

ACTG 364- Nelfinavir (NFV) and/or Efavirenz (EFV) in Combination with New nRTIs in Nucleoside Experienced Subjects: Week 144 Results

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Introduction

BACKGROUND

The optimal alternative therapy for subjects with nRTI experience who develop viral rebound remains uncertain. ACTG 364 examined long-term virologic and immune responses of quadruple vs triple antiretroviral (ART) therapy regimens in exclusively nRTI-treated subjects

Study Objectives

PRIMARY STUDY OBJECTIVES

- To evaluate plasma HIV RNA responses across the three study arms at 16 weeks
- To evaluate the safety and tolerability of NFV and/or EFV in combination with nucleoside analog-containing regimens

SECONDARY STUDY OBJECTIVES

- To assess durability of viral suppression through 48 weeks and 144 weeks
- To determine time to virologic failure (confirmed HIV-1 RNA ≥ 200 c/mL at week 16 or later)
- To compare CD4 cell count responses across the study arms at 16 weeks and 144 weeks

Study Design

INCLUSION CRITERIA

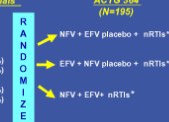
- Participation in ACTG 302/303 with original randomization to d4T monotherapy or combination nucleoside analog therapy and maintenance of that regimen until randomization in ACTG 364
- Screening HIV RNA ≥ 500 c/mL
- Acceptable laboratory values

EXCLUSION CRITERIA

- Protease inhibitor exposure
- Non-nucleoside reverse transcriptase inhibitor (NNRTI) exposure
- History of acute or chronic pancreatitis
- Peripheral neuropathy \geq grade 2
- Malignancy requiring systemic chemotherapy
- Pregnancy
- Acute infection or medical illness

Phase II, Randomized, Partially Double-Blind

ACTG 302/303 Rollover Trials



Statistical Methods

- Intent-to-treat analysis
- Analyses included all randomized subjects who had any study treatment dispensed and available follow-up through week 144
- Safety data censored within 56 days of date of last dose
- Primary efficacy assessed on the basis of plasma HIV-1 RNA levels
- Analyses of proportion of subjects with HIV-1 RNA below 500 (50) c/mL evaluated using Cochran-Mantel-Haenszel test
- Stratification factor: ACTG 302/303 nucleoside therapy
- Time to event analyses estimated using method of Kaplan and Meier
- To evaluate association between baseline factors and treatment failure (confirmed HIV RNA ≥ 200 c/mL at week 16 or later), Kaplan Meier curves and Cox proportional hazards regression models were used to assess the time to virologic failure.

Monitoring

- Clinical Assessment: baseline, and weeks 2, 4, 8, 12, and 16; then every 8 weeks through week 144
- Standard Safety/Laboratory Tests: baseline, and weeks 2, 4, 8, 12, and 16; then every 8 weeks through week 144
- Plasma HIV RNA assays:
 - Standard Roche Amplicor Monitor[®] assay through week 48 then later timepoints used Roche UltraSensitive assay
 - Viral load samples < 500 c/mL retrospectively analyzed using Roche UltraSensitive assay (lower limit of detection: 50 c/mL)
 - Later timepoints after week 48 used Roche UltraSensitive assay
- CD4 cell counts

Table 1: Baseline Characteristics

Characteristic	Total N=195	NFV +RTIs N=66	EFV +RTIs N=65	NFV+EFV N=64
Male sex: No (%)	171 (88%)	60 (91%)	53 (82%)	58 (91%)
Age - yr (Mean)	41.1	39.5	43.4	40.3
Race or ethnic group: No (%)				
White, non hispanic	145 (74%)	48 (73%)	48 (71%)	51 (80%)
African American	28 (14%)	7 (11%)	13 (20%)	8 (13%)
Hispanic	18 (9%)	9 (14%)	6 (9%)	3 (5%)
Asian Pacific or other	4 (2%)	2 (3%)	- (%)	2 (3%)
Injection drug use- No (%)	9 (5%)	3 (5%)	2 (3%)	4 (6%)
Hemophilia- No (%)	14 (7%)	5 (8%)	4 (6%)	5 (8%)
Median CD4 Count (cells/mm ³)	350	336	343	379
Range (cells/mm ³)	0-1590	24-635	0-1004	42-1590
Baseline Median HIV RNA (c/mL)	7776	8690	7999	5776
Range	< 500->	< 500->	< 500->	< 500->
	750,000	>750,000	421,511	348,422
Median duration of prior nRTI therapy (yrs)	5.6 yrs			

Follow-Up and Treatment Status at 144 Weeks

- Of the 195 subjects, 171 (88%) completed the protocol
 - Among the protocol-completers, 49% (83/171) were followed to week 144
- 120 subjects (62%) completed the study treatment
 - 30 in the NFV arm, 44 in the EFV arm, and 46 in the NFV+EFV arm
- A total of 75 (38%) subjects permanently discontinued study treatment during 144 weeks of follow-up
 - Protocol defined clinical events and virologic failure accounted for permanent study treatment discontinuation in 36 (18%) of 195 subjects with 21 in the NFV arm, 10 in the EFV arm, and 5 in the NFV+EFV arm
 - The majority (81%; 29/36) of these treatment discontinuations were attributed to virologic failure

Table 2: Time to Permanent Treatment Discontinuation

Treatment arm	N	%	Treatment arm	2-way p
NFV	34/66	52%	vs EFV	0.003
EFV	19/65	29%	vs NFV+EFV	0.75
NFV+EFV	17/64	27%	vs NFV	< 0.001

3-way p < 0.001

Proportion of Subjects with HIV RNA < 50 c/mL

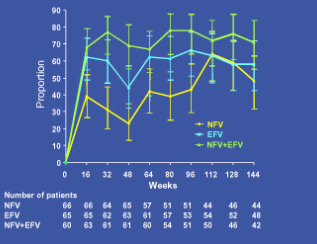
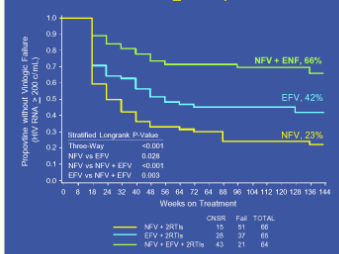


Table 3: Comparison of Treatment Arms at 144 Weeks (< 50 c/mL)

Treatment Arm	N	%	Treatment arm	2-way P
NFV	21/44	48%	vs EFV	0.241
EFV	28/48	58%	vs NFV+EFV	0.187
NFV+EFV	30/42	71%	vs NFV	0.016

3-way P=0.045

Time to HIV RNA ≥ 200 Copies/mL



Median CD4 Cell Count Change from Baseline

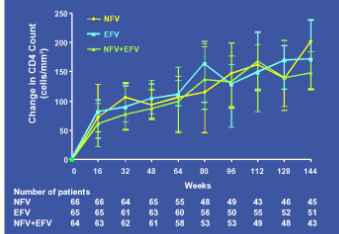


Table 4: Predictors of Virologic Failure (HIV RNA ≥ 200 c/mL at Week 144): Cox Proportional Hazards Model

Baseline Factors	Hazards Ratio	95% Confidence Interval	P-values
Baseline HIV RNA (\log_{10} c/mL)*	1.75	1.37-2.23	< 0.001
302/303 Treatment**	Referent		
ZDV/ddI/3TC:			
d4T	0.25	0.09- 0.71	0.009
ZDV+3TC	0.66	0.42- 1.06	0.086
ZDV+ddI	0.19	0.10- 0.36	< 0.001
ZDV+ddC+3TC	0.79	0.43- 1.45	0.450
ZDV+ddC	0.31	0.12- 0.79	0.014
2 vs 1 new nRTI**	0.44	0.29-0.67	< 0.001

Based on Cox proportional hazards model:
 * Adjusting for randomized 364 treatment
 ** Adjusting for randomized 364 treatment and \log_{10} HIV RNA

Table 5: Predictors of Virologic Failure (HIV RNA ≥ 200 c/mL at Week 144): Final Model

Baseline Factors	Hazards Ratio	95% Confidence Interval	P-values
Baseline HIV RNA (\log_{10} c/mL)	2.14	1.66- 2.76	< 0.001
ACTG 364 Treatment			
NFV	3.60	2.15- 6.05	< 0.001
EFV	2.25	1.31- 3.86	0.003
NFV+EFV	referent		
3TC-naïve at entry*	0.28	0.17- 0.45	< 0.001

*ACTG 302/303 treatments grouped into single baseline factor which assessed whether patients were 3TC-naïve or experienced at ACTG 364 study entry

Adverse Clinical Events

- There were no significant differences among the three treatment arms to onset of first \geq grade 3 sign/symptom
- 11 of 195 (6%) subjects experienced ≥ 2 peripheral neuropathy
 - 5 subjects in the NFV, 2 in the EFV, and 4 in the NFV+EFV arms, respectively
- 48 of 195 (25%) subjects developed at least one grade 3 or higher clinical sign/symptom
 - 14 subjects in the NFV, 14 in the EFV, and 20 in the NFV+EFV arms, respectively
- The most common sign/symptoms were:
 - Ache/pain/discomfort in 18 (9%) subjects overall
 - Diarrhea/loose stools in 9 (5%) subjects

Adverse Laboratory Events

- There were no significant differences among the three study arms to time to onset of first \geq grade 3 laboratory toxicity
- 81 of 195 (42%) subjects experienced at least one grade 3 or higher laboratory toxicity:
 - 30 in the NFV, 26 in the EFV, and 25 in the NFV+EFV arms, respectively
- The most common laboratory toxicities were:
 - Grade 3 or higher triglycerides: 32 of 195 subjects (16%)
 - \geq Grade 3 elevated CPK levels: 30 of 195 subjects (15%)

Deaths Observed through Week 144

- Six deaths occurred on study: 2 each in the NFV, EFV, and NFV+EFV arms, respectively
- Causes of death included:
 - Respiratory arrest
 - Lung cancer
 - Unknown
 - Pancreatitis with coincident biliary colic
 - Lung cancer with metastatic disease
 - Post-operative sepsis
- None of the deaths were attributed to HIV infection

Conclusions

- PLASMA HIV RNA RESPONSES
 - In this nRTI-experienced, selected population, virologic suppression (HIV RNA < 50 c/mL) was achieved in 59% (79/134) of subjects at week 144
 - A significant difference in virologic suppression was observed among the three treatment arms at week 144 (3-way p=0.045)
 - This difference was less significant compared to that seen at weeks 40-48 and week 96, respectively (3-way p=0.001; 3-way p=0.001)
 - In pairwise comparisons at week 144:
 - The proportion of subjects achieving viral suppression was greater in the quadruple NFV+EFV arm compared to the triple NFV arm (p=0.016)
 - There were no significant differences in viral suppression seen in the NFV+EFV vs EFV arms or in the EFV vs NFV triple arms
- DURABILITY OF VIRAL LOAD RESPONSES
 - In time to virologic failure (confirmed HIV RNA ≥ 200 c/mL at week 16 or later) analyses, a highly significant difference in durability of viral suppression was observed among the three treatment arms at 144 weeks (three-way p < 0.001)
 - The patients in the quadruple NFV+EFV arm took a significantly longer time to experience virologic failure compared to those randomized to the NFV triple arm (p < 0.001) and to the triple EFV arm (p=0.003)
 - The EFV triple arm had superior durability of viral load suppression compared to the NFV triple arm (p=0.028)

BASILINE PREDICTORS OF VIROLOGIC OUTCOME:

- COX PROPORTIONAL HAZARDS REGRESSION MODEL
 - Baseline factors that were highly predictive of virologic outcome (HIV RNA ≥ 200 c/mL) at 144 weeks:
 - Baseline HIV RNA (1 \log_{10} c/mL higher) was associated with virologic failure
 - Receipt of 3 vs 4 drug ACTG 364 randomized regimen was associated with increased risk of virologic failure
 - Being 3TC-naïve at study entry was associated with reduced risk of virologic failure

CD4 CELL COUNT CHANGE

- No significant short-term or long-term differences in CD4 cell count responses were observed among the three treatment arms at week 16 or week 144
- Overall, a median CD4 cell count rise of 70 cells/mm³ and 171 cells/mm³ was seen at week 16 and week 144, respectively

ACTG 364: CONCLUSIONS

- This study showed that the addition of at least two new classes of ART drugs in an alternative 4-drug regimen achieved superior durability of viral load suppression vs three-drug regimens for patients with extensive nucleoside experience who developed viral rebound.
- The benefits of achieving potent viral suppression with 4 drug vs three drug regimens have to be balanced with the risks of limiting future treatment options and incurring long-term toxicities
- Partially suppressive regimens in extensively nRTI-experienced patients may still provide substantial long-term increases in CD4 cell counts and confer clinical benefit