

CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

NDA 21-453

Statistical Review(s)



Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

Medical Division: Division of Antiviral Drug Products (HFD-530)

Biometrics Division: Division of Biometrics III (HFD-725)

NEW DRUG APPLICATION (NDA):	21-453
SERIAL NUMBER:	000
NAME OF DRUG:	ZERIT [®] ER Extended Release Capsules (d4T, Stavudine)
DOSAGE FORM:	37.5, 50, 75, 100 mg tablets
INDICATION(S):	Treatment of HIV infection
APPLICANT:	Bristol-Myers Squibb Co.
SUBMISSION DATE:	January 24, 2003
PRESCRIPTION DRUG USER FEE ACT (PDUFA) DATE:	January 9, 2003
DOCUMENTS REVIEWED:	Volumes 18, 24 (paper copies) file:\\cdsesub1\21453\000\2001-12-10 file:\\cdsesub1\21453\000\2002-05-30A file:\\cdsesub1\21453\000\2002-09-23 file:\\cdsesub1\21453\000\2002-10-24
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STATISTICAL KEY WORDS:	Non-inferiority, TAD, imputation, Wilcoxon test

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1. EXECUTIVE SUMMARY OF STATISTICAL FINDINGS

The applicant conducted two randomized, controlled, double-blind, multinational clinical trials AI455-096, a pilot study, and AI455-099, a pivotal study. These studies enrolled treatment-naïve HIV-infected subjects. Both studies were carried out with a single-substitution design matching ER to IR stavudine, in combination with lamivudine (3TC) and efavirenz (EFV). In these studies, 3TC and EFV were administered 'open label'.

The pilot study, AI455-096, was conducted in North America, South America and Africa. The pivotal study, AI455-099, was carried out at sites in Europe, North America, South America, Africa and Asia. The duration of these trials was 48 weeks for Study AI455-096 and 56 weeks for Study AI455-099.

The study subjects were predominantly male (70%). The median age of these subjects was 33 years. Non-white racial groups comprised approximately 53% of the study population. Overall, the median baseline HIV RNA level was 4.79 log₁₀ c/mL for ER vs. 4.77 log₁₀ c/mL for IR. The proportion of subjects with HIV RNA ≥ 30,000 c/mL at baseline was 66% for ER and IR treatment groups. The median baseline CD4+ cell count was 294 cells/mm³ for the ER treatment group and 269 cells/mm³ for the IR group.

Based on available data through Week 48 and beyond, we reached the following conclusions:

1. Using TLOVR algorithm the Study AI455-099 demonstrated similarity of the proportion of subjects with HIV RNA below 400 c/mL in the d4T ER + 3TC + EFV treatment arm (79%), as compared to d4T IR + 3TC + EFV arm (76%). The difference of the two treatment arms (2.9%) had a lower 95% CI bound (-3.0%) above -12%, meeting the pre-specified non-inferiority level.
2. The temporal trend of plasma HIV RNA was similar for the ER and the IR regimens. Plasma HIV RNA had a sharp drop of about 2.0 log₁₀ prior to Week 4 and this decline continued at a slower pace until Week 24. At Week 8, the mean change from baseline in plasma HIV RNA reached -2.5~-2.6 log₁₀ in the ER and IR regimens with qualifying HIV RNA ≥ 30,000 c/mL, and -2.1 log₁₀ in the ER and IR regimens with qualifying HIV RNA < 30,000 c/mL, respectively. The estimated time-weighted average change from baseline in plasma HIV RNA through Week 48 adjusting for qualifying HIV RNA [TAD_{ER-IR}] was less than 0.01 log₁₀ c/mL with a 95% confidence interval of (-10.0,8.5) by the LOCF method.
3. Immunological response, measured by mean increase from baseline in CD4+ cell count through Week 48 was similar in the d4T ER and the d4T IR

regimen. Based on the LOCF method, the estimated time-weighted average change from baseline in CD4+ cell count (TAD in cells/mm³) through Week 48 were: 143 for the ER regimen and 140 for the IR regimen for qualifying HIV RNA \geq 30,000 c/mL; 105 for the ER regimen and 90 for the IR regimen for qualifying HIV RNA < 30,000 c/mL. The difference between the two regimens (ER-IR) was 6.1 with a 95% confidence interval of (-8.7,20.9).

4. The similarity of treatment effects between the d4T ER and the d4T IR regimen was also supported by the comparisons of the proportion of subjects with HIV RNA below 50 c/mL through Week 48.
5. HIV RNA measurements were associated with specimen shipment status. Alternative analyses on the primary endpoint stratified by specimen shipment procedures supported similar treatment effects between the d4T ER and the d4T IR regimen.
6. Subgroup analyses on the primary efficacy endpoint showed that the ER regimen was doing slightly worse than the IR regimen for those subjects in sites where specimens did not need transportation, and those subjects whose specimens were shipped frozen during study period.
7. Longitudinal assessment of change from baseline in plasma HIV RNA showed that the mean change from baseline in plasma HIV RNA was significantly associated with gender, race and baseline weight in some of the treatment regimen and qualifying HIV RNA strata, in early phase of the study.
8. Longitudinal assessment of change from baseline in CD4+ cell count showed that the treatment regimen was statistically significantly associated with gender, race, age, and baseline weight in the following situations.
 - Among those with qualifying HIV RNA \geq 30,000 c/mL,

Males in the ER regimen had an additional significant increase of 53 cells/mm³ than those in the IR regimen at Week 12, and an additional significant increase of 59 cells/mm³ at Week 48;

Younger subjects in the ER regimen had significant greater increases in CD4+ cell count at Week 8 and Week 16 than the younger subjects in the IR regimen;

Among subjects with higher weight at baseline, those in the ER regimen had significant greater increases in CD4+ cell count: 62 cells/mm³ at Week 12 and 57 at Week 48, than the subjects with higher weight at baseline in the IR regimen.
 - Among those with qualifying HIV RNA <30,000 c/mL,

Hispanic subjects in the ER regimen had significant increases CD4+ cell count ranging 27-104 during the study than those in the IR regimen during the study;

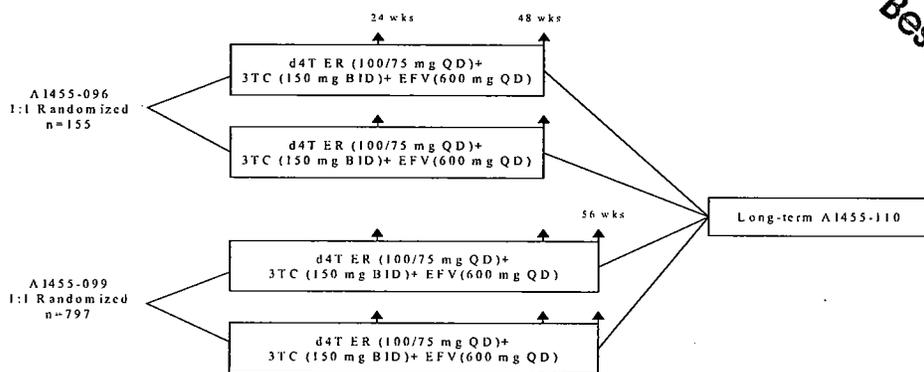
Older subjects in the ER regimen had significant greater increases in CD4+ cell count at Week 48 than the older subjects in the IR regimen.

9. Subgroup analyses showed that change from baseline in CD4+ cell count was statistically significantly associated with race, age, and baseline weight in the following situations.
 - During the study, for subjects in the ER regimen with qualifying HIV RNA <30,000 c/mL, Hispanic subjects had significant greater mean increase in CD4+ cell count, the maximum was 230 cells/mm³, greater than White (189) and Black subjects (114).
 - During the study, for subjects in the ER regimen with qualifying HIV RNA ≥30,000 c/mL, Hispanic subjects had significant greater mean increase in CD4+ cell count, the maximum was 267 cells/mm³, greater than White (212) and Black subjects (169).
 - Between Week 12 and Week 40, for subjects in the IR regimen with qualifying HIV RNA ≥30,000 c/mL, Hispanic subjects had significant greater mean increase in CD4+ cell count, the maximum was 247 cells/mm³, greater than White (182) and Black subjects (195).
 - During the study, among subjects in the ER regimen with qualifying HIV RNA ≥30,000 c/mL, younger subjects had significant greater mean increase in CD4+ cell count than the older subjects. However, the maximum mean difference of 55 cells/mm³ is less than the mean difference of 65 cells/mm³ at baseline.
10. Subgroup analyses showed subjects with frequent diarrhea may be associated with virologic suppression. For those in qualifying HIV RNA <30,000 c/mL, at Week 4 subjects with no diarrhea or less frequent diarrhea had greater reduction in HIV RNA than those with frequent diarrhea.

2. INTRODUCTION AND BACKGROUND

This is a standard review of the New Drug Application (NDA 21-453) which seeks approval for ZERIT® ER Extended Release Capsules 37.5 mg, 50 mg, 75 mg and 100 mg of stavudine (d4T) for the treatment of both treatment-naïve and treatment-experienced HIV-infected patients. Previously, two dosage forms of stavudine are currently marketed: ZERIT® (stavudine) Immediate Release Capsules (IR) and ZERIT® (stavudine) for Oral Solution. ZERIT® IR was approved under NDA # 20-412 and ZERIT® (stavudine) for Oral Solution was approved under NDA # 20-413.

The sponsor conducted two-randomized, controlled, double-blinded, multinational clinical trials AI455-096 (096), a pilot study, and AI455-099 (099), a pivotal study, in treatment-naïve HIV-infected subjects, both with a single-substitution design matching ER to IR stavudine, in combination with lamivudine (3TC) and efavirenz (EFV). The pilot study AI455-096 was conducted multinationally in North America, South America and Africa. The pivotal study AI455-099 was carried out globally from sites in Europe, North America, South America, Africa and Asia. The duration of study period is 48 weeks for Study AI455-096 and 56 weeks for the Study AI455-099. The study objective was to provide the safety and efficacy of the ER formulation of stavudine. Upon completion of studies, participants from both studies will be eligible to enter a long-term Study AI455-110. Figure 1 below summarizes the study design for these studies.



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Figure 1: Study AI455-096 and Study AI455-099

The statistical review will focus on clinical efficacy data from the pivotal efficacy study AI455-099.

2.1 Data Analyzed and Sources

2.1.1 Study AI455-096

Title: "Evaluation of the Safety and Antiretroviral Activity of Stavudine Extended Release Formulation as Compared to Stavudine Immediate Release Formulation, Each as Part of Potent Antiretroviral Combination Therapy". The study period for AI455-096 was between October 11, 1999 to February 28, 2001.

The Study AI455-096 was a multi-center, double-dummy, randomized 1:1 comparison of d4T ER (100 mg QD) and d4T IR (40 mg BID) in combination with 3TC and EFV in antiretroviral naïve HIV-infected subjects with plasma HIV viral load $\geq 5,000$ c/mL and CD4+ cell count ≥ 100 cells/mm³. Randomization was stratified by screening HIV viral load of $< 30,000$ c/mL or $\geq 30,000$ c/mL. Antiviral response was assessed at 12 and 48 weeks. Treatment continued until the last enrolled subject completes 48 weeks of therapy.

2.1.1.1 Sample Size and Study Population

The sample size of 60 per arm for Study AI455-096 was obtained to demonstrate that the antiviral activity of d4T ER/3TC/EFV would have been similar to d4T IR/3TC/EFV. The similarity level in the antiviral activity was based on an upper 95% confidence limit of $0.5 \log_{10}(\text{ER-IR})$ for the comparison of the Time-Average Difference (TAD) in \log_{10} HIV RNA change from baseline over 48 weeks of therapy between the two study arms with a power of 90%. The TAD within subject variance was $0.5 \log_{10}$ and between subject variance was $0.8 \log_{10}$.

AI455-096 was conducted in 27 sites: 25 sites in the United States and Canada, and 2 sites in South America. The median age was 34, and the median weight was 68.9. At entry, 28% subjects had CD4+ cell count below 200 cells/mm³. The baseline median HIV RNA was $4.65 \log_{10}$ and the median CD4+ cell count was 285.

2.1.1.2 Efficacy Analysis

The primary variable was the comparison between treatment groups of the change in plasma HIV-1 RNA from baseline over 48 weeks of therapy, expressed as the Time-Averaged Difference (TAD) in \log_{10} from baseline through 48 weeks of

therapy. Secondary variables were proportion of subjects with HIV RNA < 400 c/mL at 48 weeks, < 50 c/mL at 48 weeks, and changes in CD4 cell counts over 48 weeks.

HIV RNA data at baseline and at Week 2 from the standard assay, and from the ultrasensitive assay from the Week 4 visit onward was used for efficacy analysis.

2.1.2 Study AI455-099

AI455-099 was a Phase III, multi-center, double-blind, double-dummy, randomized 1:1 comparison of d4T ER (100 mg QD) and d4T IR (40 mg BID) in combination with 3TC and EFV in antiretroviral treatment naïve, HIV-infected individuals. EFV and 3TC were administered as open-label supplies and the d4T IR and d4T ER formulations were double-blinded. Randomization was stratified by screening HIV viral load of <30,000 c/mL or \geq 30,000 c/mL and site. Treatment was continued for a period of 56 weeks.

The 3TC and EFV were administered open label. The dosage of d4T was based on weight and adjusted for peripheral Neuropathy. Participants who developed Grade 2 or greater peripheral neuropathy were permitted to interrupt d4T treatment and resume treatment at one half the original dose once symptoms resolved to Grade 1 or baseline. Participants who were unable to tolerate efavirenz (EFV) were allowed to substitute with nelfinavir (NFV). The HIV infected pregnant women were treated with marketed antiretrovirals for the duration of pregnancy only. The study subjects with newly active tuberculosis infection were treated with rifampin and EFV. The dose of EFV may be increased.

2.1.2.1 Sample Size and Study Population

The sample size of 365 per arm was based on a power of 90%, type I error of 0.05, to demonstrate similarity of antiviral activity within 12% (a non-inferiority delta) between d4T ER/3TC/EFV and d4T IR/3TC/EFV for the primary endpoint of proportion of participants with HIV RNA < 400 c/mL at week 24, assuming that 77% of d4T regimen patients on study would still have HIV RNA < 400 c/mL at week 24, and a 10% dropout prior to Week 24 visit. The sample size was also powered to account for a 17% dropout prior to Week 24 or Week 48 and a response rate of 65%.

The study was conducted by 71 investigators in the USA, Canada, Mexico, Brazil, Argentine, Puerto Rico, South Africa, Thailand, Singapore, Belgium, France,

Italy, Portugal, Russia, Spain and Israel. The study enrolled 1030 antiretroviral naïve HIV-1 infected subjects at least 12 years of age with plasma HIV RNA levels ≥ 2000 c/mL and CD4+ cell count ≥ 100 cells/mm³. Among them, 797 subjects were randomized: 399 for the ER regimen and 398 for the IR regimen, of which 783 subjects received treatment: 392 for the ER regimen and 391 for the IR regimen.

2.1.2.2 Efficacy Analysis

The primary variable was the comparison of the proportion of subjects who have levels of plasma HIV RNA < 400 copies/mL at Week 24 between the ER and IR regimens with a confirmatory analysis at Week 48. Secondary variables were proportion of subjects who have levels of plasma HIV-RNA < 50 c/mL at Week 24 & Week 48.

The analyses of efficacy endpoints were primarily based on treated population, defined as all study subjects randomized and who received at least one dose of study drug: 98.2% (392/399) for ER and IR (391/398), respectively.

Three approaches were used for the evaluation of primary and secondary efficacy endpoints.

- (1) The Virologic Response - Treated Subjects (VR-T) analysis is based on the single HIV RNA measurement closest to the Week 48 visit. The evaluable VR-T cohort consists of all treated subjects.
- (2) The Virologic Response - Completers (VR-C) analysis is also based on the single HIV RNA measurement closest to the Week 48 visit but the evaluable cohort consists of subjects who remained on treatment at the time of their Week 48 visit.
- (3) The Treatment Response Without Prior Failure (TRWPF) analysis uses a response definition of a minimum of two sequential HIV RNA measurements < LOQ maintained through Week 48 without intervening replicated rebounds, CDC Class C AIDS events or treatment discontinuations.

The proportion of responders from the VR-C analysis is greater than for the VR-T analysis since dropouts are removed from the denominator.

2.1.2.3 HIV RNA Measurements

For the evaluation of plasma HIV-1 RNA levels, Roche Amplicor HIV-1 Monitor™ Test (the standard assay) and Roche UltraSensitive HIV-1 Monitor™ Test (the ultrasensitive assay) were used. The limits of detection (LOQ) are 400 c/mL and 50 c/mL for the standard assay and the ultrasensitive assay, respectively.

The following summarizes how HIV RNA measurements were obtained and how

HIV RNA data were generated.

- Plasma samples shipped frozen and/or ambient were sent for processing of HIV RNA levels. Samples from North America were tested at a central laboratory within the United States where version 1.0 of the Roche assays was used. Samples outside of North America were tested in central or local laboratories outside of the United States where version 1.5 of the Roche assays was used.
- HIV RNA data at screening and at baseline were obtained using the standard assay. From Week 2 onward HIV RNA plasma were measured using the ultra sensitive assay.
- If a sample with HIV RNA value > 75,000 c/mL using the ultrasensitive assay, then this sample was tested using the standard assay. If any of the on-treatment HIV RNA values < 400 c/mL from the standard assay, then the sample was tested using the ultrasensitive assay.
- HIV RNA values outside the upper (or the lower limit) of quantification were assigned a value of one more (or one less) than the limit.
- When there were more than one HIV RNA measurements on a visit date, a single baseline HIV RNA value was determined by selecting *the smallest value* and a single on-study HIV RNA value was determined by choosing *the largest value*. A baseline HIV RNA value in Study AI455-096 was determined by the ambient sample if a patient had both HIV RNA values from frozen sample and ambient sample.
- When there were more than one HIV RNA measurements per subject in a time window of baseline or follow-up visit, a baseline HIV RNA was chosen with the test date closest to Day 1, and an on-study HIV RNA value for a study visit week was determined as the measurement closest to that visit week.

2.1.2.4 Problems in Handling Specimens

During the review, issues related to plasma-handling and the usage of diagnostic assays were revealed and questioned by the FDA review team.

Throughout the conduct of the d4T ER studies, not only version 1.5 of AMPLICOR HIV-1 MONITOR™ Test with standard and UltraSensitive methodologies, but also the [] of AMPLICOR HIV-1 MONITOR™ Test with standard and UltraSensitive methodologies, was offered by Roche Diagnostics. Version 1.0 and 1.5 with standard and UltraSensitive

methodologies were approved by the FDA, while the [] methodologies are currently under review by the FDA.

In study AI455-099, three sites (2 Thailand, 1 Singapore) used conventional [] tubes that were recommended by the ACTG. All other sites in AI455-099 used [] tubes – an [] equivalent tube contains [] as the anticoagulant and an additional inert material for the formation of a stable barrier separating the plasma from the cellular blood components. Other changes in handling specimens were also made, including the change of centrifugation force and duration.

The applicant used 24-hour ambient shipping initially, and observed that ambient shipping of [] tubes was consistently associated with a small, positive bias towards higher values relative to frozen shipping. A decision was made by the applicant to switch specimen shipment from shipping ambient to shipping frozen.

Note all the above problems were not mentioned in correspondence with the FDA at the time of a methodology change or at the interim report.

This reviewer performed statistical analyses to examine discrepancies between different specimen shipment status and their relationship with the primary endpoints in Section 4. The applicant provided additional sensitivity analyses on the primary endpoints due to the change in specimen shipment status (Section 3).

2.1.2.5 Time to Loss-of-Virologic-Response Algorithm

An algorithm suggested by the Division of Antiviral Drug Products (DAVDP)/FDA, was used to perform the final efficacy analyses and present the results in the d4T ER label. This algorithm has been used to determine the “success” status of patients at any visit and to compute the time to loss-of-virologic response because not all visits occur as scheduled and sometimes there are multiple evaluations for a given visit. The FDA algorithm will appear in the updated version of a Guidance for Industry (Clinical considerations for Accelerated and Traditional Approval of Antiretroviral Drugs Using Plasma HIV RNA Measurements).

Different from sponsor’s definition, this algorithm classifies a patient who is suppressed virologically without discontinuing therapy as a success regardless of whether a CDC Class C event occurred or not. In this algorithm, failures are carried forward.

Time to Loss-of-Virologic-Response Algorithm (defined by DAVDP/FDA)

For NDAs with 48-week virologic data, one analysis for computing time to

virologic failure may be assessed using the following algorithm.

1. In what follows, visit means visit with an observed viral load. All available visits, including off-schedule visits and post Week 48 visits, should be used for the calculation. Data should not be interpolated for visits or time points with missing data.
2. Subjects who never achieved confirmed HIV RNA levels below the assay limit (on two consecutive visits) before any of the following events will be considered to have failed at time 0.
 - a) Death
 - b) Discontinuation or switching of study medications. Temporary discontinuation or dose reduction of study medications may be ignored. Discontinuation or dose reduction of background therapies in blinded studies can be ignored. The handling of other changes in background therapies should be pre-specified in the protocol and discussed with the division.
 - c) Last available visit
3. For all subjects who have confirmed HIV RNA levels below an assay limit, the time to failure is the earliest of the choices below, with modification specified in 4.
 - a) Time of the event as described in 2b
 - b) Time of loss to follow-up
 - c) Time of confirmed levels above an assay limit. Confirmed is defined as two consecutive levels greater than an assay limit or one visit greater than an assay limit followed by loss to follow-up.
 - d) Time of death.
4. If the time to virologic failure defined above is immediately preceded by a single missing scheduled visit or multiple consecutive missing scheduled visits, then the time of virologic failure is replaced by the time of the first such missing visit.

Based on the algorithm above, the Week 48 virological responses and status of subjects are summarized.

3. STATISTICAL EVALUATION OF EVIDENCE ON EFFICACY: APPLICANT'S RESULTS

3.1 Demographics and Baseline Characteristics

The Study AI455-099 was conducted in 69 sites: 25 sites in North America, 11 in South America, 25 in Europe, 3 in Asia, and 5 in Africa. Baseline values for plasma HIV RNA, laboratory and physical measurements were identified as the last value measured prior to or on the day of the start of study therapy. The qualifying HIV RNA values were measured prior to randomization and used for stratification. Baseline CD4+ cell count was obtained as the average of the last two pretreatment measurements, or the pretreatment measurement if only one CD4+ cell count was available.

Table 1 shows demographics and baseline characteristics. Overall, the treated population was predominantly male (69%), with a median age 33 years. Caucasian (34%) was the lead group, followed by Black patients (24%), Hispanic (23%), Asian (9%), and other origin (<1%). At baseline, the median plasma HIV RNA was 4.80 log₁₀ c/mL and the median CD4+ cell counts was 277 cells/mm³. 28% of the subjects had baseline CD4+ cell count below 200 cells/mm³. In general, there was equal distribution of populations between treatment regimens. Comparisons of CD4+ cell count and HIV RNA level between treatment groups, no differences were statistically significant.

3.2 Patient Disposition and Study Discontinuation

797 subjects were randomized, 14 of which had never received treatment. The duration of dosing was similar between groups with a median time on therapy of 56 weeks for both groups. The overall study completion rate was excellent with 86% of those who started treatment completing 48 weeks of therapy (88% ER; 85% IR). Subjects discontinued at a similar rate from both treatment regimens. The hazard ratio and 95% CI for time on therapy was 0.94 (0.80, 1.09), favoring the ER treatment arm.

Table 2 lists the disposition through Week 48. Note that investigative sites provided only one reason for study discontinuation per subject.

Reviewer's Comments

The sponsor reported updated subject disposition and study discontinuation as requested by the FDA (Source: May 30A, 2002: 93001762). 65% for the ER regimen and 63% for the IR regimen completed therapy. A total of 54 (13%) in the d4T ER regimen and 72 (18%) in the d4T IR regimen were discontinued when data were submitted. Among those who discontinued the study, it

appeared that subjects in d4T IR regimen had more adverse events and loss to follow-up than the d4T ER regimen. Discontinuation due to noncompliance, subject withdrew, etc., were similar between these two groups.

Table 1. Demographics and Baseline Characteristics in Study AI455-099[§]

Characteristic	d4T ER/3TC/EFV N = 392	d4T IR/3TC/EFV N = 391	Total N = 783
Age (years):			
Mean (SE)	34.4 (0.4)	34.2 (0.5)	34.3 (0.3)
Median (Range)	33 (18-69)	33 (18-68)	33 (18-69)
Gender: N (%)			
Male	267 (68)	273 (70)	540 (69)
Female	125 (32)	118 (30)	243 (31)
Race: N (%)			
White	168 (43)	163 (42)	331 (42)
Black ^a	99 (25)	91 (23)	190 (24)
Hispanic/Latino	86 (22)	98 (25)	184 (23)
Asian/Pacific Islander	36 (9)	38 (10)	74 (9)
Other (< 1)	1 (< 1)	4 (< 1)	
Region: N (%)			
North America	135 (34)	133 (34)	268(34)
Europe	87 (22)	90 (23)	177 (23)
South America	80 (20)	75 (19)	155 (20)
Africa	57 (15)	58 (15)	115 (15)
Asia	33 (8)	35 (9)	68 (9)
IV Drug Use: N (%)			
	16 (4)	22 (6)	38 (5)
AIDS: N (%)			
	14 (4)	8 (2)	22 (3)
HIV RNA (log₁₀ c/mL)			
Mean (SE)	4.79 (0.03)	4.75 (0.03)	4.77 (0.02)
Median (Range)	4.80 (2.8-5.9)	4.80 (2.6-5.9)	4.80 (2.6-5.9)
HIV RNA Level Distribution^b: N (%)			
< 30,000	114 (29)	113 (29)	227 (29)
≥ 30,000	278 (71)	278 (71)	556 (71)
CD4 Cell Count (cells/mm³):			
Mean (SE)	313 (9)	324 (10)	319 (6)
Median (Range)	285 (62-1044)	272 (61-1215)	277 (61-1215)
CD4 Cell Count Distribution: N (%)			
< 200	105 (27)	116 (30)	221 (28)
200 - < 350	143 (36)	134 (34)	277 (35)
350 - < 500	93 (24)	70 (18)	163 (21)
≥ 500	51 (13)	70 (18)	121 (15)
Missing	--	1 (< 1)	1 (< 1)

[§] Source: Tables 8.3A and 8.3 B (May 30, 2002: 93001557).

^a Including mixed/biracial subjects. ^b Randomization strata.

Table 2. AI455-099: Subject Disposition— Through Week 48^S

	d4T ER/3TC/EFV	d4T IR/3TC/EFV	Total
	N = 399	N = 398	N = 797
Randomized	399 (100)	398 (100)	797(100)
Never treated	7 (2)	7 (2)	14 (2)
Treated	392 (98)	391 (98)	783 (98)
<i>Discontinued on or before Week 48 assessment</i>	49 (12)	59 (15)	108 (14)
Adverse event	15 (4)	16 (4)	31 (4)
Lost to follow-up	11 (3)	19 (5)	30 (4)
Subject withdrew	6 (2)	9 (2)	15 (2)
Pregnancy ^a	5 (1)	8 (2)	13 (2)
Protocol violation while on study	4 (1)	3 (< 1)	7 (< 1)
Death ^b	3 (< 1)	2 (< 1)	5 (1)
Noncompliance	2 (< 1)	2 (< 1)	4 (< 1)
Treatment Failure/Lack of Efficacy	2 (< 1)	--	2 (< 1)
Administrative Decision	1 (< 1)	--	1 (< 1)
<i>Discontinued after Week 48</i>	5 (1)	13 (3)	18 (2)
Lost to follow-up	3 (< 1)	2 (< 1)	5 (< 1)
Subject withdrew	2 (< 1)	--	2 (< 1)
Adverse event	--	5 (1)	5 (< 1)
Noncompliance	--	3 (< 1)	3 (< 1)
Pregnancy ^a	--	2 (< 1)	2 (< 1)
Other	--	1 (< 1)	1 (< 1)
<i>Completed Treatment</i>	261 (65)	252 (63)	513 (64)
<i>Continuing on Study</i>	77 (19)	67 (17)	144 (18)

^S. Sources: Table 2 (May 30A,2002: 93001762).

a. % refers to percent of total randomized subjects, not % randomized female subjects.

b. One additional IR death (metastatic breast cancer) was not appearing in this table.

c. Those who completed 40 weeks of therapy.

3.3 Time to Loss of Virologic Response (TLOVR)

The sponsor conducted additional efficacy analysis based on the updated definition of virologic failure provided by the Division of Antiviral Drug Products (DAVDP), using Time to Loss-of-Virologic Response (TLOVR) algorithm. The efficacy analyses were performed for HIV RNA level LOQ=400 c/mL and then LOQ=50 c/mL. The following TLOVR results were submitted under 2002-05-30A, 93001762.

3.3.1 Treatment Outcomes (TLOVR) at Week 48 (LOQ = 400 c/mL)

Table 3 below summarizes the proportion of patients who were virologically suppressed (<400 c/mL) through Week 48 in Study AI455-099.

Table 3. AI455-099: Treatment Outcomes (TLOVR) at Week 48 (LOQ = 400 c/mL)^S

	d4T ER/3TC/EFV	d4T IR/3TC/EFV
	N = 392	N = 391
Responder	309 (79)	297 (76)
Virologic failure	3	8 (10)
Rebound	21 (5)	25 (6)
No confirmed response	17 (4)	15 (4)
Death or disease progression	3 (<1)	2 (<1)
Death	3 (<1)	2 (<1)
Discontinued due to adverse events	15 (4)	13 (3)
Discontinued due to other reasons	27 (7)	39 (10)
Administrative decision	1 (<1)	--
Lost to Follow-up	10 (3)	19 (5)
Non-compliance	2 (<1)	2 (<1)
Pregnancy	5 (1)	7 (2)
Protocol violation while on study	4 (1)	3 (<1)
Subject withdrew	5 (1)	8 (2)

^S. Sources: Table 3 (Page 40, May 30A, 2002: 93001762).

a. Number (%).

3.3.2 TLOVR Curves (Kaplan-Meier) Through Week 48 (LOQ = 400 c/mL)

Figures 2 and 3 show the proportion of successes through Week 48 for HIV RNA <400 c/mL and < 50 c/mL, respectively (Sources: Figure 3 on Page 25 and Figure 4 on Page 26, May 30A, 2002: 93001762). The TLOVR rates over time showed similar results between the two treatment arms.

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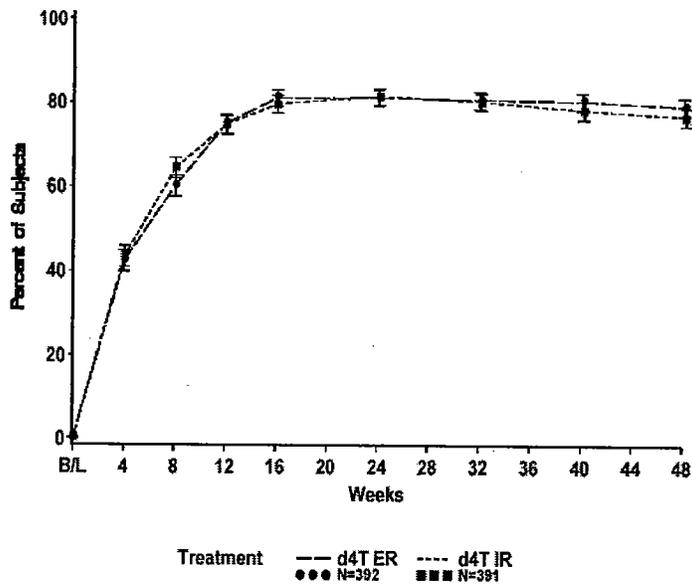


Figure 2: AI455-099: TLOVR (<400 c/mL) Through Week 48

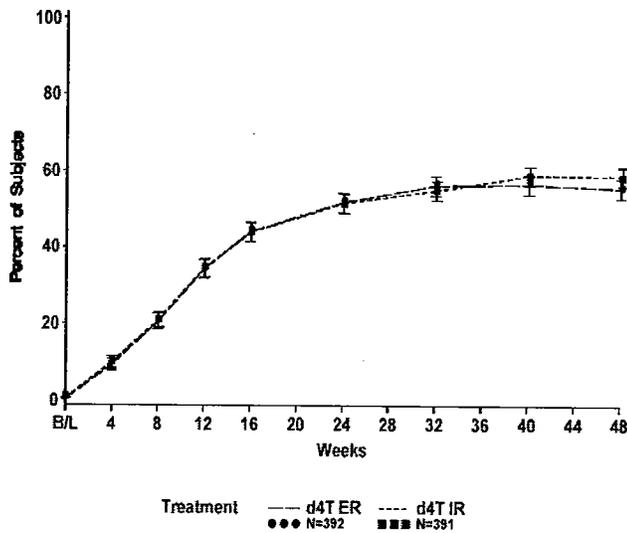


Figure 3: AI455-099: TLOVR (<50 c/mL) Through Week 48

3.3.3 Overall TLOVR at Week 24 and Week 48 (LOQ = 400 c/mL)

Table 4 shows TLOVR adjusting for qualifying HIV RNA strata at Weeks 24 and 48. At Week 48, 79% of the subjects in the ER regimen and 81% of the subjects in the IR regimen had HIV RNA <400 c/mL. The corresponding success rates for < 50 c/mL were lower, approximately 55% and 57% of the subjects in the ER and IR regimens, respectively.

Table 5 shows hazard ratio adjusting for qualifying HIV RNA strata and study sites. The hazard ratio adjusting for qualifying HIV RNA was 0.95 and 1.00, respectively, for LOQ=400 c/mL and 50 c/mL.

Table 4. Virologic Response Rate (TLOVR) at Week 24 & Week 48*

	d4T ER (%)	d4T IR (%)	Difference (%)	95% CI (%)
LOQ=400 c/mL				
Week 24	317/392 (81)	297/391 (76)	0.0	-5.5,5.6
Week 48	309/392 (79)	316/391 (81)	2.9	-3.0,8.7
LOQ=50 c/mL				
Week 24	201/392 (51)	197/391 (50)	0.9	-6.1,7.8
Week 48	215/392 (55)	224/391 (57)	-2.5	-9.4,4.5

*. Difference estimates are stratifying by qualifying HIV RNA strata. P-value > 0.05 by the CMH tests for the comparisons of response rates between d4T ER and d4T IR. Sources: Table 3 on Page 19, 2002-05-30A,93001762.

Table 5. Hazard Ratio and 95% Confidence Interval for TLOVR

LOQ	Method	Estimate d4T ER: d4T IR	95% CI
LOQ=400	HIV RNA < 30,000 c/mL	0.82	0.48,1.38
	HIV RNA ≥ 30,000 c/mL	1.02	0.73,1.42
	Overall stratifying by HIV RNA	0.95	0.72,1.27
	Overall stratifying by site	0.91	0.68,1.23
LOQ=50	HIV RNA < 30,000 c/mL	0.81	0.54,1.21
	HIV RNA ≥ 30,000 c/mL	1.07	0.85,1.35
	Overall stratifying by HIV RNA	1.00	0.82,1.22
	Overall stratifying by site	1.03	0.83,1.27

Sources: Table 4 on Page 20, 2002-05-30A,93001762.

3.3.4 Efficacy Results Using HIV RNA from Frozen Shipped or Local Transferred Specimens

As requested by the FDA, the sponsor further provided two efficacy analyses: (1) Analysis 1 included HIV RNA data points from frozen shipped specimens; and (2) Analysis 2 included HIV RNA data points from frozen shipped specimens as well as those from local specimens. The sponsor believed that Analysis 2 reflected only data points for which the study-specified or implemented process for the pre-laboratory handling of HIV RNA specimens was in accordance with Roche AMPLICOR assay specifications.

The results of Analysis 1 demonstrated that the relationship between the two treatment groups remains consistent with the previous analysis that ignored specimen shipment status. The estimated difference in response rate (ER-IR) and 95% CI at Week 48 was 1.4 (-5.6, 8.4) for TLOVR and 3.7 (-3.3, 10.7) for the Virologic Response - Treated Subjects (VR-T) analysis based on the single HIV RNA measurement closest to the Week 48 visit using LOQ = 400 c/mL.

However, the response rates for the frozen-only analysis were generally lower. The lower response rates were caused by the fact that all subjects with ambient-shipped specimens were considered failures.

Reviewer's comment

It may be appropriate to exclude those subjects in the denominators in calculation of these response rates.

In Analysis 2, the Week 48 results were comparable to those in the previous submission, with response rates falling within $\pm 1\%$ of those generated by the full dataset. Given the small difference estimates in all analyses presented, it is reasonable to conclude that the AI455099 data support the conclusion that treatment with stavudine ER is non-inferior to treatment with stavudine IR with respect to antiviral efficacy.

3.4 Efficacy Results: Interim Analysis

The sponsor reported interim efficacy results at Week 24. This reviewer summarized the interim efficacy results in Tables 6 and 7. Three types of efficacy analyses were performed for primary endpoint on all treated subjects. Note a total of 707 (90%) were completed 24 weeks of therapy.

The Virologic Response - Treated Subjects (VR-T) analysis was based on the single HIV RNA measurement closest to the Week 24 visit.

The Virologic Response - Observed Cases (VR-OC) analysis was also based on the Week 24 visit but the evaluable cohort consists of subjects who remained on treatment at the time of their Week 24 visit.

The Treatment Response Without Prior Failure (TRWPF) analysis uses a response definition of a minimum of two sequential HIV RNA measurements < LOQ maintained through Week 24 without interviewing replicated rebounds, CDC Class C AIDS events or treatment discontinuations.

The applicant performed TAD analyses including (1) analysis when missing data were replaced with Last Observation Carried Forward (LOCF); (2) subgroups analysis which stratified qualifying HIV RNA; (3) subgroups analysis which stratified different regions due to different version in HIV RNA assays: version 1.0 in North America and version 1.5 in other regions; and (4) covariate analysis assuming investigator site to be a random effect or fixed effect.

A) Proportion HIV RNA < 400 c/mL

The Treatment Response Without Prior Failure (TRWPF) rate was 79% in the d4T ER versus 81% in the d4T IR regimen (estimated difference [ER - IR] of -1.2%, 95% CI: -6.8%, 4.4%).

B) Plasma HIV RNA

Both treatment regimens exhibited a rapid decrease in HIV RNA levels immediately following treatment initiation. By Week 8, both groups had achieved median decreases greater than 2.4 log₁₀; this reduction in viral load was sustained through Week 24 in both treatment groups, with a median decrease of 2.84 log₁₀ in the ER regimen and 2.87 log₁₀ in the IR regimen. The median HIV RNA levels of the d4T ER and the d4T IR regimens decreased to below 50 c/mL (< 1.70 log₁₀ c/mL) level at Week 16. The overall magnitude and pattern of response was similar between the two treatment regimens at all time points.

For data stratified by qualifying HIV RNA, the overall Time-Averaged Difference Change from baseline in log₁₀ HIV RNA through Week 24 TAD (ER - IR) was -0.01 with a 95% CI of (-0.08, 0.06). The 95% confidence upper limit 0.06 was less than the pre-specified non-inferiority margin 0.5.

In these analyses, the 95% confidence upper limit ranged from 0.06 to 0.13, less than the non-inferiority margin 0.5. The applicant declared that these data supported the conclusion of similarity.

C) CD4+ Cell Count

Last part of Table 6 shows the results of change from baseline (TAD) in CD4+ Cell Count (cells/mm³). Both treatment groups were associated with a substantial increase in CD4+ cell counts over 24 weeks of follow-up. The mean increase at Week 24 was 142 c/mm³ in the ER regimen and 135 c/mm³ in the IR regimen. The magnitude and rate of the CD4+ Cell Count increase for the two regimens were comparable. The TAD through Week 24 was 6.9 favoring the ER regimen.

D) Other Secondary Endpoints

Other secondary endpoints were evaluated including (1) treatment outcomes at Week 24; (2) proportion of subjects who responded at all times; and (3) Time to Treatment Failure. They were all evaluated based on TRWPF. Table 7 shows the treatment outcome and other secondary efficacy results.

At Week 24, response rates in the ER and IR groups were comparable, 79% vs. 81% for LOQ=400 c/mL, and 49% vs. 48% for LOQ=50 c/mL, respectively. The rates of virologic failure ER vs. IR were also comparable: 11% vs. 9% for LOQ=400 c/mL and 41% vs. 43% for LOQ=50 c/mL.

For time to treatment failure analyses, the hazard ratios (ER vs. IR) were 0.95 and 1.03 for LOQ=400 c/mL and 50 c/mL, respectively. Subjects in both regimens were likely to experience treatment failure at a comparable rate.

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Table 6. Study AI455-099: Efficacy Results at Week 24-Part I^s

Primary Endpoint				
1. Proportions of HIV RNA <400 c/mL (Tables 10.1.1.)				
	n/N (P_{ER}%)	n/N (P_{IR}%)	P_{ER-IR}%	95% CI of P_{ER-IR}%
VR-T	315/392 (80)	320/391 (82)	-1.5	(-7.0,4.0)
VR-OC	315/366 (86)	320/360 (89)	-2.9	(-7.7,1.9)
TRWPF	311/392 (79)	315/391 (81)	-1.2	(-6.8,4.4)
Secondary Endpoint				
2. Proportions of HIV RNA <50 c/mL (Tables 10.1.5.)				
VR-T	216/392 (55)	214/391 (55)	0.3%	(-6.6,7.3)
VR-OC	216/366 (59)	214/366 (59)	-0.6%	(-7.6,6.5)
TRWPF	195/392 (49)	188/392 (48)	1.1%	(-5.8,8.0)
3. Time Average Difference in log₁₀ HIV RNA Change from Baseline Through Week 24³				
Method			TAD_{ER-IR}	95% CI of TAD_{ER-IR}
Overall (stratified by HIV RNA)			-0.01	(-0.08,0.06)
Last observation carried forward			0.01	(-0.06,0.08)
<30,000 c/mL			-0.05	(-0.20,0.10)
≥30,000 c/mL			0.01	(-0.08,0.09)
North America			0.01	(-0.12,0.13)
Other Regions			-0.01	(-0.11,0.07)
Site as fixed effect			-0.01	(-0.09,0.06)
Site as random effect			-0.01	(-0.09,0.06)
4. TAD in CD4 Cell Counts (cells/mm³) Change from Baseline⁴				
			TAD_{CD4}	95% CI
Overall (stratified by HIV RNA)			6.9	(-7.2,21.0)
Last observation carried forward			6.0	(-8.1,20.1)
<30,000 c/mL			16.4	(-12.0,44.8)
≥30,000 c/mL			3.1	(-13.1,19.2)
Site as fixed effect			5.9	(-8.3,20.1)
Site as random effect			3.7	(-10.9,18.2)

^s Sources: Vol. 1.24.

Table 7. AI455-099: Efficacy Results at Week 24-Part II^S

5. Treatment Outcomes (Tables 10.1.2 &10.1.6)								
	LOQ=400 c/mL		LOQ=50 c/mL					
	ER: n(%)	IR: n(%)	ER: n(%)	IR: n(%)				
Responder	311 (79)	315 (81)	193 (49)	188 (48)				
Virologic Failure	43 (11)	37 (9)	161 (41)	167 (43)				
Death of Disease Progression	5 (1)	2 (<1)	5 (1)	2 (<1)				
Discontinued								
Adverse Events	12 (3)	9 (2)	12 (3)	8 (2)				
Other Reasons	21 (5)	28 (7)	21 (5)	26 (7)				
6. Responses at All Times (Tables S.10.1.3A-C)								
	LOQ=400 c/mL		LOQ=50 c/mL					
	Range:P_{ER-IR} %	Range:Low Limit 95% CI	Range:P_{ER-IR} %	Range: Low Limit 95% CI				
VR-T	(-3.3,1.1)	(-9.7,-4.6)	(-1.9,1.4)	(-6.6,-4.8)				
VR-OC	(-3.3,0.8)	(-9.7,-4.9)	(-1.9,1.1)	(-7.6,-4.8)				
TRWPF	(-4.6,1.1)	(-11.1,-4.6)	(-0.4,1.1)	(-6.2,-4.1)				
7. Time to Treatment Failure (Tables S.10.1.4 & S.10.1.8)								
	LOQ=400 c/mL		LOQ=50 c/mL					
	Hazard Ratio	95% CI of HR	Hazard Ratio	95% CI of HR				
TRWPF	HR=0.95	(0.71,1.27)	HR=1.03	(0.85,1.26)				
8. Log₁₀ HIV RNA Level Over Time (Table S.10.2A)								
Time Point	ER				IR			
	n	Median	Mean	SE	N	Median	Mean	SE
Baseline	392	4.80	4.77	0.03	391	4.80	4.74	0.03
Week 4	372	2.60	2.62	0.03	376	2.63	2.61	0.03
Week 8	364	2.23	2.36	0.03	368	2.20	2.31	0.03
Week 12	365	1.88	2.13	0.03	359	1.88	2.16	0.03
Week 16	363	1.69	2.03	0.03	361	1.69	2.02	0.03
Week 24	356	1.69	1.98	0.03	355	1.69	1.96	0.03
9. Change in Log₁₀ HIV RNA Level from Baseline (Table S.10.2B)								
Week 4	372	-2.20	-2.15	0.03	376	-2.16	-2.13	0.03
Week 8	364	-2.47	-2.41	0.03	368	-2.44	-2.44	0.03
Week 12	365	-2.64	-2.63	0.04	359	-2.60	-2.59	0.04
Week 16	363	-2.78	-2.74	0.04	361	-2.76	-2.73	0.04
Week 24	356	-2.84	-2.79	0.04	355	-2.87	-2.79	0.04

^S Sources: Vol. 1.24.

3.5 Applicant's Summary

1. The TLOVR for AI455099 showed similar response rates between the two treatment regimens over time. The Week 48 estimate and 95% CI was 2.9 (-3.0,8.7) for IOQ=400 c/mL and -2.5 (-9.4,4.5) for LOQ=50 c/mL. The TLOVR estimates were consistent with the other assessments of virologic

response (VR-T,VR-C,TRWPF) presented in the CSRs.

2. Analyses of the primary efficacy outcome (proportion with Week 24 HIV RNA < 400 c/mL) demonstrated the similarity of the d4T ER and d4T IR containing regimens. The Treatment Response Without Prior Failure (TRWPF) rate was 79% for d4T ER versus 81% for d4T IR (estimated difference [ER - IR] of -1.2%, 95% CI: -6.8%, 4.4%).
3. Analyses of the primary efficacy outcome (proportion with Week 48 HIV RNA < 400 c/mL) demonstrated the similarity of the d4T ER and d4T IR containing regimens. The Treatment Response Without Prior Failure (TRWPF) rate was 78% for d4T ER versus 73% for d4T IR (estimated difference [ER - IR] of 4.9%, 95% CI: -1.1%, 10.9%).
4. All methods of assessing the proportion of subjects with HIV RNA below the level of quantification fall well within the pre-specified criterion for similarity. The similarity of d4T ER to d4T IR is supported by multiple analyses including: the proportions achieving HIV RNA levels < 400 c/mL according to the Virologic Response for Treated Subjects (VR-T) and Virologic Response for Completers (VR-C) analysis methods; the proportion of subjects achieving HIV RNA levels < 50 c/mL according to all three analysis methods; the Time Averaged Difference (TAD) analysis for HIV RNA; and the TAD analysis for change in CD4 cell count.

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4. STATISTICAL EVALUATION OF EVIDENCE ON EFFICACY: STATISTICAL REVIEWER'S FINDINGS

The statistical reviewer verified sponsor's fundamental findings that: (1) the virologic response was similar for the ER study regimen and equivalent IR reference regimen; (2) the virologic response was sustained through Week 48; and (3) the virologic response was associated with a significant rise in CD4+ cell count.

As mentioned in Section 2.1.2.4, during the review, issues related to specimen handling in Study AI455-096 and plasma shipment handling in Study AI455-099 were revealed. Due to significant differences in longitudinal HIV RNA measurement by specimen shipment status, it was decided by the statistical review team to report efficacy analyses on TLOVR stratified by three specimen shipment status and qualifying HIV RNA strata.

Section 4.1 summarized paired HIV RNA data analyses in Study AI455-096 and provided sensitivity analyses on TAD in plasma HIV RNA. Sections 4.2 to 4.5 are topics related to Study AI455-099. Section 4.2 summarized data analysis in Study AI455-099 regarding plasma HIV RNA and specimen shipment status. Section 4.3 summarized results from sensitivity analyses based on TLOVR algorithm adjusting for specimen shipment status and qualifying HIV RNA. The corresponding subgroup analyses regarding specimen shipment was also included. In Sections 4.4 and 4.5, this reviewer performed TAD analyses on plasma HIV RNA and CD4+ cell count.

4.1 Study AI455-096: HIV RNA Data from Frozen and Ambient Samples

Per FDA's request, the applicant provided the reasons for duplicated specimens in 2002-09-23 document. At study start, the applicant instructed the AI455-096 sites to ship the samples in an ambient state to the central laboratory via overnight priority express courier for arrival within 24 hours. Sites were instructed that for each visit where a specimen was drawn and sent for testing at the central laboratory, a second specimen should be drawn and remain locally available in a freezer as an eventual HIV RNA back-up sample.

This reviewer summarized the descriptive statistics of HIV RNA measurements by frozen or ambient samples and performed TAD sensitivity analyses using HIV RNA data sets generated by different rules in order to examine the efficacy in Study AI455-096.

In Study AI455-096, there were substantial numbers of HIV RNA measurements from both ambient and frozen samples per subject per visit date, including 775 HIV RNA paired measurements from ambient and frozen samples of the same patient collected on an identical visit date. From these, 108 pairs were prior to or at Day 1, and 667 were on study measurements. It was also noted that about 45% of these were obtained from North America labs. At baseline, 95.3% (143/150) and 39.3% (59/150) study subjects had HIV RNA measurements from ambient samples and frozen samples, respectively.

If HIV RNA dataset was generated follow the statement the submission: “When available, results from frozen samples were used” (see page 130, item 8, Vol. 1.), then a TAD analysis should have included HIV RNA values from 39.3% frozen samples and 60.7% ambient samples. However, when generating HIV RNA data, a SAS program stated that the rule of selection was ‘largest, ambient or frozen’. Thus, the actual HIV RNA value at a study visit date was determined by ambient samples when both were presented. The impact of such method was not known.

Figure 4 shows scatter plot and two marginal histograms for 108 HIV RNA pairs prior to or at Day 1. The solid line is identity line ‘ $x=y$ ’ and the dotted lines denoted median values. More data points were below a line ‘ $x=y$ ’, indicating that HIV RNA values from frozen specimens were more likely smaller than their paired ambient specimens. The median HIV RNA from frozen specimens was $4.6 \log_{10}$, $0.25 \log_{10}$ less than ambient samples (median = $4.85 \log_{10}$).

Figure 5 contains scatter plots of the paired HIV RNA data by follow-up visits. Overall, the median difference (Ambient-Frozen) in HIV RNA is $0.19 \log_{10}$ and mean (std) is $0.33 (0.56) \log_{10}$. At Week 4, more HIV RNA values were below 50 c/mL ($<1.7 \log_{10}$) from the frozen specimens than from the ambient specimens. The median values were reduced and reached to below $1.7 \log_{10}$ level from Week 12 onward in frozen specimens, and from Week 32 onward in ambient specimens.

Table 8 shows the basic statistics of paired HIV RNA measurements by study time (pre or post baseline), and region (North America and South America). Comparing the HIV RNA from paired ambient and frozen samples in each stratum, HIV RNA measurements from ambient samples were statistically significantly higher than the frozen samples, $p < 0.001$, by the Wilcoxon signed rank tests. HIV RNA values were well correlated between ambient and frozen pairs prior to treatment; and this correlation was weakened as the length of therapy increased. HIV RNA below assay limit (LOQ=50 c/mL) from frozen samples was about 15% higher than ambient samples during the first 8 weeks of therapy. The gap increased to approximate 30% after 8 weeks of therapy.

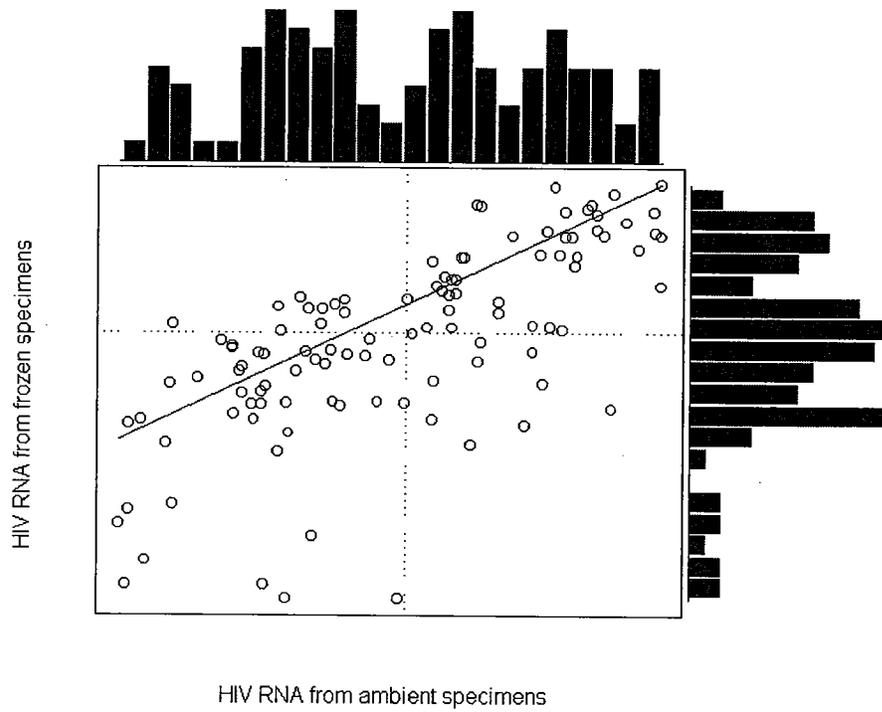


Figure 4: AI455-096: Paired HIV RNA Data Prior to Treatment

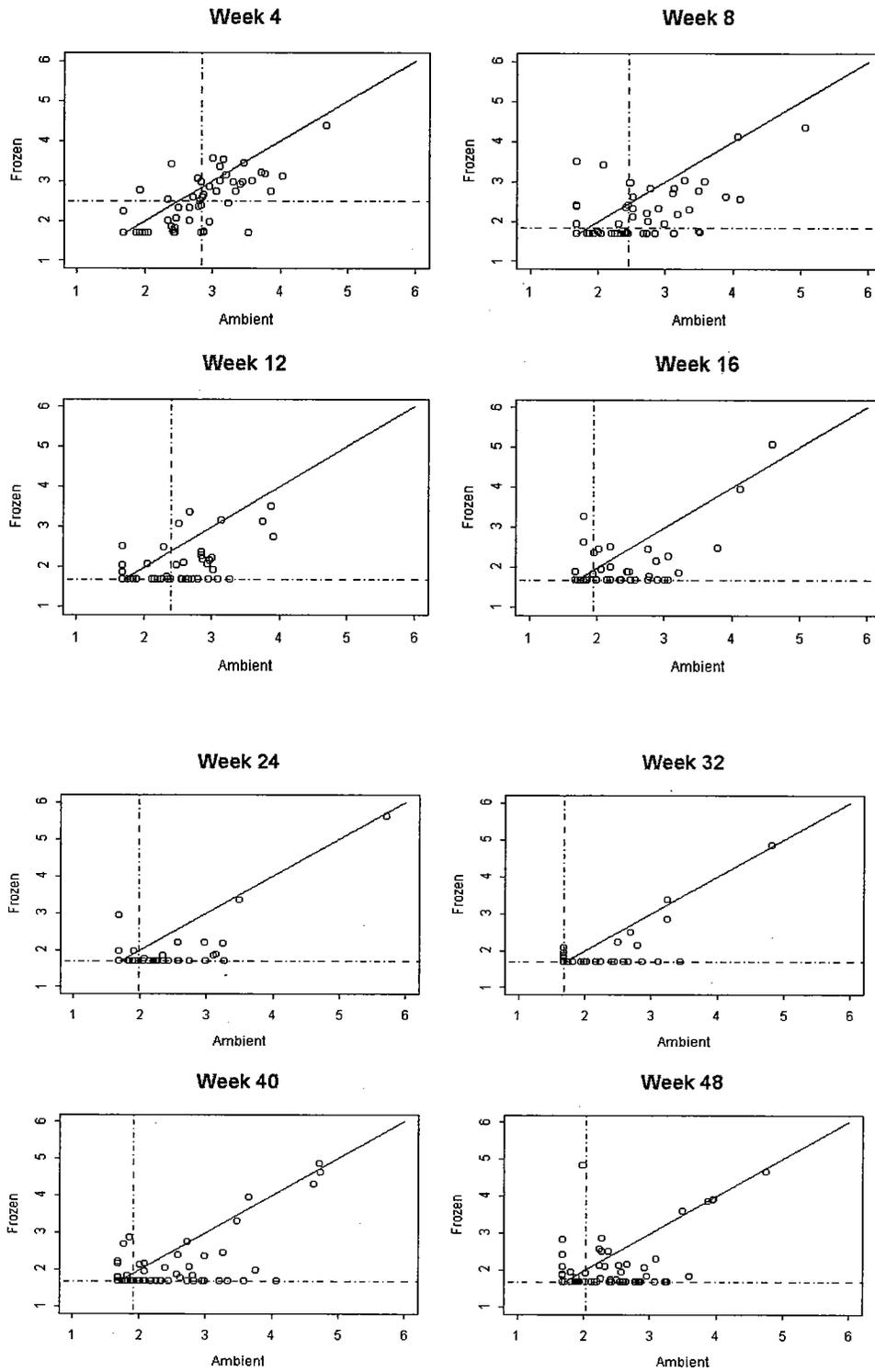


Figure 5: A1455-096: Paired HIV RNA Data By Follow-up Visits

Table 8. HIV RNA from Frozen and Ambient Samples

	Prior to Treatment	On Study	Total	
1. Overall				
Frozen	120	777	897	
Ambient	301 (71.5%)	1460 (65.3%)	1761	
Pair	108	667	775	
2. HIV RNA from paired frozen and ambient samples in treated population				
North America	23	393	416	
South America	29	274	303	
3. Comparisons among paired HIV RNA (frozen and ambient) in treated population				
Study Week	n	Spearman r	% <LOQ (50c/mL)	
			Ambient	Frozen
Prior to Treatment	52	0.73	0.0	0.0
≤8 weeks	124	0.63	5.7	20.2
>8-≤24 weeks	152	0.51	29.0	60.0
>24-≤48 weeks	207	0.38	42.0	73.0
>48 weeks	184	0.42	38.0	65.2

4.1.1 Sensitivity Analysis: TAD in HIV RNA using Different HIV RNA Data Sets

The impact of the results using frozen samples when both frozen and ambient samples were available, on the efficacy endpoint is not known. This reviewer performed TAD analyses using algorithm different from the sponsor's to examine the strength of this study. The TAD was computed within the qualifying HIV RNA strata using observed measurements and combined using a weighted average with weights proportional to stratum size Cochran-Mantel-Haenszel weighting. Time in days since baseline was used for TAD analyses. TAD through Week 48 included HIV RNA data between 44 and 52 weeks since treatment initiation. Three approaches were applied:

- no imputation when an HIV RNA measurement was missing, i.e., last TAD carry forward (LTadCF) and subjects with only baseline HIV RNA were excluded;
- imputing an HIV RNA using subject's baseline HIV RNA measurement (BVCF) if the last HIV RNA was observed prior to Week 40;
- imputing an HIV RNA at using subject's last non-missing HIV RNA measurement (LOCF) if the last HIV RNA was observed prior to Week 40.

To generate HIV RNA data sets the following methods were used:

- The average of the two when both available;
- The value from an ambient sample whenever available; and
- The value from a frozen sample when available.

Table 9 shows the TAD adjusted by qualifying HIV RNA. For an imputation method, it appears that difference between two TADs is less than 0.01 and the difference in two standard errors of TADs is about 0.01. Using same data set, the standard error is the greatest by the BVCF, followed by the LOCF and the LtadCF approach. Therefore, the 95% CIs of TAD are widest by the BVCF approach. Note that this reviewer's results by LTadCF were very close to sponsor's results despite that fact that different ways of generating data sets were applied. Lastly, the upper bound of 95% CI ranging from 0.12 to 0.21, they are all less than 0.5, indicating the similarity between ER and IR regimens regarding time average difference in log₁₀ HIV RNA change from baseline through Week 48.

Different from the applicant's method, this analysis used all on study data points within the time intervals while the applicant's dataset was created to include one data point per visit week, i.e., closest to the follow-up week. Note that the applicant selected *the largest value* of results from ambient samples whenever ambient samples were available, or otherwise a *largest value* of results from frozen samples whenever ambient samples were not available, for a HIV RNA. Time variable in days was used by this reviewer and in weeks by the sponsor.

Table 9: AI455-096: Time Average Difference in log₁₀ HIV RNA Change from Baseline Through Week 48 Stratified by Qualifying HIV RNA*

Method	TAD _{ER-IR}	95% CI
1. No imputations in HIV RNA – Last TAD Carry Forward (n=144)		
Average	-0.031	(-0.22,0.15)
Ambient first	-0.029	(-0.21,0.16)
Frozen first	-0.033	(-0.24,0.18)
2. Baseline HIV RNA Value Carry Forward (n=150)		
Average	-0.134	(-0.39,0.12)
Ambient first	-0.133	(-0.38,0.12)
Frozen first	-0.135	(-0.40,0.13)
3. Last Observation Carry Forward (n=150)		
Average	-0.044	(-0.28,0.19)
Ambient first	-0.043	(-0.28,0.19)
Frozen first	-0.044	(-0.30,0.21)

*. No imputations for subjects with at least 40 weeks follow-up.

4.1.2 Sensitivity Analysis: TAD in HIV RNA Through Week 24, 36 and 48

This reviewer obtained three types of estimated TAD through Week 24, 36 and 48 using average HIV RNA value when there were multiple measurements on a visit date. Time windows are +/- 4 weeks. The methods are similar to those described in Section 4.1.1. Table 10 shows the estimated TAD by different time point and method. Again, the estimated overall TAD, denoted by TAD_{ER-IR}, is a weighted average of TAD adjusting for qualifying HIV RNA strata. The findings are as follows.

Overall, variations of the estimated TAD_{ER-IR} and standard error were observed. For a given time interval, larger variation of TAD_{ER-IR} was associated with BVCF and LOCF methods. For a given method, estimated TAD_j (j=1 for qualifying HIV RNA ≥ 30,000 c/mL; and j=2 otherwise) and TAD_{ER-IR} were stable. The TAD_{ER-IR} through Week 48 are -0.03 by LTadCF, 0.04 by LOCF and -0.13 by BVCF with upper limit of 95% CI ranging between 0.12 to 0.19. These estimates are somewhat analogous to applicant's results although different methods were used for computations.

TAD_{ER-IR} values are all negative, indicating that ER regimen was doing slightly better in general. This was due to that fact that (1) the estimated TAD₁ are all negative for subjects in qualifying HIV RNA ≥ 30,000 c/mL; (2) the estimated TAD₂ are all positive for subjects in qualifying HIV RNA < 30,000 c/mL; and (3) more weights were obtained from subgroups in qualifying HIV RNA ≥ 30,000 c/mL because of the sample sizes are larger than those in subgroups of qualifying HIV RNA < 30,000 c/mL.

Table 10. AI455-096: Time-Average Difference Change From Baseline in log₁₀ HIV RNA Adjusting for Qualifying HIV RNA[§]

Through week	TAD ₁	Se(TAD ₁)	TAD ₂	Se(TAD ₂)	TAD _{ER-IR}	Se(TAD _{ER-IR})	95% CL
1. Last TAD Carry Forward (n=144)							
24	-0.122	0.108	0.170	0.118	-0.021	0.081	(-0.181,0.139)
36	-0.104	0.120	0.177	0.122	-0.006	0.089	(-0.181,0.168)
48	-0.144	0.129	0.184	0.122	-0.031	0.094	(-0.216,0.155)
2. Baseline HIV RNA Value Carry Forward (n=150)							
24	-0.212	0.136	0.162	0.154	-0.083	0.104	(-0.286,0.121)
36	-0.198	0.148	0.177	0.159	-0.069	0.111	(-0.287,0.149)
48	-0.312	0.173	0.204	0.175	-0.134	0.128	(-0.385,0.118)
3. Last HIV RNA Value Carry Forward (n=150)							
24	-0.194	0.134	0.161	0.154	-0.071	0.103	(-0.273,0.130)
36	-0.181	0.146	0.169	0.159	-0.060	0.110	(-0.275,0.156)
48	-0.189	0.160	0.231	0.170	-0.044	0.120	(-0.279,0.191)

§ TAD₁ – TAD(ER-IR) for qualifying HIV RNA ≥ 30,000 c/mL;
 TAD₂ – TAD(ER-IR) for qualifying HIV RNA < 30,000 c/mL.

4.2 Study AI455-099: HIV RNA Data and Specimen Shipment Status

In the following, several important characteristics to quantify an HIV RNA value in Study AI455-099 were discussed.

First, HIV RNA data in the Study AI455-099 had less frequent replicated HIV RNA measurements per subject per visit, i.e., approximately 1% of the total study HIV RNA measurements. After combining data from central and local labs standard assay along with ultra sensitive assays, there were four subjects with more than one measurement per visit date, and the sponsor choose the *largest* HIV RNA value to generate an on study HIV RNA data set. Additionally there were sixty-nine follow-up windows with more than one HIV RNA value from different visit dates of a study subject, five had one value below and one had one value above LOQ (=50 c/mL) at weeks 24 and 48 that may have influenced the efficacy. However based on the rule selecting HIV RNA on a visit date closest to the study visit date, only one was chosen to be below LOQ. This method of generating HIV RNA data set appears to be reasonable in evaluating efficacy endpoints.

Originally, two variables 'PREPM' and 'FORMENT' in an HIV RNA dataset were used to code an HIV RNA value. The 'PREPM' specifies whether an HIV RNA value was obtained using Roche Amplicor standard assay (PREPM=1) or an ultra-sensitive assay (PREPM=2). The 'FORMENT' specifies the actual method of transfer and entry: e-transfer (FORMENT='VIRAL_LOAD_OUT'), on paper CRF (FORMENT='VIRAL_LOAD'), or on paper follow-up CRF (FORMENT='VIRAL_LOAD_FU'), respectively.

After this reviewer identified the systemic bias between paired HIV RNA data from ambient and frozen specimens in the Study AI455-096, the review team requested that the applicant provide more information regarding specimen shipment in the study AI455-099. The sponsor updated HIV RNA dataset, adding two new variables -'TRANSPRT' and 'EXPENT' into the HIV RNA dataset. The term 'TRANSPRT' indicates whether a specimen was ambient shipped, shipped frozen, or not shipped, i.e., local transfer. The information was obtained from a site-by-site review of HIV RNA specimen handling procedure, not a specimen-by-specimen review of their actual documented in handling procedure. The term 'EXPENT' indicates the expected method of data transfer and entry as to whether or not it was obtained from a local laboratory, and whether or not the data were e-transferred: 1=e-transfer, 2=CRF. In order to identify the local specimens, it is necessary to use both EXPENT and FORMENT variables. Local specimens were those when expected and actual methods of data transfer and entry do not agree, i.e., EXPENT = 1 (e-transfer) and FORMENT = 'VIRAL_LOAD' (CRF).

4.2.1 HIV RNA: Analysis of Effect of Specimen Shipment by Subject

This reviewer examined the effects of specimen shipment status on HIV RNA measurements. Please note that triplets HIV RNA using different shipment per subject per visit date were not available, therefore, comparisons were limited to the group comparisons controlling for qualifying HIV RNA strata. The following analyses included all HIV RNA data points from baseline to Week 48 for 781 patients who had at least one treatment.

The frequencies of subjects' specimens by different shipment during study period are shown in Part I of Table 11 where the analysis was based on individual subject. Overall, the number of subjects (%) whose specimen shipment were always ambient, frozen or local during the study period were 32 (4.2%), 126 (16.1%), and 255 (32.7%), respectively. There were 368 (47.1%) of study subjects who had specimen shipment status change from ambient to frozen during the study period - including approximately 50% of the study subjects in ER group and 47% in IR regimen for qualifying HIV RNA $\geq 30,000$ c/mL, 48% in ER group and 58% in IR regimen for qualifying HIV RNA $< 30,000$ c/mL. The study subjects with their specimen shipment status changed or not is balanced with treatment regimens for both qualifying HIV RNA strata, $p > 0.05$, by the Chi-square tests.

The frequencies of specimen by different shipment during study period are shown in Part II of Table 11 - note that this analysis was based on individual specimen. The proportion of specimens by ambient shipping, frozen shipping or local transfer were similar between treatment groups for qualifying HIV RNA $\geq 30,000$ c/mL stratum, $p > 0.05$, by the Chi-square test. On the contrary, for qualifying HIV RNA $< 30,000$ c/mL stratum, there were 4% more ambient-shipped specimens and 4% more frozen+shipped specimens in the IR group, respectively, than those in the ER group, $p = 0.0002$, by the Chi-square test.

4.2.2 HIV RNA: Analysis of Effect of Specimen Shipment by Qualifying HIV RNA, Treatment and Follow-up Visit

There are a total of 6478 specimens with specimen shipment information available between baseline to Week 48. To compare HIV RNA values in \log_{10} between the ER and the IR groups, the analysis would be stratified by qualifying HIV RNA (2 strata), different shipment (3 strata), and follow-up visit (9 strata). Using the Wilcoxon rank tests, a total of 54 comparisons ($2 \times 3 \times 9$) would be made. A significant difference was found among those subjects with qualifying HIV RNA $\geq 30,000$ c/mL and their specimens were frozen shipped: p value was 0.0384 at Week 16. The HIV RNA values in the ER regimen were significantly higher than in the IR regimen. However, adjusting for multiple comparisons, HIV RNA between the two treatment regimens would not be statistically significantly

different.

This reviewer further compared HIV RNA values between specimen shipment status stratified by qualifying HIV RNA and follow-up visit, combining the two treatment regimens. For qualifying HIV RNA $\geq 30,000$ c/mL, p-values were all < 0.0001 , by the Wilcoxon rank tests. Prior to Week 24, the median HIV RNA values by ambient-shipped specimens were consistently higher than frozen-shipped or local-transferred specimens. From Week 32 onward, the number of specimens with ambient shipping reduced to below 20. Therefore, the comparisons were made between frozen-shipped specimens and local-transferred specimens. HIV RNA measurements by frozen-shipped specimens were more likely greater than those from local-transferred specimens. Similar results were observed for subjects with qualifying HIV RNA $< 30,000$ c/mL, p-values were < 0.001 up to Week 16 by the Wilcoxon rank tests.

Figures 6 & 7 show mean \pm standard error of \log_{10} HIV RNA by different shipment and follow-up visits, for qualifying HIV RNA strata, respectively. Circle, triangle and diamond denote mean HIV RNA values for ambient shipping, frozen shipping and local transfer, respectively. Table 12 lists mean difference in $\log_{10}(\text{HIV RNA})$ between specimen shipment status subgroups by follow-up visits up to Week 24.

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Table 11. AI455-099: Distribution of Specimen Shipment by Qualifying HIV RNA and Treatment Groups

Specimen Shipment	d4T ER		d4T IR	
	n	%	n	%
Part I-Analysis Was Based on Study Subject				
Qualifying HIV RNA \geq 30,000 c/mL*				
Ambient only	10	3.6	8	2.9
Ambient to Frozen	140	50.4	132	47.5
Frozen only	37	13.3	40	14.4
Local only	91	32.7	98	35.3
Total	278	100.0	278	100.0
Qualifying HIV RNA < 30,000 c/mL*				
Ambient only	8	7.0	7	6.2
Ambient to Frozen	56	48.3	66	58.4
Frozen only	13	11.4	12	10.6
Local only	38	33.3	28	24.8
Total	114	100.0	113	100.0
Part II- Analysis Was Based on Individual Specimen				
Qualifying HIV RNA \geq 30,000 c/mL*				
Ambient	483	20.8	446	19.3
Frozen	1041	44.7	1006	43.5
Local	802	34.5	860	37.2
Total	2326	100	2312	100
Qualifying HIV RNA < 30,000 c/mL**				
Ambient	183	19.6	218	24.1
Frozen	419	44.8	444	49.1
Local	333	35.6	243	26.8
Total	935	100	905	100

*. $P > 0.05$ **. $P = 0.0002$, by the Chi-square tests.

Table 12. AI455-099: Mean Difference in Log₁₀(HIV RNA)

	Week						
	-2	0	4	8	12	16	24
Qualifying HIV RNA ≥ 30,000 c/mL							
Ambient-Frozen	0.01	-0.06	0.21	0.21	0.35	0.08	-0.07
Ambient-Local	0.13	0.12	0.39	0.42	0.60	0.37	0.18
Frozen-local	0.12	0.19	0.18	0.21	0.26	0.29	0.25
Qualifying HIV RNA < 30,000 c/mL							
Ambient-Frozen	0.05	0.02	0.31	0.34	0.24	0.06	-0.15
Ambient-Local	0.06	0.12	0.38	0.30	0.43	0.28	-0.01
Frozen-local	0.00	0.10	0.07	-0.04	0.19	0.22	0.13

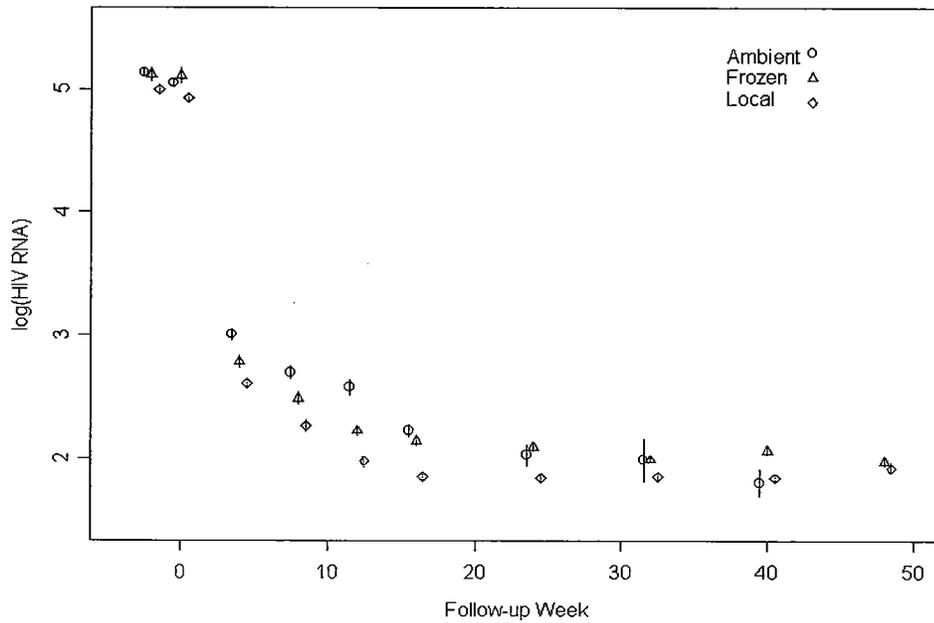


Figure 6. AI455-099: HIV RNA in Log₁₀ by Specimen Shipment for Qualifying HIV RNA ≥ 30,000 c/mL

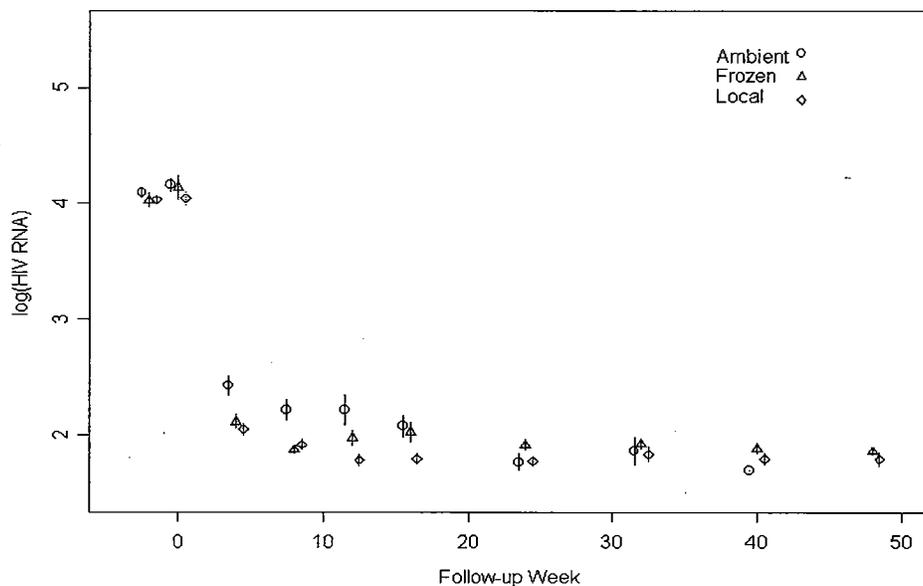


Figure 7. AI455-099: HIV RNA in Log₁₀ by Different Shipment for Qualifying HIV RNA < 30,000 c/mL

4.3 Primary Endpoints: Stratified by Qualifying HIV RNA and Status of Specimen Shipment

This reviewer performed sensitivity analyses and subgroup analyses on two efficacy endpoints - the proportion of subjects with HIV RNA < 400 c/mL through Week 48, and the proportion of subjects with HIV RNA < 50 c/mL through Week 48. The sensitivity analyses adjusting for specimen shipment status were performed in order to examine whether the triple combination regimen d4T ER/3TC/EFV would be similar to the d4T ER/3TC/EFV regimen on these primary endpoints using TLOVR algorithm.

Subjects in AI455-099 were stratified into three groups according to their specimen shipment status: (1) subjects with their specimens shipped ambient first and then subsequently shipped frozen later; (2) subjects with all specimens shipped frozen during entire study period; and (3) subjects with specimens processed locally without shipment. In the first stratum, only those HIV RNA values from frozen-shipped specimens were used, meaning that those HIV RNA measurements obtained from ambient-shipped specimens were set as missing. This analysis excluded 33 subjects with only ambient-shipped specimen: 18 in the ER regimen and 15 in the IR regimen. None of them completed 48 weeks of

treatment.

4.3.1 Comparisons of TLOVR Curves Between ER and IR Regimen By Qualifying HIV RNA and Specimen Shipment

For each of six strata, TLOVR curves between the ER and the IR regimens were compared using SAS Proc LifeTest. Figures 6-7 show the TLOVR curves for HIV RNA < 400 c/mL by qualifying HIV RNA strata, respectively. P-values which test the equality of survival curves between the two treatment regimens ranging from 0.0571 to 0.6389, by the log-rank tests. Figures 8-9 show the TLOVR curves for HIV RNA < 50 c/mL by qualifying HIV RNA strata, respectively. Likewise, no significant treatment difference in survival curves were found for that efficacy: the corresponding p-values range from 0.0774 to 0.7198, by the Logrank tests.

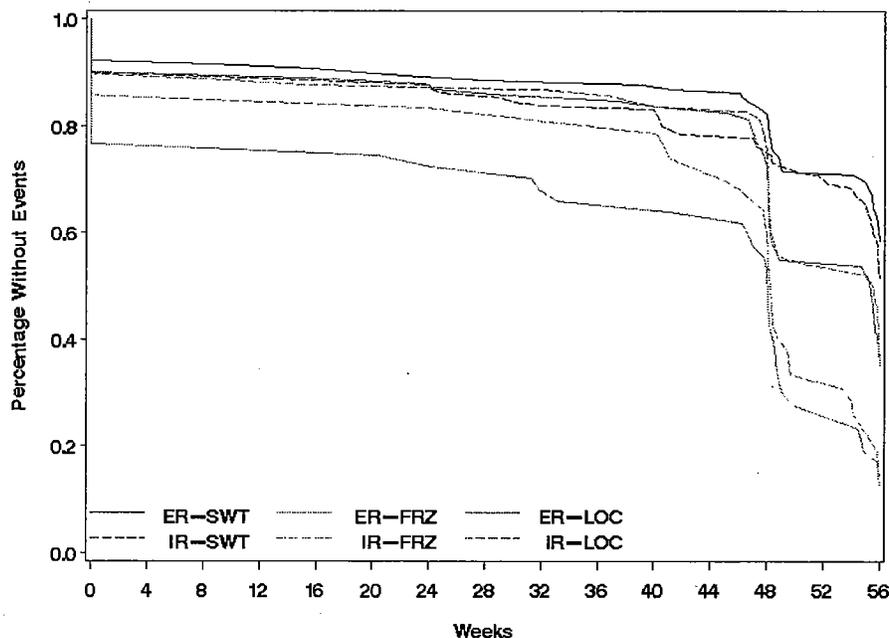


Figure 8: AI455-099: TLOVR Curves (LOQ=400 c/mL) by Specimen Shipping for Qualifying HIV RNA $\geq 30,000$ c/mL

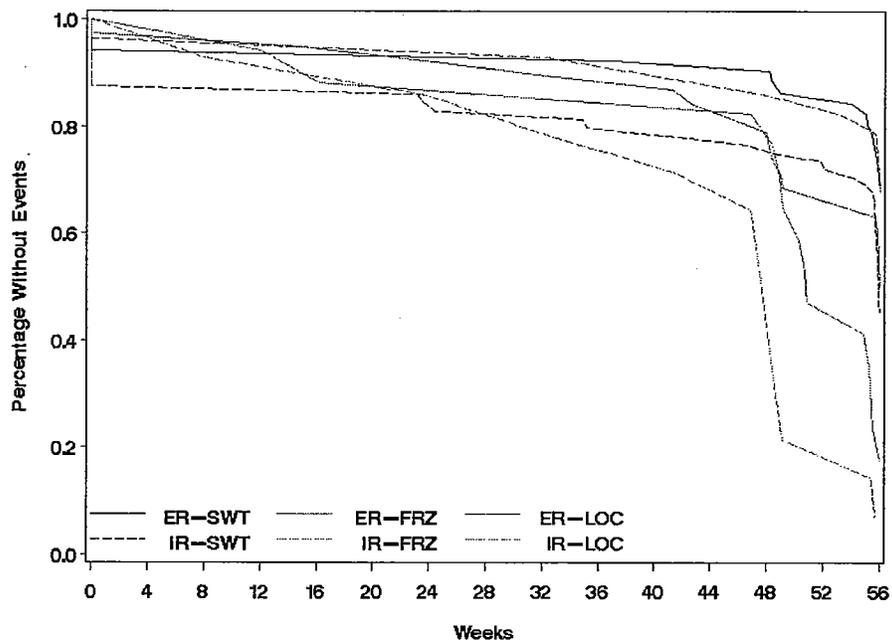


Figure 9: AI455-099: TLOVR Curves (LOQ=400 c/mL) by Specimen Shipping for Qualifying HIV RNA < 30,000 c/mL

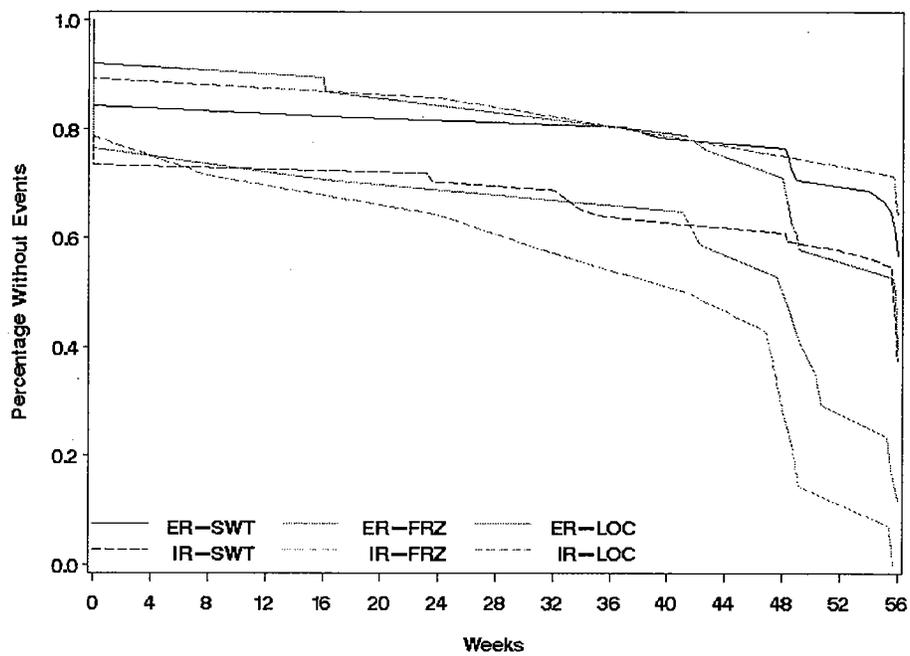


Figure 10: AI455-099: TLOVR Curves (LOQ=50 c/mL) by Specimen Shipping for Qualifying HIV RNA \geq 30,000 c/mL

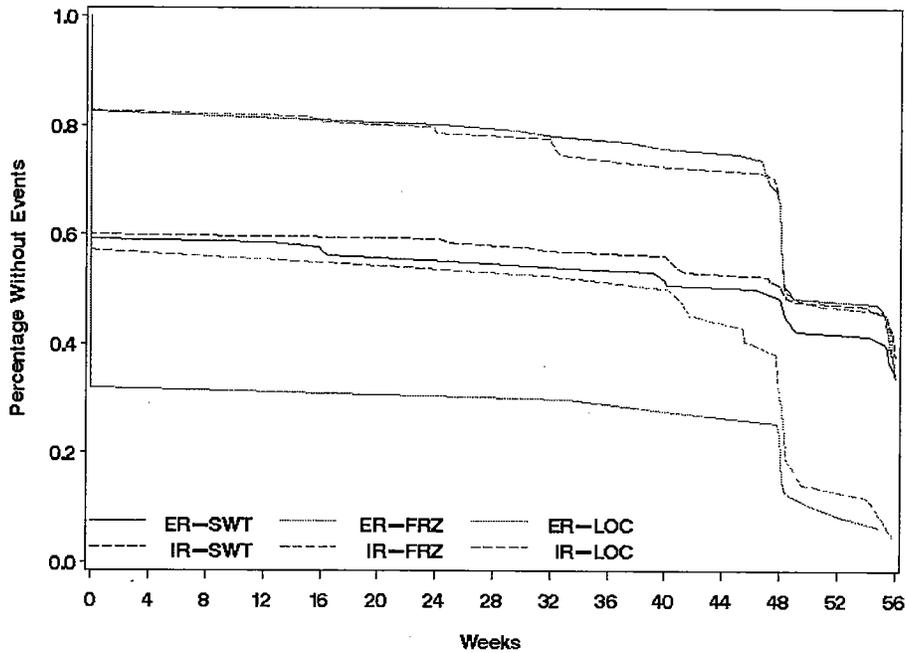


Figure 11: AI455-099: TLOVR Curves (LOQ=50 c/mL) by Specimen Shipping for Qualifying HIV RNA < 30,000 c/mL

4.3.2 Comparisons of TLOVR Curves Among Specimen Shipment Subgroups by Treatment Regimen

The following summarizes results in comparison of TLOVR curves among three specimen shipment subgroups stratifying by treatment regimen and qualifying HIV RNA.

For LOQ=400 c/mL, the TLOVRs through Week 48 were statistically significantly higher for subgroup with specimen shipment switched from ambient to frozen than 'Local' and 'Frozen' subgroups, p-values < 0.0001 by the log-rank tests, in the ER and the IR regimens with qualifying HIV RNA \geq 30,000 c/mL, and in the IR regimen with qualifying HIV RNA < 30,000 c/mL respectively. TLOVR curves in the ER regimen with qualifying HIV RNA < 30,000 c/mL were not statistically significant different.

Analogous results were found for LOQ=50 c/mL, in comparison of the TLOVR curves among three specimen shipment subgroups, stratifying by treatment regimen and qualifying HIV RNA.

Table 13 summarizes observed (Part I) and adjusted (Part II) response rates using TLOVR algorithm. Second and third columns in Table 13 show the TLOVRs by

six subgroups using LOQ=400 c/mL, and the fourth and fifth columns list those using LOQ=50 c/mL, respectively.

The findings for LOQ=400 c/mL are as follows.

The TLOVRs were led by three subgroups in the ER regimen and the other three were led by three subgroups in the IR regimen. The overall differences (ER-IR) in TLOVR at Week 48 were -0.3% and -0.6%, respectively, for shipment 'Local' and 'Frozen' subgroups, and was 0.8% for 'Ambient to Frozen' subgroup.

TLOVR (ER-IR) response rates were computed within the qualifying HIV RNA strata and combined using Cochran-Mantel-Haenszel (CMH) weighting approach with weights proportional to stratum size. The TLOVR (ER-IR) at Week 48 adjusting for qualifying HIV RNA were the same as the unadjusted ones, and the lower bounds of 95% CI of TLOVR (ER-IR) was 0.0% for 'Ambient to Frozen', -12.5% for 'Local' and -20.5% for 'Frozen' subgroup.

- Note that the lower bound of 95% CI in the 'Frozen' subgroup exceeded -12%. This may be due to small sample sizes in qualifying HIV RNA < 30,000 c/mL: n=17 for d4T ER and n=14 for d4T IR regimens.
- In the 'Frozen' subgroup, the TLOVR at Week 48 was greater in the IR regimen than in the ER regimen for qualifying HIV RNA ≥ 30,000 c/mL, and was vice versa for qualifying HIV RNA < 30,000 c/mL. However, this qualitative interaction is not statistically significant by the Chi-square test.

The overall TLOVRs at Week 48 were 83.4% and 81.6% in the ER and the IR regimens, respectively. The overall TLOVRs adjusting for qualifying HIV RNA and specimen shipment were 83.6% and 81.8% in the ER and the IR regimens, respectively. The overall difference TLOVR (ER-IR) at Week 48 adjusting for qualifying HIV RNA and specimen shipment was 1.8% with a lower bound of 95% CI of -3.6%, indicating that the two treatment regimens had similar efficacy.

4.3.3 Comparisons of TLOVR at Week 48 Between Treatment Regimens for Those Who Had Ambient-shipped Specimens

One drawback of the above method was that the HIV RNA information from ambient-shipped specimens were discarded. This reviewer performed additional analysis for a subgroup of subjects who had ambient-shipped specimen during study period. This analysis included 33 subjects who had only ambient-shipped specimens and 375 subjects with specimen shipment status change from ambient to frozen. For LOQ=400 c/mL, the adjusted TLOVRs were reduced to 80.4% and 73.3% in the ER and the IR regimens. However, the TLOVR(ER-IR) estimate and 95% CI adjusting for qualifying HIV RNA was 7.0% (-1.2%,15.2%), close to

the results where HIV RNA from ambient-shipped specimens were ignored in Table 13. For LOQ=50 c/mL, the TLOVR(ER-IR) estimate and 95% CI adjusting for qualifying HIV RNA was -0.9% (-10.6%,8.8%).

**Table 13: TLOVR: Proportions of HIV RNA < LOQ at Week 48
 by Specimen Shipment**

Specimen Shipment	% of HIV RNA < 400 c/mL		% of HIV RNA < 50 c/mL			
	ER n/N (%)	IR n/N (%)	ER n/N (%)	IR n/N (%)		
Part I: Observed TLOVR at Week 48						
Qualifying HIV RNA ≥ 30,000 c/mL						
Local	74/91(81)	<u>80/98(82)</u>	65/91 (71)	71/98 (72)		
Frozen-shipped Only	32/47 (68)	<u>33/42 (79)</u>	12/47 (26)	16/42 (38)		
Ambient to Frozen	112/130 (86)	105/130 (81)	64/130 (49)	69/130 (53)		
Qualifying HIV RNA < 30,000 c/mL						
Local	32/38 (84)	<u>27/28 (96)</u>	28/38 (74)	24/28 (86)		
Frozen-shipped Only	15/17 (88)	11/14 (79)	9/17 (53)	9/14 (64)		
Ambient to Frozen	47/51(92)	51/64 (80)	39/51 (76)	40/64 (63)		
Overall						
Local	106/129 (82)	107/126 (85)	93/129 (72)	95/126 (75)		
Frozen-shipped Only	47/64 (73)	44/56 (79)	21/64 (33)	25/56 (45)		
Ambient to Frozen	159/181 (88)	156/194 (80)	103/181 (57)	109/194 (56)		
Total	312/374 (84)	307/376 (82)	217/374 (58)	229/376 (61)		
Part II: TLOVR(ER-IR) Adjusting for Qualifying HIV RNA and Specimen Shipment						
	P _{ER} -P _{IR}	P _{ER} IR	95%CI	P _{ER} -P _{IR}	P _{ER} IR	95%CI
Local	82.1-85.5	-3.4	-12.5,5.7	72.0-75.9	-3.9	-14.7,6.9
Frozen	73.7-78.6	-5.3	-20.5,10.0	32.6-44.8	-12.2	-29.2,4.7
Ambient to Frozen	88.0-80.4	7.6	0.0,15.0	57.6-56.0	1.6	-8.3,11.5
Total*	83.6-81.8	1.8	-3.6,7.2	58.5-61.0	-2.5	-9.2,4.3

*. Adjusting for qualifying HIV RNA and specimen shipment (six strata).

Additional sensitivity analyses were performed to stratify specimen shipment status as 'Local', 'Frozen-shipped only' and 'Ever Ambient-shipped'. The third group includes subjects who had at least one ambient-shipped specimen. The results of TLOVR (ER-IR) are listed in Table 14. For LOQ=400 c/mL, the overall difference TLOVR (ER-IR) estimate at Week 48 and 95% CI adjusting for qualifying HIV RNA and specimen shipment was 1.8% (-3.9%,7.5%). For LOQ=50 c/mL, the overall difference TLOVR (ER-IR) estimate at Week 48 and 95% CI adjusting for qualifying HIV RNA and specimen shipment was -3.6% (-10.3%,3.1%).

Table 14: TLOVR: Proportions of HIV RNA < LOQ at Week 48 for Those Subjects Who Had Ambient-shipped Specimen*

	% of HIV RNA < 400 c/mL		% of HIV RNA < 50 c/mL			
	ER n/N (%)	IR n/N (%)	ER n/N (%)	IR n/N (%)		
Qualifying HIV RNA						
≥ 30,000 c/mL	113/140 (81)	104/138 (75)	65/140 (46)	70/138 (51)		
< 30,000 c/mL	47/59 (80)	49/71 (69)	37/59 (63)	40/71 (56)		
	P_{ER}-P_{IR}	P_{ER}-IR	95%CI	P_{ER}-P_{IR}	P_{ER}-IR	95%CI
Adjusted**	80.4-73.3	7.0	-1.2,15.2	51.6-52.5	-0.9	-10.6,8.8
Total***	79.8-78.1	1.8	-3.9,7.5	55.3-59.0	-3.6	-10.3,3.1

*. Using all HIV RNA data points from subjects with ambient-shipped specimens (n=33) and those with specimen shipment switched from ambient to frozen (n=275). **. Adjusting for qualifying HIV RNA.

***Adjusting for three specimen shipment status and qualifying HIV RNA.

4.4 Temporal Trend and Time-Averaged Difference Change from Baseline in log₁₀ HIV RNA

The temporal trend in the mean change from baseline in plasma HIV RNA (log₁₀ c/mL) is shown in Figure 12 for the ER and IR regimens stratified by qualifying HIV RNA as higher (H_{rna}: ≥ 30,000 c/mL) and lower (L_{rna}: <30,000 c/mL). The HIV RNA data set was generated using the updated HIV RNA data set received on May 30, 2002. Please note at Week 48, HIV RNA data were available in approximately 86% of the study population.

Plasma HIV RNA had a sharp drop of about 2.0 log₁₀ prior to Week 4; this decline continued in a slower pace until Week 24. At week 8, the mean change from baseline in plasma HIV RNA was -2.5 to -2.6, for qualifying HIV RNA ≥ 30,000 c/mL strata, and -2.1 for both qualifying HIV RNA < 30,000 c/mL strata.

This reviewer conducted three types of TAD analyses at different time intervals: through Week 8, 16, 24, 32, 40 and 48. A visit window was defined from Day 1 of therapy to the midpoints between the two consecutive scheduled visits. An overall TAD was a weighted one adjusting for qualifying HIV RNA strata for subjects in the treated population. Calculation methods were defined as:

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

Table 15 illustrates the TAD results in terms of plasma HIV RNA. Overall, the TAD_{ER-IR} estimate and the standard error depend on the method of calculation. For a given time interval, a large variation of TAD_{ER-IR} is associated with the

BVCF method.

For qualifying HIV RNA $\geq 30,000$ c/mL, majority of the estimated TAD_1 values are positive. Conversely, TAD_2 values are predominately negative. The absolute TAD_{ER-IR} values are all less than 0.05 with the upper limits of 95% CI of the TAD_{ER-IR} adjusting for qualifying HIV RNA are all less than 0.1, supporting the similar effect between the ER and the IR regimens on HIV RNA suppression during 48 weeks of treatment.

Through Week 24, the largest estimated $|TAD_{ER-IR}|$ was obtained from the BVCF, where $TAD_{ER-IR} = 0.014$ with 95% CI of (-0.11,0.08); the smallest $|TAD_{ER-IR}|$ was obtained from the LOCF, where $TAD_{ER-IR} = 0.0066$ with 95% CI of (-0.08,0.09). These estimates were analogous with the sponsor's result: $TAD_{ER-IR} = 0.01$ with 95% CI (-0.08,0.06).

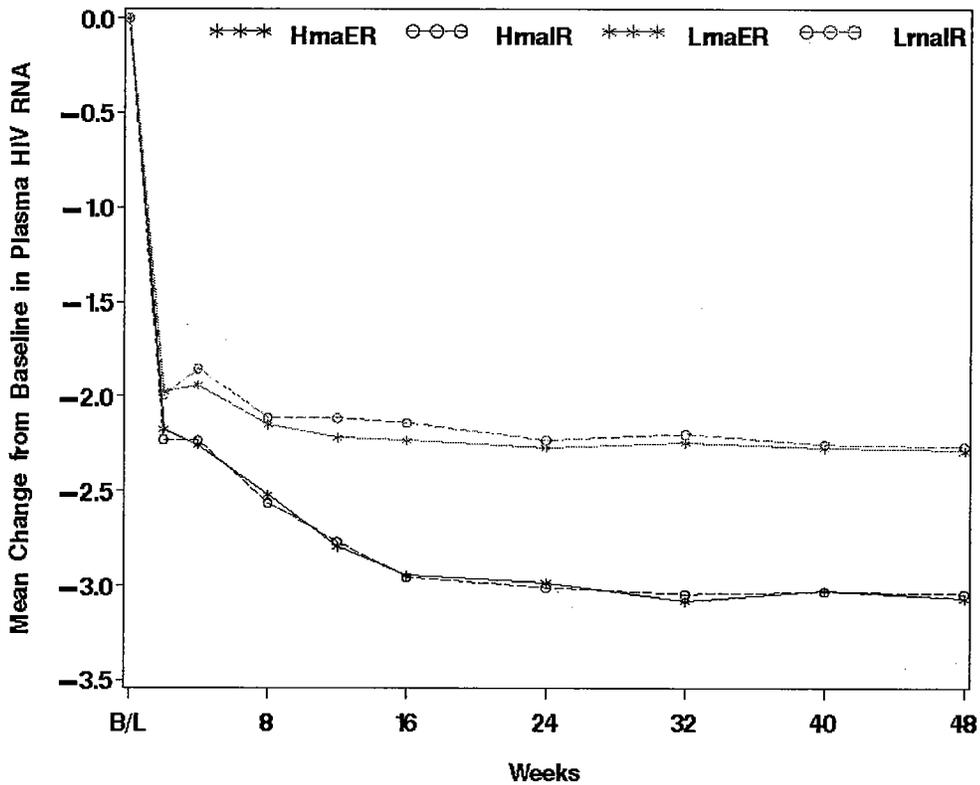


Figure 12: AI455-099: Mean Change from Baseline in Plasma HIV RNA (\log_{10} c/mL) by Treatment Regimen and Qualifying HIV RNA

Table 15. AI455-099: Time-Average Difference Change From Baseline in log₁₀ HIV RNA Adjusting for Qualifying HIV RNA

Through Week	TAD ₁	Se(TAD ₁)	TAD ₂	Se(TAD ₂)	TAD _{ER-IR}	Se(TAD _{ER-IR})	95%CL
Last TAD Carry Forward (n=766)							
8	-0.0132	0.0381	-0.0515	0.0698	-0.0242	0.0338	(-0.0905, 0.0420)
16	0.0042	0.0397	-0.0625	0.0721	-0.0151	0.0351	(-0.0839, 0.0537)
24	0.0082	0.0423	-0.0728	0.0750	-0.0151	0.0371	(-0.0878, 0.0575)
32	0.0066	0.0445	-0.0696	0.0770	-0.0154	0.0387	(-0.0994, 0.0604)
40	-0.0031	0.0460	-0.0665	0.0785	-0.0214	0.0398	(-0.0966, 0.0566)
48	-0.0071	0.0473	-0.0652	0.0795	-0.0239	0.0407	(-0.1037, 0.0560)
Last Observation Carry Forward (n=781)							
8	0.0137	0.0402	0.0199	0.0661	0.0155	0.0344	(-0.0519, 0.0829)
16	0.0048	0.0463	-0.0019	0.0749	0.0028	0.0394	(-0.0744, 0.0801)
24	0.0124	0.0492	-0.0075	0.0793	0.0066	0.0418	(-0.0753, 0.0886)
32	0.0046	0.0516	-0.0012	0.0821	0.0029	0.0437	(-0.0827, 0.0886)
40	-0.0017	0.0532	0.0042	0.0840	0.0000	0.0449	(-0.0881, 0.0881)
48	-0.0040	0.0546	0.0059	0.0852	-0.0011	0.0460	(-0.0912, 0.0890)
Baseline Value Carry Forward (n=781)							
8	-0.0132	0.0462	0.0079	0.0805	-0.0071	0.0402	(-0.0859, 0.0718)
16	0.0130	0.0509	-0.0468	0.0838	-0.0043	0.0435	(-0.0897, 0.0810)
24	0.0042	0.0571	-0.0583	0.0899	-0.0139	0.0482	(-0.1084, 0.0806)
32	0.0050	0.0625	-0.0822	0.0943	-0.0203	0.0521	(-0.1225, 0.0818)
40	-0.0073	0.0666	-0.0873	0.0978	-0.0305	0.0551	(-0.1385, 0.0776)
48	-0.0288	0.0707	-0.0984	0.1015	-0.0489	0.0582	(-0.1630, 0.0651)

TAD₁ – TAD for baseline HIV RNA ≥ 30,000 c/mL. TAD₂ - TAD for baseline HIV RNA < 30,000 c/mL.

4.5 Temporal Trend and Time-Average Difference Change from Baseline CD4+ Cell Count

The temporal trend in the mean change from baseline in CD4+ cell count (cells/mm³) is shown in Figure 13 using observed CD4+ cell count data. Denoted by Hrna and Lrna for qualifying HIV RNA ≥ 30,000 c/mL and < 30,000 c/mL, and ER and IR as treatment regimens respectively, four lines in Figure 13 are for HrnaER, LrnaER, HrnaIR and LrnaIR groups. There is one subject with no baseline CD4+ cell count, a CD4=534 cells/mm³ was replaced by the CD4 at Week 4 (615) adjusting for the group mean increment (81).

Different from HIV RNA data, mean change from baseline in CD4+ cell count increased in the entire study period. At week 48, CD4+ cell count data were available in approximately 82% of the treated subjects, the mean change from baseline in CD4+ cell count was 213, 204, 176 and 124 for HrnaER, HrnaIR, LrnaER and LrnaIR groups. For Hrna strata, no significant difference in mean CD4+ cell count change from baseline was found between the ER and the IR groups by the Wilcoxon test. For Lrna strata, the ER regimen appears to have

better treatment responses than the IR regimen from Week 12 onward. By the Wilcoxon test, the statistically significant differences between treatment regimens were reached at Week 12 ($p=0.0131$) and at Week 48 ($p=0.0064$).

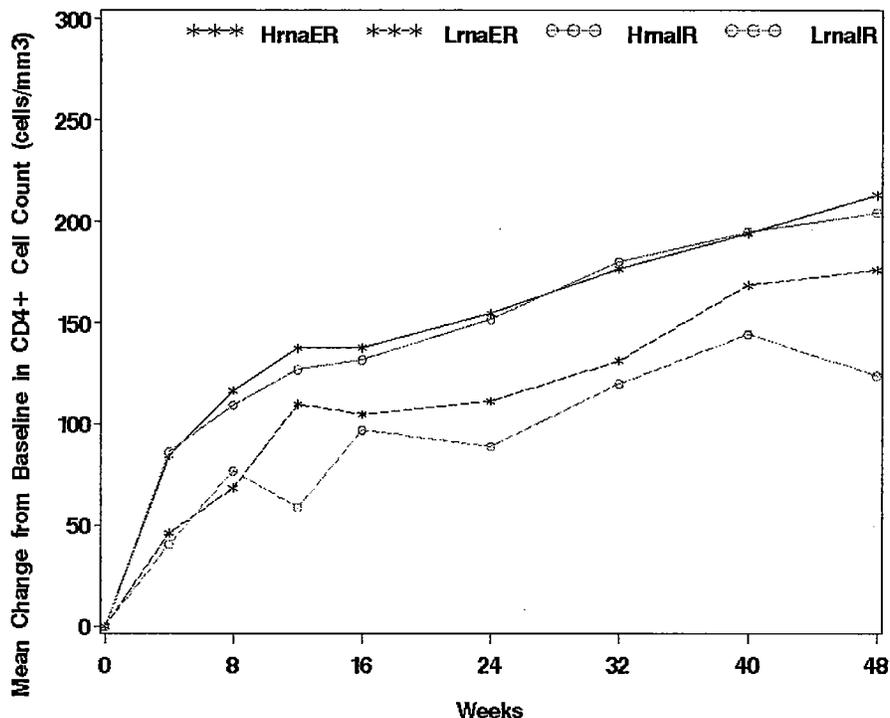


Figure 13: AI455-099: Mean Change from Baseline in CD4+ Cell Count (cells/mm³) by Treatment Regimen and Qualifying HIV RNA

Similar to TAD analyses for HIV RNA, this reviewer applied three methods to obtain TAD change from baseline CD4+ cell count through Weeks 8, 16, 24, 32, 40 and 48 for subjects with at least one treatment. Likewise, the overall TAD_{ER-IR} values are those adjusting for qualifying HIV RNA.

The findings are as follows. From Week 16 onward, the estimated TAD₁(ER-IR) for qualifying HIV RNA $\geq 30,000$ c/mL (Hrna), TAD₂(ER-IR) for qualifying HIV RNA $< 30,000$ c/mL (Lrna), and the overall TAD_{ER-IR} adjusting for qualifying HIV RNA were predominately positive and stable. The mean TAD estimates through Week 48 by the LOCF were 143, 140, 105 and 90 (cells/mm³) for HrnaER, HrnaIR, LrnaER, and LrnaIR subgroups.

Comparing among three methods, the overall TAD_{ER-IR} and 95% CI estimates through Week 48 were 6.7 with 95% CI of (-8.0,21.5) by the LTadCF, 6.1 (-8.7,20.9) by the LOCF, and 8.8 (-6.0,23.5) by the BVCF. Note that the TAD_{ER-IR}

estimates were all less than 9 cells/mm³, not significantly from zero by the Wald tests, $p > 0.05$, indicating that the treatment effects in CD4+ cell count increase were not statistically significantly different between the ER and the IR regimens.

In addition, the TAD_{ER-IR} and standard error estimates through Week 24 adjusting for qualifying HIV RNA strata by the reviewer were close to sponsor's results, despite the fact that different approaches were used for calculations.

Table 16: Time-Average Difference Change From Baseline CD4 Cell Counts[§]

Through Week	TAD ₁	Se(TAD ₁)	TAD ₂	Se(TAD ₂)	TAD _{ER-IR}	Se(TAD _{ER-IR})	95%CL
Last TAD Carry Forward							
8	-1.14	5.94	-0.05	11.08	-0.83	5.30	(-11.22,9.56)
16	2.44	6.95	15.53	12.64	6.21	6.14	(-5.83,18.26)
24	3.04	7.41	17.64	13.32	7.25	6.53	(-5.54,20.04)
32	2.05	7.80	16.14	14.24	6.12	6.91	(-7.42,19.65)
40	0.47	8.26	17.45	14.89	5.37	7.28	(-8.89,19.64)
48	0.37	8.62	22.43	15.08	6.73	7.52	(-8.01,21.47)
Last Observation Carry Forward							
8	-0.21	6.03	0.84	11.23	0.10	5.38	(-10.44,10.64)
16	3.88	6.86	10.35	12.51	5.75	6.07	(-6.15,17.65)
24	4.42	7.37	9.52	13.36	5.90	6.51	(-6.86,18.67)
32	3.35	7.80	10.25	14.16	5.35	6.89	(-8.16,18.86)
40	2.13	8.27	11.63	14.89	4.89	7.29	(-9.40,19.17)
48	2.40	8.65	15.31	15.14	6.14	7.55	(-8.65,20.94)
Baseline Value Carry Forward							
8	-6.98	7.71	2.53	15.54	-4.22	7.09	(-18.11,9.67)
16	1.78	7.02	16.92	12.14	6.17	6.10	(-5.79,18.12)
24	2.76	7.64	18.99	14.78	7.47	6.91	(-6.08,21.02)
32	2.18	8.01	18.77	14.06	6.99	7.00	(-6.72,20.70)
40	2.64	8.25	20.45	14.74	7.81	7.25	(-6.40,22.01)
48	2.82	8.71	23.30	14.65	8.75	7.50	(-5.95,23.46)

[§]TAD₁-TAD(ER-IR) for qualifying HIV RNA $\geq 30,000$ c/mL. TAD₂-TAD(ER-IR) for qualifying HIV RNA $< 30,000$ c/mL.

4.6 Reviewer's Summary

The following summarizes the association between HIV RNA measurements and specimen process status and specimen shipment status.

1. In Study AI455-096, a positive bias (median=0.19 log₁₀, mean=0.33 log₁₀) was observed using the paired HIV RNA data. Sensitivity analyses on TAD in HIV RNA adjusting for qualifying HIV RNA strata sustained a similar effect between the ER and the IR regimens through Week 48. The upper

limits of 95% CI of the adjusted TAD estimates were all less than 0.5 in \log_{10} , the non-inferiority margin. The estimated TAD values using different methods of generating HIV RNA data sets due to repeated measurements, including those from frozen and ambient-paired samples, showed differences possibly not great enough to negate non-inferiority.

In Study AI455-099,

2. For each follow-up visit, the HIV RNA measurements were not statistically significantly different between the ER and the IR regimens, adjusting for qualifying HIV RNA strata and specimen shipment using a type I error level adjusting for multiple comparisons.
3. The HIV RNA measurements were associated with specimen shipment status: $p < 0.0001$ for qualifying HIV RNA $\geq 30,000$ c/mL and $p < 0.001$ for qualifying HIV RNA $< 30,000$ c/mL, respectively, by the Wilcoxon tests.
4. For qualifying HIV RNA $\geq 30,000$ c/mL, the mean HIV RNA measurement for ambient-shipped specimens appeared to be statistically significantly greater than those specimen shipped frozen and those with local transfer. The mean difference of HIV RNA between ambient-shipped specimens and frozen-shipped specimen ($\Delta\mu$) ranging from 0.2 to 0.35 through Week 12; $\Delta\mu$ (ambient shipping - local transfer) ranging from 0.4 to 0.6 through Week 16; $\Delta\mu$ (frozen shipping - local transfer) ranging from 0.2 to 0.3 between Week 0 and Week 24.
5. Similar findings were observed for qualifying HIV RNA $< 30,000$ c/mL. The mean HIV RNA measurement by ambient-shipped specimens appeared to be statistically significantly higher than those by frozen-shipped specimens and local-transferred specimens. $\Delta\mu$ (ambient-shipped – frozen-shipped specimens) had a range from 0.2 to 0.3 between Week 4 and Week 12; $\Delta\mu$ (ambient-shipped – local-transferred specimens) had a range from 0.3 to 0.4 between Week 0 and Week 16; $\Delta\mu$ (frozen-shipped – local-transferred specimens) had a range from 0.2 to 0.3 between Week 4 to Week 16. At baseline, however, the mean HIV RNA was not statistically significantly different between frozen-shipped specimens and ambient-shipped specimens.
6. A maximum mean difference of 0.60 and 0.43 \log_{10} c/mL between ambient-shipped specimens and local-transferred specimens were observed at Week 12 for qualifying HIV RNA $\geq 30,000$ c/mL and $< 30,000$ c/mL, respectively. In other words, the mean HIV RNA value at Week 12 for ambient-shipped specimens *may be* four times as high as local-transferred specimens: *The reasons for such a difference are not clear. These observed data were not collected to show sources of variation.* Lew J. et al. reported a total average standard deviation (std) 0.6 \log_{10} c/mL which includes variations from intra-assay (std=0.2 \log_{10}), inter-assay, and biological (Lew J. et al. Minireview:

Determinations of Levels of Human Immunodeficiency Virus Type I RNA in Plasma: Reassessment of Parameters Affecting Assay Outcome. *J. Clin. Microbiol* 1998, 36 (6): 1471-1479.

The following summarizes sensitivity and subgroup analyses regarding efficacy endpoints in Study AI455-099.

1. Adjusting for specimen shipment status and qualifying HIV RNA, the TLOVR (LOQ=400 c/mL) difference estimate of and 95% CI at Week 48 were 1.8% (-3.6%,7.2%) for analyses ignoring those who had only ambient-shipped specimens; and 1.8% (-3.9%,7.5%) for analyses including those who had only ambient-shipped specimens.
2. Subgroup analyses on TLOVR with LOQ=400 c/mL showed that the ER regimen was doing slightly worse than the IR regimen for those subjects in sites where specimens did not need transportation, and those subjects whose specimens were shipped frozen during study period.
3. Longitudinal virologic suppression measured by TAD change from baseline in HIV RNA through Week 48 showed that the absolute TAD_{ER-IR} values were all less than 0.05. The upper limits of 95% CI of the adjusted TAD were all less than 0.1 ($<0.5\log_{10}$). No treatment effect was found on reduction in plasma HIV RNA by the Wald t-tests ($p>0.05$).
4. Longitudinal immunologic response measured by TAD change from baseline in CD4+ cell count estimates (cells/mm³) through Week 48 using LOCF were: 143 in the ER regimen and 140 in the IR regimen for qualifying HIV RNA $\geq 30,000$ c/mL; 105 in the ER regimen and 90 in the IR regimen for qualifying HIV RNA $< 30,000$ c/mL. The overall TAD(ER-IR) estimate and 95% CI was 6.1 (-8.7,20.9) for treatment population. No treatment difference between the ER and IR regimens was found on increase in CD4+ cell count.

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5. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

Subgroup analysis were performed to investigate:

- (1) Whether the temporal patterns in virologic suppressions and immunologic responses were consistent with the overall pattern in gender, race, age, and weight subgroups
- (2) Whether there were treatment differences among gender, race, age, and weight subgroups and
- (3) Whether subjects in subgroups of gender, race, age and weight had different response to the ER or IR regimen.

In the following analysis the ethnic subgroup subjects consist of White, Black and Hispanic subjects, representing 90% of the entire study population. Using a median age of 33 years old as the cut-point, younger age group is for subjects with age < 33; and older is for age \geq 33. Baseline weight has two strata: < 60 kg and \geq 60 kg.

Section 5.1 offers a comparison of baseline plasma HIV RNA and CD4+ cell count among demographic characteristics for data sets by qualifying HIV RNA and treatment regimens.

Section 5.2 summarizes comparisons of longitudinal virologic suppression by gender, race, age and weight subgroups.

Section 5.3 summarizes comparisons of longitudinal immunologic responses by gender, race, age and weight subgroups.

Section 5.4 looks at associations between subjects' diarrhea status and longitudinal virologic and immunologic response.

Sections 5.5-5.6 investigate longitudinal virologic and immunologic responses by alternative subgroups of baseline HIV RNA and baseline CD4+ cell count.

5.1 Comparisons of Baseline Plasma HIV RNA and CD4+ Cell Count among Gender, Race, Age, and Weight Subgroups

Baseline plasma HIV RNA and CD4+ cell count may be associated with a change from baseline in plasma HIV RNA and CD4+ cell count. Therefore, this reviewer has summarized baseline plasma HIV RNA and CD4+ cell count and gender, race and age subgroups stratifying by qualifying HIV RNA and treatment regimens.

The Wilcoxon test was used for the comparisons of baseline plasma HIV RNA and CD4+ cell count among subgroups of concern.

Tables 17 and 18 show basic statistics of baseline \log_{10} HIV RNA (c/mL) and CD4+ cell count (cells/mm³) by baseline demographic characteristics using data sets stratified by qualifying HIV RNA and treatment regimen..

For baseline plasma HIV RNA, no significant differences were found among gender, race, age or weight subgroups, respectively.

For baseline CD4+ cell counts, no significant difference was found among gender, or race subgroups.

At baseline, younger age group had greater mean CD4+ cell count than the older age group. The mean differences Δ_{CD4} were:

- for subjects with qualifying HIV RNA $\geq 30,000$ c/mL, $\Delta_{CD4} = 65$ cells/mm³, $p=0.0006$, in the ER regimen; $\Delta_{CD4}=24$ ($P>0.05$) in the IR regimen;
- for subjects with qualifying $<30,000$ c/mL: $\Delta_{CD4}=71$ in the ER regimen ($p=0.0412$) and $\Delta_{CD4}=85$ ($p=0.0118$) in the IR regimen, respectively.

At baseline, for subjects in the IR regimen with qualifying HIV RNA $\geq 30,000$ c/mL, the mean (median) CD4+ cell count was 68 cells/mm³ (43) greater in higher weight group than those in the lower weight group ($p=0.0145$).

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Table 17: Baseline Plasma HIV RNA in log₁₀ by Gender, Race* and Age Subgroups

STRATA [§]			n	mean	std	minimum	maximum	median
1	ER	Male	197	5.03	0.48	3.48	5.88	5.04
1	ER	Female	81	5.04	0.56	3.15	5.88	5.06
1	IR	Male	203	5.02	0.47	3.67	5.88	5.04
1	IR	Female	75	4.95	0.54	3.40	5.88	4.98
2	ER	Male	70	4.18	0.56	2.79	5.85	4.19
2	ER	Female	44	4.06	0.40	3.17	5.07	4.08
2	IR	Male	70	4.13	0.50	2.60	5.61	4.13
2	IR	Female	43	4.05	0.57	2.87	5.88	4.01
1	ER	White	127	5.07	0.50	3.94	5.88	5.04
1	ER	Black	64	5.01	0.57	3.15	5.88	5.09
1	ER	Hispanic	52	5.00	0.43	3.98	5.88	5.01
1	IR	White	116	5.04	0.48	3.78	5.88	5.03
1	IR	Black	57	5.04	0.51	3.40	5.88	5.01
1	IR	Hispanic	64	4.97	0.44	3.98	5.86	4.98
2	ER	White	41	4.16	0.42	3.35	5.30	4.16
2	ER	Black	27	4.23	0.42	3.40	5.07	4.24
2	ER	Hispanic	34	4.09	0.66	2.79	5.85	4.11
2	IR	White	47	4.19	0.52	3.16	5.61	4.16
2	IR	Black	18	4.07	0.61	3.18	5.88	3.99
2	IR	Hispanic	34	4.03	0.54	2.60	5.37	4.10
1	ER	<33	125	5.01	0.55	3.15	5.88	5.00
1	ER	≥33	153	5.06	0.46	3.94	5.88	5.10
1	IR	<33	137	4.99	0.49	3.40	5.88	5.06
1	IR	≥33	141	5.01	0.49	3.62	5.88	5.01
2	ER	<33	59	4.09	0.38	3.35	5.03	4.14
2	ER	≥33	55	4.18	0.61	2.79	5.85	4.16
2	IR	<33	56	4.06	0.52	2.60	5.88	4.02
2	IR	≥33	57	4.14	0.54	2.87	5.61	4.13
1	ER	<60kg	60	5.07	0.47	4.06	5.88	5.03
1	ER	≥60kg	218	5.03	0.51	3.15	5.88	5.05
1	IR	<60kg	69	5.05	0.51	3.62	5.88	5.13
1	IR	≥60kg	209	4.99	0.48	3.40	5.88	5.00
2	ER	<60kg	23	4.02	0.53	2.79	5.07	4.09
2	ER	≥60kg	91	4.16	0.50	3.19	5.85	4.16
2	IR	<60kg	30	4.03	0.62	2.87	5.88	4.00
2	IR	≥60kg	83	4.13	0.49	2.60	5.61	4.11

*. Race: Other racial groups were excluded due to small sample sizes.

§ Strata: 1- qualifying HIV RNA ≥30,000c/mL; 2- qualifying HIV RNA <30,000c/mL.

Table 18: Baseline CD4+ Cell Count by Gender, Race* and Age Subgroups

STRATA [§]			n	mean	std	minimum	maximum	median
1	ER	Male	197	293.97	163.48	62.00	968.00	247.00
1	ER	Female	81	269.69	163.03	65.00	1044.00	233.00
1	IR	Male	203	296.00	163.41	61.00	877.00	246.00
1	IR	Female	75	280.31	166.58	61.00	836.00	259.00
2	ER	Male	70	361.49	173.38	67.00	1022.00	354.50
2	ER	Female	44	400.66	157.50	105.00	854.00	417.00
2	IR	Male	70	422.44	228.79	85.00	1215.00	379.00
2	IR	Female	43	380.28	193.82	96.00	879.00	349.00
1	ER	White	127	307.59	188.36	62.00	1044.00	276.00
1	ER	Black	64	261.25	127.53	65.00	574.00	230.50
1	ER	Hispanic	52	295.46	156.32	77.00	812.00	265.00
1	IR	White	116	298.36	164.06	61.00	877.00	263.50
1	IR	Black	57	310.93	172.94	81.00	836.00	259.00
1	IR	Hispanic	64	302.69	171.16	78.00	812.00	252.50
2	ER	White	41	352.44	152.13	99.00	660.00	352.00
2	ER	Black	27	350.37	128.79	109.00	616.00	357.00
2	ER	Hispanic	34	392.82	198.04	67.00	1022.00	352.00
2	IR	White	47	462.09	251.59	85.00	1215.00	452.00
2	IR	Black	18	335.72	144.42	96.00	674.00	301.50
2	IR	Hispanic	34	412.94	199.50	125.00	986.00	442.00
1	ER	<33	125	322.82	176.16	65.00	1044.00	296.00
1	ER	≥33	153	257.55	146.39	62.00	968.00	220.00
1	IR	<33	137	304.12	170.82	61.00	877.00	276.00
1	IR	≥33	141	279.77	157.01	73.00	812.00	230.00
2	ER	<33	59	410.68	172.82	105.00	1022.00	412.00
2	ER	≥33	55	340.05	155.64	67.00	854.00	347.00
2	IR	<33	56	449.04	213.88	85.00	1215.00	450.00
2	IR	≥33	57	364.51	212.11	109.00	879.00	266.00
1	ER	<60kg	60	258.02	139.02	76.00	809.00	228.50
1	ER	≥60kg	218	294.92	168.85	65.00	1044.0	255.50
1	IR	<60kg	69	240.58	113.19	61.00	593.00	221.00
1	IR	≥60kg	209	308.47	174.73	61.00	877.00	264.00
2	ER	<60kg	23	423.70	237.36	99.00	1022.0	381.00
2	ER	≥60kg	91	364.64	144.54	67.00	807.00	358.00
2	IR	<60kg	30	365.53	158.85	85.00	601.00	375.00
2	IR	≥60kg	83	421.17	232.62	125.00	1215.0	357.00

*. Race: Other racial groups were excluded due to small sample sizes.

§ Strata: 1- qualifying HIV RNA ≥30,000c/mL; 2- qualifying HIV RNA <30,000c/mL.

5.2 Mean Change from Baseline in Plasma HIV RNA

In the following, this reviewer examined gender, age, race and baseline weight difference in efficacy by comparing mean change from baseline in HIV RNA longitudinally. Note: no significant difference was found at baseline among gender, race, and age, or baseline weight subgroups, stratified by qualifying HIV RNA and treatment regimen, *for example* the mean difference (male-female) in HIV RNA is around 0.08 log₁₀ for both qualifying HIV RNA strata.

5.2.1 Gender Comparisons

The gender difference in virologic response is of concern since women infected with HIV-1 consistently had lower levels of plasma HIV RNA than men at a similar stage of HIV infection (**Brian Boyle: Patient Gender Really Does Matter When It Comes to HIV Viral Load Levels**).

In this study, all four mean HIV RNA curves are extremely close to each other from Week 16 forward, for qualifying HIV RNA < 30,000 c/mL. Seemingly, no further analyses will be needed.

Figure 14 shows the mean for subjects with qualifying HIV RNA ≥30,000 c/mL curves by gender and treatment regimens.

- No significant treatment difference was found by gender subgroup, though a mean difference (i.e., **ER - IR**) in change from baseline HIV RNA among females was discovered a **-0.3** for **Week 24** and a **-0.27** for **Week 48**, respectively.
- Females had a range of **0.17 – 0.28 log₁₀** more reductions in mean change from baseline HIV RNA in the **IR** regimen than males during **Week 4** to **Week 24**, **p-values** range from **0.03** to **0.0004** by the Wilcoxon tests.
- In the **ER** regimen, **no significant gender difference** was found.

5.2.2 Race Comparisons

Figures 15 and **16** show the trend of the mean change from baseline in plasma HIV RNA by race and treatment, respectively, for qualifying HIV RNA strata. **Table 19** list **p-values** by the Wilcoxon tests for the comparisons of change from baseline plasma HIV RNA among race subgroups.

- No significant difference in change from baseline in plasma HIV RNA was found between treatment regimens in each qualifying HIV RNA and racial stratum.
- No significant difference in change from baseline plasma HIV RNA was

found among racial groups in subjects with qualifying HIV RNA <30,000 c/mL and the ER or the IR regimen, respectively.

- Black subjects had greater reduction in plasma HIV RNA than White or Hispanic subjects for qualifying HIV RNA $\geq 30,000$ c/mL subgroups. Significant differences were reached at **Week 8** and at **Week 12** for subjects in the ER regimen, and at **Weeks 4 to 16** for the subjects in the IR regimen.
- The inter-racial differences in mean change from baseline in plasma HIV RNA that exceed $0.2 \log_{10}$ were found Black-White at **Week 12** in the ER regimen; Black-White and Black-Hispanic at **Week 4** and **Week 8**, and Black-White at **Week 12** in the IR regimen. A maximum of $0.34 \log_{10}$ was found between Black and Hispanic subjects at **Week 4** in the IR regimen.

Table 19: P-values for the Comparisons of Change from Baseline Plasma HIV RNA among Racial Groups*

HIV RNA Week	$\geq 30,000$ c/mL		<30,000c/mL	
	ER	IR	ER	IR
0	NS	NS	NS	NS
4	NS	0.0093	NS	NS
8	0.0020	0.0043	NS	NS
12	0.0245	0.0330	NS	NS
16	NS	0.0218	NS	NS
24	NS	NS	NS	NS
32	NS	NS	NS	NS
40	NS	NS	NS	NS
48	NS	NS	NS	NS

* P-values by the Wilcoxon test.

5.2.3 Age Comparisons

No significant difference in mean change from baseline in plasma HIV RNA was observed between the two age groups by qualifying HIV RNA and treatment regimen. No significant difference in change from baseline in plasma HIV RNA was found between treatment regimens in each qualifying HIV RNA and age stratum.

5.2.4 Baseline Weight Subgroups

Figure 17 shows HIV RNA curves.

- No significant difference in change from baseline in plasma HIV RNA was found between treatment regimens in each qualifying HIV RNA and baseline weight stratum.

- No significant difference in change from baseline HIV RNA between weight subgroups was found as stratified by qualifying HIV RNA and treatment regimen, with two exceptions.

For subjects in the ER regimen with qualifying HIV RNA $\geq 30,000$ c/mL, those with lower weight (<60 kg) at baseline had greater reductions in HIV RNA at Week 4 than those with higher weight ($p = 0.0223$).

For subjects in the IR regimen with qualifying HIV RNA $\geq 30,000$ c/mL, subjects with lower weight (<60 kg) at baseline had greater reductions in HIV RNA at **Week 8** than those in higher weight group ($p = 0.0337$).

In both cases, the differences in mean reduction were $<0.2 \log_{10}$ and the differences in median reduction were $0.23 \log_{10}$.

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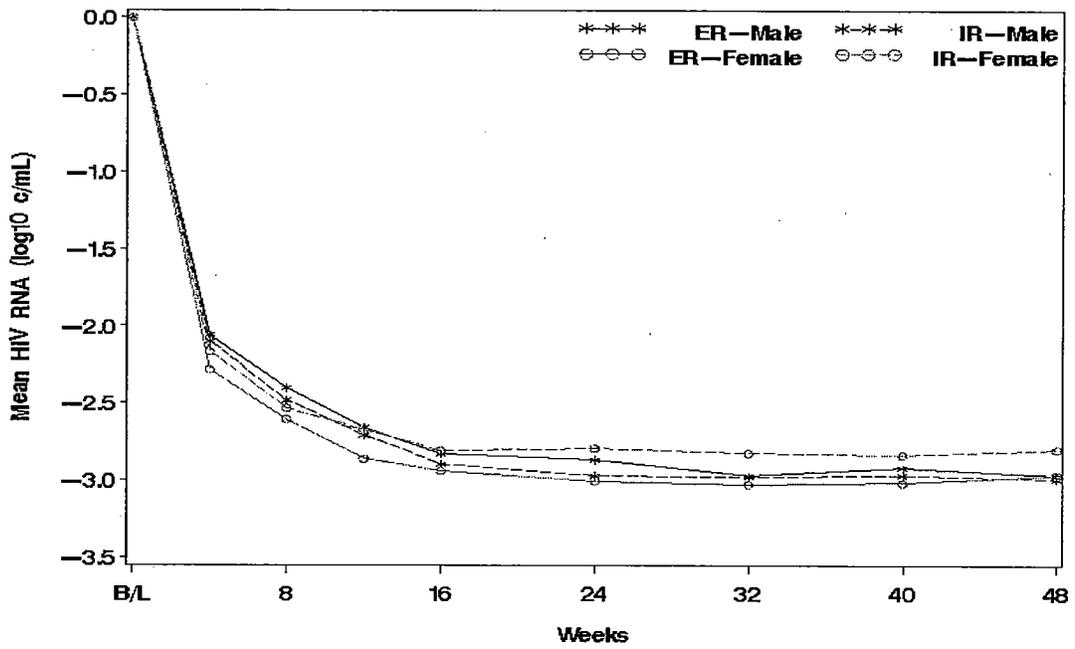


Figure 14: AI455-099: Mean Change from Baseline Plasma HIV RNA By Gender for Qualifying HIV RNA $\geq 30,000$ c/mL

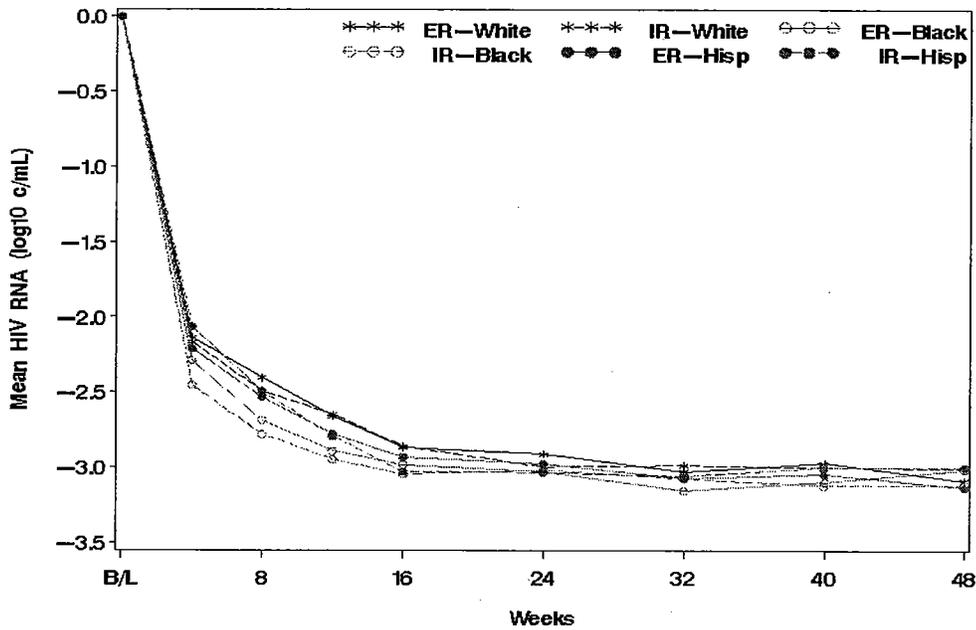


Figure 15: AI455-099: Mean Change from Baseline in HIV RNA By Race for Qualifying HIV RNA $\geq 30,000$ c/mL

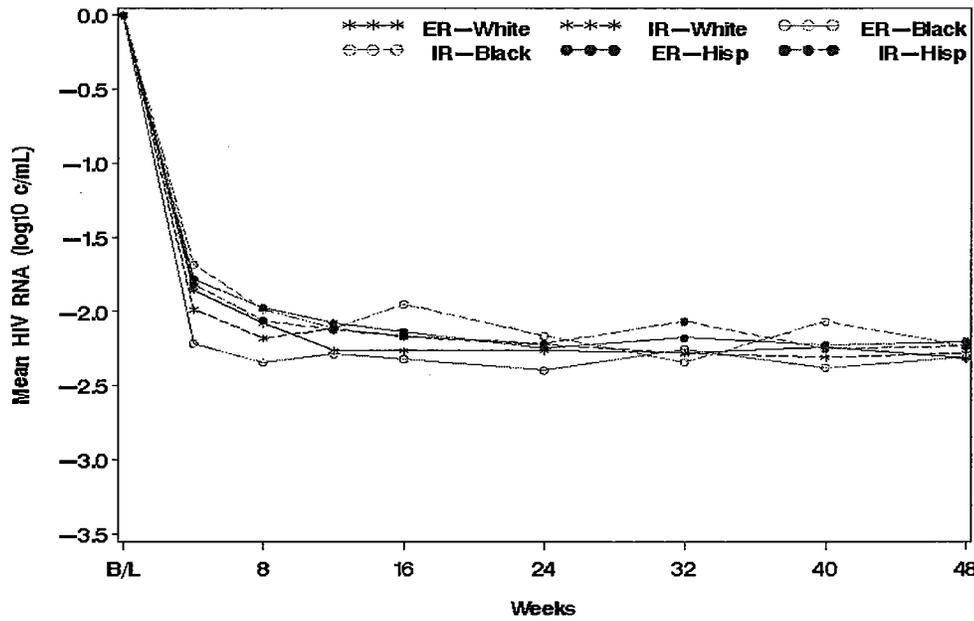
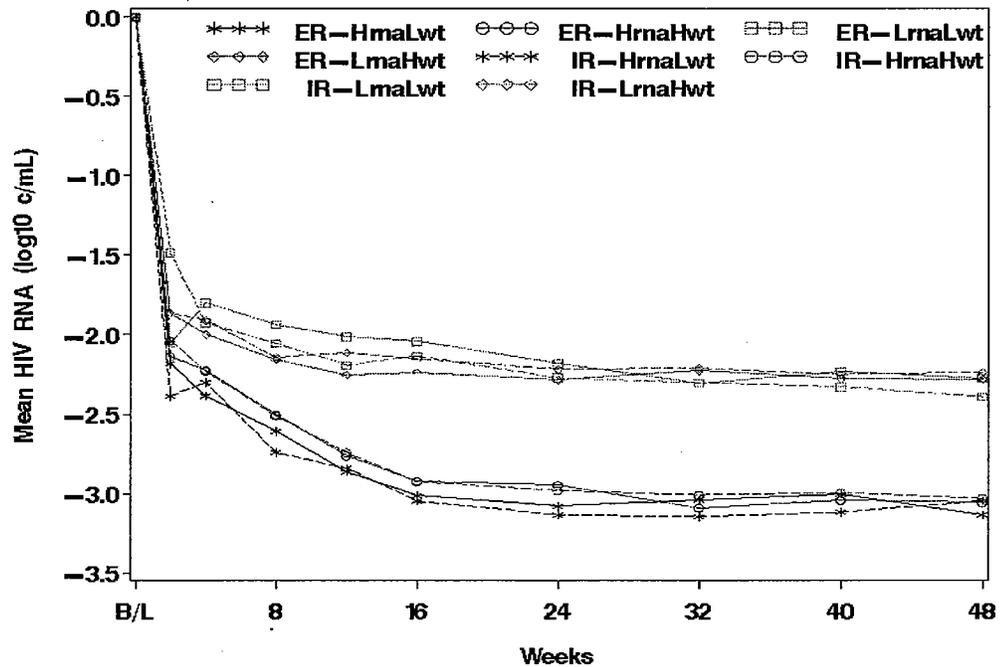


Figure 16: AI455-099: Mean Change from Baseline in HIV RNA By Race for Qualifying HIV RNA <30,000 c/mL



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Figure 17: AI455-099: Mean Change from Baseline HIV RNA By Weight

5.3 Mean Change from Baseline in CD4+ Cell Count

5.3.1 Gender Comparisons

Figure 18 shows change from baseline CD4+ cell count stratifying by gender, treatment regimen for subjects in qualifying HIV RNA $\geq 30,000$ c/mL. No significant gender or treatment difference was found.

Figure 19 shows mean CD4+ curves for subjects in qualifying HIV RNA $< 30,000$ c/mL. No significant gender difference in change from baseline CD4+ cell count was found. No significant treatment difference in change from baseline CD4+ cell count was found except for the two situations.

- At Week 12 males in the ER regimen had an additional mean increase of 53 cells/mm³ CD4+ cell count than males in the IR regimen, $p=0.0368$ by the Wilcoxon test.
- At Week 48, males in the ER regimen had an additional mean increase of 59 cells/mm³ CD4+ cell count than males in the IR regimen, $p=0.0098$ by the Wilcoxon test.

5.3.2 Race Comparisons

Figure 20 shows the mean change from baseline in CD4+ cell count stratifying by race (White, Black and Hispanic) and treatment regimen for subjects with qualifying HIV RNA $\geq 30,000$ c/mL. No significant differences are found except for the following:

- In the ER regimen, Hispanic subjects had greater mean increase in CD4+ cell counts up to 267 cells/mm³, followed by White (212) and Black (169) during the 48 weeks study. The significant differences were reached between Week 8 to Week 48.
- In the IR regimen, Hispanic subjects had greater mean increase in CD4+ cell count up to 247 cells/mm³, followed by Black (195) and White (182). The significant differences were reached between Week 12 to Week 40.

Figure 20 shows the mean change from baseline in CD4+ cell count for subjects with qualifying HIV RNA $< 30,000$ c/mL. No significant differences are found except for the following:

- Hispanic subjects in the ER regimen had greater mean increase in CD4+ cell count than those in the IR regimen - 27 cells/mm³ at Week 8, 104 at Week 24, and 87 at Week 48. The significant differences were reached between

Week 8 to Week 48 (See Table 20).

- In the ER regimen, Black subjects had less mean increase in CD4+ cell count with the maximum of 114 cells/mm³, followed by White (189) and Hispanic (230) subjects, the significant differences were reached from Week 12 to Week 48.

Table 20 shows the p-values by the Wilcoxon test for the comparisons of change from baseline CD4+ cell count among racial groups by qualifying HIV RNA. The last column lists the p-values for the comparisons of change from baseline CD4+ cell count between treatment regimen for Hispanic subjects with qualifying HIV RNA $\geq 30,000$ c/mL.

Table 20: P-values for the Comparisons of Change from Baseline CD4 Cell Counts Among Racial Group or Treatment Regimen*

Subgroup	Race		Race		ER/IR
	Race		Race		ER/IR
HIV RNA	$\geq 30,000$ c/mL		$< 30,000$ c/mL		$\geq 30,000$ c/mL
Week	ER	IR	ER	IR	Hispanic
0	NS	NS	NS	NS	NS
4	NS	NS	NS	NS	NS
8	0.0156	NS	NS	NS	0.0432
12	NS	0.0246	0.0234	NS	0.0072
16	0.0233	0.0108	0.0002	NS	0.0515
24	NS	0.0161	0.0008	NS	0.0096
32	0.0012	0.0011	0.0011	NS	0.0392
40	0.0103	0.0072	0.0009	NS	NS
48	0.0292	NS	0.0274	NS	0.0157

* P-values by the Wilcoxon test.

5.3.3 Age Comparisons

Table 21 shows p-values by the Wilcoxon test for the comparisons of baseline CD4+ cell count, and change in CD4+ cell count among treatment regimen or age subgroups. Figures 22 and 23 show the longitudinal change in CD4+ cell count by qualifying HIV RNA strata, respectively.

For subjects with qualifying HIV RNA $\geq 30,000$ c/mL:

- During the 48 week study, in the ER regimen younger subjects (< 33) had greater mean increase in CD4+ cell count than the older subjects (≥ 33): the maximum mean increase is 243 in the younger group and 188 in the older

group. Note that this mean difference of 55 cells/mm³ may be associated with baseline CD4+ cell count. The mean difference at baseline is 65 cells/mm³: mean baseline CD4+ cell count in the younger subjects = 323 cells/mm³ vs a mean of 258 cells/mm³ in the older group.

- Younger subjects in the ER regimen had greater increase in CD4+ cell count than those in the IR regimen. The significant differences were reached at Week 8 and Week 16.

For subjects with qualifying HIV RNA < 30,000c/mL:

- No significant difference in change from baseline CD4+ cell count was found between age subgroups during the study although the mean baseline CD4+ cell count was higher in the younger group than the older subjects.
- Older subjects in the ER regimen had greater increase in CD4+ cell count than those in the IR regimen. The significant differences were reached at Week 48.

Table 21: P-values for the Comparisons of Change from Baseline CD4 Cell Counts Among Age Group or Treatment Regimen*

Subgroup HIV RNA Week	Age ≥30,000c/mL		Age <30,000c/mL		ER/IR	
	ER	IR	ER	IR	≥30,000c/mL Age <33	<30,000c/mL Age ≥33
0	0.0006	NS	0.0418	0.0118	NS	NS
4	NS	NS	NS	NS	NS	NS
8	0.0005	NS	NS	NS	0.0041	NS
12	0.0312	NS	NS	NS	NS	NS
16	0.0046	NS	NS	NS	0.0367	NS
24	0.0091	NS	NS	NS	NS	NS
32	0.0001	NS	NS	NS	NS	NS
40	NS	NS	NS	NS	NS	NS
48	0.0382	NS	NS	NS	NS	0.0357

* P-values by the Wilcoxon test.

5.3.4 Baseline Weight Subgroups

The mean change from baseline in CD4+ cell count by qualifying HIV RNA, treatment regimen and baseline weight strata (60 kg or ≥ 60 kg) are shown in Figure 24.

Stratifying by qualifying HIV RNA and baseline weight strata, no significant difference in change from baseline CD4+ cell count between the ER and the IR regimens was found with two exceptions among those with qualifying HIV RNA < 30,000 c/mL and higher weight (≥ 60 kg) at baseline:

- at Week 12, subjects in the ER regimen had a mean (median) increase of 118 cells/mm³ (93) whereas those in the IR regimen had a mean (median) increase of 56 cells/mm³ (75), $p=0.0220$;
- at Week 48, subjects in the ER regimen had a mean (median) increase of 185 cells/mm³ (166) whereas those in the IR regimen had a mean (median) increase of 128 cells/mm³ (88), $p=0.0053$.

Stratifying by qualifying HIV RNA and treatment regimen, no significant difference in change from baseline HIV RNA between weight subgroups was found. Please note that subjects in the IR regimen with qualifying HIV RNA $\geq 30,000$ c/mL had greater baseline CD4+ cell count (68) than those in the lower weight group ($P<0.05$).

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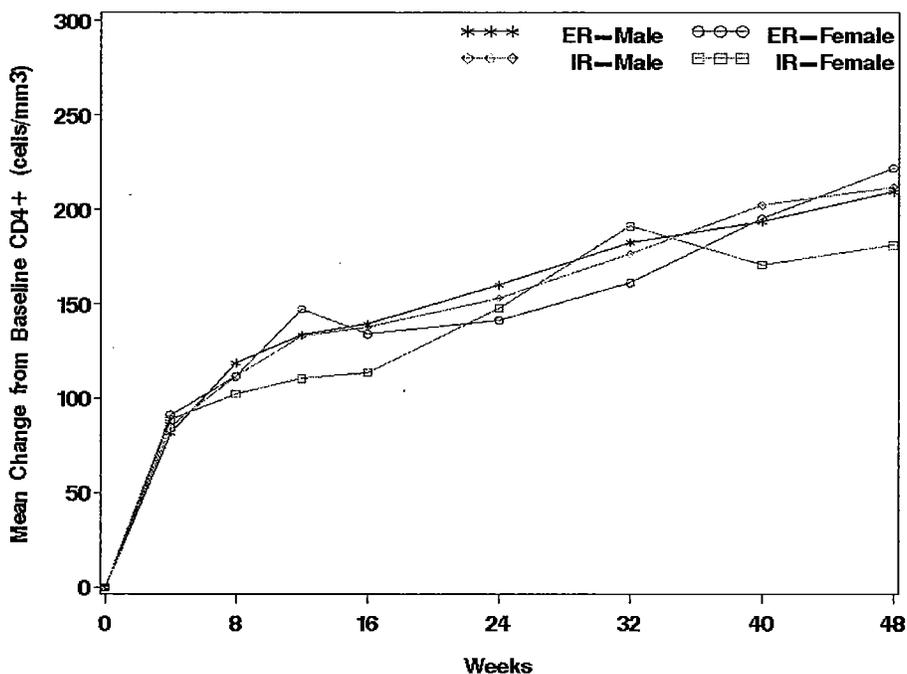


Figure 18: AI455-099: Mean Change from Baseline in CD4+ Cell Count By Gender for Qualifying HIV RNA $\geq 30,000$ c/mL

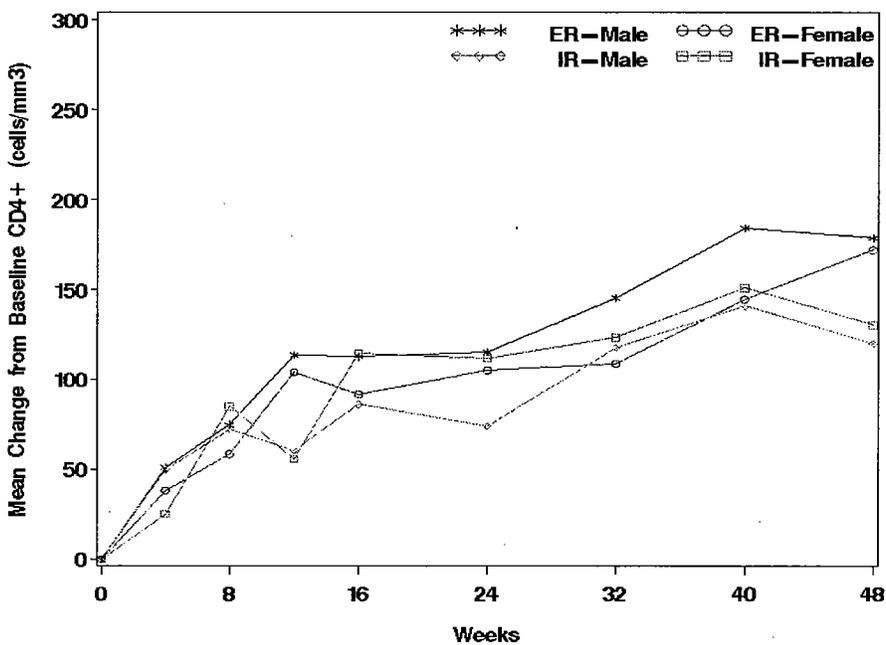


Figure 19: AI455-099: Mean Change from Baseline in CD4+ Cell Count By Gender for Qualifying HIV RNA < 30,000 c/mL

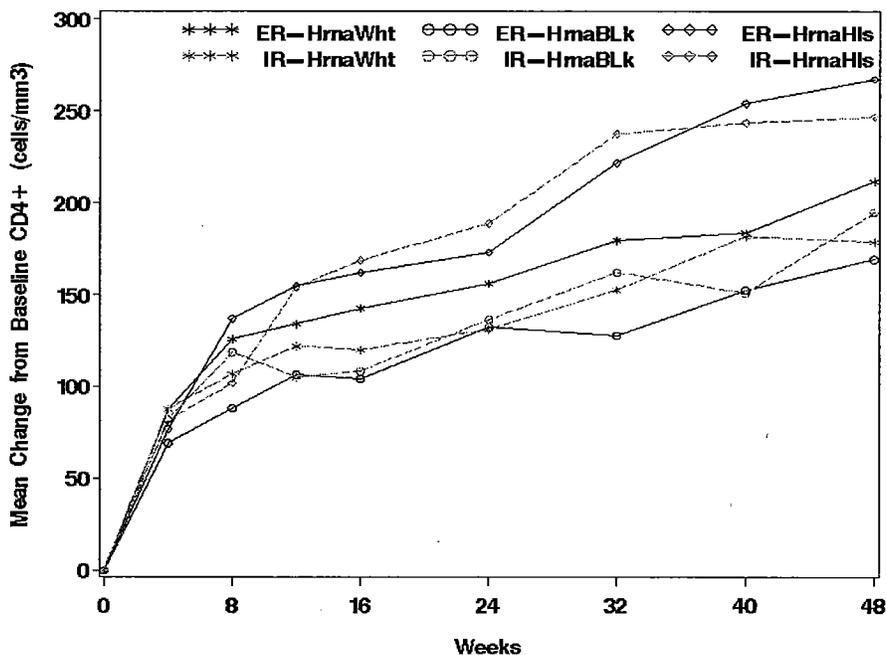


Figure 20: AI455-099: Mean Change from Baseline CD4+ Cell Count By Race for Qualifying HIV RNA $\geq 30,000$ c/mL

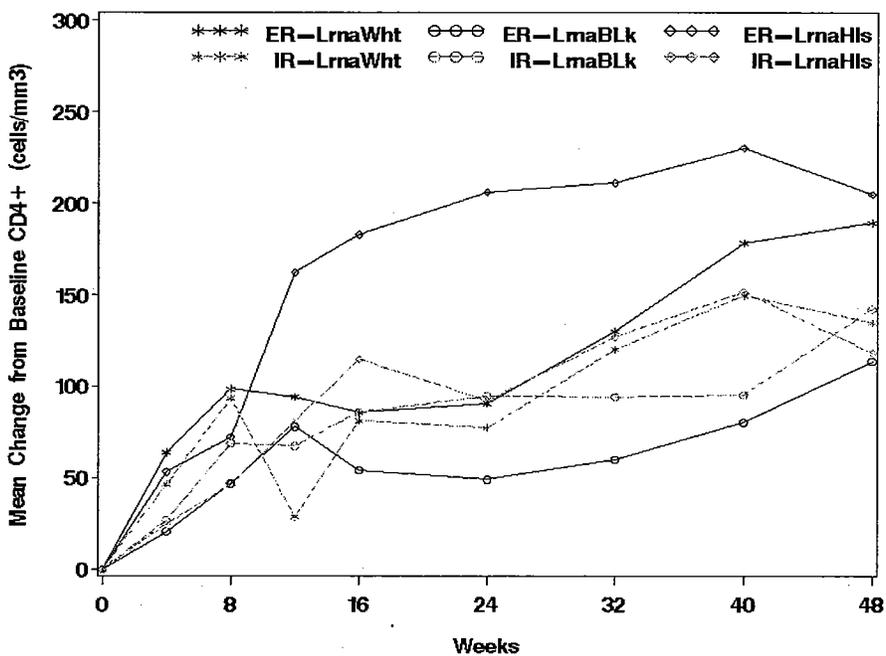


Figure 21: AI455-099: Mean Change from Baseline CD4 By Race for Qualifying HIV RNA $< 30,000$ c/mL

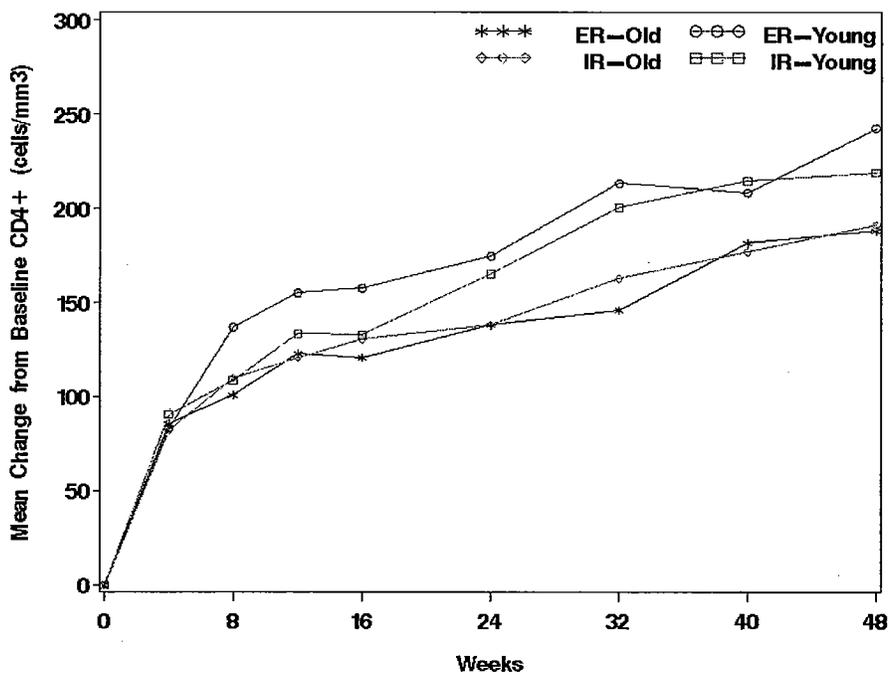


Figure 22: AI455-099: Mean Change from Baseline in CD4+ Cell Count By Age for Qualifying HIV RNA $\geq 30,000$ c/mL

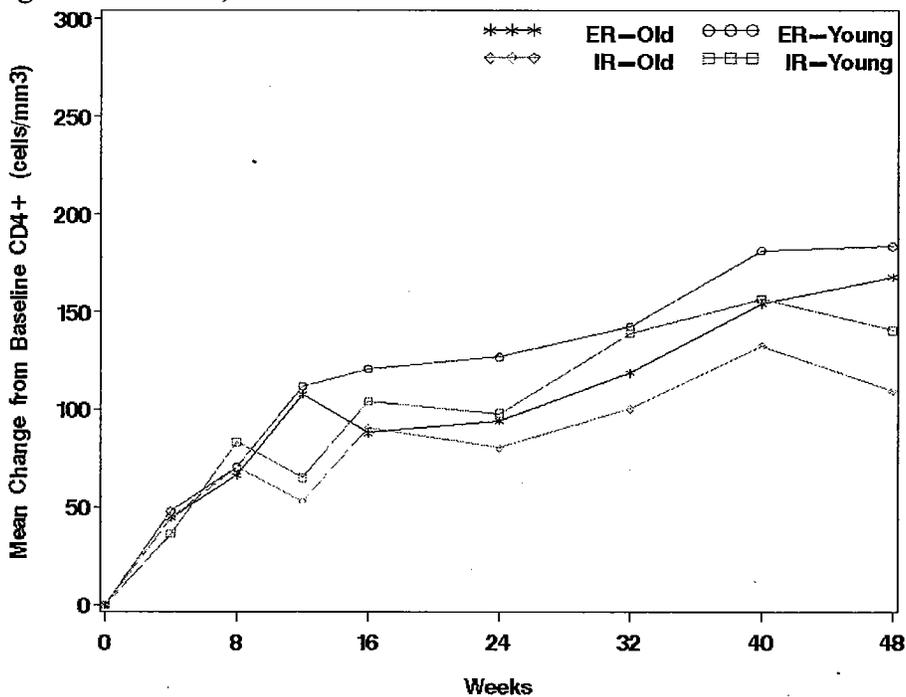


Figure 23: AI455-099: Mean Change from Baseline in CD4+ Cell Count By Age for Qualifying HIV RNA $< 30,000$ c/mL

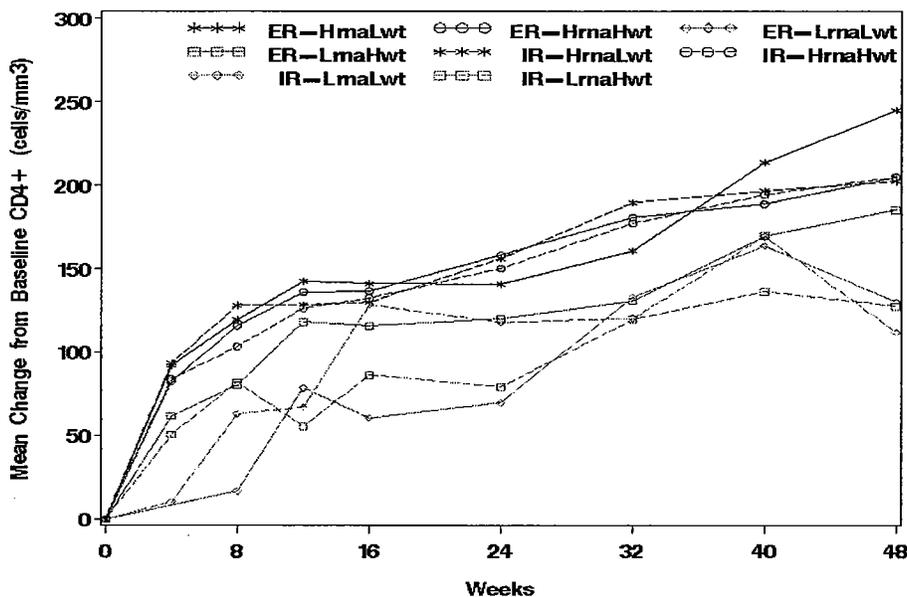
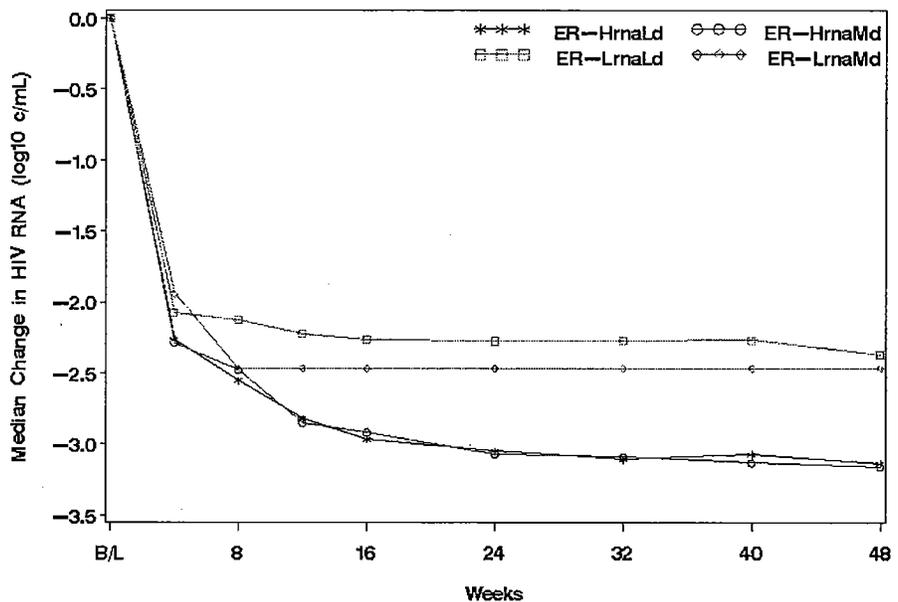


Figure 24: AI455-099: Mean Change from Baseline CD4+ Cell Count By Baseline Weight

5.4 Diarrhea Subgroups

It was concerned that diarrhea and vomiting might have negative effects on subjects' efficacy, especially for those who were treated with d4T ER. For Study AI455-099, diarrhea or vomiting (diarrhea) occurred in 200 (25%) of the study subjects during the follow-up period with a maximum number of nine times. There was no significant difference in frequency of diarrhea (0,1,2+) between the ER and the IR regimens by qualifying HIV RNA strata, $p > 0.05$, by the chi-square tests.

In the following, the results of comparison of change from baseline HIV RNA by subjects with frequent diarrhea or vomiting subgroups are summarized. Subjects were grouped as less frequent group (Ld: 0-1) and frequent (Md: 2+). For cross-sectional comparisons in HIV RNA, the Wilcoxon test was used.



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Figure 25: AI455-099: Median Change from Baseline in HIV RNA By ER Diarrhea Subgroups

The median change from baseline HIV RNA by frequent diarrhea or vomiting strata (Ld: 0-1 versus Md:2+) for the d4T ER groups is shown in Figure 25. No significant difference was found between the two diarrhea subgroups or between treatment regimens for subjects with qualifying HIV RNA $\geq 30,000$ c/mL. For subjects with qualifying HIV RNA $< 30,000$ c/mL, there is only one situation that a significant difference was found:

- at Week 4, subjects in Ld had greater reduction in HIV RNA than those in Md, $p=0.0192$, by the Wilcoxon test.

The alternative analysis was also performed to stratify study subjects into no diarrhea or vomiting (Nd: 0) or not (Yd:>0). For qualifying HIV RNA $< 30,000$ c/mL d4T ER subgroups (Lrna), no diarrhea (Nd) subgroup had less change in HIV RNA than subjects with ever diarrhea, the only significant difference was found at Week 40, $p=0.0373$, by the Wilcoxon test.

5.5 Discordance in Screen and Baseline Plasma HIV RNA

Plasma HIV RNA measurements were obtained within 14 days prior to randomization in Study AI455-096, and within 21 days in Study AI455-099. The discordant between screening and baseline (day1 or Week 0) HIV RNA occurred in 15.5% of the subjects (24/155) in Study AI455-096 and 15.8% of the subjects (126/797) in Study AI455-099. Table 22 shows the frequencies of concordance and discordance by treatment regimen for these studies. There were more subjects with screening HIV RNA $\geq 30,000$ c/mL and baseline HIV RNA $< 30,000$ c/mL than the reversed status, with a risk ratio of 2.43 and 1.56, respectively in AI455-096 and AI455-099, although such discordance was well balanced between the ER and the IR regimens.

Table 22: Screening and Baseline HIV RNA

HIVRNA		ER		IR	
Screen	Week 0	n	%	n	%
AI455-096					
<30,000	<30,000	25	16.13	22	14.19
$\geq 30,000$	$\geq 30,000$	40	25.81	44	28.39
$\geq 30,000$	<30,000	7	4.52	10	6.45
<30,000	$\geq 30,000$	3	1.94	4	2.58
AI455-099					
<30,000	<30,000	90	11.29	91	11.42
$\geq 30,000$	$\geq 30,000$	247	30.99	243	30.49
$\geq 30,000$	<30,000	37	4.64	41	5.14
<30,000	$\geq 30,000$	25	3.14	23	2.89

5.5.1 Mean Change from Baseline in Plasma HIV RNA for AI455-099

Figure 26 shows the mean change from baseline in plasma HIV RNA for Study AI455-099.

- It appears that the HIV RNA suppression has three different temporal patterns. The top two curves are those for concordant HIV RNA $< 30,000$ c/mL at screening and at Week 0 (legend:Lrna) for subjects in the ER and IR regimens, and the bottom two curves are those for the concordant HIV RNA $\geq 30,000$ c/mL at screening and at Week 0 (legend:Hrna). Two curves in the middle of Figure 26 are those for those with discordant HIV RNA at screening and at baseline (legend:Drna).
- No significant treatment difference was observed except for the two

discordant groups: from Week 8 to Week 32, the subjects in the ER regimen responded to virologic suppression slightly better than those in the IR regimen.

5.5.2 Mean Change from Baseline in CD4+ Cell Count for AI455-099

Figure 27 shows the mean change from baseline in CD4+ cell count in Study AI455-099 by treatment regimen and concordance HIV RNA at entry. All six subgroups show increase in CD4+ cell count. Subjects with concordant HIV RNA $\geq 30,000$ c/mL at entry had a greater increase in CD4+ cell count during the study period than subjects in the other subgroups. No significant treatment difference in change from baseline CD4+ cell count was observed except for the following.

- From Week 24 onward, CD4+ cell count increase seems favor ER regimen for concordant HIV RNA $<30,000$ c/mL at entry.

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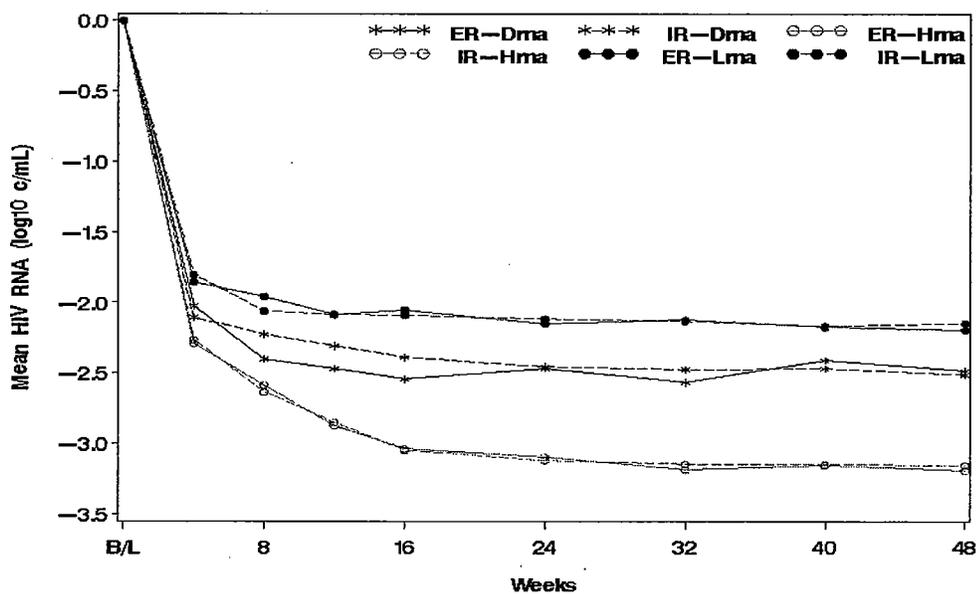


Figure 26: AI455-099: Mean Change from Baseline in Plasma HIV RNA By Concordance Status of Screening and Baseline HIV RNA

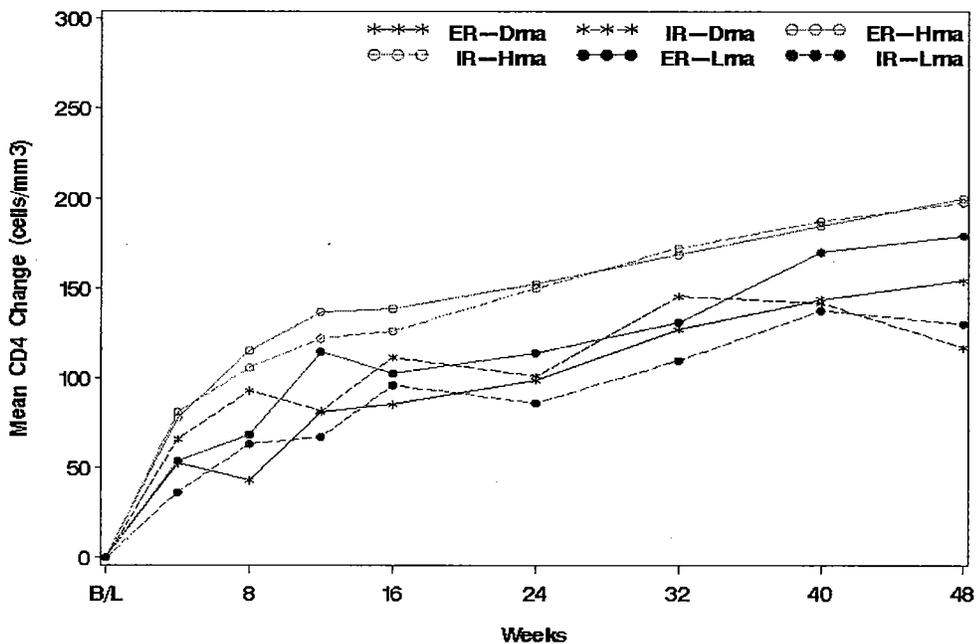


Figure 27: AI455-099: Mean Change from Baseline CD4+ Cell Count By Concordance of Screening and Baseline HIV RNA

5.6 Change from Baseline HIV RNA by Baseline CD4+ Cell Count and Qualifying HIV RNA

It was noticed that entire efficacy analyses regarding HIV RNA suppression didn't take the baseline CD4+ cell count into account. To evaluate the associations between baseline CD4+ cell counts and HIV RNA suppression, CD4+ cell count at baseline was stratified by '<300' and '≥300' cells/mm³. The cut point of 300 is in between the median 277 and mean 320 in Study AI455-099. Therefore, four strata by baseline CD4+ cell count and qualifying HIV RNA were used in the analyses.

Figures 28 and 29 show mean change from baseline plasma HIV RNA by treatment regimens and CD4+ cell count at baseline. The findings are as follows.

- The patterns of decline in HIV RNA are different for different strata of HIV RNA at entry. For subjects with qualifying HIV RNA <30,000 c/mL, the mean change from baseline in plasma log₁₀ HIV RNA maintains a level between -2.5 to -2.2 from Week 12 onward, after a significant decline since treatment initiation. For subjects with qualifying HIV RNA ≥ 30,000 c/mL, the mean change from baseline in plasma log₁₀ HIV RNA continues its decline to below -3.0 at Week 24, after a significant decline since treatment initiation.
- No significant treatment difference was found as stratified by baseline CD4+ cell count and qualifying HIV RNA strata.
- Among those in the ER regimen with qualifying HIV RNA < 30,000 c/mL, subjects with baseline CD4+ cell count <300 had greater reductions than those with baseline CD4+ cell count ≥ 300: at Week 24, a significant mean reduction of 0.22 log₁₀ was reached, p=0.0058, by the t-test adjusting for unequal variances between the two baseline CD4+ cell count subgroups.

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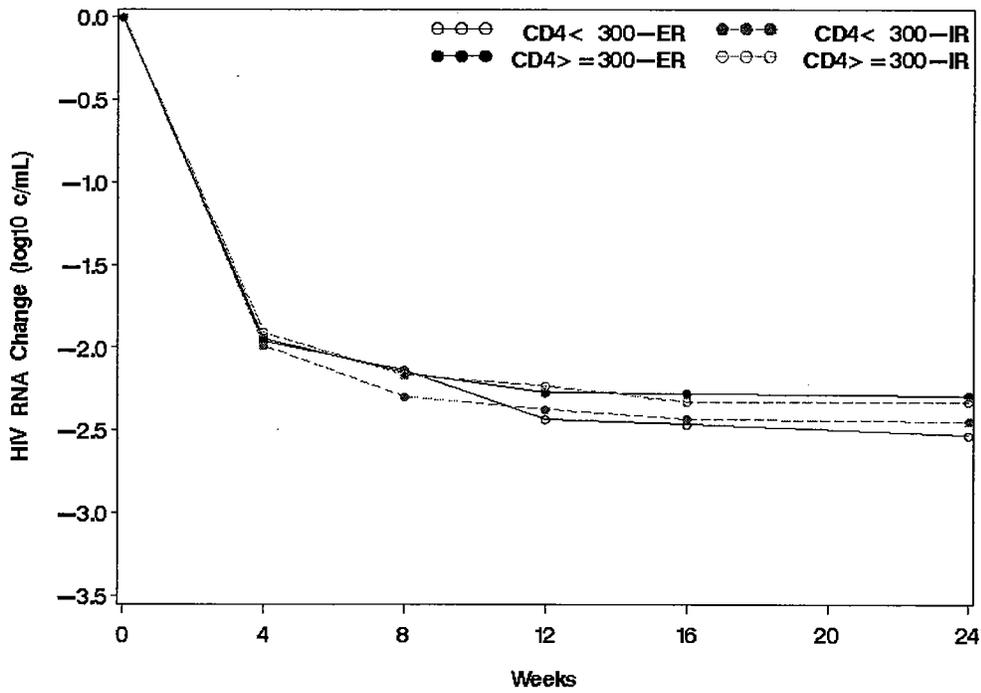


Figure 28: AI455-099: Mean Change from Baseline in Plasma HIV RNA for Qualifying HIV RNA < 30,000 c/mL

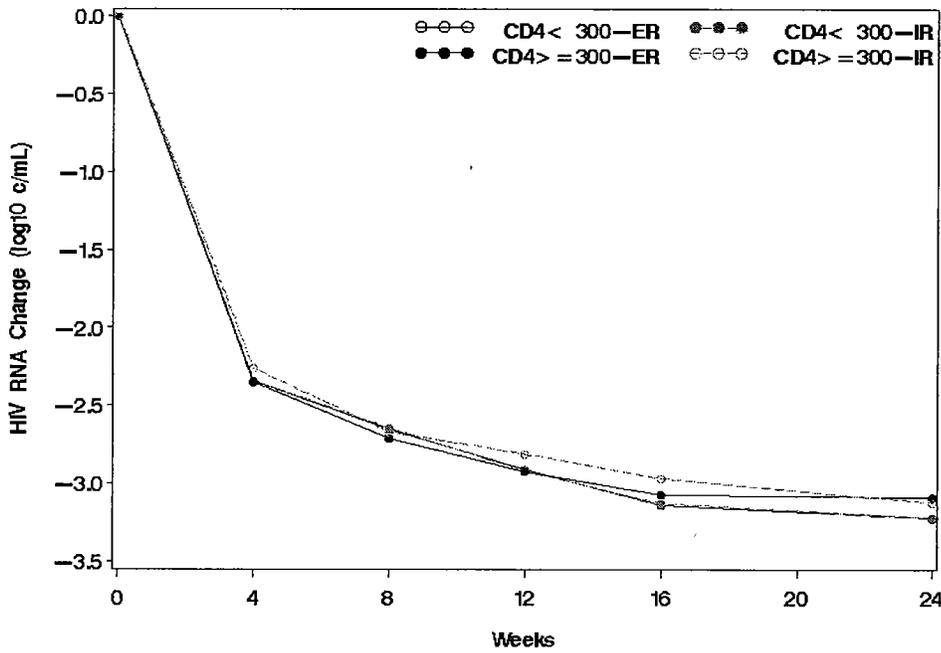


Figure 29: AI455-099: Mean Change from Baseline in Plasma HIV RNA for Qualifying HIV RNA ≥ 30,000 c/mL

6. CONCLUSIONS AND RECOMMENDATIONS

The applicant conducted two randomized, controlled, double-blind, multinational clinical trials AI455-096, a pilot study, and AI455-099, a pivotal study. These studies enrolled treatment-naïve HIV-infected subjects. Both studies were carried out with a single-substitution design matching ER to IR stavudine, in combination with lamivudine (3TC) and efavirenz (EFV). In these studies, 3TC and EFV were administered 'open label'.

The pilot study, AI455-096, was conducted in North America, South America and Africa. The pivotal study, AI455-099, was carried out at sites in Europe, North America, South America, Africa and Asia. The duration of these trials was 48 weeks for Study AI455-096 and 56 weeks for Study AI455-099.

The study subjects were predominantly male (70%). The median age of these subjects was 33 years. Non-white racial groups comprised approximately 53% of the study population. Overall, the median baseline HIV RNA level was 4.79 \log_{10} c/mL for ER vs. 4.77 \log_{10} c/mL for IR. The proportion of subjects with HIV RNA \geq 30,000 c/mL at baseline was 66% for ER and IR treatment groups. The median baseline CD4+ cell count was 294 cells/mm³ for the ER treatment group and 269 cells/mm³ for the IR group.

Based on available data through Week 48 and beyond, we reached the following conclusions:

1. Using TLOVR algorithm the Study AI455-099 demonstrated similarity of the proportion of subjects with HIV RNA below 400 c/mL in the d4T ER + 3TC + EFV treatment arm (79%), as compared to d4T IR + 3TC + EFV arm (76%). The difference of the two treatment arms (2.9%) had a lower 95% CI bound (-3.0%) above -12%, meeting the pre-specified non-inferiority level.
2. The temporal trend of plasma HIV RNA was similar for the ER and the IR regimens. Plasma HIV RNA had a sharp drop of about 2.0 \log_{10} prior to Week 4 and this decline continued at a slower pace until Week 24. At Week 8, the mean change from baseline in plasma HIV RNA reached -2.5~-2.6 \log_{10} in the ER and IR regimens with qualifying HIV RNA \geq 30,000 c/mL, and -2.1 \log_{10} in the ER and IR regimens with qualifying HIV RNA < 30,000 c/mL, respectively. The estimated time-weighted average change from baseline in plasma HIV RNA through Week 48 adjusting for qualifying HIV RNA was $|\text{TAD}_{\text{ER-IR}}| < 0.01 \log_{10}$ c/mL with a 95% confidence interval of (-9.1, 8.9) by the LOCF method.
3. Immunological response, measured by mean increase from baseline in CD4+ cell count at Week 48 was similar in the d4T ER and the d4T IR regimen. The estimated time-weighted average change from baseline in CD4+ cell count (TAD in cells/mm³) at Week 48 by the LOCF method were: 143 for the

ER regimen and 140 for the IR regimen for qualifying HIV RNA $\geq 30,000$ c/mL; 105 for the ER regimen and 90 for the IR regimen for qualifying HIV RNA $< 30,000$ c/mL. The difference between the two regimens (ER-IR) was 6.1 with a 95% confidence interval of (-8.7,20.9).

4. The similarity of treatment effects between the d4T ER and the d4T IR regimen was also supported by the comparisons of the proportion of subjects with HIV RNA below 50 c/mL through Week 48.
5. HIV RNA measurements were associated with specimen shipment status. Alternative analyses on the primary endpoint stratified by specimen shipment procedures supported similar treatment effects between the d4T ER and the d4T IR regimen.
6. Subgroup analyses on the primary efficacy endpoint showed that the ER regimen was doing slightly worse than the IR regimen for those subjects in sites where specimens did not need transportation, and those subjects whose specimens were shipped frozen during study period.
7. Longitudinal assessment of change from baseline in plasma HIV RNA showed that the interactions between treatment regimen (ER-IR) and gender, race, age, and baseline weight were not statistically significantly different from zero. Mean change from baseline in plasma HIV RNA was significantly associated with gender, race and baseline weight in some of the treatment regimen and qualifying HIV RNA strata as follows.

Prior to Week 24, among those with qualifying HIV RNA $\geq 30,000$ c/mL,

- in the IR regimen,

Black subjects had a maximum of 0.34 \log_{10} and 0.30 \log_{10} greater reduction than Hispanic and White subjects, respectively;

Females had 0.17 to 0.28 \log_{10} statistically significantly greater reduction than males;

Subjects in the lower weight at baseline had statistically significantly greater mean reduction in HIV RNA at Week 8 than subjects in the higher weight group. However, the mean reductions were less than 0.2 \log_{10} .

- in the ER regimen,

Black subjects had a maximum of 0.25 \log_{10} greater reduction than White subjects;

Subjects in the lower weight at baseline had statistically significantly greater reduction in HIV RNA at Week 4 than subjects in the higher

weight group.

8. Longitudinal assessment of change from baseline in CD4+ cell count showed that the treatment regimen was statistically significantly associated with gender, race, age, and baseline weight in the following situations.

- Among those with qualifying HIV RNA $\geq 30,000$ c/mL,

Males in the ER regimen had an additional significant increase of 53 cells/mm³ than those in the IR regimen at Week 12, and an additional significant increase of 59 cells/mm³ at Week 48;

Younger subjects in the ER regimen had significant greater increases in CD4+ cell count at Week 8 and Week 16 than the younger subjects in the IR regimen;

Among subjects with higher weight at baseline, those in the ER regimen had significant greater increases in CD4+ cell count: 62 cells/mm³ at Week 12 and 57 at Week 48, than the subjects with higher weight at baseline in the IR regimen.

- Among those with qualifying HIV RNA $< 30,000$ c/mL,

Hispanic subjects in the ER regimen had significant increases CD4+ cell count ranging 27-104 during the study than those in the IR regimen during the study;

Older subjects in the ER regimen had significant greater increases in CD4+ cell count at Week 48 than the older subjects in the IR regimen.

9. Subgroup analyses showed that change from baseline in CD4+ cell count was statistically significantly associated with race, age, and baseline weight in the following situations.

- During the study, for subjects in the ER regimen with qualifying HIV RNA $< 30,000$ c/mL, Hispanic subjects had significant greater mean increase in CD4+ cell count, the maximum was 230 cells/mm³, greater than White (189) and Black subjects (114).
- During the study, for subjects in the ER regimen with qualifying HIV RNA $\geq 30,000$ c/mL, Hispanic subjects had significant greater mean increase in CD4+ cell count, the maximum was 267 cells/mm³, greater than White (212) and Black subjects (169).
- Between Week 12 and Week 40, for subjects in the IR regimen with qualifying HIV RNA $\geq 30,000$ c/mL, Hispanic subjects had significant greater mean increase in CD4+ cell count, the maximum was 247

cells/mm³, greater than White (182) and Black subjects (195).

- During the study, among subjects in the ER regimen with qualifying HIV RNA $\geq 30,000$ c/mL, younger subjects had significant greater mean increase in CD4+ cell count than the older subjects. However, the maximum mean difference of 55 cells/mm³ is less than the mean difference of 65 cells/mm³ at baseline.
10. Subgroup analyses showed subjects with frequent diarrhea may be associated with virologic suppression. For those in qualifying HIV RNA for $< 30,000$ c/mL, at Week 4 subjects with no diarrhea or less frequent diarrhea had greater reduction in HIV RNA than those with frequent diarrhea.

Based on available data through Week 48 and beyond from the pivotal study AI455-099, this reviewer found that the virologic response was similar in the ER study regimen and equivalent IR reference regimen. The virologic response was sustained through Week 48 and the virologic response was associated with a significant rise in CD4+ cell count.

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