	0.648%	0.655	0.459	0.851	63
TRIAL_380	PLAC	TRV				
<90%	4.847%	2.355%	0.514	-0.283	1.311	7
>=90%	1.876%	0.434%	0.769	0.617	0.920	58

For neither of the trials is there any evidence that the hazard ratio varies with self-reported compliance level. One should note that self-reported compliance in trial 380 is so high that no confidence can be placed in the results for the group with compliance <90%.

TABLE 3.1.2 B
RISK REDUCTION RATIOS OF ACTIVE TO PLACEBO
BY RISK BEHAVIOR

HIGH_RISK_BEHAVIOR			RISK			
TRIAL_288	PLAC	TRV	REDUCTION	LOWER	UPPER	INF
No_URAI	2.686%	3.217%	-0.198	-1.504	1.108	13
URAI	5.776%	2.716%	0.530	0.338	0.722	106
#_ANAL_SEX_ACTS,BY_QUARTILE						
<=13	3.259%	1.624%	0.502	0.050	0.954	21
13-27	4.289%	2.632%	0.386	-0.057	0.830	31
27-61	3.694%	1.814%	0.509	0.139	0.879	31
61<	5.318%	3.395%	0.362	-0.008	0.731	48
#_SEX_ACTS_WITH_MEN,BY_QUARTILE						
<=14	3.615%	1.973%	0.454	-0.014	0.923	23
14-30	3.911%	2.391%	0.389	-0.058	0.835	30
30-66	4.044%	1.672%	0.587	0.268	0.905	32
66<	4.977%	3.440%	0.309	-0.097	0.715	46
EXCHANGED_SEX_FOR_MONEY						
NO	4.438%	2.179%	0.509	0.269	0.749	73
YES	3.854%	2.677%	0.305	-0.058	0.668	58
TRIAL_380						
ANY_UNPROTECTD_SEX						
	PLAC	TDF				
NO	1.502%	0.719%	0.521	0.217	0.825	44
YES	3.596%	0.455%	0.874	0.721	1.026	25
	PLAC	TRV				
NO	1.502%	0.404%	0.731	0.521	0.941	38
YES	3.596%	0.781%	0.783	0.572	0.994	27

One will notice from this table that, as would be expected, the risk of infection tends to go up with more risky behavior by most measures used and in both trials. However, the rate of infection tends to go up in both placebo and active arms: there is no consistent pattern of steadily decreasing hazard ratio with increased risk. One may infer from this pattern that, although TDF and Truvada prophylaxis are effective, they are not perfect. The risk of infection with Truvada and high risk behavior is lower than that of placebo and high risk behavior but it is comparable to (sometimes, even higher than) the risk with placebo and low risk behavior.

In table 3.1.2 C, we explored the possibility of interactions between compliance, risky behavior, and efficacy. This table shows nothing that was already present in the two preceding tables. Risky behavior inflates the risk on both arms. There is no particular evidence that compliance improves with riskier behavior or that even such happened, that it has any effect on efficacy.

TABLE 3.1.2 C
RISK REDUCTION OF ACTIVE TO PLACEBO
BY RISK BEHAVIOR AND COMPLIANCE

TRIAL_288		RISK					
COMPLY	RISKBEH	PLAC	TRV	REDUCTION	LOWER	UPPER	INF
<90%	No_URAI	3.646%	2.318%	0.364	-0.773	1.502	5
	URAI	6.905%	3.395%	0.508	0.193	0.824	42
>=90%	No_URAI	2.126%	3.807%	-0.791	-3.355	1.773	8
	URAI	5.231%	2.382%	0.545	0.304	0.785	64
TDF_380		RISK					
COMPLY	ANYUNPSX	PLAC	TDF	REDUCTION	LOWER	UPPER	INF
<90%	NO	2.653%	1.075%	0.595	-0.378	1.568	3
	YES	10.80%	0				
>=90%	NO	1.457%	0.702%	0.518	0.202	0.835	41
	YES	3.254%	0.486%	0.851	0.669	1.033	22
TRV_380		RISK					
COMPLY	ANYUNPSX	PLAC	TRV	REDUCTION	LOWER	UPPER	INF
<90%	NO	2.653%	1.695%	0.361	-1.173	1.895	3
	YES	10.80%	3.855%	0.643	-0.165	1.451	4
>=90%	NO	1.457%	0.365%	0.750	0.542	0.957	35
	YES	3.254%	0.651%	0.800	0.584	1.016	23

TABLE 3.1.2 D
RISK REDUCTION OF ACTIVE TO PLACEBO
BY STI'S

TRIAL_288			RISK			
SYPHILIS	PLAC	TRV	REDUCTION	LOWER	UPPER	INF
YES	2.973%	1.881%	0.367	0.073	0.661	75
NO	8.426%	4.161%	0.506	0.233	0.779	56
TRIAL_380			RISK			
SYPHILIS	PLAC	TDF	REDUCTION	LOWER	UPPER	INF
YES	2.440%	0				3
NO	1.993%	0.688%	0.655	0.464	0.845	66
SYPHILIS	PLAC	TRV	REDUCTION	LOWER	UPPER	INF
YES	2.440%	0.849%	0.652	-0.136	1.440	4
NO	1.993%	0.482%	0.758	0.606	0.911	61
TRIAL_288			RISK			
HSV2	PLAC	TRV	REDUCTION	LOWER	UPPER	INF
YES	5.521%	3.688%	0.332	0.055	0.609	92
NO	2.876%	1.034%	0.641	0.382	0.899	39
TRIAL_380			RISK			
HSV2	PLAC	TDF	REDUCTION	LOWER	UPPER	INF
YES	2.169%	0.557%	0.743	0.544	0.942	40
NO	1.754%	0.670%	0.618	0.285	0.952	25
HSV2	PLAC	TRV	REDUCTION	LOWER	UPPER	INF
YES	2.169%	0.428%	0.803	0.631	0.975	38
NO	1.754%	0.641%	0.635	0.316	0.954	25

TABLE 3.1.2 D (continued)
RISK REDUCTION OF ACTIVE TO PLACEBO
BY STI'S

TRIAL_288							
STI_WITH_ULCER	PLAC	TRV	RISK REDUCTION	LOWER	UPPER	INF	
YES	10.90%	4.969%	0.544	0.083	1.006	16	
NO	3.853%	2.237%	0.419	0.199	0.640	115	
DIAGNOSED_WTIH_STI							
YES	7.420%	4.936%	0.335	0.335	0.003	0.667	64
NO	3.052%	1.496%	0.510	0.510	0.260	0.760	67

Tables 3.1.2 D explores the possibility of interactions between STI's and efficacy. There is no discernible pattern of HIV risk associated with syphilis (the risk goes down for syphilitics in trial 288; there are too few syphilitics in trial 380 to discern anything.) For placebo subjects, risk goes up in both trials with HSV2 infection and with ulcerous STI's in trial 288. The truvada risk, however, also goes up in trial 288 while the risk with either TDF or truvada goes down in trial 380. It is difficult to believe that any firm conclusions can be drawn from these data with respect to relative benefit of TDF/truvada to placebo.

TABLE 3.1.2 E
RISK REDUCTION OF ACTIVE TO PLACEBO
BY SEVERITY OF PARTNER'S HIV, TRIAL 380

			RISK REDUCTION	LOWER	UPPER	INF	
CD4 Count	PLAC	TDF					
	<350	1.951%	1.562%	0.199	-0.545	0.944	18
	>=350	2.004%	0.430%	0.785	0.631	0.940	51
	PLAC	TRV					
	<350	1.951%	0.776%	0.602	0.141	1.063	14
	>=350	2.004%	0.428%	0.786	0.633	0.940	51
Viral Load	PLAC	TDF					
	>=50_K	3.928%	0.895%	0.772	0.526	1.019	22
	<50_K	1.510%	0.614%	0.594	0.331	0.856	45
	PLAC	TRV					
	>=50_K	3.928%	0.897%	0.772	0.524	1.019	22
	<50_K	1.510%	0.421%	0.721	0.515	0.927	41

Risk of HIV infection more than doubles for placebo between the low and high levels of partner's viral load. However, we again see, as with other risk factors, risk of infection also increases on the active drug arms. Risk doubles with truvada between high and low levels of partner's viral load and increases 40% with TDF. This produces little change in the hazard ratio. It is another manifestation of the phenomenon that although truvada and TDF are beneficial, they are not perfect and that higher risk situations still produce higher risk with active prophylaxis. The risk on the active arms is still lower than with placebo in both high and low risk subgroups.

Table 3.1.2 F explores the interaction with contraceptive use by the at-risk partner in trial 380. Contraceptive use increased risk in placebo and TRV arms while lowering it in the TDF arm. It seems unlikely that anything substantive should be made of this.

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TABLE 3.1.2 F
 RISK REDUCTION OF ACTIVE TO PLACEBO
 BY CONTRACEPTIVE USE, TRIAL 380

Contra_Use	PLAC	TDF	RISK REDUCTION	LOWER	UPPER	INF
NO	2.416%	1.088%	0.550	0.108	0.991	18
YES	3.199%	0.452%	0.859	0.651	1.066	18
	PLAC	TRV				
NO	2.416%	0.419%	0.826	0.567	1.086	14
YES	3.199%	1.500%	0.531	0.115	0.948	23

Several other covariates were also examined, including age, education level, male circumcision. Nothing particularly interesting or likely to cast doubt on efficacy was found. A brief summary of the various analyses by covariates is given in section 4 below.

3.2.2 Effect of Post Exposure Prophylaxis

Thirty-three subjects in trial 288 received a course of multi-drug post exposure prophylaxis (PEP) during the trial. The drugs used included lamivudine, lopinavir/ritonavir, stavudine (the three most common choices), zidovudine, tenofovir, emtricitibine, abacavir, nevirapine, efavirenz, atazanavir, and raltegravir. One may be concerned that this occurrence may have contaminated the results by preventing infections that would have occurred had only the protocol specified drugs been used. Table 3.2,2 A documents the arms, HIV status, and duration of PEP for these 33 subjects.

TABLE 3.2.2 A
PEP IN TRIAL 288

ARM	HIV	#_SUBJECTS	#_DAYS_ON_PEP	DAYS_TOTAL
Placebo	NON	20	675	17044
Truvada	NON	12	400	7418=20.3 yrs
Truvada	INF	1	31	473

Since PEP can only reduce the risk of seroconversion and obviously wasn't beneficial in any case where seroconversion occurred anyway, the most stringent contingency analysis would be to assume that all 12 truvada subjects who received PEP would have become HIV infected on the day PEP began if PEP had not been given and that there would have been no change in the number and timing of the placebo infections.

This is almost certainly too extreme: there is no reason to expect that whatever event prompted the PEP would have led to infection in the truvada arm but not in the placebo arm. A second possibility is to discard those 12 truvada subjects who received PEP and did not seroconvert while retaining all 20 placebo subjects who received PEP and the one truvada subject who became infected some time after PEP ended. The results of these sensitivity analyses, using infections per person exposed is given in table 3.2.2 B. Even the unreasonable analysis that considers all truvada subjects receiving PEP as infected does not quite result in statistically insignificant difference and even for that method, the p-value is still a significant .045.

TABLE 3.2.2 B
ALTERNATIVE ANALYSES OF EFFICACY IN TRIAL 288
RATES PER PERSON

ARM	INFECTION RATE	RISK REDUCT	95% BOUNDS		P-VALUE
			LOWER	UPPPER	
Original analysis					
Placebo	83/1218=7.313%				
TRV	48/1224=4.082%	.442	.196	.612	.0017
PEP=Infect-TRV only					
Placebo	83/1218=7.313%				
TRV	60/1224=5.155%	.295	.008	.499	.0451
PEP=Infect-Both					
Placebo	103/1218=9.271%				
TRV	60/1224=5.155%	.442	.225	.598	.0005
Discard PEP-TRV only					
Placebo	83/1218=7.313%				
TRV	48/1212=4.124%	.436	.188	.608	.002

The other endpoint is infection per person year exposed and this endpoint permits one additional sensitivity analysis in which the 12 truvada subjects who receive PEP (and don't subsequently become HIV+) are considered as censored at the time PEP began. The results of these sensitivity analyses are given in table 3.2.2 C

TABLE 3.2.2 C
ALTERNATIVE ANALYSES OF EFFICACY IN TRIAL 288
RATES PER PERSON YEAR

ARM	INFECTION RATE	RISK REDUCT	95% BOUNDS		P-VALUE
			LOWER	UPPPER	
Original analysis					
Placebo	83/1986.4 = 4.18%				
TRV	48/1998.1 = 2.40%	.425	.221	.629	.0001
PEP=Infect-TRV only					
Placebo	83/1986.4 = 4.18%				
TRV	60/1989.5 = 3.02%	.278	.039	.518	.023
Discard PEP-TRV only					
Placebo	83/1986.4 = 4.18%				
TRV	48/1957.5 = 2.45%	.413	.205	.622	.0001

Using this endpoint even the extremely harsh assumption that all and only truvada subjects with PEP are counted as HIV+ at the end results in a finding of statistically significant superiority of truvada at the two-sided .05 level, although the lower bound (.039) is just barely above zero.

Thus, no reasonable adjustment for the PEP changes the overall conclusion of efficacy of truvada or even changes the risk reduction very far from .44 (using subjects) or .42 (using person years).

In addition, one could well argue that the PEP used already approved drugs and would presumably be applied post approval of truvada prophylaxis in ways similar to what was seen in the trial. On this argument, one could simply ignore the PEP and consider that the trial estimates the difference between placebo and truvada rates in the presence of potential use of PEP.

3.2.3 Effect of Index Case Use of ARVs

In trial 380, 1472 index cases initiated anti-retrovirals (ARV) post randomization; 1314 of them started ARV during the trial. If ARV therapy lower viral load or even suppressed it to below limit of quantitation (BLQ), then the risk of HIV transmission to the partner would be reduced. It will be noted that 8 subjects acquired HIV infection even though their index partner had started ARV earlier so the protection of ARV is not absolute.

The FDA statistical reviewer has conducted a sensitivity analysis, in which it was assumed that any prophylaxed subject was censored at the start of his index case's ARV therapy unless he became HIV+ after the start of his partner's ARV. Given that the trial is randomized and double blind, one would expect approximately the same amount of time on ARV's in both arms, leading to no change in the hazard ratio and risk reduction. In the second, all subjects whose index partner used ARV were excluded, unless the subject became HIV+. Table 3.2.3 A shows the number of subjects whose partners used ARV and number of days at risk by those subjects in the original analysis and in the sensitivity analysis treating ARV start as censoring. Subjects who became infected have no change in their days at risk, of course.

TABLE 3.2.3 A
ARV USE BY INDEX PARTNER, TRIAL 380
NUMBER ARV

TRT	HIV+	INDEX SUBJECTS EVER	INDEX SUBJECTS BEFORE END	DAYS AT RISK SENSITIVITY	DAYS AT RISK ORIGINAL
Placebo	NON	474	429	186367	308541
Placebo	INF	21	5	6829	6829
TDF	NON	493	451	190334	313822
TDF	INF	7	3	2586	2586
Truvada	NON	475	426	186756	320824
Truvada	INF	2	0	225	225

Table 3.2.3 B gives the comparison of the risk in the original and the sensitivity analysis. One can see that the discarding of exposure time after initiation of ARV simply

elevates the risk in all arms, essentially equally. This is what one would expect from a successfully blinded trial. The second part of the table shows that the hazard ratio actually shifts a small amount further in favor of the two active arms. One should also point out that the above analysis censors subjects at the start of infected partner's ARV. If one allowed 1-3 months of ARV to achieve suppression before censoring, the effect on all conclusions would be even smaller.

TABLE 3.2.3 B
EFFECT OF ARV USE ON EFFICACY TRIAL 380

ARM	INFECTIONS	PERSONS	PERSON_YRS	RATE PER YR
ORIGINAL ANALYSIS				
Placebo	52	1578	2608.8	1.993%
TDF	17	1579	2605.4	0.652%
Truvada	13	1576	2618.2	0.497%
SENSITIVITY ANALYSIS				
Placebo	52	1578	2274.1	2.287%
TDF	17	1579	2267.1	0.750%
Truvada	13	1576	2250.9	0.578%

ARM	RISK_REDUCT	95% LOWER BOUND	95% UPPER BOUND
ORIGINAL ANALYSIS			
TDF	0.681	0.445	0.816
TRV	0.756	0.55	0.868
SENSITIVITY ANALYSIS			
TDF	0.672	0.493	0.851
TRV	0.747	0.595	0.900

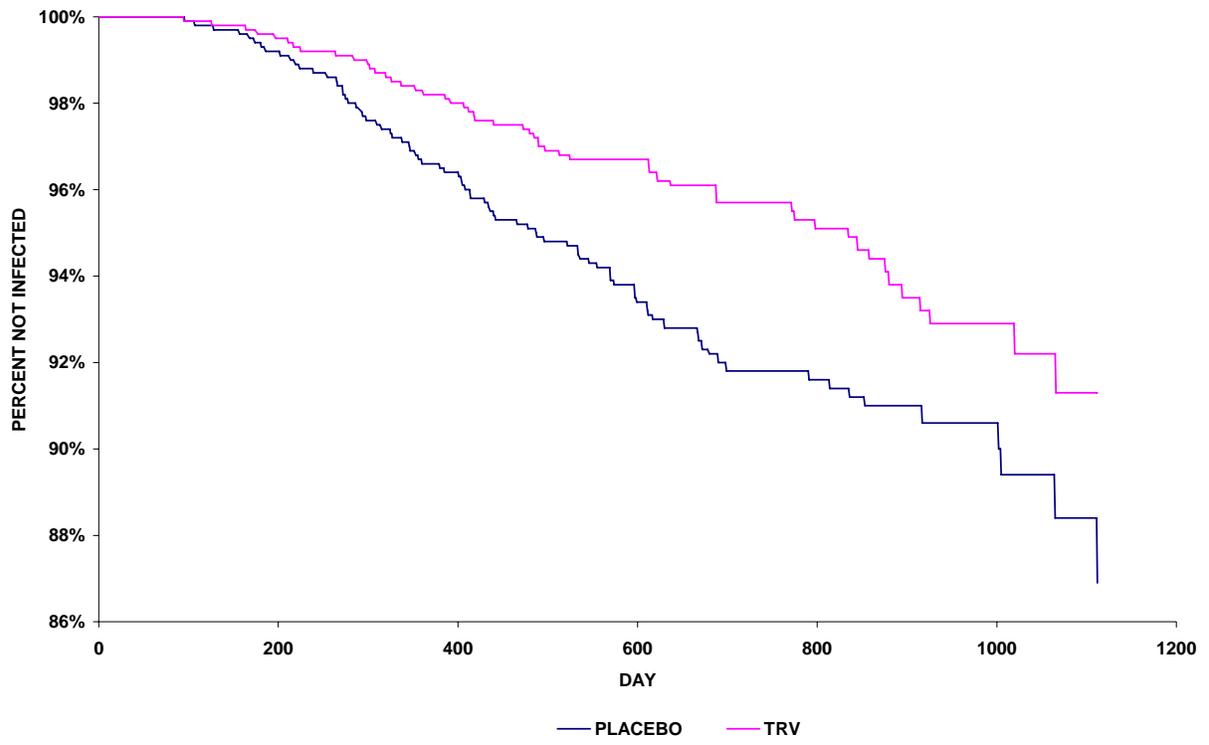
One should observe that the same general caution applies to the analyses in this section as in the discussion of PEP in section 3.2.2. One can expect that in the post-approval world HIV infected partners will initiate ARV therapy on the basis of their own health and regardless of their uninfected partner's prophylaxis. The fact that the efficacy of truvada or TDF is demonstrated in the presence of such action and both with and without adjustment for such action supports the overall conclusion of efficacy.

There is reason to believe that ARV treatment resulting in successful viral suppression may reduce the need for prophylaxis. See the results in table 3.1.2 D above. However, this trial by itself was not intended to estimate the risk reduction associated with viral suppression in the infected partner so caution should be used in making recommendations about prophylaxis in the absence of other data.

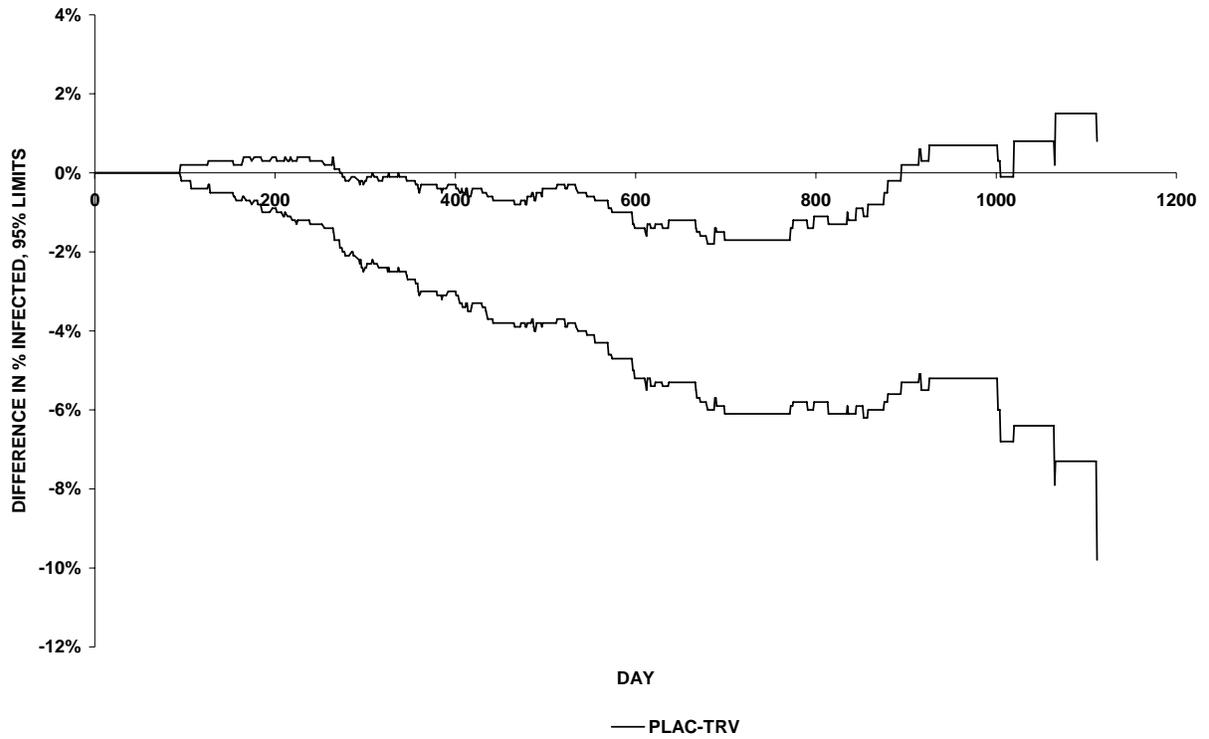
3.2.4 Time Course of Infection Risk

The following graphs give 1) the Kaplan-Meier curve for percent infection free on both arms in trial 288, 2) the 95% confidence bands for the difference in percent infection free between the arms of trial 288, 3) the Kaplan-Meier for percent infection free on all three arms in trial 380, 4) the 95% confidence bands for the difference in percent infection free between placebo and active drug in trial 380. One can clearly see in graphs 2 and 4 that the confidence bands for the difference between all three active arms and their respective placebos lie mostly below zero, indicating superiority of the active arms to placebo.

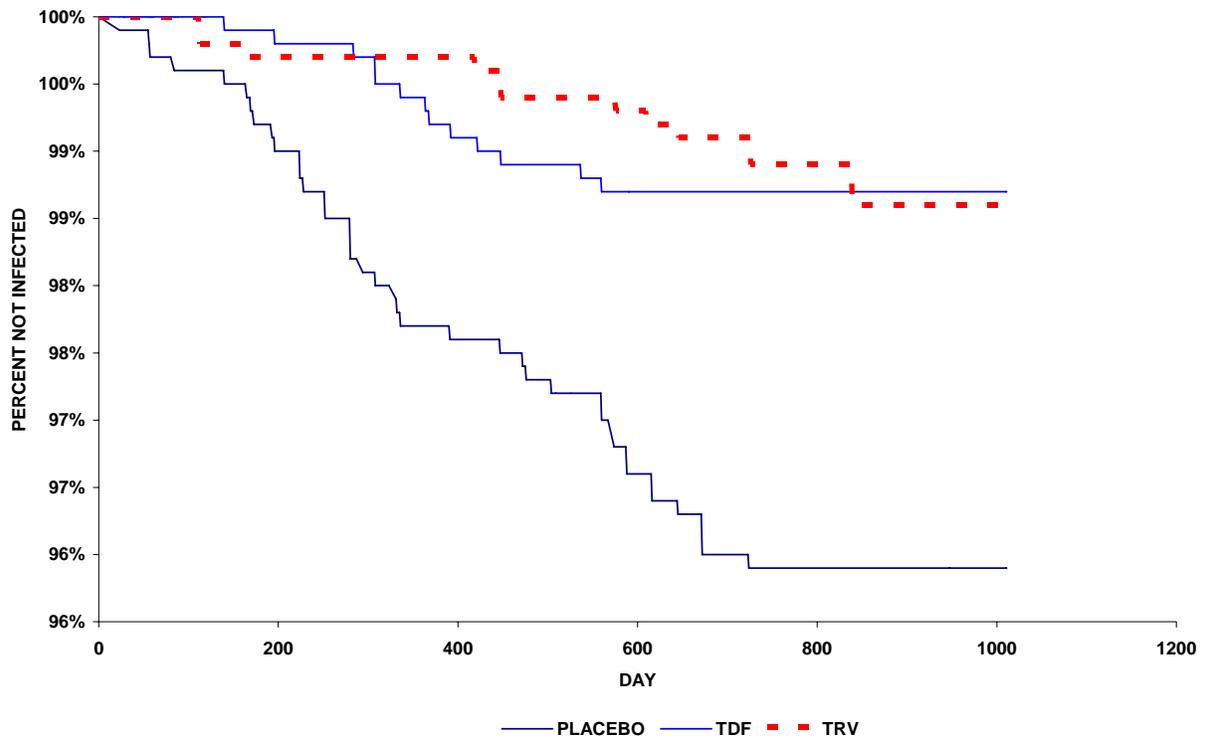
TRIAL_288



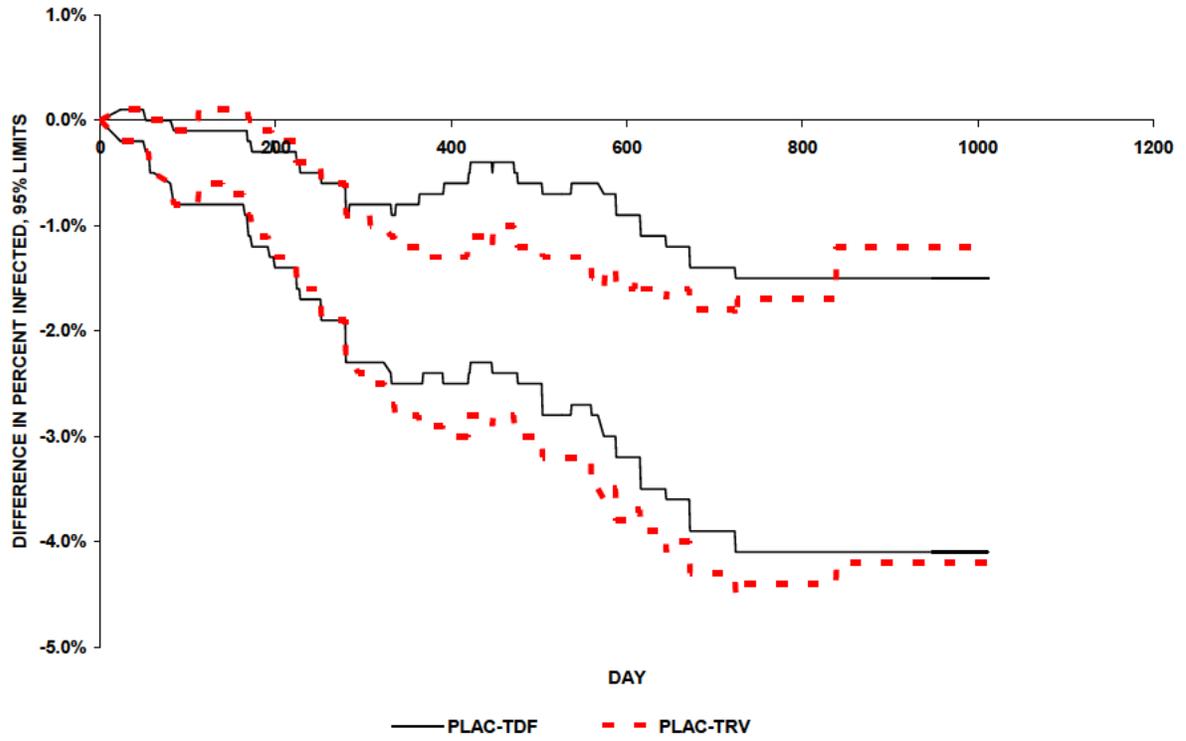
TRIAL_288



TRIAL 380

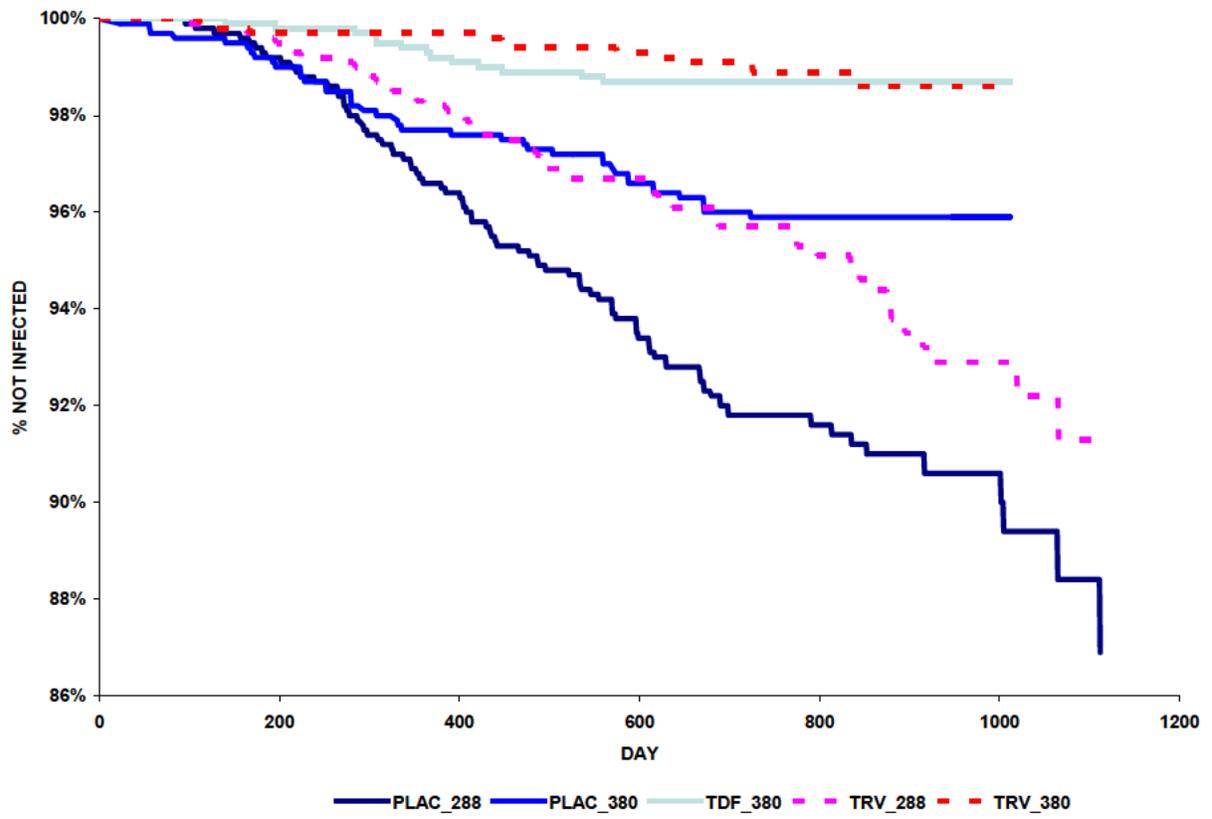


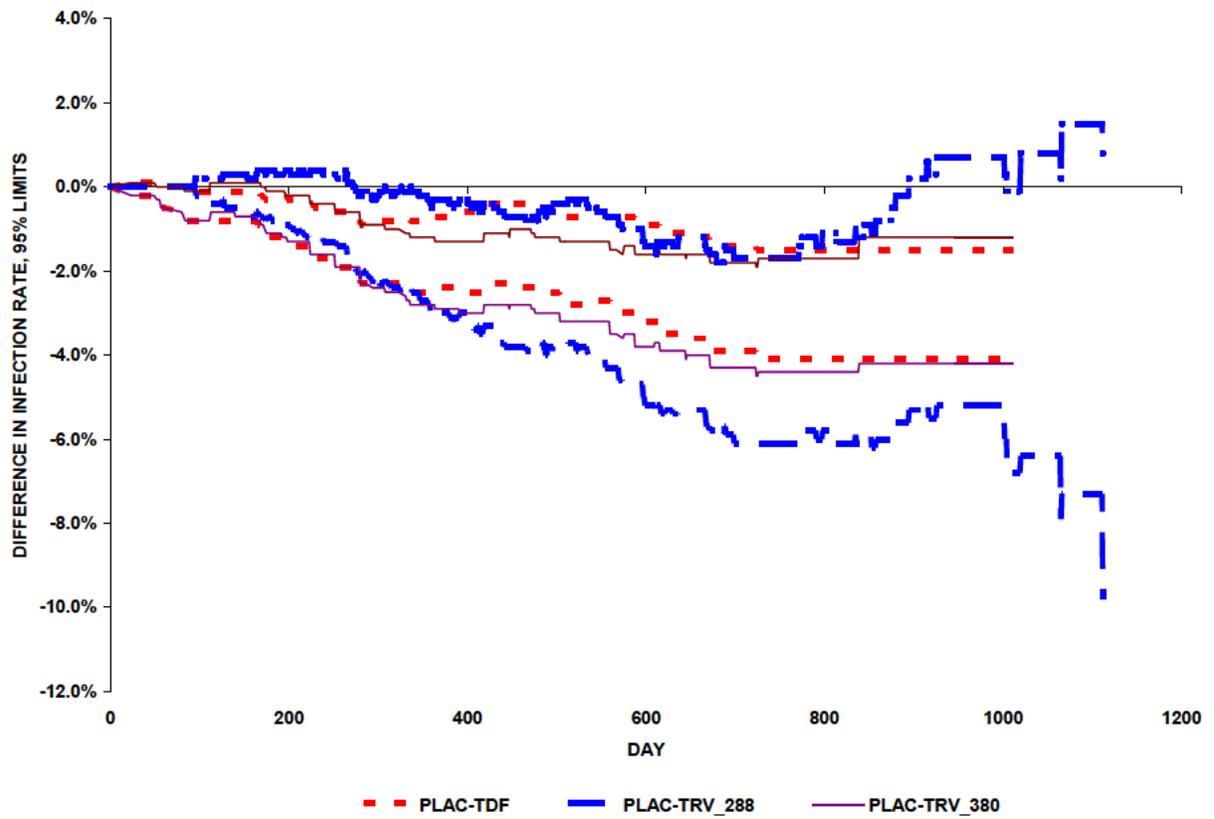
TRIAL 380



Graphs 7 and 8 give the five Kaplan-Meier curves for all arms in both trials plotted against the same vertical scale. One will notice in this graph that the placebo arm for trial 380 tracks very closely to the truvada arm in trial 288 and that both are noticeably higher than the curve for the placebo arm in trial 288. This indicates that the risk in the population in trial 288 was higher than that for the population in trial 380. It also provides another example of evidence that although truvada prophylaxis is effective, it is not perfect: being on placebo in a low risk group can be as safe as being on truvada in a high risk group and both are safer than being of placebo in a high risk group.

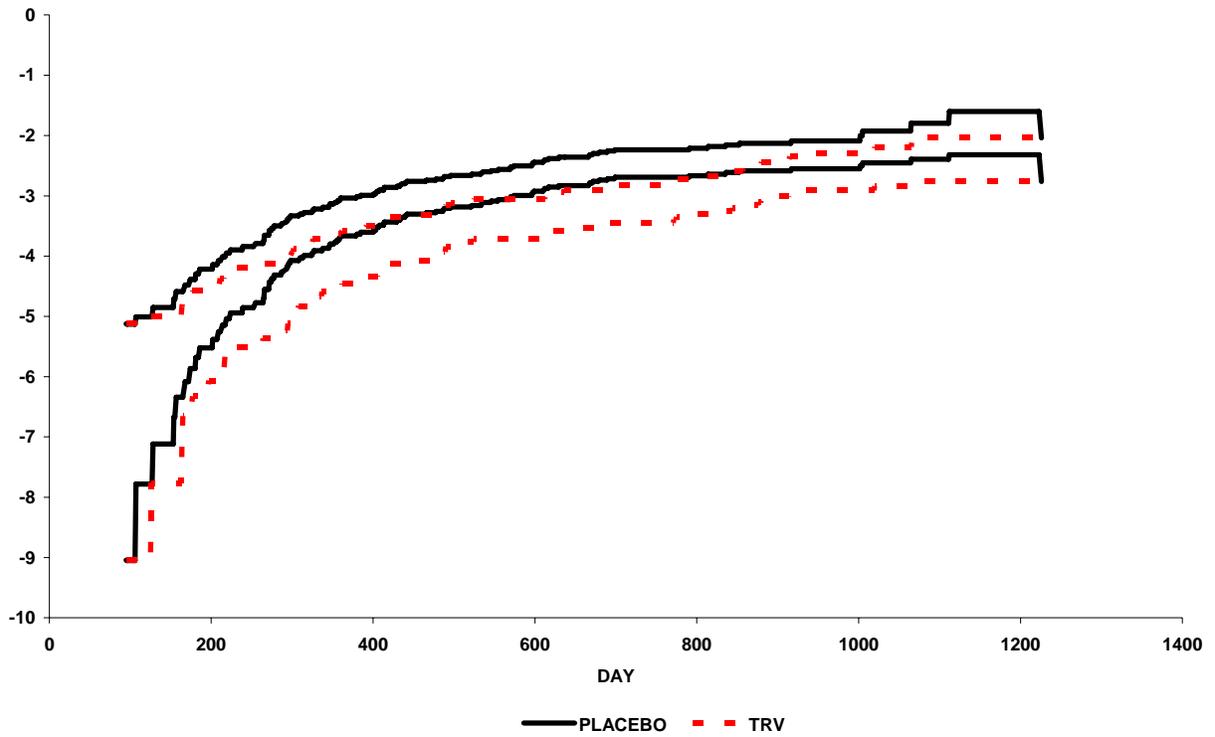
Graph 8 shows the three 95% confidence bands for all three active arms in the two trials against their respective placebos. One can see that the magnitude of the difference in risk is comparable in all three comparisons against placebo. (Note that these are differences in risk, not ratios as in most of the tables above.)



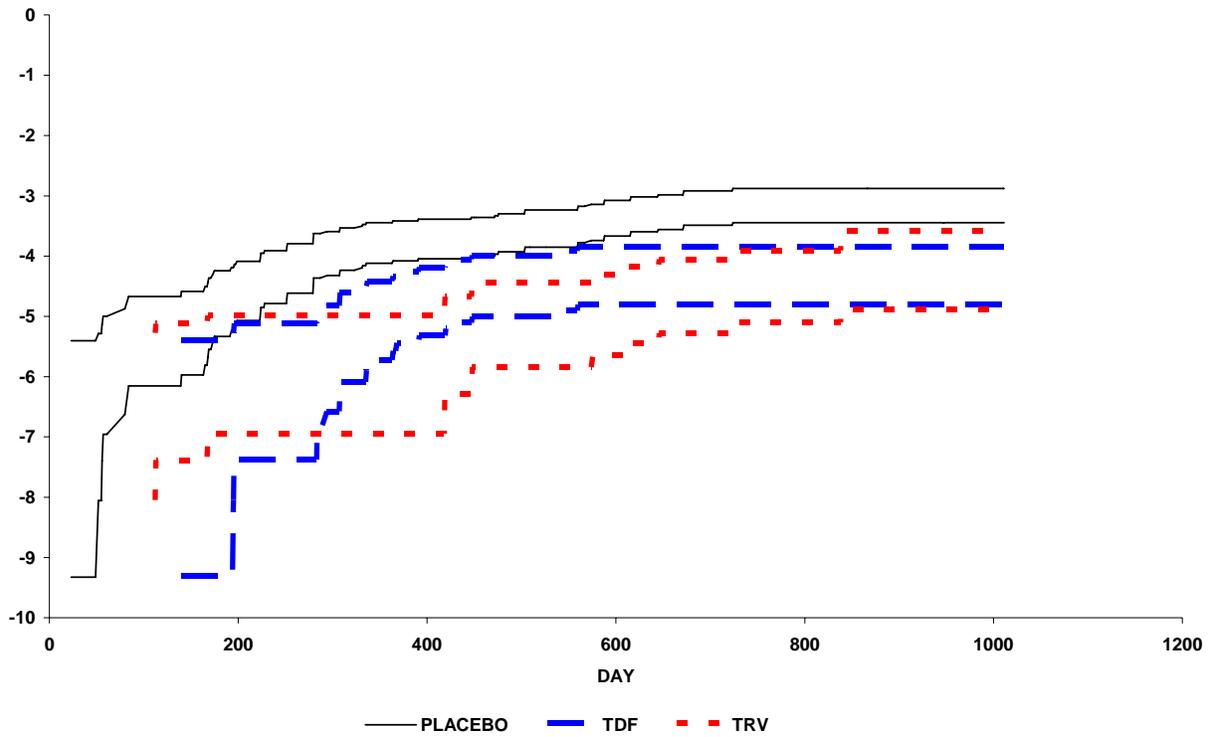


Another question which arises in examining the time course of risk is whether the hazard rate (roughly, the probability of being infected tomorrow given that one is not infected today) is constant. If it were increasing, two conceivable explanations would be that compliance decreased over time or that risky behavior increased over time. A visual test for constancy of the hazard rate for an arm is to see whether a horizontal line can be fit between the upper and lower 95% confidence bounds. As one can see from the following two graphs, the hazard rate in all three arms in both trials is increasing: there is no chance that a horizontal line would fit between any of the five pairs of confidence bounds on either graph. (The vertical scale on these graphs is logarithmic since that makes it easier to see hazard rates that vary from 10^{-7} to 10^{-2} . Nonetheless, constant risk would still accommodate a horizontal line between the confidence bounds.)

TRIAL 288 LOG HAZARD RATES,95% LIMITS

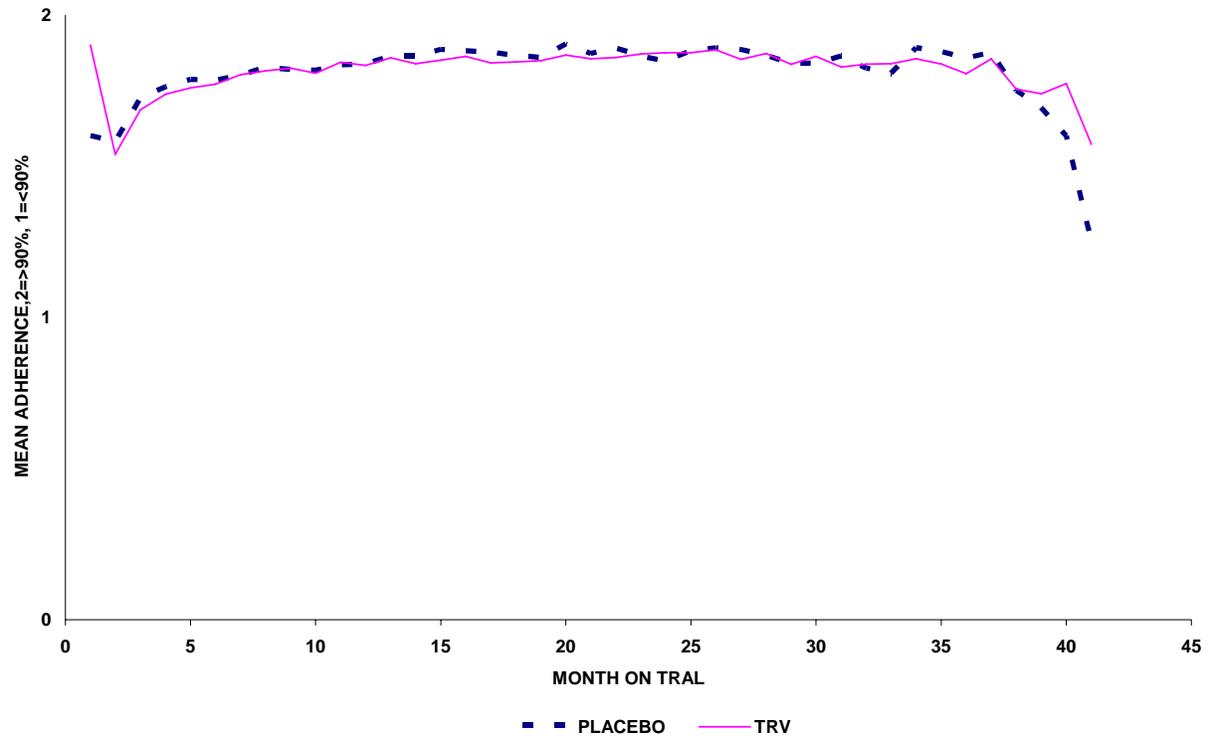


TRIAL 380 LOG HAZARD RATES, 95% LIMITS

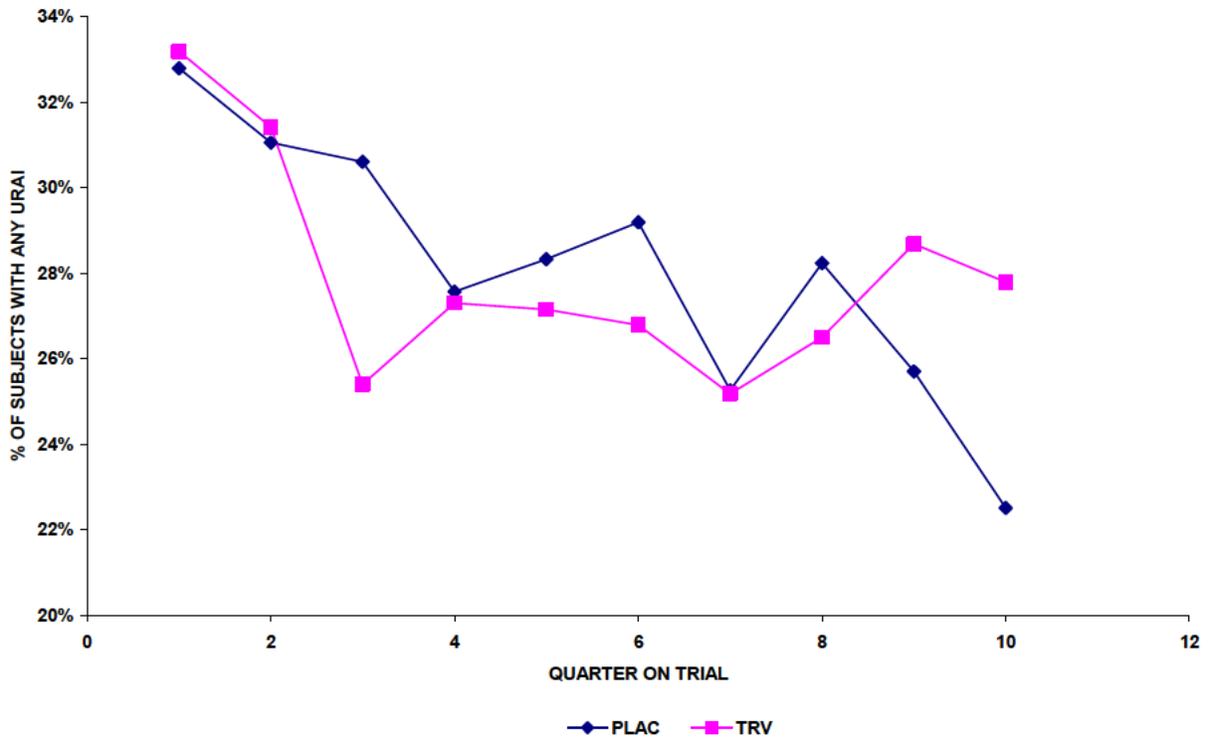


The next two graphs explore the question as to whether the increasing hazard rates can be explained by changes in compliance or behavior. The first of these two graphs looks at self-reported adherence in successive monthly visits averaged over all subjects in trial 288. (2=90-100% adherence, 1 = <90% adherence). One can see that the curves are essentially flat. The second curve shows risk behavior, measured as the number of reported acts of unprotected receptive anal intercourse at each visit, again averaged over all subjects in trial 288. As with the adherence graph, there is no pattern of increased risk taking over time. Whatever the reason for the increase in hazard rate, it is not something readily detectable from this dataset.

ADHERENCE OVER TIME, TRIAL 288



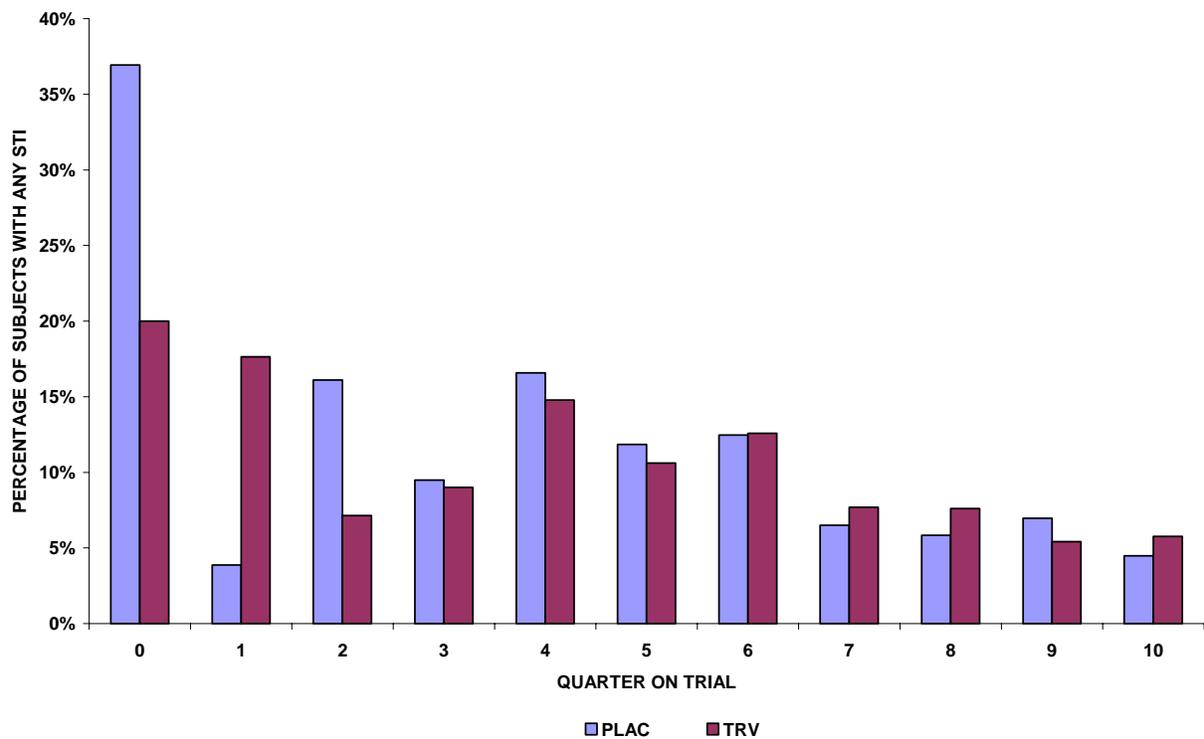
TRIAL 288



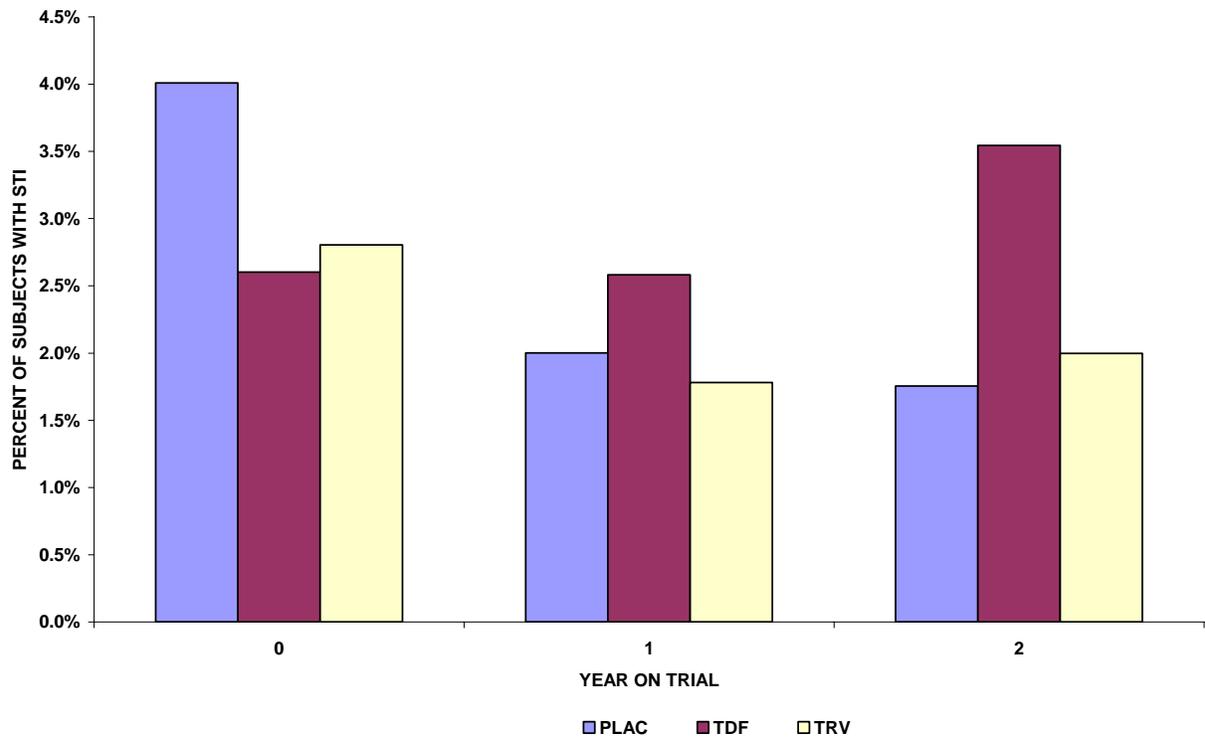
(There is a graph provided by the applicant that shows percentage of URAI acts as essentially constant. That graph is computed using a different denominator. The applicant's graph uses number of subjects with URAI divided by number of subjects with RAI, protected or not, and focuses on rate of condom use. This graph uses number of subjects with URAI divided by number of subjects, with or without RAI, and focuses simply on frequency of the high risk act.)

Both of the two above graphs use self-reported variables. As an additional, more objective measure of risk over time, the FDA statistical reviewer provides the following two graphs, which show the incidence of STIs (syphilis, gonorrhea, chlamydia, and HSV2) in both trials. The pattern of the data suggested that trial 380 collected this data less frequently than trial 288. Therefore, total number of STIs is graphed by quarter on trial and by year on trial and arm in trial 380. Quarter 0 and year 0 are baseline.

TRIAL 288

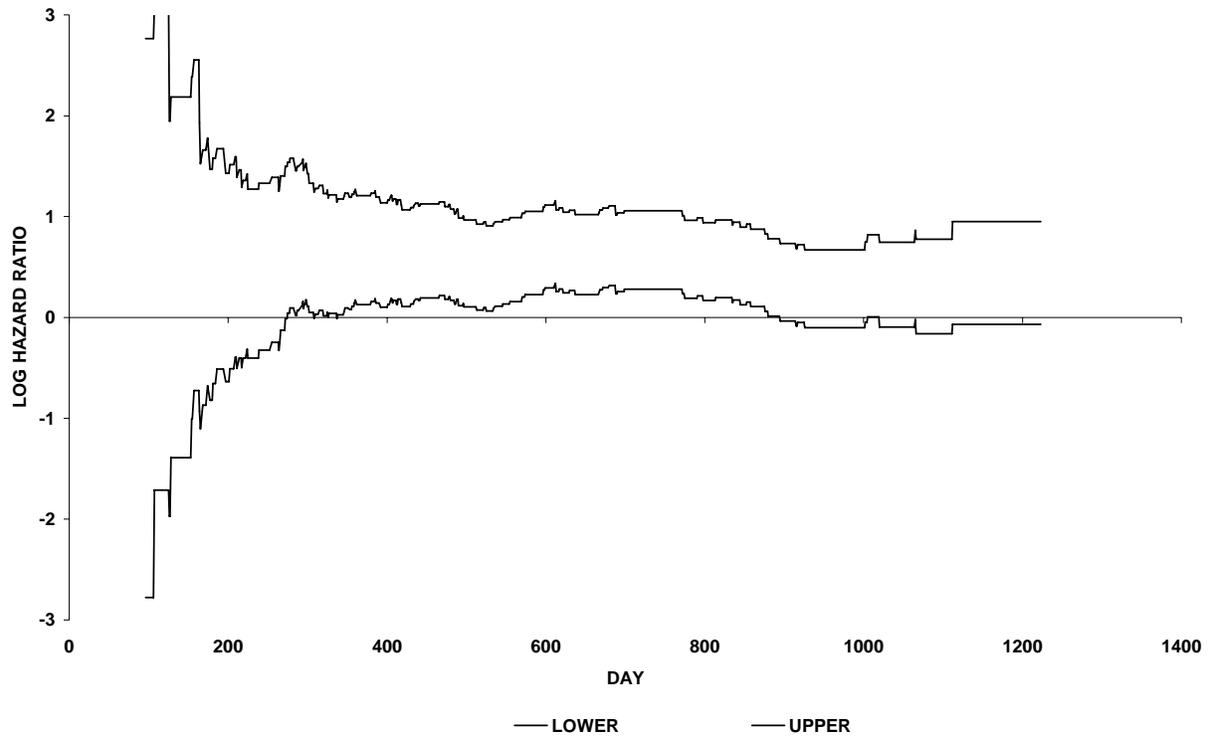


TRIAL 380

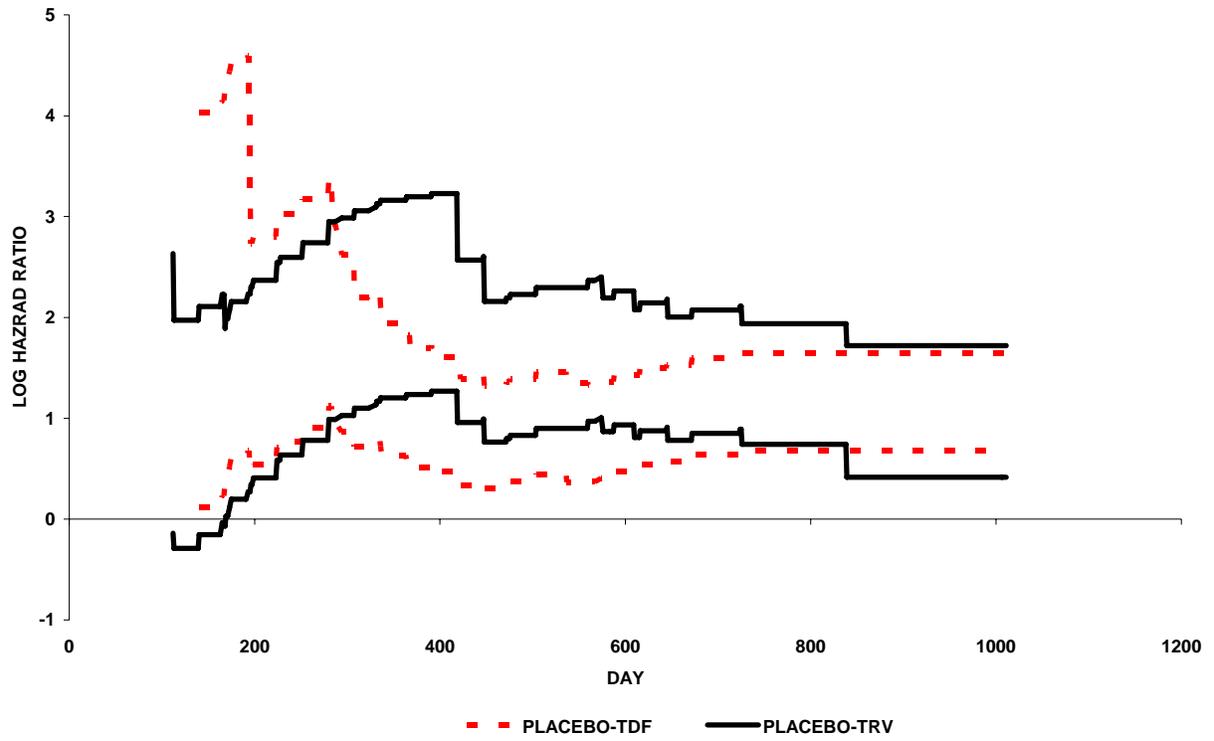


The next two graphs look at further details of the pattern of risk over time. They show the plots of the hazard ratios of placebo to active drug in trials 288 (the first graph) and 380 (the second graph). The ratios are computed so that values above one show superiority for the active drug. One can see that in all three comparisons, the hazard ratio is constant and most of the time statistically significantly in favor of the active drug. The most important conclusion to be drawn from the examination of the temporal pattern of risk is that truvada and TDF are statistically significantly better than placebo and that the hazard ratios are likely constant over the duration of the trial.

LOG HAZARD RATIO, 95% LIMITS



LOG HAZARD RATIOS, 95% LIMITS



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 show the infection rate per person year for placebo and either TRV or TDF, the odds-ratio for active drug divided by placebo, the lower and upper 95% confidence limits for the hazard ratio, and the number of infected in the category. Table 4.1 gives the results for all subjects and for age categories and gender for the TRV placebo comparison in trial 288 and for both the TDF-placebo and TRV-placebo comparisons in trial 380. (All subjects in trial 288 are male; the vast majority of subjects in trial 288 are mixed race; all subjects in trial 380 are black. Therefore, these gender and race comparisons cannot be done.)

The most interesting thing to note here is that the hazard ratios for both males and females in trial 380 show statistically significant superiority of both TDF and TRV to placebo. The evidence from this one trial at least supports efficacy in both genders. There is no confirmatory trial for efficacy in females.

TABLE 4.1 A
RISK COMPARISONS BY AGE AND GENDER, BOTH TRIALS

TRIAL_288	TRT	FAIL	LOWER	UPPER	RISK REDUCT	LOWER	UPPER	INFECTED
ALL	Placebo	4.178%	3.280%	5.077%
	Truvada	2.402%	1.723%	3.082%	0.425	0.221	0.629	131
AGECAT								
<40	Placebo	4.505%	3.524%	5.486%
	Truvada	2.565%	1.824%	3.307%	0.431	0.225	0.637	127
>=40	Placebo	1.062%	-0.410%	2.534%
	Truvada	0.976%	-0.377%	2.330%	0.081	-1.721	1.882	4
AGECAT2								
<25	Placebo	4.482%	3.201%	5.764%
	Truvada	3.214%	2.064%	4.365%	0.283	-0.046	0.611	77
>=25	Placebo	3.839%	2.585%	5.093%
	Truvada	1.691%	0.910%	2.472%	0.560	0.310	0.809	54
TRIAL_380_TDF								
ALL	Placebo	1.993%	1.451%	2.535%
	TDF	0.652%	0.342%	0.963%	0.673	0.493	0.852	69
AGE_CAT								
<25	Placebo	4.034%	1.534%	6.535%
	TDF	1.071%	-0.141%	2.282%	0.735	0.392	1.077	13
>=25	Placebo	1.779%	1.241%	2.317%
	TDF	0.602%	0.287%	0.918%	0.662	0.457	0.866	56
AGE_QUARTILE								
<=28	Placebo	4.071%	2.442%	5.700%
	TDF	1.300%	0.399%	2.200%	0.681	0.425	0.936	32
28-33	Placebo	1.800%	0.684%	2.915%

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	TDF	0.462%	-0.061%	0.985%	0.743	0.412	1.074	13
33-40	Placebo	1.455%	0.632%	2.278%
	TDF	0.561%	0.011%	1.111%	0.614	0.178	1.051	16
40<	Placebo	0.939%	0.188%	1.691%
	TDF	0.319%	-0.123%	0.761%	0.661	0.118	1.204	8
GENDER								
Female	Placebo	2.809%	1.768%	3.849%
	TDF	0.805%	0.247%	1.362%	0.714	0.488	0.939	36
Male	Placebo	1.489%	0.893%	2.085%
	TDF	0.559%	0.194%	0.924%	0.625	0.337	0.912	33

TABLE 4.1 A (continued)
RISK COMPARISONS BY AGE AND GENDER, BOTH TRIALS

TRV_380	TRT	FAIL	LOWER	UPPER	RISK REDUCT	LOWER	UPPER	INFECTED
ALL	Placebo	1.993%	1.451%	2.535%
	Truvada	0.497%	0.227%	0.766%	0.751	0.600	0.902	65
AGE_CAT <25	Placebo	4.034%	1.534%	6.535%
	Truvada	2.335%	0.467%	4.203%	0.421	-0.165	1.007	16
AGE_CAT ≥25	Placebo	1.779%	1.241%	2.317%
	Truvada	0.296%	0.077%	0.516%	0.833	0.700	0.967	49
AGE_QUARTILE ≤28	Placebo	4.071%	2.442%	5.700%
	Truvada	0.971%	0.194%	1.748%	0.761	0.548	0.975	30
AGE_QUARTILE 28-33	Placebo	1.800%	0.684%	2.915%
	Truvada	0.174%	-0.167%	0.515%	0.903	0.704	1.102	11
AGE_QUARTILE 33-40	Placebo	1.455%	0.632%	2.278%
	Truvada	0.404%	-0.053%	0.862%	0.722	0.370	1.074	15
AGE_QUARTILE 40<	Placebo	0.939%	0.188%	1.691%
	Truvada	0.439%	-0.058%	0.935%	0.533	-0.114	1.180	9
GENDER Female	Placebo	2.809%	1.768%	3.849%
	Truvada	0.954%	0.331%	1.577%	0.660	0.405	0.915	37
GENDER Male	Placebo	1.489%	0.893%	2.085%
	Truvada	0.239%	0.005%	0.473%	0.840	0.670	1.009	28

4.2 Other Baseline Covariates

Results for other baseline covariates are presented here. The most interesting results have already been discussed in section 3.2.2 above. The entries in the tables are the same as in section 4.1. Table 4.2 A gives the results for the comparison of TRV and placebo in trial 288. Table 4.2 B gives the results for the comparison of the TDF and placebo arms in trial 380. Table 4.2 C gives the results for the comparison of the TRV and placebo arms in trial 380.

Some of the variable names in the following tables may not be completely self-explanatory. Here are their meanings.

LIVE = living status
MARITAL = marital status
STI_DIAG = diagnosis of STI at baseline
STI_ULCER = STI with ulcer
RISKBEH = high risk behavior (unprotected receptive anal sex)
ANSEXMENQ = # of receptive anal sex acts with men since last visit, by quartile
SEXWTMENQ = # of sex acts with men since last visit, by quartile
CD4_Count = infected partner's CD4 count, either < or \geq 350, or by quartile
Part.VL and Viral_Load = infected partner's HIV viral level, either < or \geq 50K or by quartile
YRSHIVQ = years infected partner with HIV, by quartile
YRSWPTNRQ = years partners together, by quartile
CURABL STI = curable STI at baseline
ANYUNPSX = any unprotected sex acts since last visit
OTHERSEX = any sex acts with other person than partner since last visit
SEXACTSQ = # of sex acts since last visit, by quartile
ANYINCOM = Subject has any income
YRSEDUCQ = years of education
CONTRA = contraceptive use
CIRC = circumcised (fully/partially vs none)
MALECIRC = circumcised (fully vs partially/none)
(females are missing for the latter two variables)

TABLE 4.2 A
RISK RESULTS IN TRIAL 288, BY SUBGROUPS

	TRT	FAIL	LOWER	UPPER	RISKRED	LOWER	UPPER	INFECTED
ALL	Placebo	4.178%	3.280%	5.077%
	Truvada	2.402%	1.723%	3.082%	0.425	0.221	0.629	131
REGION	TRT	FAIL	LOWER	UPPER	RISKRED	LOWER	UPPER	INFECTED
Africa	Placebo	5.270%	-2.034%	12.57%
	Truvada	4.755%	-1.835%	11.34%	0.098	-1.671	1.866	4
Asia	Placebo	5.760%	-0.758%	12.28%
	Truvada	3.672%	-1.417%	8.761%	0.363	-0.778	1.503	5
N_America	Placebo	1.356%	-0.523%	3.236%
	Truvada	0.682%	-0.655%	2.018%	0.497	-0.709	1.704	3
S_America	Placebo	4.346%	3.369%	5.323%
	Truvada	2.450%	1.718%	3.183%	0.436	0.225	0.647	119
COUNTRY	TRT	FAIL	LOWER	UPPER	RISKRED	LOWER	UPPER	INFECTED
Brazil	Placebo	5.490%	2.087%	8.893%
	Truvada	2.169%	0.043%	4.295%	0.605	0.147	1.063	14
Ecuador	Placebo	6.945%	3.644%	10.25%
	Truvada	3.957%	1.372%	6.543%	0.430	-0.030	0.891	26
Peru	Placebo	3.707%	2.669%	4.744%
	Truvada	2.234%	1.434%	3.033%	0.397	0.124	0.671	79
South	Africa	Placebo	5.270%	-2.034%	12.57%	.	.	.
	Truvada	4.755%	-1.835%	11.34%	0.098	-1.671	1.866	4
Thailand	Placebo	5.760%	-0.758%	12.28%
	Truvada	3.672%	-1.417%	8.761%	0.363	-0.778	1.503	5
USA	Placebo	1.356%	-0.523%	3.236%
	Truvada	0.682%	-0.655%	2.018%	0.497	-0.709	1.704	3

TABLE 4.2 A(continued)
RISK RESULTS IN TRIAL 288, BY SUBGROUPS

SITENAME	TRT	FAIL	LOWER	UPPER	RISKRED	LOWER	UPPER	INFECTED
Boston	Placebo	1.845%	-1.771%	5.461%
	Truvada	1
S_Francisco	Placebo	1.072%	-1.029%	3.174%
	Truvada	1.091%	-1.047%	3.230%	-0.017	-2.838	2.803	2
Cape_Town	Placebo	5.270%	-2.034%	12.57%
	Truvada	4.755%	-1.835%	11.34%	0.098	-1.671	1.866	4
Chiang_Mai	Placebo	5.760%	-0.758%	12.28%
	Truvada	3.672%	-1.417%	8.761%	0.363	-0.778	1.503	5
Guayaquil	Placebo	6.945%	3.644%	10.25%
	Truvada	3.957%	1.372%	6.543%	0.430	-0.030	0.891	26
Iquitos	Placebo	2.019%	0.700%	3.338%
	Truvada	1.600%	0.415%	2.785%	0.208	-0.575	0.990	16
Lima_INMENZA								
Lima_Impacta	Placebo	4.707%	2.740%	6.674%
	Truvada	2.968%	1.413%	4.522%	0.370	-0.053	0.792	36
Lima_Impacta								
Rio_Praça_Onze	Placebo	4.403%	2.369%	6.437%
	Truvada	2.075%	0.719%	3.430%	0.529	0.152	0.906	27
Rio_Praça_Onze								
Rio_FIOCRUZ	Placebo	7.273%	-0.957%	15.50%
	Truvada	4.624%	-1.784%	11.03%	0.364	-0.773	1.502	5
Rio_FIOCRUZ								
Sao_Paulo	Placebo	4.773%	0.589%	8.957%
	Truvada	1.919%	-0.741%	4.579%	0.598	-0.061	1.257	7
Sao_Paulo	Placebo	5.532%	-2.135%	13.20%
	Truvada	2

TABLE 4.2 A(continued)
RISK RESULTS IN TRIAL 288, BY SUBGROUPS

AGECAT	TRT	FAIL	LOWER	UPPER	RISKRED	LOWER	UPPER	INFECTED
<40	Placebo	4.505%	3.524%	5.486%
	Truvada	2.565%	1.824%	3.307%	0.431	0.225	0.637	127
≥40	Placebo	1.062%	-0.410%	2.534%
	Truvada	0.976%	-0.377%	2.330%	0.081	-1.721	1.882	4
AGECAT2	TRT	FAIL	LOWER	UPPER	RISKRED	LOWER	UPPER	INFECTED
<25	Placebo	4.482%	3.201%	5.764%
	Truvada	3.214%	2.064%	4.365%	0.283	-0.046	0.611	77
≥25	Placebo	3.839%	2.585%	5.093%
	Truvada	1.691%	0.910%	2.472%	0.560	0.310	0.809	54
COMPLIANCE	TRT	FAIL	LOWER	UPPER	RISKRED	LOWER	UPPER	INFECTED
<90%	Placebo	4.806%	3.141%	6.472%
	Truvada	2.736%	1.506%	3.966%	0.431	0.108	0.754	51
≥90%	Placebo	3.862%	2.802%	4.922%
	Truvada	2.225%	1.415%	3.034%	0.424	0.161	0.687	80

TABLE 4.2 A(continued)
RISK RESULTS IN TRIAL 288, BY SUBGROUPS

EDUCATION	TRT	FAIL	LOWER	UPPER	RISKRED	LOWER	UPPER	INFECTED
not_completed_secondary								
	Placebo	3.926%	2.753%	5.100%
	Truvada	2.684%	1.723%	3.644%	0.317	-0.002	0.635	73
completed_secondary_school								
	Placebo	3.219%	1.533%	4.905%
	Truvada	2.344%	0.891%	3.797%	0.272	-0.319	0.863	24
beyond_secondary								
	Placebo	5.698%	3.508%	7.888%
	Truvada	1.764%	0.542%	2.986%	0.690	0.445	0.936	34

TABLE 4.2 A(continued)
RISK RESULTS IN TRIAL 288, BY SUBGROUPS

LIVE	TRT	FAIL	LOWER	UPPER	RISKRED	LOWER	UPPER	INFECTED
with_family_or_friends	Placebo	4.724%	3.648%	5.800%
	Truvada	2.691%	1.877%	3.505%	0.430	0.215	0.646	116
other	Placebo	2.143%	0.743%	3.544%
	Truvada	1.371%	0.274%	2.469%	0.360	-0.301	1.021	15
MARITAL	TRT	FAIL	LOWER	UPPER	RISKRED	LOWER	UPPER	INFECTED
single	Placebo	4.669%	3.583%	5.755%
	Truvada	2.239%	1.486%	2.991%	0.520	0.324	0.717	105
with_partner,_not_married	Placebo	2.878%	1.250%	4.506%
	Truvada	3.223%	1.535%	4.912%	-0.120	-0.984	0.744	26

TABLE 4.2 A(continued)
RISK RESULTS IN TRIAL 288, BY SUBGROUPS

SYPHILIS	TRT	FAIL	LOWER	UPPER	RISKRED	LOWER	UPPER	INFECTED
YES	Placebo	2.973%	2.114%	3.832%
	Truvada	1.881%	1.197%	2.566%	0.367	0.073	0.661	75
NO	Placebo	8.426%	5.711%	11.14%
	Truvada	4.161%	2.290%	6.032%	0.506	0.233	0.779	56
HSV2	TRT	FAIL	LOWER	UPPER	RISKRED	LOWER	UPPER	INFECTED
YES	Placebo	5.521%	4.048%	6.993%
	Truvada	3.688%	2.515%	4.860%	0.332	0.055	0.609	92
NO	Placebo	2.876%	1.829%	3.923%
	Truvada	1.034%	0.393%	1.674%	0.641	0.382	0.899	39
STI_DIAG	TRT	FAIL	LOWER	UPPER	RISKRED	LOWER	UPPER	INFECTED
YES	Placebo	7.420%	5.061%	9.780%
	Truvada	4.936%	3.039%	6.834%	0.335	0.003	0.667	64
NO	Placebo	3.052%	2.160%	3.944%
	Truvada	1.496%	0.871%	2.121%	0.510	0.260	0.760	67
STI_ULCER	TRT	FAIL	LOWER	UPPER	RISKRED	LOWER	UPPER	INFECTED
YES	Placebo	10.90%	4.143%	17.65%
	Truvada	4.969%	0.993%	8.944%	0.544	0.083	1.006	16
NO	Placebo	3.853%	2.969%	4.737%
	Truvada	2.237%	1.561%	2.914%	0.419	0.199	0.640	115

TABLE 4.2 A(continued)
RISK RESULTS IN TRIAL 288, BY SUBGROUPS

RISK_BEH	TRT	FAIL	LOWER	UPPER	RISKRED	LOWER	UPPER	INFECTED
No_URAI	Placebo	2.686%	0.537%	4.835%
	Truvada	3.217%	0.834%	5.599%	-0.198	-1.504	1.108	13
URAI	Placebo	5.776%	4.442%	7.110%
	Truvada	2.716%	1.803%	3.629%	0.530	0.338	0.722	106
ANSEXMENQ	TRT	FAIL	LOWER	UPPER	RISKRED	LOWER	UPPER	INFECTED
<=13	Placebo	3.259%	1.552%	4.966%
	Truvada	1.624%	0.421%	2.827%	0.502	0.050	0.954	21
13-27	Placebo	4.289%	2.361%	6.218%
	Truvada	2.632%	1.143%	4.121%	0.386	-0.057	0.830	31
27-61	Placebo	3.694%	2.114%	5.273%
	Truvada	1.814%	0.690%	2.938%	0.509	0.139	0.879	31
61<	Placebo	5.318%	3.383%	7.254%
	Truvada	3.395%	1.868%	4.922%	0.362	-0.008	0.731	48
SEXWTMENQ	TRT	FAIL	LOWER	UPPER	RISKRED	LOWER	UPPER	INFECTED
<=14	Placebo	3.615%	1.786%	5.445%
	Truvada	1.973%	0.606%	3.341%	0.454	-0.014	0.923	23
14-30	Placebo	3.911%	2.104%	5.718%
	Truvada	2.391%	1.038%	3.744%	0.389	-0.058	0.835	30
30-66	Placebo	4.044%	2.392%	5.697%
	Truvada	1.672%	0.579%	2.764%	0.587	0.268	0.905	32
66<	Placebo	4.977%	3.099%	6.854%
	Truvada	3.440%	1.893%	4.986%	0.309	-0.097	0.715	46

TABLE 4.2 A(continued)
RISK RESULTS IN TRIAL 288, BY SUBGROUPS

COMPLIANCE	RISKBEH	TRT	FAIL	LOWER	UPPER	RISKRED	LOWER	UPPER	INFECTED
<90%	No_URAI	Placebo	3.646%	-0.480%	7.772%
		Truvada	2.318%	-0.894%	5.529%	0.364	-0.773	1.502	5
	URAI	Placebo	6.905%	4.347%	9.463%
		Truvada	3.395%	1.617%	5.174%	0.508	0.193	0.824	42
≥90%	No_URAI	Placebo	2.126%	-0.280%	4.531%
		Truvada	3.807%	0.470%	7.145%	-0.791	-3.355	1.773	8
	URAI	Placebo	5.231%	3.686%	6.777%
		Truvada	2.382%	1.338%	3.426%	0.545	0.304	0.785	64
COMPLIANCE <90%	AGECAT <40	Placebo	5.017%	3.251%	6.784%
		Truvada	2.816%	1.515%	4.116%	0.439	0.113	0.765	49
	AGECAT ≥40	Placebo	2.086%	-2.003%	6.175%
		Truvada	1.811%	-1.739%	5.360%	0.132	-2.274	2.538	2
COMPLIANCE ≥90%	AGECAT <40	Placebo	4.237%	3.062%	5.411%
		Truvada	2.426%	1.528%	3.325%	0.427	0.162	0.692	78
	AGECAT ≥40	Placebo	0.712%	-0.684%	2.109%
		Truvada	0.668%	-0.642%	1.978%	0.062	-2.539	2.662	2
COMPLY <90%	AGECAT2 <25	Placebo	6.196%	3.717%	8.675%
		Truvada	3.087%	1.263%	4.911%	0.502	0.146	0.857	35
	AGECAT2 ≥25	Placebo	2.873%	0.882%	4.864%
		Truvada	2.366%	0.726%	4.005%	0.177	-0.630	0.984	16
COMPLY ≥90%	AGECAT2 <25	Placebo	3.478%	2.057%	4.900%
		Truvada	3.293%	1.812%	4.774%	0.053	-0.522	0.629	42
	AGECAT2 ≥25	Placebo	4.247%	2.674%	5.820%
		Truvada	1.376%	0.523%	2.229%	0.676	0.442	0.910	38

TABLE 4.2 B
RISK RESULTS IN TRIAL 380, BY SUBGROUPS

		TDF ARM VS PLACEBO ARM						
	TRT	FAIL	LOWER	UPPER	RISKRED	LOWER	UPPER	INFECTED
ALL	Placebo	1.993%	1.451%	2.535%
	TDF	0.652%	0.342%	0.963%	0.673	0.493	0.852	69
AGE25 <25	Placebo	4.034%	1.534%	6.535%
	TDF	1.071%	-0.141%	2.282%	0.735	0.392	1.077	13
>=25	Placebo	1.779%	1.241%	2.317%
	TDF	0.602%	0.287%	0.918%	0.662	0.457	0.866	56
AGE_QRT <=28	Placebo	4.071%	2.442%	5.700%
	TDF	1.300%	0.399%	2.200%	0.681	0.425	0.936	32
28-33	Placebo	1.800%	0.684%	2.915%
	TDF	0.462%	-0.061%	0.985%	0.743	0.412	1.074	13
33-40	Placebo	1.455%	0.632%	2.278%
	TDF	0.561%	0.011%	1.111%	0.614	0.178	1.051	16
40<	Placebo	0.939%	0.188%	1.691%
	TDF	0.319%	-0.123%	0.761%	0.661	0.118	1.204	8
GENDER Female	Placebo	2.809%	1.768%	3.849%
	TDF	0.805%	0.247%	1.362%	0.714	0.488	0.939	36
Male	Placebo	1.489%	0.893%	2.085%
	TDF	0.559%	0.194%	0.924%	0.625	0.337	0.912	33

TABLE 4.2 B(continued)
RISK RESULTS IN TRIAL 380, BY SUBGROUPS
TDF ARM VS PLACEBO ARM

CD4_COUNT	TRT	FAIL	LOWER	UPPER	RISKRED	LOWER	UPPER	INFECTED
<350	Placebo	1.951%	0.742%	3.160%
	TDF	1.562%	0.480%	2.644%	0.199	-0.545	0.944	18
≥350	Placebo	2.004%	1.398%	2.610%
	TDF	0.430%	0.149%	0.711%	0.785	0.631	0.940	51
CD4_Count ≤375	Placebo	2.040%	0.971%	3.109%
	TDF	1.314%	0.456%	2.173%	0.356	-0.184	0.895	23
375-496	Placebo	1.875%	0.814%	2.935%
	TDF	0.157%	-0.151%	0.464%	0.916	0.746	1.087	13
496-663	Placebo	2.320%	1.146%	3.493%
	TDF	0.620%	0.012%	1.228%	0.733	0.438	1.028	19
663<	Placebo	1.730%	0.708%	2.753%
	TDF	0.470%	-0.062%	1.002%	0.728	0.381	1.075	14
Part_VL <50_K	Placebo	1.510%	0.987%	2.033%
	TDF	0.614%	0.280%	0.947%	0.594	0.331	0.856	45
≥50_K	Placebo	3.928%	2.114%	5.743%
	TDF	0.895%	0.018%	1.771%	0.772	0.526	1.019	22

TABLE 4.2 B(continued)
RISK RESULTS IN TRIAL 380, BY SUBGROUPS
TDF ARM VS PLACEBO ARM

Viral_Load	TRT	FAIL	LOWER	UPPER	RISKRED	LOWER	UPPER	INFECTED
<=1504	Placebo	0.610%	0.012%	1.208%
	TDF	0.449%	-0.059%	0.957%	0.264	-0.837	1.366	7
1504-7596	Placebo	1.079%	0.280%	1.879%
	TDF	0.442%	-0.058%	0.942%	0.590	0.036	1.144	10
7596-31795	Placebo	2.883%	1.587%	4.180%
	TDF	0.657%	0.013%	1.300%	0.772	0.527	1.018	23
31795<	Placebo	3.407%	1.983%	4.831%
	TDF	1.078%	0.279%	1.877%	0.684	0.414	0.953	29
YRSHIVQ	TRT	FAIL	LOWER	UPPER	RISKRED	LOWER	UPPER	INFECTED
<=0.083	Placebo	2.667%	0.053%	5.280%
	TDF	4
0.083-0.42	Placebo	2.722%	1.731%	3.713%
	TDF	1.010%	0.413%	1.606%	0.629	0.372	0.887	40
0.42-2	Placebo	1.617%	0.702%	2.532%
	TDF	0.389%	-0.051%	0.830%	0.759	0.455	1.064	15
2<	Placebo	1.075%	0.279%	1.871%
	TDF	0.482%	-0.063%	1.027%	0.552	-0.055	1.158	10

TABLE 4.2 B(continued)
 RISK RESULTS IN TRIAL 380, BY SUBGROUPS
 TDF ARM VS PLACEBO ARM

YRSWPTNRQ	TRT	FAIL	LOWER	UPPER	RISKRED	LOWER	UPPER	INFECTED
<=3	Placebo	3.356%	1.954%	4.759%
	TDF	1.662%	0.680%	2.644%	0.505	0.147	0.863	33
3-7	Placebo	2.172%	0.943%	3.400%
	TDF	0.504%	-0.066%	1.074%	0.768	0.474	1.062	15
7-14	Placebo	1.499%	0.613%	2.384%
	TDF	0.291%	-0.112%	0.694%	0.806	0.514	1.098	13
14<	Placebo	1.050%	0.272%	1.828%
	TDF	0.151%	-0.145%	0.448%	0.856	0.554	1.158	8
COMPLIANCE	TRT	FAIL	LOWER	UPPER	RISKRED	LOWER	UPPER	INFECTED
<90%	Placebo	4.847%	0.598%	9.095%
	TDF	0.738%	-0.709%	2.185%	0.848	0.521	1.175	6
>=90%	Placebo	1.876%	1.339%	2.412%
	TDF	0.648%	0.330%	0.965%	0.655	0.459	0.851	63

TABLE 4.2 B(continued)
RISK RESULTS IN TRIAL 380, BY SUBGROUPS
TDF ARM VS PLACEBO ARM

CURABL	STI	FAIL	LOWER	UPPER	RISKRED	LOWER	UPPER	INFECTED	
YES		Placebo	2.946%	0.589%	5.303%	.	.	.	
		TDF	6	
NO		Placebo	1.949%	1.386%	2.513%	.	.	.	
		TDF	0.582%	0.277%	0.887%	0.702	0.523	0.880	60
SYPHILIS	TRT	FAIL	LOWER	UPPER	RISKRED	LOWER	UPPER	INFECTED	
		Placebo	2.440%	-0.321%	5.201%
YES		TDF	3	
		Placebo	1.993%	1.435%	2.552%
NO		TDF	0.688%	0.361%	1.015%	0.655	0.464	0.845	66
		TRT	FAIL	LOWER	UPPER	RISKRED	LOWER	UPPER	INFECTED
HSV2	YES	Placebo	2.169%	1.418%	2.921%
		TDF	0.557%	0.171%	0.944%	0.743	0.544	0.942	40
NO		Placebo	1.754%	0.944%	2.565%
		TDF	0.670%	0.174%	1.167%	0.618	0.285	0.952	25

TABLE 4.2 B(continued)
RISK RESULTS IN TRIAL 380, BY SUBGROUPS
TDF ARM VS PLACEBO ARM

ANYUNPSX	TRT	FAIL	LOWER	UPPER	RISKRED	LOWER	UPPER	INFECTED
NO	Placebo	1.502%	0.965%	2.040%
	TDF	0.719%	0.343%	1.096%	0.521	0.217	0.825	44
YES	Placebo	3.596%	2.093%	5.099%
	TDF	0.455%	-0.060%	0.970%	0.874	0.721	1.026	25
OTHERSEX	TRT	FAIL	LOWER	UPPER	RISKRED	LOWER	UPPER	INFECTED
NO	Placebo	2.119%	1.538%	2.701%
	TDF	0.635%	0.314%	0.956%	0.700	0.528	0.873	66
YES	Placebo	0.494%	-0.474%	1.462%
	TDF	0.825%	-0.318%	1.969%	-0.671	-4.682	3.340	3
SEXACTSQ	TRT	FAIL	LOWER	UPPER	RISKRED	LOWER	UPPER	INFECTED
<=2	Placebo	1.390%	0.528%	2.251%
	TDF	0.583%	0.012%	1.153%	0.581	0.095	1.067	14
2-4	Placebo	2.450%	1.349%	3.552%
	TDF	0.862%	0.223%	1.501%	0.648	0.343	0.953	26
4-8	Placebo	1.766%	0.671%	2.860%
	TDF	0.664%	0.013%	1.315%	0.624	0.188	1.060	14
8<	Placebo	2.374%	1.083%	3.664%
	TDF	0.396%	-0.153%	0.946%	0.833	0.584	1.082	15

TABLE 4.2 B(continued)
RISK RESULTS IN TRIAL 380, BY SUBGROUPS
TDF ARM VS PLACEBO ARM

ANYINCOM	TRT	FAIL	LOWER	UPPER	RISKRED	RLOWER	RUPPER
NO	Placebo	2.581%	1.229%	3.933%	.	.	.
	TDF	0.581%	-0.076%	1.238%	0.775	0.494	1.056
YES	Placebo	1.839%	1.254%	2.424%	.	.	.
	TDF	0.670%	0.319%	1.021%	0.636	0.412	0.859
YRSEDUCQ <=4	Placebo	2.995%	1.714%	4.277%	.	.	.
	TDF	0.714%	0.088%	1.341%	0.761	0.529	0.994
4-7	Placebo	1.593%	0.692%	2.495%	.	.	.
	TDF	0.492%	0.010%	0.974%	0.691	0.342	1.041
7-10	Placebo	2.080%	0.903%	3.257%	.	.	.
	TDF	1.123%	0.225%	2.022%	0.460	-0.069	0.989
10<	Placebo	1.212%	0.314%	2.109%	.	.	.
	TDF	0.358%	-0.138%	0.855%	0.704	0.239	1.169
CONTRA NO	Placebo	2.416%	1.049%	3.783%	.	.	.
	TDF	1.088%	0.217%	1.958%	0.550	0.108	0.991
YES	Placebo	3.199%	1.631%	4.766%	.	.	.
	TDF	0.452%	-0.174%	1.078%	0.859	0.651	1.066

TABLE 4.2 B(continued)
RISK RESULTS IN TRIAL 380, BY SUBGROUPS
TDF ARM VS PLACEBO ARM

CIRC	TRT	FAIL	LOWER	UPPER	RISKRED	RLOWER	RUPPER
Fully/ Partially	Placebo	1.522%	0.695%	2.349%	.	.	.
	TDF	0.698%	0.139%	1.256%	0.541	0.098	0.985
Not_circum	Placebo	1.452%	0.594%	2.309%	.	.	.
	TDF	0.400%	-0.053%	0.853%	0.724	0.372	1.076
MALECIRC	TRT	FAIL	LOWER	UPPER	RISKRED	RLOWER	RUPPER
Partially/ None	Placebo	1.441%	0.589%	2.292%	.	.	.
	TDF	0.522%	0.010%	1.034%	0.638	0.223	1.052
Fully	Placebo	1.532%	0.699%	2.365%	.	.	.
	TDF	0.593%	0.073%	1.113%	0.613	0.214	1.012

TABLE 4.2 C
RISK RESULTS IN TRIAL 380, BY SUBGROUPS
TRV ARM VS PLACEBO ARM

	TRT	FAIL	LOWER	UPPER	RISKRED	LOWER	UPPER	INFECTED
ALL	Placebo	1.993%	1.451%	2.535%
	Truvada	0.497%	0.227%	0.766%	0.751	0.600	0.902	65
AGE25 <25	TRT	FAIL	LOWER	UPPER	RISKRED	LOWER	UPPER	INFECTED
	Placebo	4.034%	1.534%	6.535%
>=25	Truvada	2.335%	0.467%	4.203%	0.421	-0.165	1.007	16
	Placebo	1.779%	1.241%	2.317%
AGE_QRT <=28	TRT	FAIL	LOWER	UPPER	RISKRED	LOWER	UPPER	INFECTED
	Placebo	4.071%	2.442%	5.700%
28-33	Truvada	0.971%	0.194%	1.748%	0.761	0.548	0.975	30
	Placebo	1.800%	0.684%	2.915%
33-40	Truvada	0.174%	-0.167%	0.515%	0.903	0.704	1.102	11
	Placebo	1.455%	0.632%	2.278%
40<	Truvada	0.404%	-0.053%	0.862%	0.722	0.370	1.074	15
	Placebo	0.939%	0.188%	1.691%
GENDER Female	TRT	FAIL	LOWER	UPPER	RISKRED	LOWER	UPPER	INFECTED
	Placebo	2.809%	1.768%	3.849%
Male	Truvada	0.954%	0.331%	1.577%	0.660	0.405	0.915	37
	Placebo	1.489%	0.893%	2.085%
	Truvada	0.239%	0.005%	0.473%	0.840	0.670	1.009	28

TABLE 4.2 C(continued)
RISK RESULTS IN TRIAL 380, BY SUBGROUPS
TRV ARM VS PLACEBO ARM

CD4_Count	TRT	FAIL	LOWER	UPPER	RISKRED	LOWER	UPPER	INFECTED
<350	Placebo	1.951%	0.742%	3.160%
	Truvada	0.776%	0.016%	1.536%	0.602	0.141	1.063	14
≥350	Placebo	2.004%	1.398%	2.610%
	Truvada	0.428%	0.148%	0.708%	0.786	0.633	0.940	51
CD4_Count ≤375	Placebo	2.040%	0.971%	3.109%
	Truvada	0.613%	0.012%	1.214%	0.699	0.365	1.033	18
375-496	Placebo	1.875%	0.814%	2.935%
	Truvada	0.587%	0.012%	1.162%	0.687	0.332	1.041	16
496-663	Placebo	2.320%	1.146%	3.493%
	Truvada	0.629%	0.013%	1.246%	0.729	0.429	1.028	19
663<	Placebo	1.730%	0.708%	2.753%
	Truvada	0.154%	-0.148%	0.456%	0.911	0.729	1.093	12
Part.VL <50_K	Placebo	1.510%	0.987%	2.033%
	Truvada	0.421%	0.146%	0.696%	0.721	0.515	0.927	41
≥50_K	Placebo	3.928%	2.114%	5.743%
	Truvada	0.897%	0.018%	1.777%	0.772	0.524	1.019	22

TABLE 4.2 C(continued)
RISK RESULTS IN TRIAL 380, BY SUBGROUPS
TRV ARM VS PLACEBO ARM

Viral_Load	TRT	FAIL	LOWER	UPPER	RISKRED	LOWER	UPPER	INFECTED
<=1504	Placebo	0.610%	0.012%	1.208%
	Truvada	0.278%	-0.107%	0.664%	0.544	-0.230	1.318	6
1504-7596	Placebo	1.079%	0.280%	1.879%
	Truvada	0.321%	-0.124%	0.765%	0.703	0.236	1.170	9
7596-31795	Placebo	2.883%	1.587%	4.180%
	Truvada	0.591%	0.012%	1.170%	0.795	0.574	1.016	23
31795<	Placebo	3.407%	1.983%	4.831%
	Truvada	0.836%	0.103%	1.569%	0.755	0.516	0.993	27
YRSHIVQ	TRT	FAIL	LOWER	UPPER	RISKRED	LOWER	UPPER	INFECTED
<=0.083	Placebo	2.667%	0.053%	5.280%
	Truvada	4
0.083-0.42	Placebo	2.722%	1.731%	3.713%
	Truvada	0.633%	0.164%	1.101%	0.768	0.576	0.959	36
0.42-2	Placebo	1.617%	0.702%	2.532%
	Truvada	0.409%	-0.054%	0.871%	0.747	0.428	1.067	15
2<	Placebo	1.075%	0.279%	1.871%
	Truvada	0.487%	-0.064%	1.037%	0.547	-0.065	1.160	10

TABLE 4.2 C(continued)
RISK RESULTS IN TRIAL 380 BY SUBGROUPS
TRV ARM VS PLACEBO ARM

YRSWPTNRQ	TRT	FAIL	LOWER	UPPER	RISKRED	LOWER	UPPER	INFECTED
<=3	Placebo	3.356%	1.954%	4.759%
	Truvada	0.579%	0.012%	1.146%	0.828	0.644	1.011	26
3-7	Placebo	2.172%	0.943%	3.400%
	Truvada	0.543%	-0.072%	1.158%	0.750	0.433	1.066	15
7-14	Placebo	1.499%	0.613%	2.384%
	Truvada	0.445%	-0.059%	0.949%	0.703	0.324	1.082	14
14<	Placebo	1.050%	0.272%	1.828%
	Truvada	0.428%	-0.056%	0.912%	0.592	0.041	1.144	10
COMPLIANCE	TRT	FAIL	LOWER	UPPER	RISKRED	LOWER	UPPER	INFECTED
<90%	Placebo	4.847%	0.598%	9.095%
	Truvada	2.355%	-0.909%	5.619%	0.514	-0.283	1.311	7
>=90%	Placebo	1.876%	1.339%	2.412%
	Truvada	0.434%	0.178%	0.691%	0.769	0.617	0.920	58

TABLE 4.2 C(continued)
RISK RESULTS IN TRIAL 380, BY SUBGROUPS
TRV ARM VS PLACEBO ARM

CURABL	STI	TRT	FAIL	LOWER	UPPER	RISKRED	LOWER	UPPER	INFECTED
YES		Placebo	2.946%	0.589%	5.303%
		Truvada	0.694%	-0.666%	2.053%	0.765	0.266	1.263	7
NO		Placebo	1.949%	1.386%	2.513%
		Truvada	0.492%	0.213%	0.770%	0.748	0.588	0.908	58
SYPHILIS		Placebo	2.440%	-0.321%	5.201%
		Truvada	0.849%	-0.815%	2.514%	0.652	-0.136	1.440	4
NO		Placebo	1.993%	1.435%	2.552%
		Truvada	0.482%	0.209%	0.755%	0.758	0.606	0.911	61
HSV2		Placebo	2.169%	1.418%	2.921%
		Truvada	0.428%	0.085%	0.770%	0.803	0.631	0.975	38
NO		Placebo	1.754%	0.944%	2.565%
		Truvada	0.641%	0.166%	1.116%	0.635	0.316	0.954	25

TABLE 4.2 C(continued)
RISK RESULTS IN TRIAL 380, BY SUBGROUPS
TRV ARM VS PLACEBO ARM

ANYUNPSX	TRT	FAIL	LOWER	UPPER	RISKRED	LOWER	UPPER	INFECTED
NO	Placebo	1.502%	0.965%	2.040%
	Truvada	0.404%	0.124%	0.685%	0.731	0.521	0.941	38
YES	Placebo	3.596%	2.093%	5.099%
	Truvada	0.781%	0.096%	1.466%	0.783	0.572	0.994	27
OTHERSEX	TRT	FAIL	LOWER	UPPER	RISKRED	LOWER	UPPER	INFECTED
NO	Placebo	2.119%	1.538%	2.701%
	Truvada	0.501%	0.218%	0.785%	0.764	0.615	0.912	63
YES	Placebo	0.494%	-0.474%	1.462%
	Truvada	0.447%	-0.429%	1.323%	0.095	-2.415	2.604	2
SEXACTSQ	TRT	FAIL	LOWER	UPPER	RISKRED	LOWER	UPPER	INFECTED
<=2	Placebo	1.390%	0.528%	2.251%
	Truvada	0.151%	-0.145%	0.447%	0.891	0.668	1.115	11
2-4	Placebo	2.450%	1.349%	3.552%
	Truvada	0.608%	0.075%	1.140%	0.752	0.508	0.996	24
4-8	Placebo	1.766%	0.671%	2.860%
	Truvada	0.322%	-0.124%	0.768%	0.818	0.541	1.094	12
8<	Placebo	2.374%	1.083%	3.664%
	Truvada	0.978%	0.121%	1.834%	0.588	0.163	1.013	18

TABLE 4.2 C(continued)
RISK RESULTS IN TRIAL 380, BY SUBGROUPS
TRV ARM VS PLACEBO ARM

ANYINCOM	TRT	FAIL	LOWER	UPPER	RISKRED	RLOWER	RUPPER
NO	Placebo	2.581%	1.229%	3.933%	.	.	.
	Truvada	0.841%	0.104%	1.579%	0.674	0.341	1.007
YES	Placebo	1.839%	1.254%	2.424%	.	.	.
	Truvada	0.395%	0.121%	0.669%	0.785	0.621	0.949
YRSEDUCQ	TRT	FAIL	LOWER	UPPER	RISKRED	RLOWER	RUPPER
<=4	Placebo	2.995%	1.714%	4.277%	.	.	.
	Truvada	0.949%	0.246%	1.653%	0.683	0.412	0.954
4-7	Placebo	1.593%	0.692%	2.495%	.	.	.
	Truvada	0.268%	-0.104%	0.640%	0.832	0.580	1.084
7-10	Placebo	2.080%	0.903%	3.257%	.	.	.
	Truvada	0.368%	-0.142%	0.878%	0.823	0.559	1.088
10<	Placebo	1.212%	0.314%	2.109%	.	.	.
	Truvada	0.338%	-0.131%	0.807%	0.721	0.282	1.160

TABLE 4.2 C(continued)
RISK RESULTS IN TRIAL 380, BY SUBGROUPS
TRV ARM VS PLACEBO ARM

CONTRA	TRT	FAIL	LOWER	UPPER	RISKRED	RLOWER	RUPPER
NO	Placebo	2.416%	1.049%	3.783%	.	.	.
	Truvada	0.419%	-0.162%	1.001%	0.826	0.567	1.086
YES	Placebo	3.199%	1.631%	4.766%	.	.	.
	Truvada	1.500%	0.389%	2.611%	0.531	0.115	0.948
CIRC	TRT	FAIL	LOWER	UPPER	RISKRED	RLOWER	RUPPER
Fully/ Partially	Placebo	1.522%	0.695%	2.349%	.	.	.
	Truvada	0.345%	-0.045%	0.735%	0.773	0.489	1.058
Not_circum	Placebo	1.452%	0.594%	2.309%	.	.	.
	Truvada	0.124%	-0.119%	0.368%	0.914	0.739	1.090
MALECIRC	TRT	FAIL	LOWER	UPPER	RISKRED	RLOWER	RUPPER
Partially/ None	Placebo	1.441%	0.589%	2.292%	.	.	.
	Truvada	0.124%	-0.119%	0.366%	0.914	0.739	1.090
Fully	Placebo	1.532%	0.699%	2.365%	.	.	.
	Truvada	0.347%	-0.046%	0.739%	0.774	0.490	1.058

TABLE 4.2 D
RISK RESULTS IN TRIAL 380, BY SUBGROUPS
CROSSED WITH COMPLIANCE
TDF ARM VS PLACEBO ARM

COMPLIANCE	ANYUNPSX	TRT	FAIL	LOWER	UPPER	RISKRED	LOWER	UPPER	INFECTED	
<90%	NO	Placebo	2.653%	-1.024%	6.331%	
		TDF	1.075%	-1.032%	3.183%	0.595	-0.378	1.568	3	
	YES	Placebo	10.80%	-1.421%	23.02%	
		TDF	3	
≥90%	NO	Placebo	1.457%	0.917%	1.997%	
		TDF	0.702%	0.320%	1.083%	0.518	0.202	0.835	41	
	YES	Placebo	3.254%	1.791%	4.717%	
		TDF	0.486%	-0.064%	1.036%	0.851	0.669	1.033	22	
COMPLIANCE	OTHERSEX	NO	Placebo	5.657%	0.698%	10.62%
			TDF	0.845%	-0.811%	2.502%	0.851	0.530	1.171	6
		YES	Placebo
			TDF
	≥90%	NO	Placebo	1.985%	1.411%	2.558%
			TDF	0.624%	0.297%	0.950%	0.686	0.498	0.874	60
		YES	Placebo	0.533%	-0.511%	1.577%
			TDF	0.888%	-0.343%	2.119%	-0.667	-4.669	3.335	3

TABLE 4.2 D(continued)
RISK RESULTS IN TRIAL 380, BY SUBGROUPS
CROSSED WITH COMPLIANCE
TDF ARM VS PLACEBO ARM

COMPLIANCE	SEXACTSQ	TRT	FAIL	LOWER	UPPER	RISKRED	LOWER	UPPER	INFECTED		
<90%	2-4	Placebo		
		TDF	2.383%	-2.288%	7.055%	.	.	.	1		
	4-8	Placebo	4.938%	-4.741%	14.62%		
		TDF	1		
	8<	Placebo	17.89%	0.358%	35.43%		
		TDF	4		
≥90%	<=2	Placebo	1.436%	0.546%	2.326%		
		TDF	0.617%	0.012%	1.221%	0.570	0.072	1.069	14		
	2-4	Placebo	2.574%	1.417%	3.732%		
		TDF	0.779%	0.156%	1.403%	0.697	0.419	0.975	25		
	4-8	Placebo	1.648%	0.571%	2.725%		
		TDF	0.694%	0.014%	1.375%	0.579	0.083	1.075	13		
	8<	Placebo	1.713%	0.594%	2.833%		
		TDF	0.421%	-0.162%	1.004%	0.754	0.378	1.131	11		
	COMPLIANCE	AGE25	TRT	FAIL	LOWER	UPPER	RISKRED	LOWER	UPPER	INFECTED	
			Placebo	15.85%	-2.086%	33.78%	
		<90%	<25	TDF	3
				Placebo	2.375%	-0.916%	5.665%
≥90%		<25	TDF	0.937%	-0.899%	2.773%	0.605	-0.342	1.553	3	
			Placebo	3.057%	0.792%	5.322%	
≥90%	>=25	TDF	1.193%	-0.157%	2.543%	0.610	0.082	1.138	10		
		Placebo	1.757%	1.212%	2.301%		
		TDF	0.586%	0.267%	0.905%	0.666	0.458	0.875	53		

TABLE 4.2 D(continued)
RISK RESULTS IN TRIAL 380, BY SUBGROUPS
CROSSED WITH COMPLIANCE
TDF ARM VS PLACEBO ARM

COMPLIANCE	AGE_QRT	TRT	FAIL	LOWER	UPPER	RISKRED	LOWER	UPPER	INFECTED
<90%	<=28	Placebo	14.27%	1.762%	26.78%
		TDF	5
	28-33	Placebo
		TDF	2.309%	-2.217%	6.835%	.	.	.	1
≥90%	<=28	Placebo	3.427%	1.886%	4.968%
		TDF	1.414%	0.434%	2.393%	0.588	0.247	0.928	27
	28-33	Placebo	1.875%	0.713%	3.037%
		TDF	0.330%	-0.127%	0.787%	0.824	0.557	1.091	12
	33-40	Placebo	1.508%	0.655%	2.361%
		TDF	0.575%	0.012%	1.139%	0.618	0.187	1.050	16
	40<	Placebo	0.964%	0.193%	1.736%
		TDF	0.332%	-0.128%	0.792%	0.656	0.105	1.207	8

TABLE 4.2 E
RISK RESULTS IN TRIAL 380, BY SUBGROUPS
CROSSED WITH COMPLIANCE
TRV ARM VS PLACEBO ARM

COMPLIANCE	ANYUNPSX	TRT	FAIL	LOWER	UPPER	RISKRED	LOWER	UPPER	INFECTED	
<90%	NO	Placebo	2.653%	-1.024%	6.331%	
		Truvada	1.695%	-1.627%	5.018%	0.361	-1.173	1.895	3	
	YES	Placebo	10.80%	-1.421%	23.02%	
		Truvada	3.855%	-3.701%	11.41%	0.643	-0.165	1.451	4	
	>=90%	NO	Placebo	1.457%	0.917%	1.997%
			Truvada	0.365%	0.095%	0.635%	0.750	0.542	0.957	35
	YES	Placebo	3.254%	1.791%	4.717%	
		Truvada	0.651%	0.013%	1.290%	0.800	0.584	1.016	23	
COMPLIANCE	OTHERSEX	TRT	FAIL	LOWER	UPPER	RISKRED	LOWER	UPPER	INFECTED	
<90%	NO	Placebo	5.657%	0.698%	10.62%	
		Truvada	2.546%	-0.982%	6.074%	0.550	-0.188	1.288	7	
	YES	Placebo	
		Truvada	
>=90%	NO	Placebo	1.985%	1.411%	2.558%	
		Truvada	0.432%	0.164%	0.699%	0.782	0.634	0.931	56	
	YES	Placebo	0.533%	-0.511%	1.577%	
		Truvada	0.460%	-0.442%	1.362%	0.136	-2.258	2.531	2	

TABLE 4.2 E(continued)
RISK RESULTS IN TRIAL 380, BY SUBGROUPS
CROSSED WITH COMPLIANCE
TRV ARM VS PLACEBO ARM

COMPLIANCE	SEXACTSQ	TRT	FAIL	LOWER	UPPER	RISKRED	LOWER	UPPER	INFECTED	
<90%	2-4	Placebo	
		Truvada	6.149%	-2.373%	14.67%	.	.	.	2	
	4-8	Placebo	4.938%	-4.741%	14.62%	
		Truvada	1	
	8<	Placebo	17.89%	0.358%	35.43%	
		Truvada	4	
	≥90%	<=2	Placebo	1.436%	0.546%	2.326%
			Truvada	0.155%	-0.149%	0.458%	0.892	0.671	1.114	11
2-4		Placebo	2.574%	1.417%	3.732%	
		Truvada	0.380%	-0.050%	0.809%	0.853	0.673	1.032	22	
4-8		Placebo	1.648%	0.571%	2.725%	
		Truvada	0.330%	-0.127%	0.788%	0.800	0.493	1.107	11	
8<		Placebo	1.713%	0.594%	2.833%	
		Truvada	1.017%	0.126%	1.908%	0.407	-0.242	1.055	14	
COMPLIANCE	AGE25	TRT	FAIL	LOWER	UPPER	RISKRED	LOWER	UPPER	INFECTED	
<90%	<25	Placebo	15.85%	-2.086%	33.78%	
		Truvada	15.33%	-5.915%	36.57%	0.033	-1.698	1.763	5	
	≥25	Placebo	2.375%	-0.916%	5.665%	
		Truvada	2	
≥90%	<25	Placebo	3.057%	0.792%	5.322%	
		Truvada	1.640%	0.033%	3.247%	0.464	-0.195	1.123	11	
	≥25	Placebo	1.757%	1.212%	2.301%	
		Truvada	0.306%	0.079%	0.532%	0.826	0.686	0.966	47	

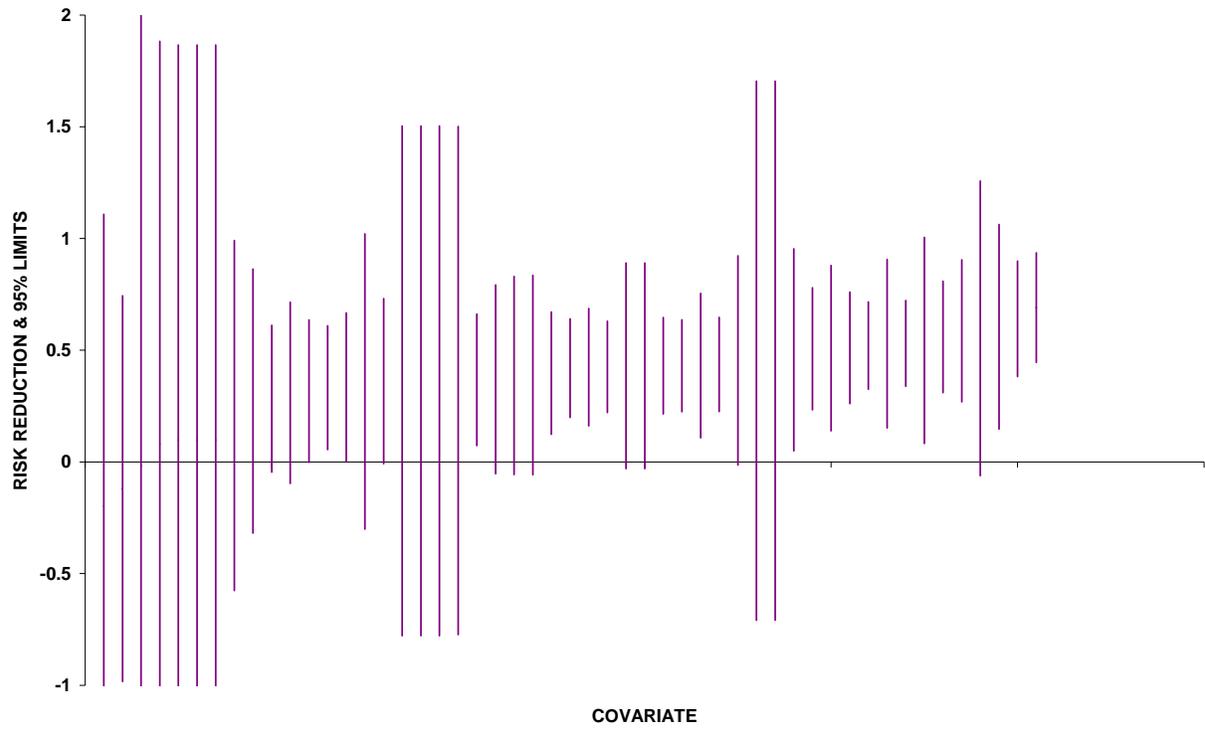
TABLE 4.2 E(continued)
RISK RESULTS IN TRIAL 380, BY SUBGROUPS
CROSSED WITH COMPLIANCE
TRV ARM VS PLACEBO ARM

COMPLIANCE	AGE_QRT	TRT	FAIL	LOWER	UPPER	RISKRED	LOWER	UPPER	INFECTED
<90%	<=28	Placebo	14.27%	1.762%	26.78%	.	.	.	
		Truvada	5.928%	-2.288%	14.14%	0.585	-0.096	1.266	7
≥90%	<=28	Placebo	3.427%	1.886%	4.968%	.	.	.	
		Truvada	0.685%	0.014%	1.356%	0.800	0.585	1.016	23
	28-33	Placebo	1.875%	0.713%	3.037%	.	.	.	
		Truvada	0.179%	-0.171%	0.528%	0.905	0.709	1.101	11
	33-40	Placebo	1.508%	0.655%	2.361%	.	.	.	
		Truvada	0.418%	-0.055%	0.890%	0.723	0.373	1.073	15
	40<	Placebo	0.964%	0.193%	1.736%	.	.	.	
		Truvada	0.447%	-0.059%	0.954%	0.536	-0.107	1.179	9

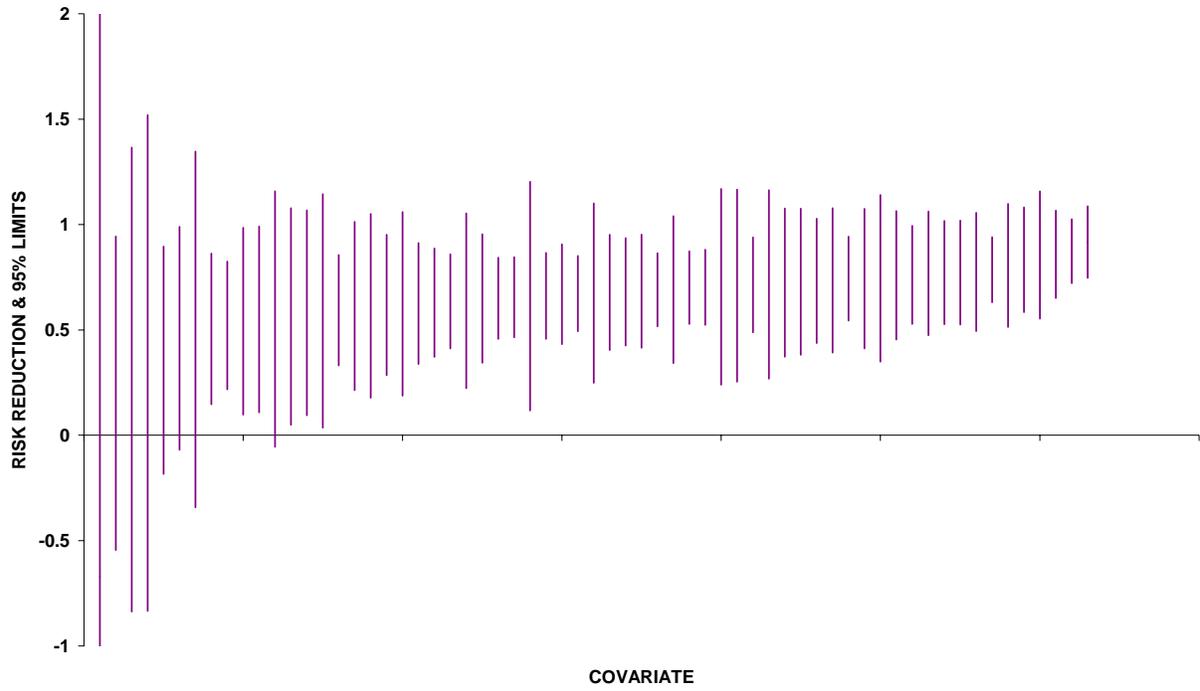
4.3 Possible Interactions Between Covariates and Efficacy

A visual picture of the above tables can be given by plotting the confidence intervals for the risk reduction for each covariate-defined subgroup. In order to get a better indication of any potential interaction with covariate and efficacy, we sort the intervals in decreasing order by point estimate of risk reduction. Any noticeable kink in the graph would suggest the possibility of an interaction. The three graphs are for trial 288, trial 380 TDF vs Placebo, and trial 380, TRV vs Placebo. One can see that, except for those intervals which are very wide because they have few events, all the risk reductions are greater zero and nothing looks like it suggests a covariate-efficacy interaction.

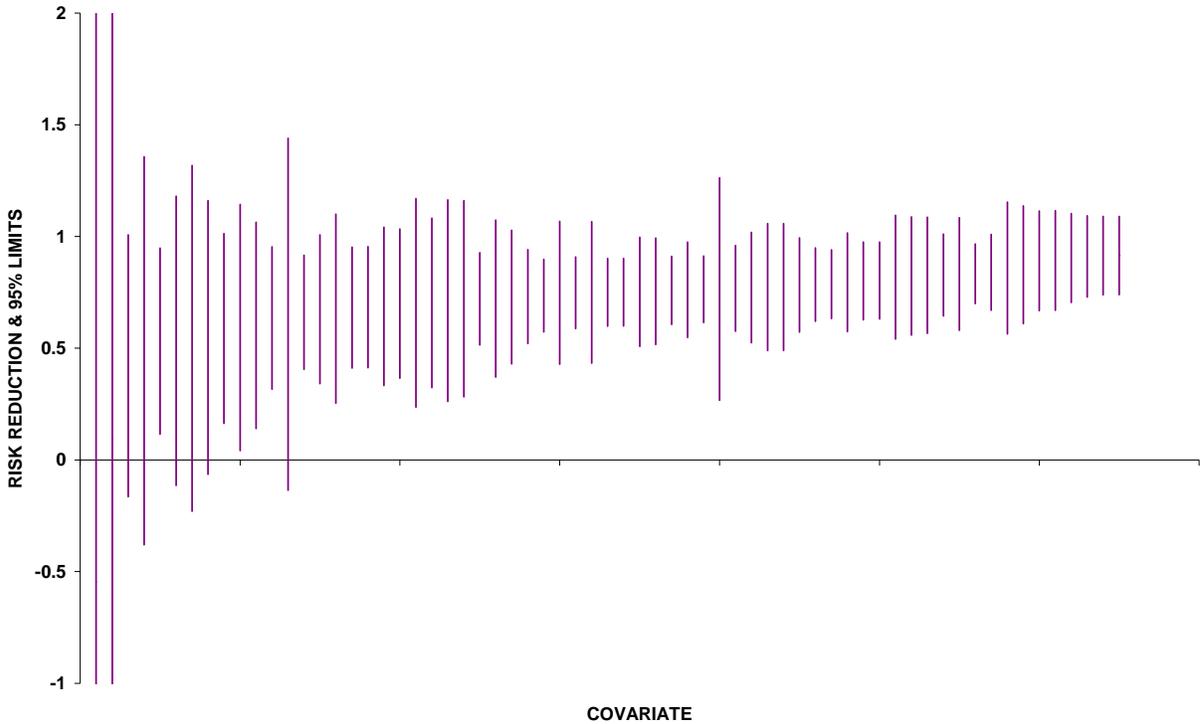
TRIAL 288



TRIAL 380, TDF



TRTIAL 380, TRV



As additional measure of exploring for interactions between covariates and efficacy, the FDA reviewer computed, for each ordinal covariate, the difference between the risk reduction at the highest level of the covariate and the risk reduction at the lowest level of the covariate. Covariates which take on only two non-missing levels were also treated as ordinal. Table 4.3 A-C gives these differences in risk reduction, together with their 95% confidence limits. One can see that the upper and lower confidence bounds for every difference in risk reduction (RISKDIFF in the table headings) straddle zero, indicating no statistically significant difference in the risk reductions at the two extreme levels of the covariate, with one exception. The covariate ANYUNPSX in the TDF arm of trial 380 showed statistically significant variability. This, of course, is without adjustment for multiple comparisons.

TABLE 4.3 A
DIFFERENCES IN RISK REDUCTION BETWEEN
HIGHEST AND LOWEST LEVELS OF COVARIATES, TRIAL 288

COVARIATE	RISKDIFF	LOWDIFF	HIDIFF
AGECAT	-0.350	-2.163	1.464
AGECAT2	0.277	-0.136	0.689
EDUC	0.374	-0.028	0.776
COMPLIANCE	-0.007	-0.423	0.410
LIVE	-0.070	-0.765	0.625
MARITAL	-0.640	-1.526	0.245
SYPHILIS	-0.139	-0.540	0.262
HSV2	0.309	-0.070	0.687
STI_DIAGNOSIS	0.175	-0.240	0.591
STI_ULCER	-0.125	-0.636	0.387
URAI_or_not	0.727	-0.593	2.047
ANSEXMENQ	-0.140	-0.724	0.444
SEXWTMENQ	-0.145	-0.765	0.474

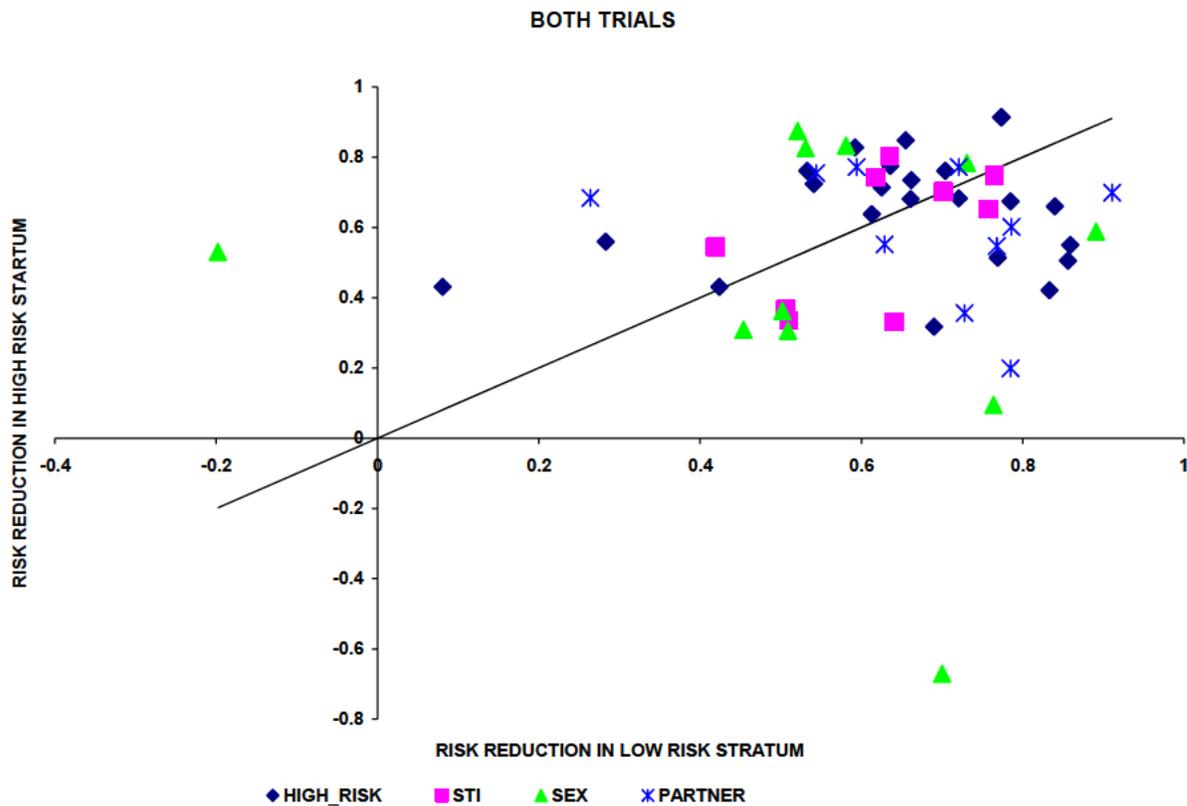
TABLE 4.3 B
DIFFERENCES IN RISK REDUCTION BETWEEN
HIGHEST AND LOWEST LEVELS OF COVARIATES, TRIAL 380, TDF ARM

COVARIATE	RISKDIFF	LOWDIFF	HIDIFF
AGE25	-0.073	-0.472	0.326
AGE_QRT	-0.020	-0.620	0.580
GENDER	-0.089	-0.454	0.276
CD4Count	0.586	-0.174	1.346
PartnerVL	0.179	-0.181	0.539
CD4_quartile	0.372	-0.269	1.014
VLQ	0.419	-0.714	1.553
YRSHIVQ	-0.078	-0.736	0.581
CURABLE	0.000	-0.253	0.253
HSV2	-0.125	-0.513	0.263
SYPHILIS	0.000	-0.269	0.269
ANYINCOM	-0.139	-0.498	0.219
YRSEDUCQ	-0.057	-0.577	0.463
COHABIT	0.000	-0.245	0.245
MARRIED	0.000	-0.273	0.273
YRSWPTNRQ	0.351	-0.118	0.820
ANYUNPSX	0.352	0.012	0.692 *
OTHERSEX	-1.372	-5.387	2.644
SEXACTSQ	0.252	-0.294	0.798
CONTRA	0.309	-0.179	0.797
CIRC	0.183	-0.383	0.749
MALECIRC	-0.025	-0.600	0.551

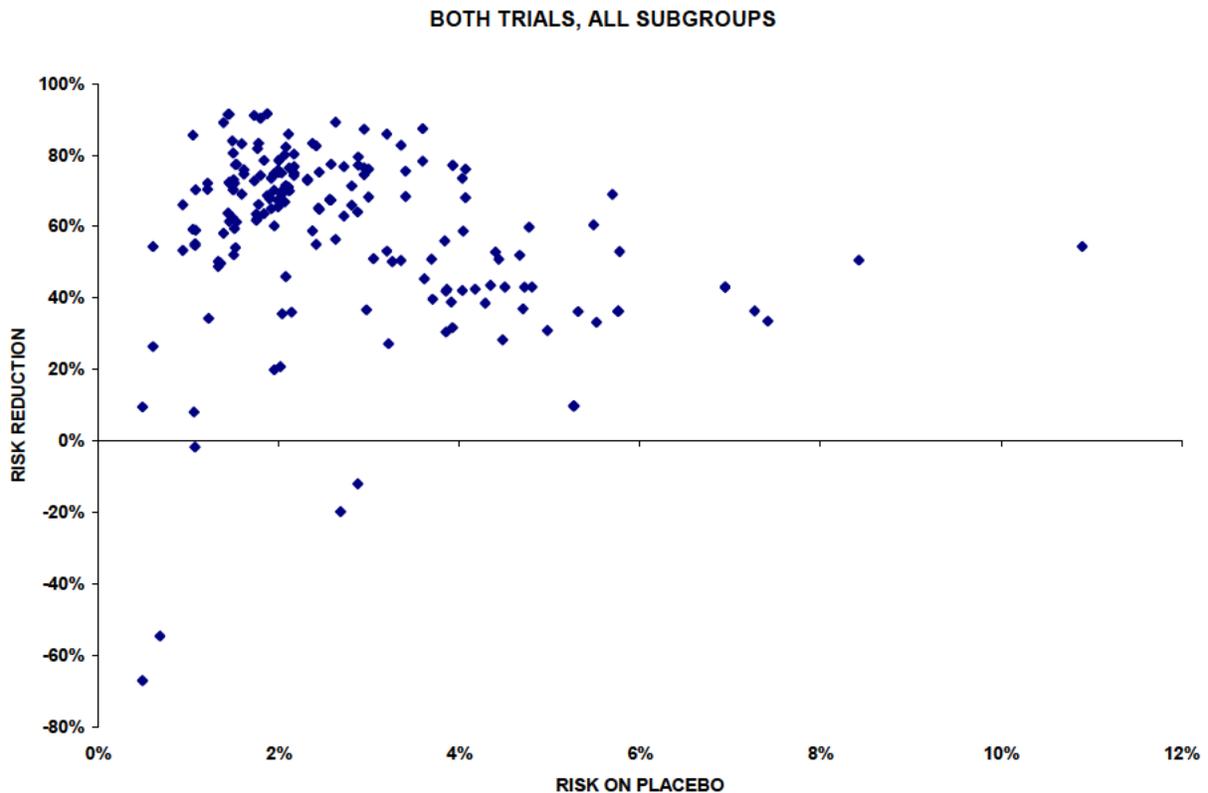
TABLE 4.3 C
DIFFERENCES IN RISK REDUCTION BETWEEN
HIGHEST AND LOWEST LEVELS OF COVARIATES, TRIAL 380 TRV ARM

COVARIATE	RISKDIFF	LOWDIFF	HIDIFF
AGE25	0.412	-0.189	1.013
AGE_QRT	-0.228	-0.910	0.453
GENDER	0.179	-0.127	0.486
CD4C350	0.184	-0.302	0.670
HIGHPVL	0.050	-0.272	0.373
CD4HIVQ	0.211	-0.169	0.592
VLQ	0.211	-0.599	1.020
YRSHIVQ	-0.220	-0.862	0.421
CURABLE	0.017	-0.507	0.540
HSV2	-0.168	-0.531	0.194
SYPHILIS	0.106	-0.696	0.909
ANYINCOM	0.111	-0.260	0.482
YRSEDUCQ	0.038	-0.478	0.553
COHABIT	0.000	-0.215	0.215
MARRIED	0.000	-0.229	0.229
YRSWPTNRQ	-0.235	-0.816	0.346
ANYUNPSX	0.052	-0.246	0.350
OTHERSEX	-0.669	-3.183	1.845
SEXACTSQ	-0.303	-0.783	0.177
CONTRA	-0.295	-0.786	0.196
CIRC	0.141	-0.193	0.475
MALECIRC	-0.140	-0.474	0.193

The following graph gives a plot of the estimated risk reduction in several binary and ordinal covariates in which, a priori, one would expect differential risk of infection. The risk reduction in the stratum with the highest anticipated risk is plotted on the y-axis against the risk reduction for the stratum with the lowest anticipated risk on the x-axis. Points below the 45° are covariates where risk reduction does not decrease with decreasing risk. Covariates associated with sexual behavior are plotted as triangles, those associated with STI's as squares, those associated with partner's HIV with stars. One does not see any systematic difference in risk reduction with higher levels of anticipated risk in any group of covariates.



As another view of the association between risk level and estimated risk reduction, the following graph shows a plot of the observed risk level in the placebo arm on the x-axis against the observed risk reduction between the active arm and the placebo arm (on the y-axis). There is one point for every subgroup defined by a covariate in trial 288 and two points (TDF vs placebo and TRV vs placebo) for every subgroup defined by a covariate in trial 380. One can see clearly that risk reduction tends to decrease with increasing risk level.



As a third method of exploring the association between risk level and risk reduction, the FDA reviewer counted the number of high risk factors for each subject in trial 288. A high risk factor is defined as any one of the following nine states:

1) yes to URAI, 2) age<-25, 3) education < secondary, 4)yes to HSV2, 5) yes to STI ulceration, 6) yes to syphilis, 7) yes to exchange sex for money or shelter, 8)>median(>=27) anal sex acts with men, and 9)>median (>=30) sex acts with men.

If one computes the risk levels for each arm and the risk reduction for number of high risk factors present, one gets the following results. The table gives the infection(failure) rate in each arm for each level, together with the upper and lower 95% confidence limits and the risk reduction, together with its upper and lower limits.

TABLE 4.3 D

RISK
FACTORS

	TRT	FAIL	LOWER	UPPER	RISKRED	LOWER	UPPER
0-2	Placebo	2.195%	0.271%	4.120%	.	.	.
	Truvada	0.437%	(0.420%)	1.294%	0.801	0.373	1.228
3	Placebo	4.785%	2.574%	6.995%	.	.	.
	Truvada	1.807%	0.468%	3.145%	0.622	0.293	0.952
4	Placebo	5.354%	3.117%	7.591%	.	.	.
	Truvada	2.145%	0.659%	3.632%	0.599	0.275	0.924
5	Placebo	6.153%	3.310%	8.995%	.	.	.
	Truvada	4.389%	2.003%	6.775%	0.287	-0.222	0.796
6-9	Placebo	9.226%	4.557%	13.90%	.	.	.
	Truvada	6.515%	2.829%	10.20%	0.294	-0.242	0.830

Again, one gets a pattern of generally decreasing risk reduction with increasing risk. A cross tabulation of # of risk factors with each of the nine contributing factors is given below.

# of RISK	FACTORS	RISKBEH7	COUNT	PERCENT
.	.	.	655	.
0-2	No	URAI	166	50.76%
		URAI	161	49.24%
3	No	URAI	88	18.41%
		URAI	390	81.59%
4	No	URAI	49	10.96%
		URAI	398	89.04%
5	No	URAI	21	6.287%
		URAI	313	93.71%
6-9	No	URAI	6	2.985%
		URAI	195	97.01%
		AGECAT2		
0-2	<	25	82	25.08%
	>=	25	245	74.92%
3	<	25	233	48.74%
	>=	25	245	51.26%
4	<	25	217	48.55%
	>=	25	230	51.45%
5	<	25	187	55.99%
	>=	25	147	44.01%
6-9	<	25	139	69.15%
	>=	25	62	30.85%
		EDUC2		
0-2	not_completed_secondary		213	65.14%
	completed_secondary_school		42	12.84%
	beyond_secondary		72	22.02%
3	not_completed_secondary		314	65.69%
	completed_secondary_school		77	16.11%
	beyond_secondary		87	18.20%
4	not_completed_secondary		273	61.07%
	completed_secondary_school		83	18.57%
	beyond_secondary		91	20.36%
5	not_completed_secondary		221	66.17%
	completed_secondary_school		64	19.16%
	beyond_secondary		49	14.67%
6-9	not_completed_secondary		160	79.60%
	completed_secondary_school		27	13.43%
	beyond_secondary		14	6.965%
		STIULCER		
0-2	YES		1	0.306%
	NO		326	99.69%
3	YES		5	1.046%
	NO		473	98.95%
4	YES		22	4.922%

19

	NO	425	95.08%
5	YES	17	5.090%
	NO	317	94.91%
6-9	YES	39	19.40%
	NO	162	80.60%
	HSV2ELI		
0-2	YES	43	13.15%
	NO	284	86.85%
3	YES	186	38.91%
	NO	292	61.09%
4	YES	269	60.18%
	NO	178	39.82%
5	YES	267	79.94%
	NO	67	20.06%
6-9	YES	190	94.53%
	NO	11	5.473%
	SYPHCONF		
0-2	YES	15	4.587%
	NO	312	95.41%
3	YES	43	8.996%
	NO	435	91.00%
4	YES	113	25.28%
	NO	334	74.72%
5	YES	151	45.21%
	NO	183	54.79%
6-9	YES	138	68.66%
	NO	63	31.34%
	ANSEXMENQ		
0-2	<=13	140	42.81%
	13-27	138	42.20%
	27-61	33	10.09%
	61<	16	4.893%
3	<=13	133	27.82%
	13-27	158	33.05%
	27-61	103	21.55%
	61<	84	17.57%
4	<=13	49	10.96%
	13-27	87	19.46%
	27-61	165	36.91%
	61<	146	32.66%
5	<=13	14	4.192%
	13-27	36	10.78%
	27-61	118	35.33%
	61<	166	49.70%
6-9	<=13	5	2.488%
	13-27	2	0.995%

19

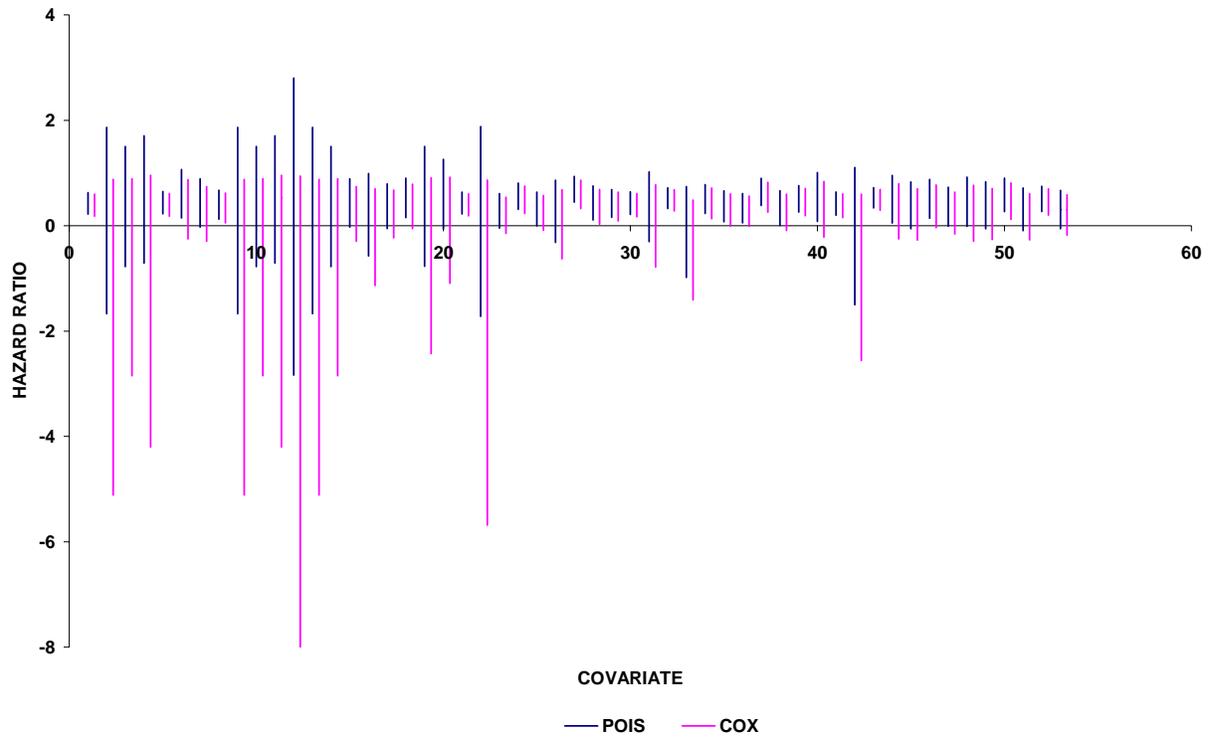
	27-61	77	38.31%
	61<	117	58.21%
	EXCHANGE		
0-2	NO	306	93.58%
	YES	21	6.422%
3	NO	402	84.10%
	YES	76	15.90%
4	NO	262	58.61%
	YES	185	41.39%
5	NO	104	31.14%
	YES	230	68.86%
6-9	NO	17	8.458%
	YES	184	91.54%
	SEXWTMENQ		
0-2	<=14	113	34.56%
	14-30	142	43.43%
	30-66	49	14.98%
	66<	23	7.034%
3	<=14	124	25.94%
	14-30	160	33.47%
	30-66	110	23.01%
	66<	84	17.57%
4	<=14	53	11.86%
	14-30	98	21.92%
	30-66	145	32.44%
	66<	151	33.78%
5	<=14	15	4.491%
	14-30	43	12.87%
	30-66	117	35.03%
	66<	159	47.60%
6-9	<=14	4	1.990%
	14-30	13	6.468%
	30-66	69	34.33%
	66<	115	57.21%

4.4 Comparison of Poisson and Cox Models on Interactions Between Covariates and Efficacy

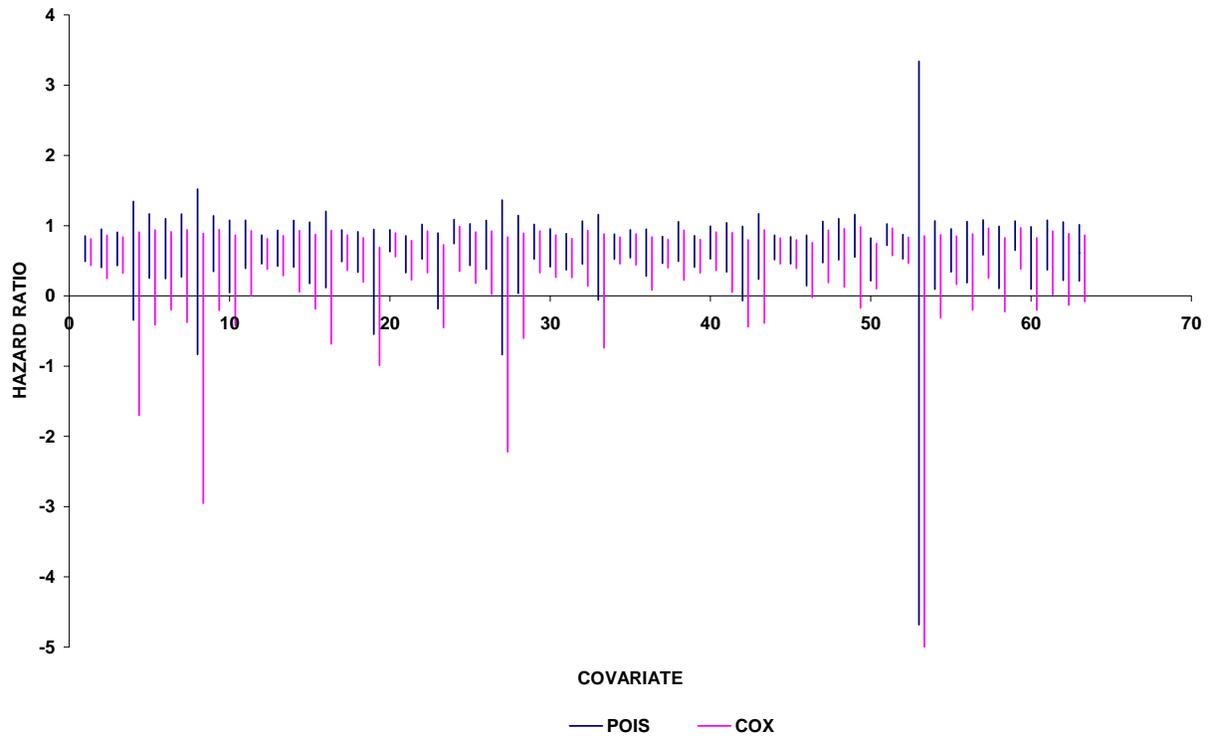
Since the Cox regression model was the primary protocol analysis, the interactions were also explored in two other ways: Cox regression separately in each stratum of the covariates and, for some of the covariates which were ordinal, not class variables, by Cox regression on all data with three predictors: treatment as a class variable, covariate, and interaction.

Tables 4.4 A-C gives the comparisons of the point estimates and 95% confidence intervals for the hazard ratio in each stratum of each covariate in trials 288 and 380, using the Poisson model of events per person year at risk and the Cox regression by stratum. The two point estimates are labeled POISSON and COX, the Poisson bounds are labeled PLOWER and PUPPER, the Cox bounds are labeled CLOWER and CUPPER. A quick visual summary of the contents of these tables are given in the following three graphs. Each of the graphs shows the confidence for hazard ratio for Poisson model and for Cox model for each level of each covariate in the tables. The three graphs cover trial 288, hazard ratios for truvada vs placebo; trial 380, hazard ratios for tenofovir vs placebo; and trial 380, hazard ratios for truvada vs placebo.

TRIAL 288 TRV VS PLACEBO



TRIAL 380, TDF VS PLACEBO



TRIAL 380 TRV VS PLACEBO

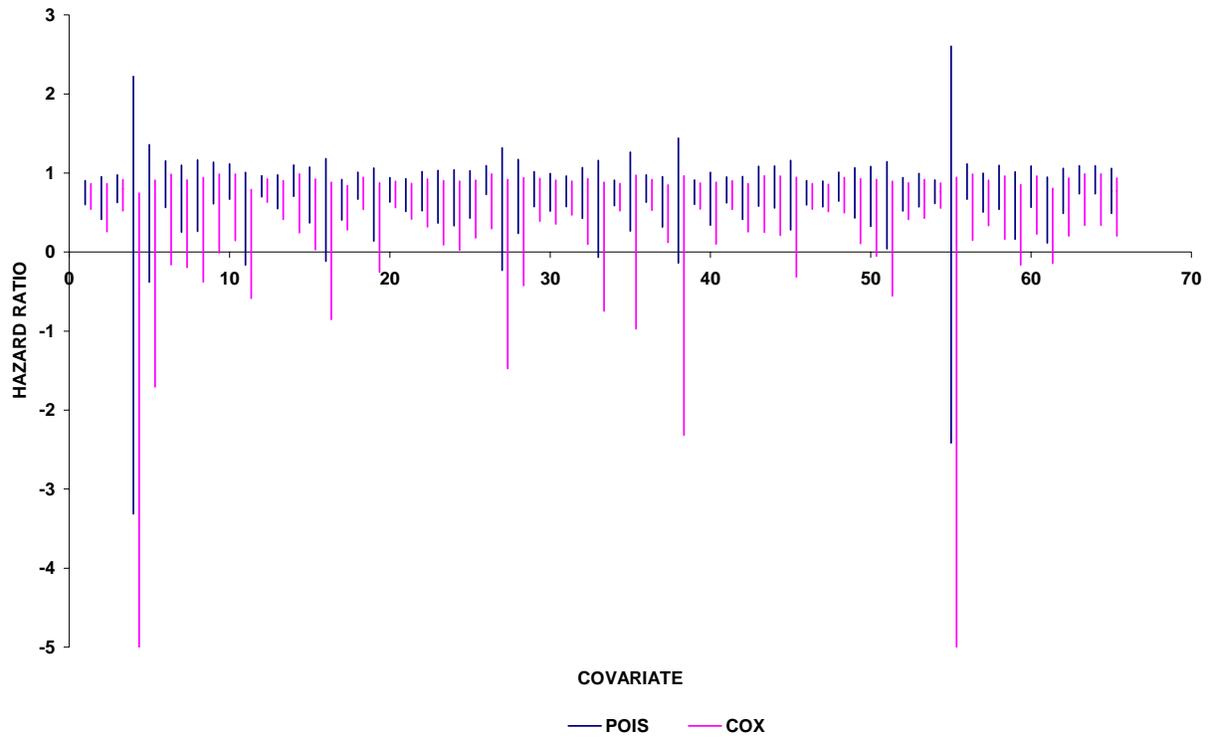


TABLE 4.4 A
 COMPARISON OF RATIOS PER PERSON YEAR WITH COX REGRESSION

COVARIATE	POISSON	COX	FLOWER	PUPPER	CLOWER	CUPPER
All	0.425	0.426	0.221	0.629	0.182	0.598
AGECAT						
<40	0.431	0.432	0.225	0.637	0.184	0.604
>=40	0.081	0.060	-1.721	1.882	-5.683	0.868
AGECAT2						
<25	0.283	0.275	-0.046	0.611	-0.146	0.542
>=25	0.560	0.563	0.310	0.809	0.230	0.752
REGION						
Africa	0.098	0.140	-1.671	1.866	-5.115	0.879
Asia	0.363	0.359	-0.778	1.503	-2.850	0.893
N_America	0.497	0.529	-0.709	1.704	-4.201	0.957
S_America	0.436	0.437	0.225	0.647	0.182	0.613
COUNTRYN						
Brazil	0.605	0.608	0.147	1.063	-0.250	0.877
Ecuador	0.430	0.423	-0.030	0.891	-0.296	0.743
Peru	0.397	0.400	0.124	0.671	0.054	0.619
S_Africa	0.098	0.140	-1.671	1.866	-5.115	0.879
Thailand	0.363	0.359	-0.778	1.503	-2.850	0.893
USA	0.497	0.529	-0.709	1.704	-4.201	0.957

TABLE 4.4 A (continued)
 COMPARISON OF RATIOS PER PERSON YEAR WITH COX REGRESSION

COVARIATE	POISSON	COX	FLOWER	PUPPER	CLOWER	CUPPER
TRIAL 288						
SITEN						
S_Francisco	-0.017	0.042	-2.838	2.803	-14.36	0.940
Cape_Town	0.098	0.140	-1.671	1.866	-5.115	0.879
Chiang_Mai	0.363	0.359	-0.778	1.503	-2.850	0.893
Guayaquil	0.430	0.423	-0.030	0.891	-0.296	0.743
Iquitos	0.208	0.205	-0.575	0.990	-1.136	0.704
Lima_INMENSA	0.370	0.371	-0.053	0.792	-0.230	0.678
Lima_Impacta	0.529	0.528	0.152	0.906	-0.052	0.788
Rio_Praça_Onze						
	0.364	0.437	-0.773	1.502	-2.429	0.907
Rio_FIOCRUZ	0.598	0.594	-0.061	1.257	-1.093	0.921
EDUC2						
not_completed_secondary						
	0.317	0.319	-0.002	0.635	-0.086	0.573
completed_secondary_school						
	0.272	0.278	-0.319	0.863	-0.626	0.680
beyond_secondary						
	0.690	0.695	0.445	0.936	0.325	0.862
SCOMPLY						
<90%	0.431	0.450	0.108	0.754	0.027	0.689
>=90%	0.424	0.424	0.161	0.687	0.092	0.635
LIVE2						
with_family_or_friends						
	0.430	0.430	0.215	0.646	0.168	0.610
other	0.360	0.365	-0.301	1.021	-0.784	0.774
MARITAL						
single	0.520	0.521	0.324	0.717	0.279	0.682
with_partner,_not_married						
	-0.120	-0.113	-0.984	0.744	-1.407	0.485

TABLE 4.4 A (continued)
 COMPARISON OF RATIOS PER PERSON YEAR WITH COX REGRESSION
 TRIAL 288

COVARIATE	POISSON	COX	PLOWER	PUPPER	CLOWER	CUPPER
SYPHCONF						
YES	0.506	0.501	0.233	0.779	0.132	0.713
NO	0.367	0.368	0.073	0.661	-0.006	0.603
HSV2ELI						
YES	0.332	0.335	0.055	0.609	-0.007	0.561
NO	0.641	0.638	0.382	0.899	0.258	0.824
STIDIAG						
YES	0.335	0.338	0.003	0.667	-0.091	0.598
NO	0.510	0.513	0.260	0.760	0.190	0.708
STIULCER						
YES	0.544	0.558	0.083	1.006	-0.218	0.839
NO	0.419	0.420	0.199	0.640	0.152	0.603
RISKBEH7						
No_URAI	-0.198	-0.196	-1.504	1.108	-2.561	0.599
URAI	0.530	0.531	0.338	0.722	0.295	0.688
ANSEXMENQ						
<=13	0.502	0.495	0.050	0.954	-0.250	0.796
13-27	0.386	0.382	-0.057	0.830	-0.273	0.700
27-61	0.509	0.512	0.139	0.879	-0.037	0.770
61<	0.362	0.351	-0.008	0.731	-0.158	0.636
SEXWTMENQ						
<=14	0.454	0.449	-0.014	0.923	-0.299	0.767
14-30	0.389	0.390	-0.058	0.835	-0.265	0.706
30-66	0.587	0.592	0.268	0.905	0.119	0.811
66<	0.309	0.294	-0.097	0.715	-0.270	0.608
EXCHANGE						
NO	0.509	0.511	0.269	0.749	0.203	0.700
YES	0.305	0.303	-0.058	0.668	-0.175	0.587

TABLE 4.4 B

COMPARISON OF RATIOS PER PERSON YEAR WITH COX REGRESSION

TRIAL_380_TDF COVARIATE	POISSON	COX	FLOWER	PUPPER	CLOWER	CUPPER
All	0.673	0.674	0.493	0.852	0.436	0.811
COUNTRYN						
Kenya	0.678	0.680	0.404	0.952	0.251	0.863
Uganda	0.669	0.670	0.432	0.906	0.324	0.838
SITEN						
Kabwohe	0.502	0.505	-0.343	1.347	-1.700	0.909
Kampala	0.710	0.707	0.254	1.166	-0.411	0.939
Kisumu	0.674	0.676	0.248	1.100	-0.196	0.912
Mbale	0.715	0.714	0.268	1.163	-0.375	0.941
Nairobi	0.343	0.340	-0.834	1.519	-2.953	0.890
Thika	0.745	0.744	0.349	1.140	-0.206	0.946
Tororo	0.564	0.562	0.050	1.078	-0.421	0.865
AGE25						
<25	0.735	0.726	0.392	1.077	0.004	0.925
>=25	0.662	0.663	0.457	0.866	0.382	0.816
AGE_QRT						
<=28	0.681	0.682	0.425	0.936	0.292	0.857
28-33	0.743	0.741	0.412	1.074	0.060	0.929
33-40	0.614	0.617	0.178	1.051	-0.187	0.877
40<	0.661	0.660	0.118	1.204	-0.685	0.931
GENDER						
Female	0.714	0.711	0.488	0.939	0.366	0.868
Male	0.625	0.627	0.337	0.912	0.197	0.827

TABLE 4.4 B (continued)

COMPARISON OF RATIOS PER PERSON YEAR WITH COX REGRESSION

TRIAL_380_TDF COVARIATE	POISSON	COX	PLOWER	PUPPER	CLOWER	CUPPER
CD4C350						
<350	0.199	0.215	-0.545	0.944	-0.989	0.690
>=350	0.785	0.785	0.631	0.940	0.558	0.895
HIGHPVL						
<50_K	0.594	0.595	0.331	0.856	0.229	0.788
>=50_K	0.772	0.773	0.526	1.019	0.330	0.923
CD4HIVQ						
<=375	0.356	0.373	-0.184	0.895	-0.450	0.728
375-496	0.916	0.916	0.746	1.087	0.354	0.989
496-663	0.733	0.729	0.438	1.028	0.182	0.910
663<	0.728	0.728	0.381	1.075	0.024	0.924
VIRAL_LOAD						
<=1504	0.264	0.279	-0.837	1.366	-2.220	0.839
1504-7596	0.590	0.586	0.036	1.144	-0.600	0.893
7596-31795	0.772	0.772	0.527	1.018	0.330	0.922
31795<	0.684	0.686	0.414	0.953	0.265	0.866
YRSHIVQ						
0.083-0.42	0.629	0.632	0.372	0.887	0.263	0.816
0.42-2	0.759	0.758	0.455	1.064	0.142	0.932
2<	0.552	0.550	-0.055	1.158	-0.739	0.884
CURABLE						
NO	0.702	0.703	0.523	0.880	0.459	0.837
HSV2						
YES	0.743	0.743	0.544	0.942	0.443	0.882
NO	0.618	0.618	0.285	0.952	0.085	0.840
SYPHILIS						
NO	0.655	0.656	0.464	0.845	0.402	0.802

TABLE 4.4 B (continued)

COMPARISON OF RATIOS PER PERSON YEAR WITH COX REGRESSION

TRIAL_380_TDF

COVARIATE	POISSON	COX	FLOWER	PUPPER	CLOWER	CUPPER
ANYINCOM						
NO	0.775	0.777	0.494	1.056	0.225	0.936
YES	0.636	0.636	0.412	0.859	0.328	0.803
YRSEDUCQ						
<=4	0.761	0.759	0.529	0.994	0.361	0.909
4-7	0.691	0.695	0.342	1.041	0.054	0.902
7-10	0.460	0.460	-0.069	0.989	-0.439	0.797
10<	0.704	0.712	0.239	1.169	-0.386	0.940
COHABIT						
YES	0.690	0.691	0.517	0.864	0.459	0.824
MARRIED						
YES	0.650	0.651	0.457	0.843	0.395	0.799
YRSWPTNRQ						
<=3	0.505	0.504	0.147	0.863	-0.023	0.759
3-7	0.768	0.772	0.474	1.062	0.192	0.936
7-14	0.806	0.806	0.514	1.098	0.126	0.957
14<	0.856	0.856	0.554	1.158	-0.170	0.982

TABLE 4.4 B (continued)

COMPARISON OF RATIOS PER PERSON YEAR WITH COX REGRESSION

TRIAL_380_TDF COVARIATE	POISSON	COX	PLOWER	PUPPER	CLOWER	CUPPER
ANYUNPSX						
NO	0.521	0.523	0.217	0.825	0.101	0.747
YES	0.874	0.873	0.721	1.026	0.576	0.962
OTHERSEX						
NO	0.700	0.701	0.528	0.873	0.468	0.832
YES	-0.671	-0.619	-4.682	3.340	-16.853	0.853
SEXACTSQ						
<=2	0.581	0.588	0.095	1.067	-0.314	0.871
2-4	0.648	0.650	0.343	0.953	0.168	0.853
4-8	0.624	0.624	0.188	1.060	-0.199	0.882
8<	0.833	0.832	0.584	1.082	0.254	0.962
CONTRA						
NO	0.550	0.541	0.108	0.991	-0.223	0.828
YES	0.859	0.859	0.651	1.066	0.385	0.967
CIRC						
Fully/Partially						
	0.541	0.544	0.098	0.985	-0.200	0.827
Not_circumcised						
	0.724	0.726	0.372	1.076	0.020	0.924
MALECIRC						
Partially/None						
	0.638	0.640	0.223	1.052	-0.130	0.885
Fully	0.613	0.615	0.214	1.012	-0.081	0.863

TABLE 4.4 C

COMPARISON OF RATIOS PER PERSON YEAR WITH COX REGRESSION

TRIAL_380_TRV COVARIATE	POISSON	COX	FLOWER	PUPPER	CLOWER	CUPPER
All	0.751	0.751	0.600	0.902	0.543	0.864
COUNTRYN						
Kenya	0.682	0.683	0.412	0.952	0.258	0.865
Uganda	0.801	0.801	0.627	0.975	0.523	0.917
SITEN						
Eldoret	-0.546	-0.522	-3.313	2.220	-8.112	0.746
Kabwohe	0.488	0.504	-0.380	1.357	-1.706	0.909
Kampala	0.859	0.857	0.564	1.154	-0.160	0.982
Kisumu	0.676	0.676	0.254	1.099	-0.195	0.912
Mbale	0.713	0.714	0.262	1.164	-0.377	0.941
Thika	0.873	0.873	0.610	1.137	-0.012	0.984
Tororo	0.892	0.892	0.669	1.115	0.146	0.986
AGE25						
<25	0.421	0.424	-0.165	1.007	-0.586	0.791
>=25	0.833	0.833	0.700	0.967	0.629	0.925
AGE_QRT						
<=28	0.761	0.760	0.548	0.975	0.413	0.902
28-33	0.903	0.904	0.704	1.102	0.247	0.988
33-40	0.722	0.727	0.370	1.074	0.031	0.923
40<	0.533	0.537	-0.114	1.180	-0.852	0.884
GENDER						
Female	0.660	0.660	0.405	0.915	0.280	0.840
Male	0.840	0.840	0.670	1.009	0.538	0.944

TABLE 4.4 C (continued)

COMPARISON OF RATIOS PER PERSON YEAR WITH COX REGRESSION

TRIAL_380_TRV COVARIATE	POISSON	COX	PLOWER	PUPPER	CLOWER	CUPPER
CD4C350						
<350	0.602	0.606	0.141	1.063	-0.255	0.877
>=350	0.786	0.786	0.633	0.940	0.561	0.896
HIGH_PVL						
<50_K	0.721	0.722	0.515	0.927	0.417	0.867
>=50_K	0.772	0.770	0.524	1.019	0.320	0.922
CD4HIVQ						
<=375	0.699	0.701	0.365	1.033	0.092	0.902
375-496	0.687	0.685	0.332	1.041	0.024	0.899
496-663	0.729	0.728	0.429	1.028	0.179	0.910
663<	0.911	0.909	0.729	1.093	0.298	0.988
VIRAL_LOAD						
<=1504	0.544	0.547	-0.230	1.318	-1.475	0.917
1504-7596	0.703	0.704	0.236	1.170	-0.424	0.939
7596-31795	0.795	0.793	0.574	1.016	0.391	0.929
31795<	0.755	0.756	0.516	0.993	0.356	0.908
YRSHIVQ						
0.083-0.42	0.768	0.768	0.576	0.959	0.471	0.898
0.42-2	0.747	0.746	0.428	1.067	0.100	0.928
2<	0.547	0.549	-0.065	1.160	-0.745	0.883
CURABLE						
NO	0.748	0.748	0.588	0.908	0.524	0.866
YES	0.765	0.763	0.266	1.263	-0.970	0.972
HSV2						
YES	0.803	0.803	0.631	0.975	0.529	0.918
NO	0.635	0.633	0.316	0.954	0.122	0.847
SYPHILIS						
YES	0.652	0.655	-0.136	1.440	-2.317	0.964
NO	0.758	0.759	0.606	0.911	0.546	0.872

TABLE 4.4 C (continued)

COMPARISON OF RATIOS PER PERSON YEAR WITH COX REGRESSION

TRIAL_380_TRV COVARIATE	POISSON	COX	PLOWER	PUPPER	CLOWER	CUPPER
ANYINCOM						
NO	0.674	0.677	0.341	1.007	0.103	0.884
YES	0.785	0.786	0.621	0.949	0.540	0.900
YRSEDUCQ						
<=4	0.683	0.684	0.412	0.954	0.256	0.866
4-7	0.832	0.832	0.580	1.084	0.251	0.962
7-10	0.823	0.824	0.559	1.088	0.213	0.961
10<	0.721	0.726	0.282	1.160	-0.317	0.943
COHABIT						
YES	0.750	0.751	0.599	0.902	0.542	0.864
MARRIED						
YES	0.735	0.735	0.573	0.897	0.512	0.856
YRSWPTNRQ						
<=3	0.828	0.827	0.644	1.011	0.499	0.941
3-7	0.750	0.748	0.433	1.066	0.108	0.929
7-14	0.703	0.706	0.324	1.082	-0.052	0.918
14<	0.592	0.598	0.041	1.144	-0.556	0.896
ANYUNPSX						
NO	0.731	0.731	0.521	0.941	0.414	0.877
YES	0.783	0.783	0.572	0.994	0.428	0.918
OTHERSEX						
NO	0.764	0.764	0.615	0.912	0.557	0.874
YES	0.095	0.129	-2.415	2.604	-12.945	0.946

TABLE 4.4 C (continued)

COMPARISON OF RATIOS PER PERSON YEAR WITH COX REGRESSION

TRIAL_380_TRV COVARIATE	POISSON	COX	PLOWER	PUPPER	CLOWER	CUPPER
SEXACTSQ						
<=2	0.891	0.891	0.668	1.115	0.149	0.986
2-4	0.752	0.752	0.508	0.996	0.337	0.908
4-8	0.818	0.817	0.541	1.094	0.163	0.960
8<	0.588	0.586	0.163	1.013	-0.162	0.852
CONTRA						
NO	0.826	0.827	0.567	1.086	0.227	0.961
YES	0.531	0.530	0.115	0.948	-0.142	0.807
CIRC						
Fully/Partially						
	0.773	0.773	0.489	1.058	0.203	0.935
Not_circumcised						
	0.914	0.915	0.739	1.090	0.339	0.989
MALECIRC						
Partially/None						
	0.914	0.915	0.739	1.090	0.338	0.989
Fully	0.774	0.773	0.490	1.058	0.204	0.935

The FDA reviewer compared three different methods of testing for the statistical significance of interactions. These results are summarized in tables 4.4 D-F. All the covariates here are either binary or ordered from lowest to highest. PVALUE1 is obtained by computing the hazard ratio from events per person year at risk at the highest and lowest levels of the covariate in question and then computing the Poisson model p-value for the difference in hazard ratios. PVALUE2 is obtained by fitting a Cox regressions to the highest and lowest levels of the covariate and then computing the Cox model p-value for the ratio of these two hazard ratios. PVALUE3 is obtained as the p-value of the interaction term in a Cox regression on all subjects with non-missing value of the covariate, using three predictors: treatment, covariate, and treatment-covariate interaction.

In these tables, the most noticeable findings are the following: In trial 288, there is a significant interaction with education by methods 1 and 2 (comparing highest to lowest levels). There is a marginally significant association with high risk vs low risk sex (URAI or not) by the two Cox methods (both p-values = .11). In trial 380 comparison of placebo to TDF, the binary variant of partner's CD4 (< or >350) was statistically significant by either Cox method and marginal by the Poisson method. But this effect was not seen in the placebo-truvada comparison and when CD4 count was classified by quartiles, no significant interaction was seen in either arm. There is also a statistically significant (or nearly so, p-values .042 to .057) for unprotected sex (but again this was only in the placebo-TDF comparison). Finally, both Cox methods found a nearly significant age interaction in the placebo-truvada comparison. Again this only occurs in one of the two comparisons in trial 380 and it is not found when one represents age by quartile. None of the findings seem to be particularly convincing.

TABLE 4.4 D
P-VALUES FOR INTERACTIONS, TRIAL 288

EFFECT	PVALUE1	PVALUE2	PVALUE3
AGE<, >40	0.70536	0.62077	0.6384
AGE<, >25	0.18825	0.17388	0.1802
EDUCATION	0.068384	0.087484	0.9045 **
COMPLIANCE	0.97433	0.90289	0.9442

LIVING_STATUS	0.84333	0.84727	0.8415
SYPHILIS	0.49734	0.52177	0.5093
HSV2	0.11039	0.15060	0.1527
STI_DIAGNOSIS	0.40825	0.39742	0.4009
STI_ULCER	0.63264	0.62403	0.6171
URAI_OR_NOT	0.28009	0.11536	0.1096 **
#_ANAL_SEX_ACTS	0.63805	0.64645	0.6312
SEX_FOR_MONEY	0.35878	0.33125	0.3371

TABLE 4.4 E
P-VALUES FOR INTERACTIONS, TRIAL 380, TDF ARM

EFFECT	PVALUE1	PVALUE2	PVALUE3
COUNTRY	0.96012	0.95500	0.9522
AGE<, >25	0.71954	0.77487	0.749
AGE_QRT	0.94762	0.94124	0.9522
GENDER	0.63384	0.64736	0.6455
PARTNER_CD4	0.13082	0.030937	0.0308 **
CD4_QRT	0.25499	0.28397	0.2801
PARTNER_VIRAL	0.33039	0.99783	0.984
PART_VL_QRT	0.25499	0.28397	0.2801
YRSHIVQ	0.81766	0.99528	0.984
CURABLE_STI	1	0.99439	0.984
HSV2	0.52800	0.50462	0.5093
SYPHILIS	1	0.99591	0.984
ANY_INCOME	0.44656	0.48850	0.4902
YRS_EDUC	0.82888	0.84959	0.2585 **
COHABIT	1	0.99830	0.984
MARRIED	1	0.99736	0.984
YRS_W_PTNR_QRT	0.14237	0.27403	0.2713
ANY_UNP_SX	0.042186	0.057189	0.0574 **
OTHER_SEX	0.50315	0.18009	0.177
#SEX_ACTS_QRT	0.36523	0.35279	0.3524
CONTRACEPT	0.21420	0.19165	0.1936
CIRC_1	0.52676	0.53147	0.5222
CIRC_2	0.93349	0.93010	0.9203

TABLE 4.4 F
P-VALUES FOR INTERACTIONS, TRIAL 380, TRV ARM

EFFECT	PVALUE1	PVALUE2	PVALUE3
COUNTRY	0.46862	0.45342	0.4533
AGE<, >25	0.17878	0.059297	0.0588 **
AGE_QRT	0.51134	0.43483	0.4295
GENDER	0.25184	0.25609	0.2585
PART_CD4	0.45786	0.37986	0.3789
CD4_QRT	0.27600	0.31527	0.3077
PART_VL	0.75899	0.99787	0.984
VL_QRT	0.61032	0.53477	0.4413
YRSHIV_QRT	0.50111	0.99518	0.984
CURABLE_STI	0.95003	0.95567	0.9442
HSV2	0.36315	0.32426	0.3271
SYPHILIS	0.79499	0.76619	0.7642
ANY_INCOME	0.55753	0.52862	0.5222
YRS_EDUC_QRT	0.88563	0.87414	0.5029
COHABIT	1	1	1
MARRIED	1	0.99739	0.984
YRS_W_PTNR_QRT	0.42779	0.33499	0.5222
ANY_UNP_SX	0.73226	0.73416	0.7414
OTHER_SEX	0.60201	0.36833	0.3576
#SEX_ACTS_QRT	0.21545	0.25493	0.2543
CONTRACEPT	0.23831	0.26041	0.2585
CIRC_1	0.40850	0.42440	0.4237
CIRC_2	0.40974	0.42580	0.4237

In these tables

PARTNER_CD4 = CD4 < or > 350

PARTNER_VIRAL = viral load < or > 50_K

Any variable ending in _QRT is quartiles of the measured quantity

CIRC_1 is circumcised FULLY_PARTIALLY vs NONE

CIRC_2 is circumcised FULLY vs PARTIALLY/NONE

5. Statistical Reviewer's Conclusions

The applicant has present analyses from two trials of oral truvada prophylaxis conducted by UCSF and the University of Washington. The analyses have demonstrated that truvada prophylaxis results in a risk reduction of 40-60% in males at risk of HIV infection. This efficacy is confirmed across sub-groups based on baseline and post-treatment covariates.

Analysis of subgroups show that although truvada is consistently superior to placebo, it is not perfect. Truvada in groups with elevated risk performs worse than truvada in groups with lower risk but still superior to placebo in groups with elevated risk.

It is more problematic whether tenofovir alone is effective and whether oral truvada is effective in women. Both of these two questions were studied only in a single trial. That trial did show statistically significant reduction in risk with respect to both at risk males using tenofovir alone and at risk females using either tenofovir alone or truvada but there is no confirmatory trial. It is also of some concern that the applicant reports the existence a second trial in women, namely, FemPrep, but does not report even a summary of the results of this trial, much less sufficient data for the FDA to analyze the results.

On the other hand, with respect to FemPrep, the failure of the conductors of this trial to make their sites available to FDA inspection and their data to FDA review may serve to cast doubt on the reliability of any findings which may contradict efficacy. Nonetheless, the absence of a confirmatory trial, possibly combined with an unreviewed, uninspected negative trial renders it problematic to approve these two specific indications.

Neither trial was powered to answer questions about efficacy within subgroups. It would be useful to be able to determine whether truvada or tenofovir was or was not sufficiently beneficial in the lower risk sub-groups to justify the burden of those drugs' toxicity. There are suggestions that those with infected partner's with high CD4 count and those not practicing

unprotected receptive anal intercourse receive minimal benefit. The FDA statistical reviewer wonders why these plausible results were not confirmed by related analyses: i.e. why are interactions not apparent with partner's viral load or with number of anal sex acts?

Mathematical Appendix

In the FDA analysis, the infection rates, the hazard ratios and their confidence intervals are computed under the model that number of infections on active drug, X , in time T are $\text{Poisson}(\lambda T)$ and that the number of infection on placebo, Y , in time S are $\text{Poisson}(\mu S)$. Then the estimates of the infection rates λ and μ are X/T with variance X/T^2 and Y/S with variance Y/S^2 . The hazard ratio is estimated by $X*S/(Y*T)$ with variance $(1+X/Y)*(X*S^2)/(Y^2*T^2)$. The variance is the approximation obtained by the delta method.

In the applicant's analysis, the time to infection, T , is assumed to be given by the formula $P(T>t) = \exp(-H(t))$ for placebo and to be given by $P(T>t) = \exp(-R * H(t))$ for the truvada arm. Here $H(t)$ is some possibly time-varying hazard function and R is the hazard ratio. The Cox regression provides an estimate of R and one can obtain an estimate of $H(t)$ as $-\log$ of the Kaplan-Meier survival function. Here t is measured as time from start of drug, not calendar time.

If $H(t)$ is linear in t , $H(t) = \mu*t$, then the Cox model implies the Poisson model for the number of events per person year. If the hazard rate = derivative of $H(t) = h(t)$ is not constant and $N(t)$ = number of subjects at risk at time t , then $X(t)$ = number events in time interval $(t, t+dt)$ is approximately $\text{Poisson}(h(t)N(t))$. If X = number of events in time interval $(0, T)$, $X = \int X(t)dt$ is also Poisson as the sum of independent Poissons. $E[X] = \int h(t)N(t)dt$. If h is constant, then $E[X] = \int h(t)N(t)dt = h \int N(t)dt = hN$ where N = total person years at risk. Non-constant $h(t)$ would mean X is Poisson with mean proportional not to person years at risk but to a weighted average of person years at risk, weighted so that years at higher hazard rate count more. Just using person years at risk should not introduce a different bias in the two arms since this a randomized double blind trial in which few subjects discontinued early in either arm.

Thomas Hammerstrom, Ph.D.
Mathematical Statistician

Concur: Dr. Soon

cc:

Archival NDA #21752 (SN 001)

HFD-530

HFD-530/Dr. Birnkrant

HFD-530/Dr. Murray

HFD-530/Dr. Marcus

HFD-530/Dr. Miele

HFD-530/Ms. Schumann

HFD-725/Dr. Hammerstrom

HFD-700/Dr. Nevius

HFD-725/Dr. Huque

HFD-725/Dr. Lin

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

/s/

THOMAS S HAMMERSTROM
05/21/2012

GUOXING SOON
05/22/2012

STATISTICS FILING CHECKLIST FOR A NEW NDA

NDA Number: 21,752S030 **Applicant:** Gilead Sciences, Inc. **Stamp Date:** 12/14/2011
Drug Name: Truvada® **NDA/BLA Type:** Priority Review
Reviewers: Susan Zhou, Ph.D.

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			See C1.
3	Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated (if applicable).	X			See C2.
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			See C3.

C1. This supplement provides safety and efficacy data from two Phase 3 studies CO-US-104-0288 and CO-US-104-0380. The cutoff date was May 11, 2010 for CO-US-104-0288 and 10 July 2011 for CO-US-104-0380.

- Study CO-US-104-0288 was a randomized, double-blind, placebo-controlled, Phase 3 study of the safety and efficacy of chemoprophylactic oral FTC/TDF in seronegative MSM at high risk for acquiring HIV-1 infection. There were 85 serconverters in CO-US-104-0288.
- Study CO-US-104-0380 was a Phase 3, multicenter, randomized, double-blind, placebo-controlled, 3 group study designed to evaluate the safety and efficacy of PrEP with either TDF or FTC/TDF when administered orally, once daily for the prevention of HIV-1 acquisition among HIV-1 uninfected individuals within a known HIV-1 serodiscordant partnership. There were 99 serconverters in CO-US-104-0380.
- Study CO-US-104-0277 (CDC 4323) was a randomized, placebo-controlled, double-blind, Phase 2 study of MSM in the US. This study was designed primarily to assess the safety, adherence, and acceptability of PrEP in subjects who used either TDF or placebo once-daily. This study was complete in July 2009. Safety data from study CO-US-104-0277 was also included in this submission. Gilead has not received a clinical study report or final datasets from the CDC 4323 study team. The CDC 4323 study showed six participants had HIV-1 seroconversion: three on placebo, and three were delayed arm participants who had not yet started drug. None of the participants in the TDF arm had seroconversion during the study. No analyses related to efficacy are presented in this study.

Protocol, synopsis and summary of clinical efficacy and safety for CO-US-104-0288, CO-US-104-0380 and CO-US-104-0277 can be found respectively, in

'~\m5\53-clin-stud-rep\535-rep-ffic-safety-stud\prep-hiv\5351-stud-rep-contr\co-us-104-0288' (1)

'~\m5\53-clin-stud-rep\535-rep-ffic-safety-stud\prep-hiv\5351-stud-rep-contr\co-us-104-0380' (2)

and

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STATISTICS FILING CHECKLIST FOR A NEW NDA

'~:\m5\53-clin-stud-rep\535-rep-effic-safety-stud\prep-hiv\5354-other-stud-rep\co-us-104-0277' (3)

In this document, we denote '~' as '\\CDSESUB1\EVSPROD\NDA21752\030'.

For example, subdirectory (1) contains sixteen documents in *.pdf formats for study CO-US-104-0288 and a subdirectory 'crf' (See Figure 1).

C2. Subgroup analyses of the primary endpoint

A pre-specified subgroup analysis was performed to investigate whether drug levels correlated with protective effect. Subjects with HIV-1 infection were matched with 2 case-control subjects, 1 from each study group, who were selected from seronegative subjects, and matched for study site and time on treatment. Plasma was tested for FTC and TFV, and peripheral-blood mononuclear cells (PBMCs) were tested for FTC triphosphate (FTC-TP) and TFV diphosphate (TFV-DP), which are the active intracellular metabolites of FTC or TFV.

Name	Size	Type	Date Modified
crf		File Folder	12/15/2011 9:05 AM
jec-irb-list.pdf	3,589 KB	Adobe Acrobat Doc...	11/15/2011 2:06 PM
investigator-list.pdf	13 KB	Adobe Acrobat Doc...	11/15/2011 2:06 PM
list-adverse-events.pdf	2,497 KB	Adobe Acrobat Doc...	11/15/2011 2:20 PM
list-comply-or-concentration.pdf	117,865 KB	Adobe Acrobat Doc...	11/15/2011 2:26 PM
list-demographic-data.pdf	4,659 KB	Adobe Acrobat Doc...	11/15/2011 2:20 PM
list-discontinued-pts.pdf	4,128 KB	Adobe Acrobat Doc...	11/15/2011 2:20 PM
list-efficacy-response.pdf	6,882 KB	Adobe Acrobat Doc...	11/15/2011 2:20 PM
list-labs-by-pts.pdf	45,992 KB	Adobe Acrobat Doc...	12/13/2011 10:25 PM
list-protocol-deviations.pdf	155 KB	Adobe Acrobat Doc...	12/13/2011 10:22 PM
protocol.pdf	1,685 KB	Adobe Acrobat Doc...	12/13/2011 10:19 PM
randomisation.pdf	172 KB	Adobe Acrobat Doc...	11/15/2011 2:06 PM
report-body.pdf	10,987 KB	Adobe Acrobat Doc...	12/13/2011 7:37 PM
sample-of.pdf	899 KB	Adobe Acrobat Doc...	11/15/2011 2:06 PM
signatures-investigators.pdf	95 KB	Adobe Acrobat Doc...	11/15/2011 2:06 PM
statistical-methods.pdf	345 KB	Adobe Acrobat Doc...	12/13/2011 10:31 PM
stf-co-us-104-0288.xml	103 KB	XML Document	12/13/2011 11:51 PM
synopsis.pdf	166 KB	Adobe Acrobat Doc...	12/6/2011 2:48 PM

Figure 1. Submitted Documents in *.pdf Formats for Study CO-US-104-0288

C3. SAS *.xpt files for efficacy and safety analyses can be found respectively, in the subdirectories
'~\m5\datasets\co-us-104-0288\tabulations\legacy\data-01may2010' (n=67) (4)

and
'~\m5\datasets\co-us-104-0288\tabulations\legacy\data-25jan2011' (n=6) (5)

for study CO-US-104-0288,

and

'~\m5\datasets\co-us-104-0380\tabulations\CO-US-104-0380' (n=67) (6)

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STATISTICS FILING CHECKLIST FOR A NEW NDA

for study CO-US-104-0380.

In addition,

'~\m5\datasets\co-us-104-0288-addendum\tabulations\legacy\data-09sep2011'(n=76) (7)

and

'~\m5\datasets\co-us-104-0288-addendum\tabulations\legacy\data-29jul2011' (n=66) (8)

contain xpt files respectively, for the cutoff dates 09 September, 2011 and 29 July, 2011.

'~\m5\ datasets\co-us-104-0277\ tabulations\legacy' contains 23 xpt files. (9)

All *.xpt files can be converted to SAS data files.

- Please note that 'define.pdf' can be found in the above subdirectories.

Two data issues were identified:

1. The sponsor failed to submit data and results from all other HIV-1 PrEP studies including the one stopped early due to unfavorable results. According to the draft document "Integrated Summary of Effectiveness (ISE) – To Industry", an overall integrated analysis should comprehensively examine the effectiveness data from all relevant individual HIV-1 PrEP clinical studies
2. The missing SAS programs and analysis datasets were requested to be submitted. After the filing meeting, this reviewer found that the sponsor did not submit indicators for 'site' and 'country' in the DEMO.XPT files (n=2) for Study CO-US-104-288. Other data problems were also found.

IS THE STATISTICAL SECTION OF THE APPLICATION FILEABLE? Yes

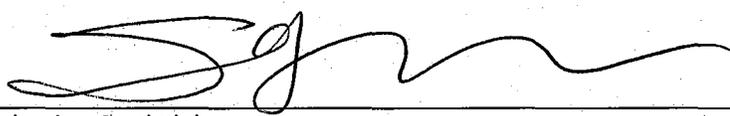
If the NDA/BLA is not fileable from the statistical perspective, state the reasons and provide comments to be sent to the Applicant.

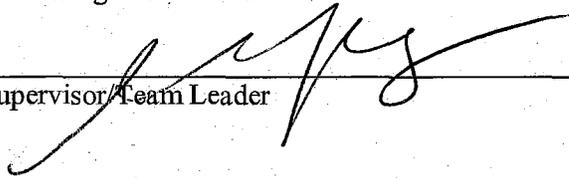
Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

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.				See C4.
Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate.	X			

C4. Please refer to the medical reviewer's comments.

STATISTICS FILING CHECKLIST FOR A NEW NDA

 Jan 4, 2012
Reviewing Statisticians Date

 1/4/2012
Supervisor/Team Leader Date

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

/s/

SUSAN Y ZHOU
01/11/2012
active reviewer for Tom Hammerstrom

GUOXING SOON
01/11/2012