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Boston, USA

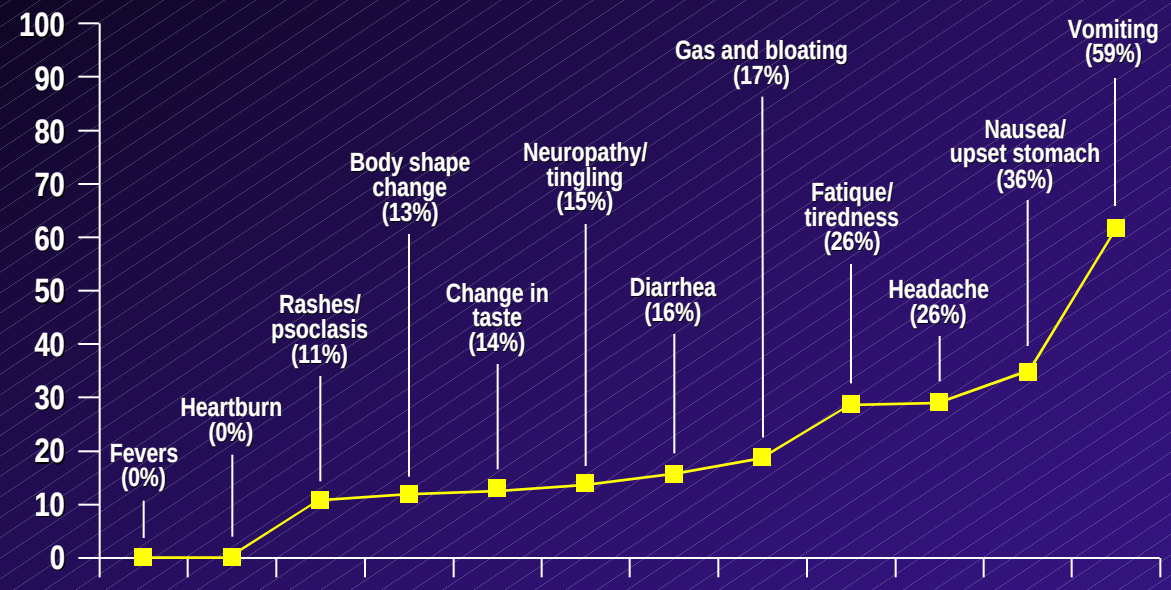
Recent data on SUSTIVA™ in PI-naïve patients

DuPont Pharma

Data that Assists in Selection Among Regimen Options

- Dosing Frequency
- Tolerability: short-term, long-term
- NC=F and Observed HIV RNA levels @ 48 weeks
- Baseline VL >100,000 copies/mL
- Ultrasensitive HIV RNA results (<50 copies/mL)

Missed Doses Due to Side Effects



POZ, vol 6 no. 2 May, 1998

Study 006 Design

Design

- Open-label, multicenter, multinational (USA, Europe, Canada) trial
- Blinded to viral load to Week 24
- 3TC, NNRTI, PI naive

Baseline Characteristics for Study 006 Extended Cohort*

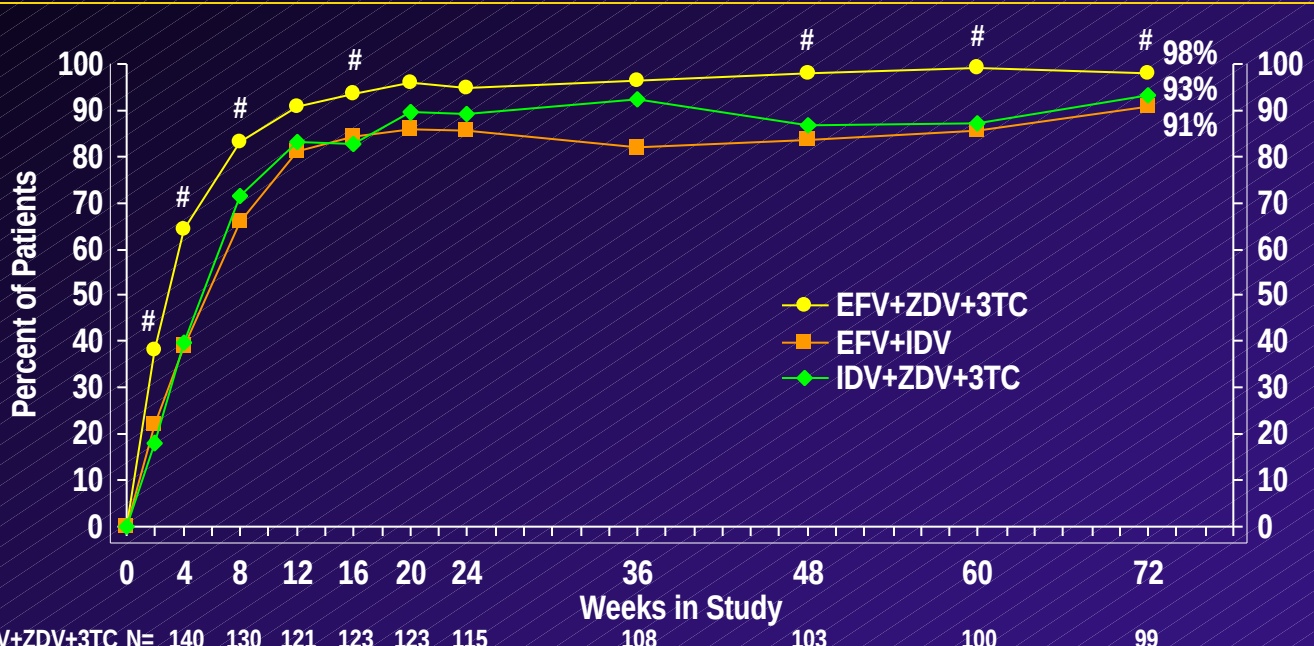
	EFV+ZDV+3TC (N=422)	EFV+IDV (N=429)	IDV+ZDV+3TC (N=415)
Antiretroviral naive (%)	83%	85%	87%
CD4 count (cells/mm^3)			
Mean	332.3 (±198.7)	340.4 (±211.0)	350.3 (±212.6)
Range	26.0–1234	2.0–1169	17.5–1198
CD4/CD8 ratio			
Mean	0.41 (±0.01)	0.41 (±0.01)	0.44 (±0.02)
HIV-1 RNA (log_{10} copies/mL)			
Mean	4.77 (±0.60)	4.80 (±0.59)	4.76 (±0.56)
Range	3.22–6.51	2.51–6.50	3.39–6.98
Geometric mean (copies/mL)	58,900	63,100	57,500

* No statistically significant differences between groups

Study 006 Initial Cohort

Amplicor Plasma HIV RNA: Percent of Patients <400 Copies/mL

Observed Data (72 Weeks)



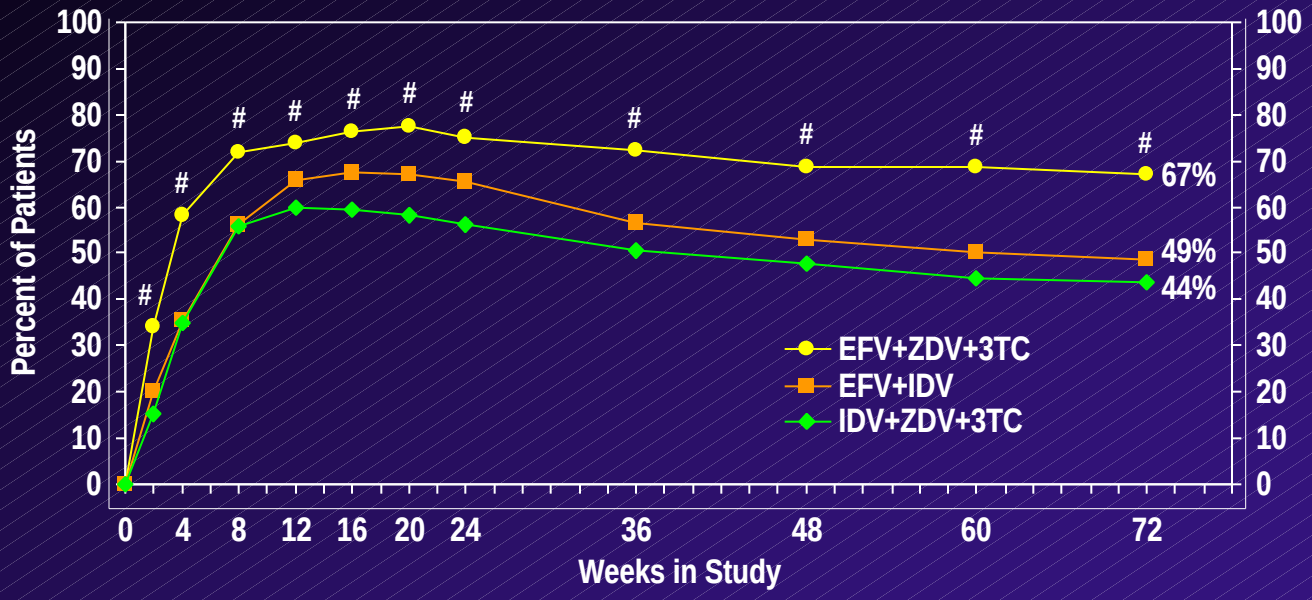
EFV+ZDV+3TC	N=	140	130	121	123	123	115	108	103	100	99
EFV+IDV	N=	133	123	117	116	114	111	95	92	84	76
IDV+ZDV+3TC	N=	131	115	106	105	96	93	79	82	77	74

Statistically significant difference between EFV+ZDV+3TC and IDV+ZDV+3TC, p≤0.05

Study 006 Initial Cohort

Amplicor Plasma HIV RNA: Percent of Patients <400 Copies/mL

Intent-to-Treat: Noncompleter = Failure (72 Weeks)



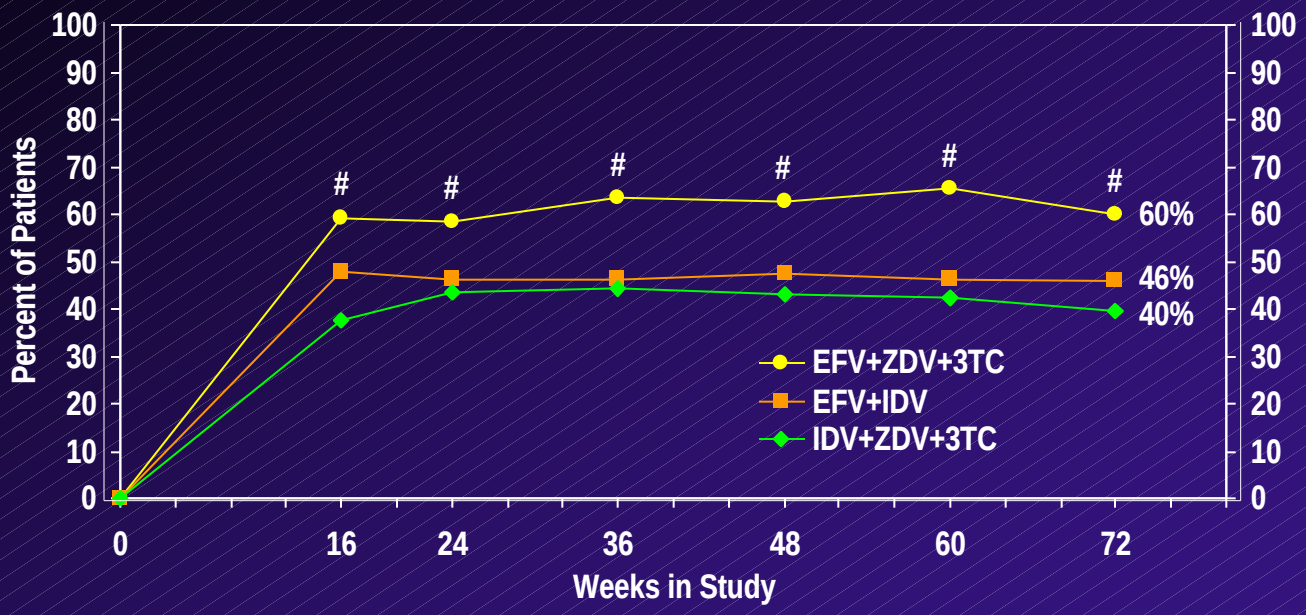
EFV+ZDV+3TC	N=	151	150	149	151	152	145	144	147	143	145
EFV+IDV	N=	147	144	145	146	145	138	129	145	144	142
IDV+ZDV+3TC	N=	148	145	145	146	146	146	142	146	146	146

Statistically significant difference between EFV+ZDV+3TC and IDV+ZDV+3TC, $p \leq 0.05$

Study 006 Initial Cohort

Ultrasensitive Plasma HIV RNA: Percent of Patients <50 Copies/mL

Intent-to-Treat: Noncompleter = Failure (72 Weeks)

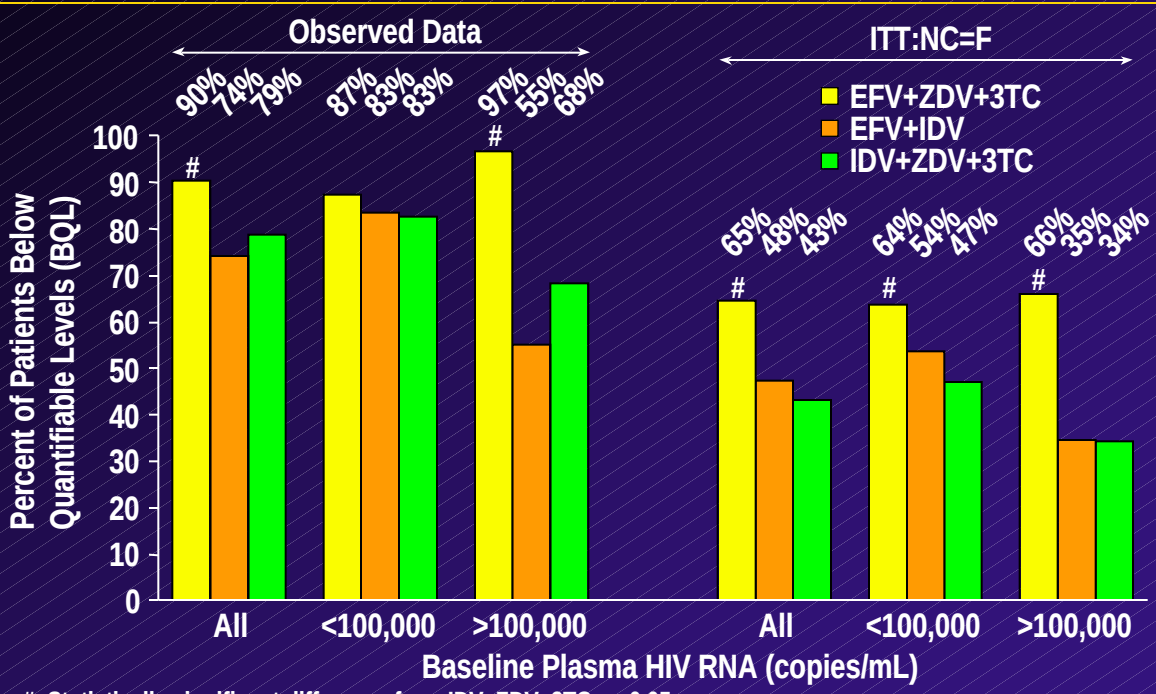


EFV+ZDV+3TC	N=	149	149	148	148	148	147
EFV+IDV	N=	144	145	140	146	145	142
IDV+ZDV+3TC	N=	144	145	144	146	146	146

Statistically significant difference between EFV+ZDV+3TC and IDV+ZDV+3TC, $p \leq 0.05$

Study 006

Ultrasensitive Plasma HIV RNA: Percent of Patients <50 Copies/mL Observed Data at Week 48



#: Statistically significant difference from IDV+ZDV+3TC, p<0.05

Tashima. *6th CROI*, 1999

Study 043 Objective and Design

Objective

- Characterize the effectiveness and safety of efavirenz (EFV) in combination with stavudine (d4T) and lamivudine (3TC) in antiretroviral therapy-naive HIV-infected patients

Design

EFV (600 mg qd) + d4T (40 mg q12h) + 3TC (150 mg q12h) (N=68)

48 Weeks

- Open-label, single-arm, multicenter trial
- 48 week duration
- 24 week data on first 42 patients enrolled

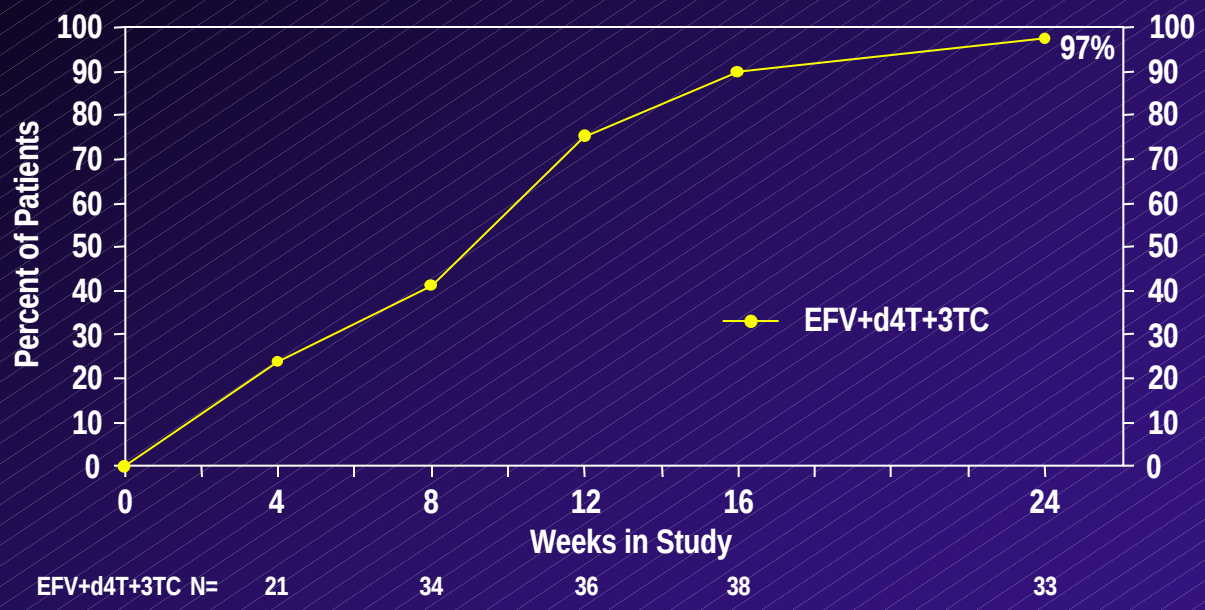
Cohen, et al. *ECCMID,* Berlin, March 1999

Disposition of Patients at 24 Weeks

	EFV+d4T+3TC (N=42)
Continuing on study	39 (93%)
Discontinuations	3 (7%)
Reason for discontinuation	
Withdrew consent	1 (2%)
Lost to follow up	2 (5%)

Study 043

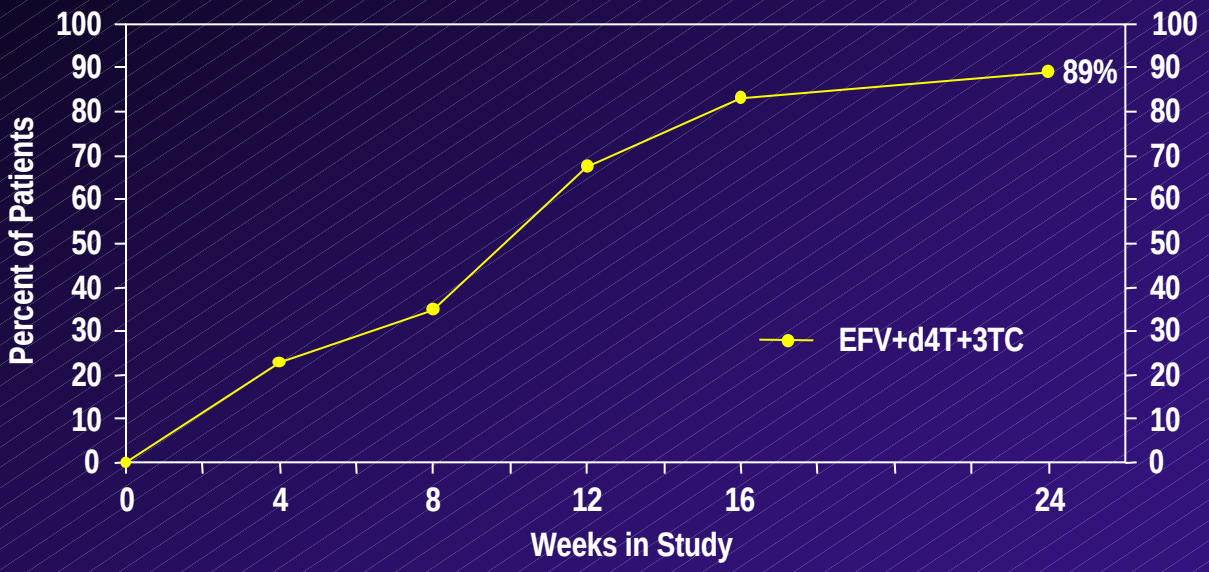
Ultrasensitive Plasma HIV RNA: Percent of Patients <50 Copies/mL Observed Data



Cohen, et al. *ECCMID,* Berlin, March 1999

Study 043

Ultrasensitive Plasma HIV RNA: Percent of Patients <50 Copies/mL
Intent-to-Treat: Noncompleter = Failure

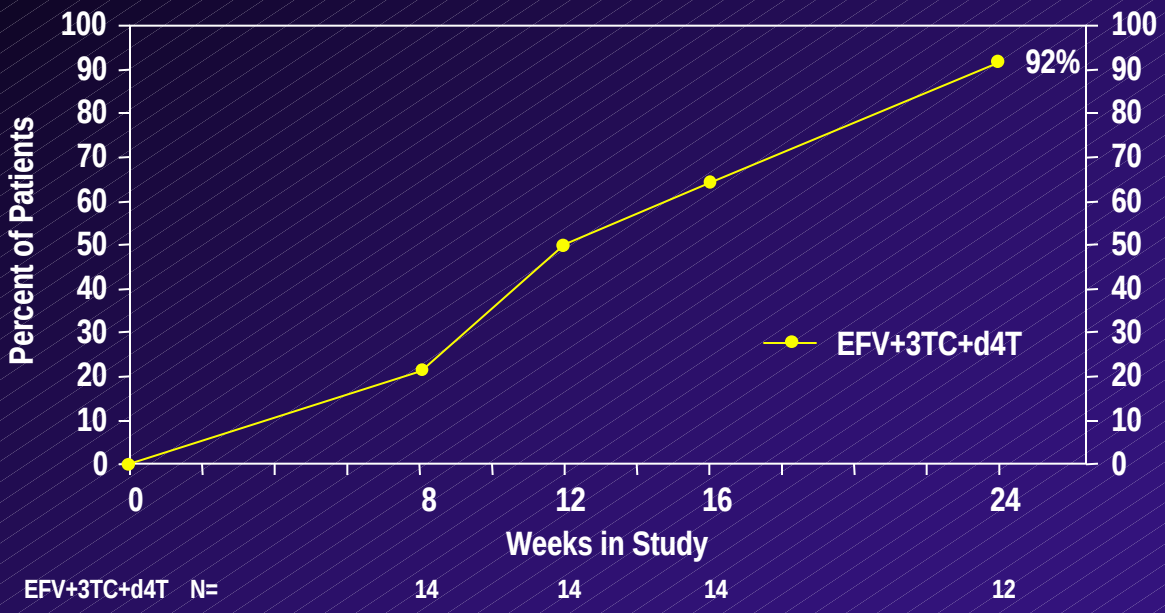


EFV+d4T+3TC N=	22	40	40	41	36

Cohen, et al. *ECCMID,* Berlin, March 1999

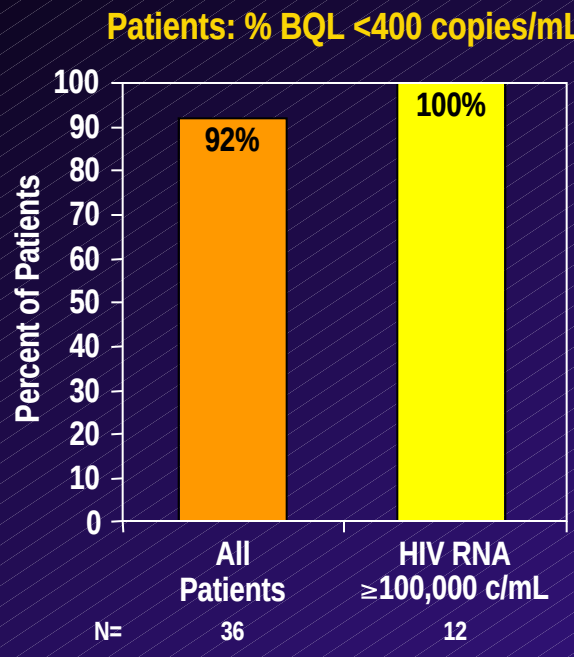
Study 043

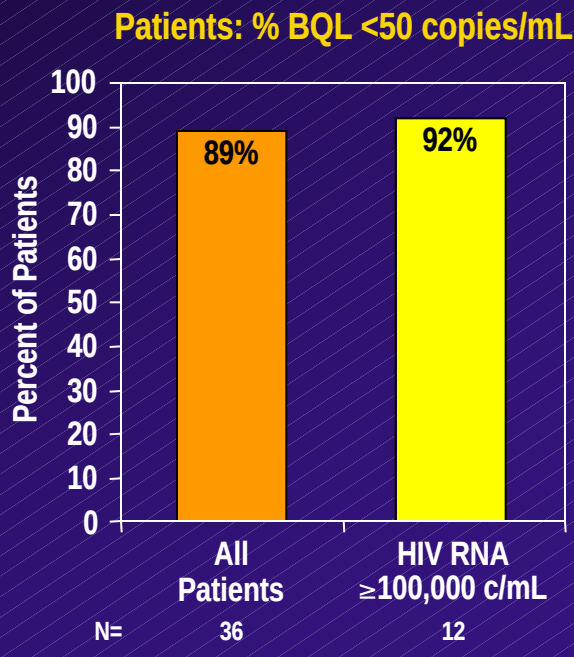
Ultrasensitive Plasma HIV RNA <50 Copies/mL
Baseline HIV RNA >100,000 Copies/mL: Noncompleter = Failure



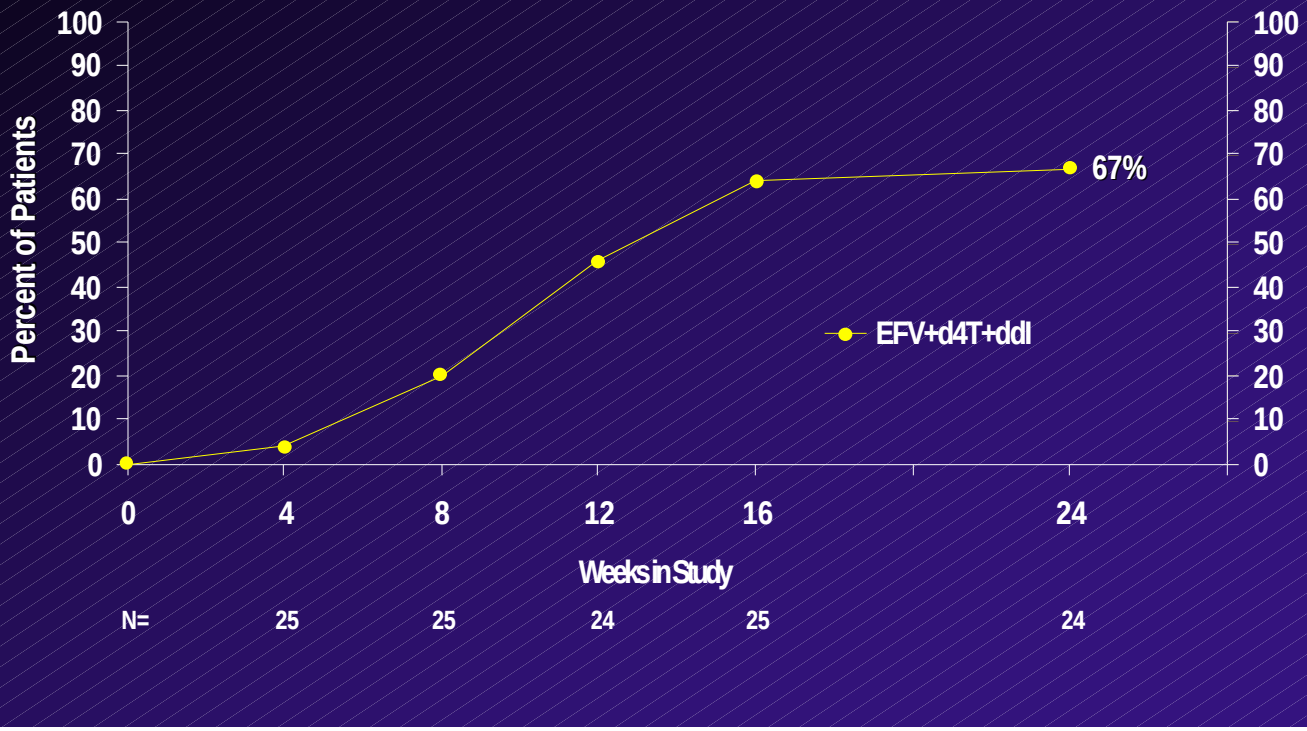
Cohen, et al. *ECCMID,* Berlin, March 1999

Plasma HIV RNA Results at 24 Weeks
Patients with Baseline HIV RNA ≥100,000 Copies/mL
Intent-to-Treat: Noncompleter = Failure



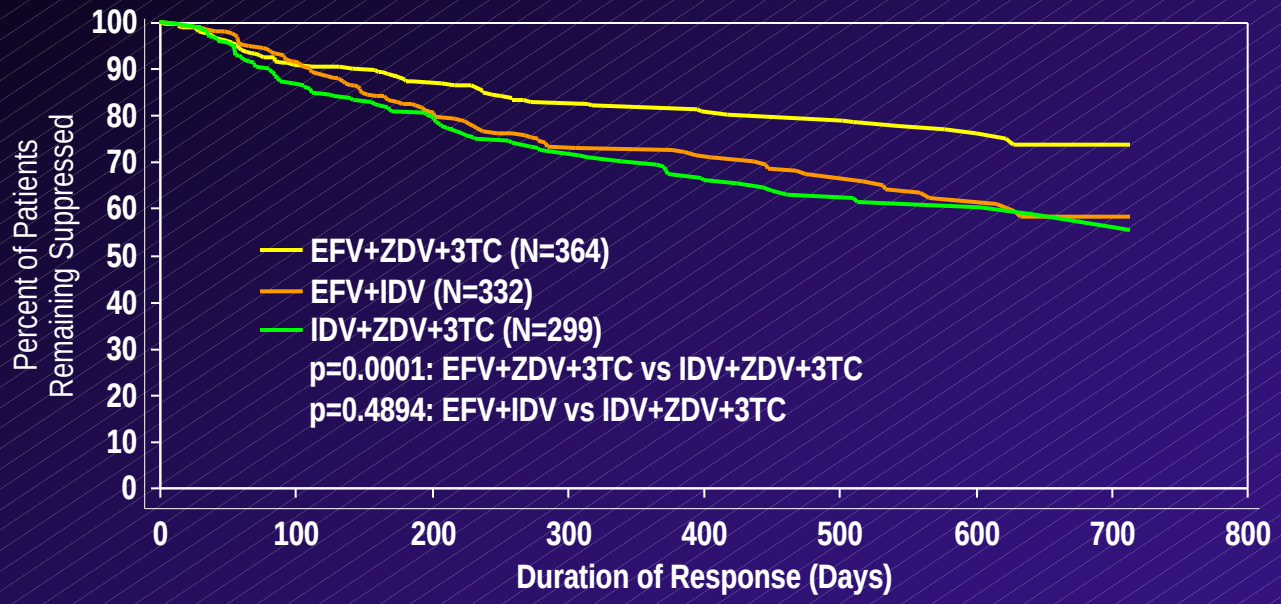


Ultrasensitive Plasma HIV-RNA Percent of Patients <50 Copies/m
Study 044: Baseline HIV-RNA ≥100,000 Copies/mL
Intent-to-Treat: Noncompleter = Failure



Study 006 Extended Cohort

Duration of Response: All Failures as Endpoint

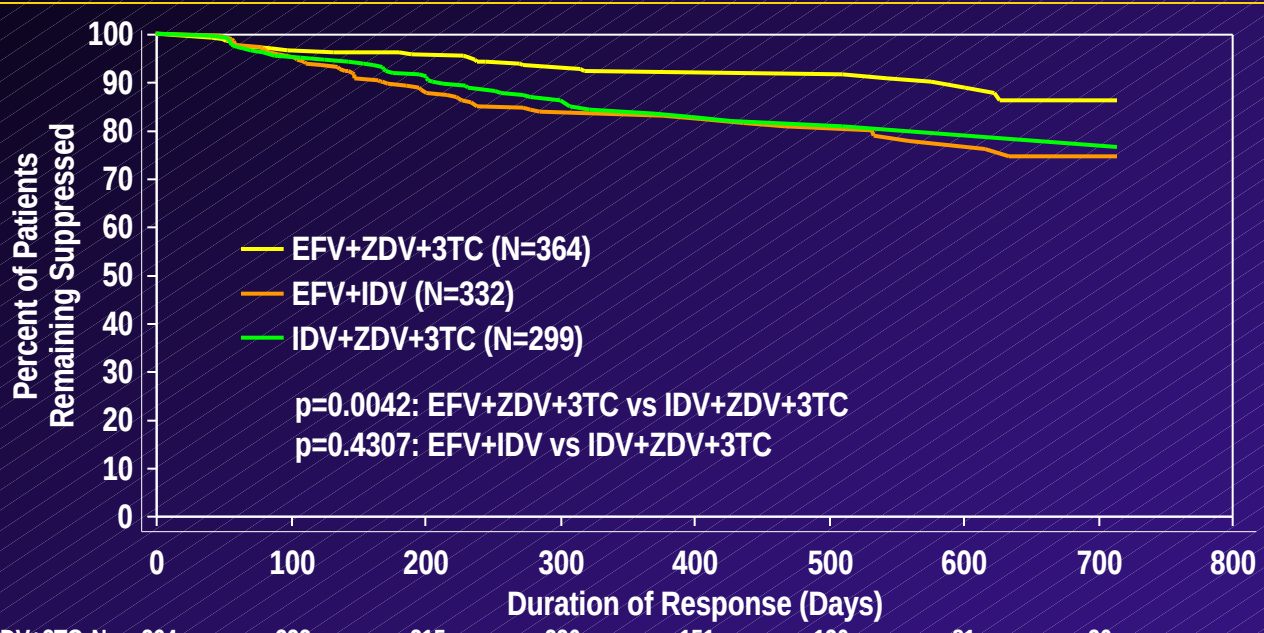


EFV+ZDV+3TC	N=	364	326	306	218	143	124	80	35
EFV+IDV	N=	332	300	265	167	114	92	50	20
IDV+ZDV+3TC	N=	299	255	229	147	94	78	51	28

Patients who discontinued, had an AIDS defining event, or had two consecutive HIV RNA results ≥400 copies/mL are considered failures

Study 006 Extended Cohort

Duration of Response: Only Virologic Failures as Endpoint



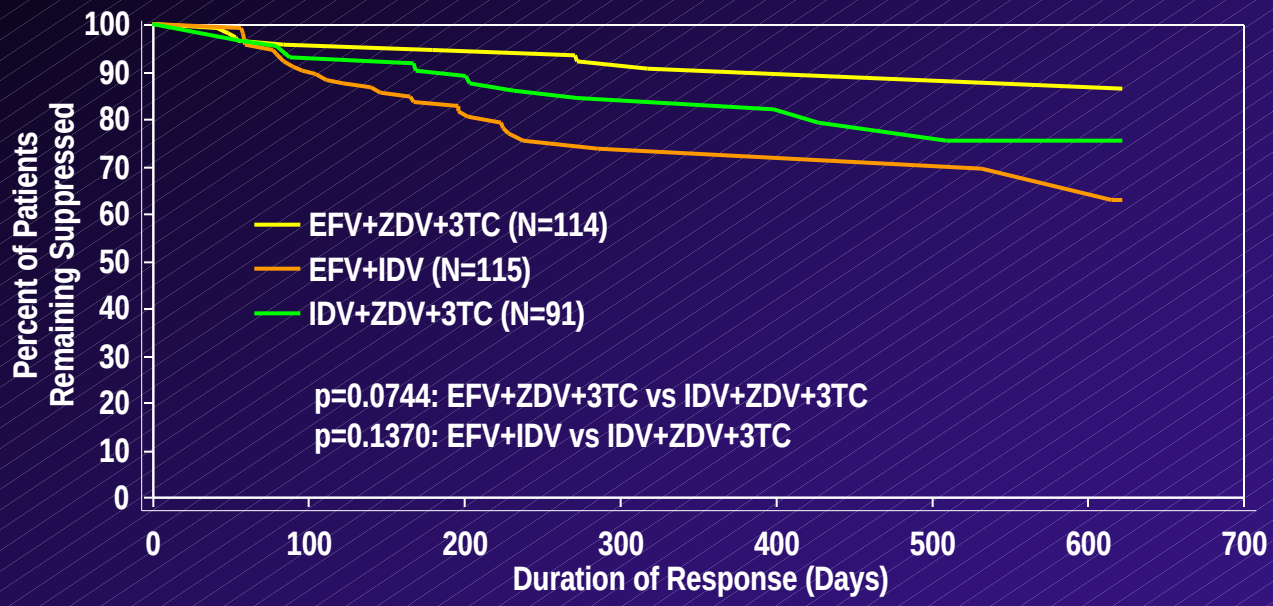
EFV+ZDV+3TC	N=	364	332	315	226	151	130	81	36
EFV+IDV	N=	332	302	267	169	116	94	51	21
IDV+ZDV+3TC	N=	299	260	233	153	98	80	53	28

Only patients who had two consecutive HIV RNA results ≥400 copies/mL are considered failures

Study 006 Extended Cohort

Duration of Response: Only Virologic Failures as Endpoint

Patients with Baseline HIV RNA ≥100,000 Copies/mL



EFV+ZDV+3TC	N=	114	102	96	70	40	34	23
EFV+IDV	N=	115	100	86	42	26	22	12
IDV+ZDV+3TC	N=	91	78	66	45	33	24	14

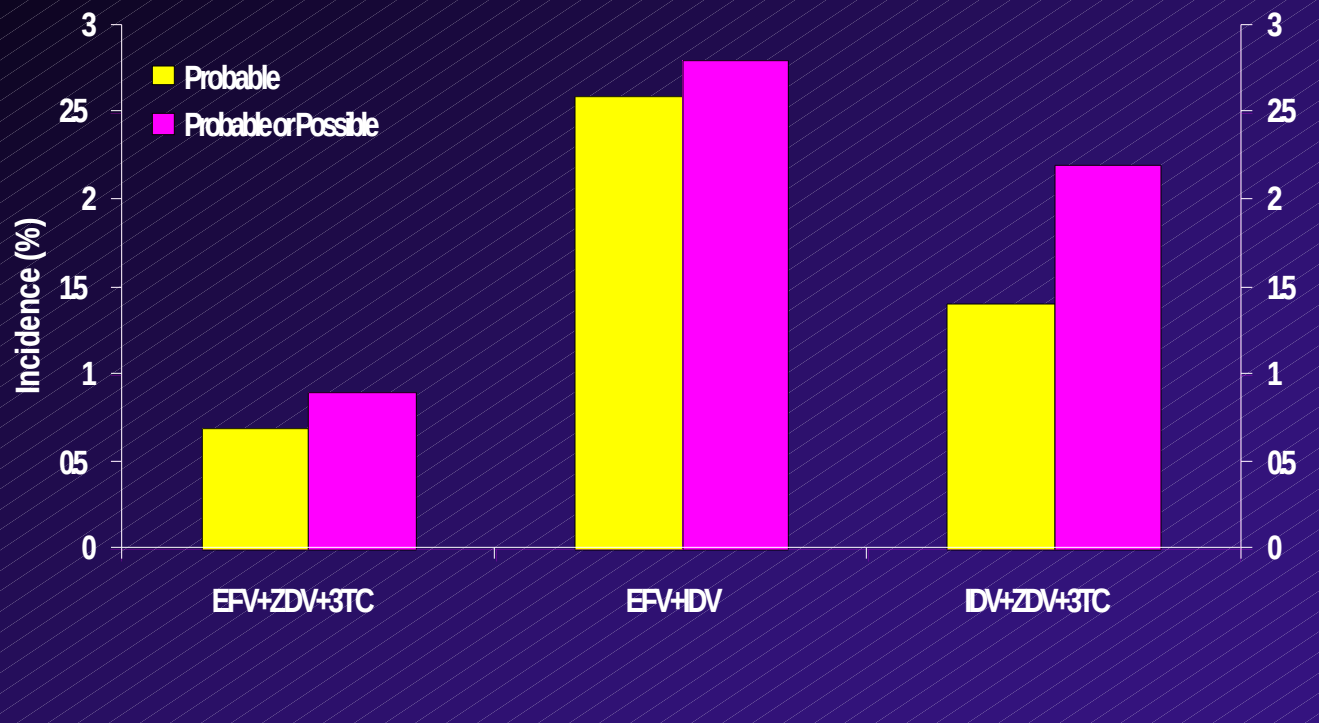
Patients who discontinued, had an AIDS defining event, or had two consecutive HIV RNA results ≥400 copies/mL are considered failures

Nervous System Symptoms: Onset and Duration Efavirenz 600 mg Daytime vs. Bedtime Dosing

	Daytime (N=27)	Bedtime (N=404)
Onset of First Symptoms (days): Median (Range)	1 (0,98)	1 (0,167)
Median Duration (days) (Range)	28 (2,>167)	15 (1,>181)

Summary: Bedtime dosing seems most favorable recommendation

Incidence of Lipodystrophy Syndromes in Study 006



Conclusions

- "As low as possible" based on
  - Reduction of viral load to <50 copies/mL in patients with a high baseline viral load (≥100,000 copies/mL)
- "In as many as possible" based on
  - High responder rates in large clinical data sets
- "For as long as possible" based on
  - Efficacy in initial cohort through 72 weeks
  - Kaplan Meier "survival" analysis in extended cohort (N=1266)


SUSTIVA
efavirenz

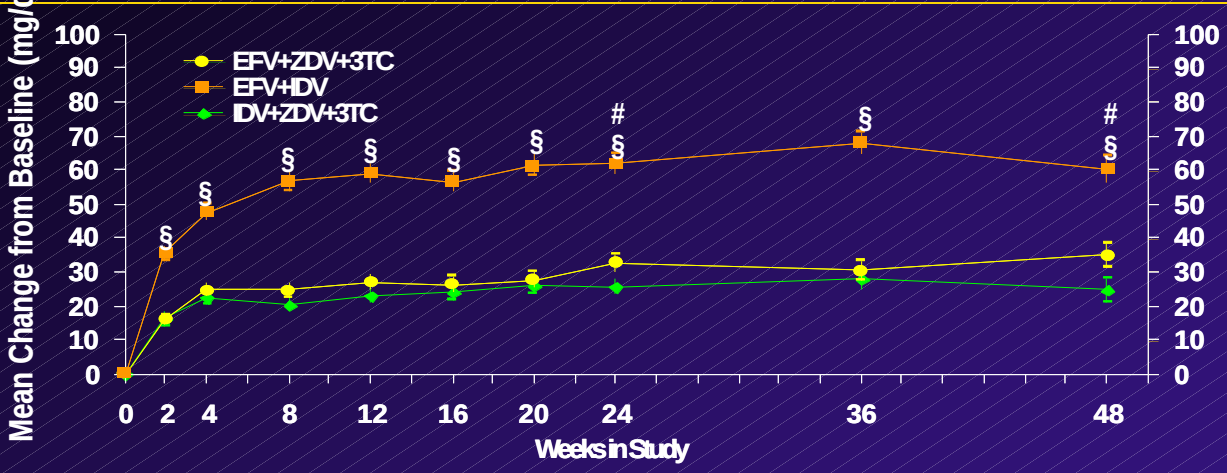
Outcome Over 48 weeks

Study Arm	n	Virologic Failure Mean # of RTM		
		<2000	>2000	
NFV	47	3/2.9	4/4.5	45%
EFV	45	3/3.2	3/4.0	60%
NFV+EFV	44	3/3.6	4/3.7	77%

Limited to subjects with >2,000 copies and ≥1 RT resistance mutation at baseline

Nonfasting Cholesterol Levels

Mean Change from Baseline



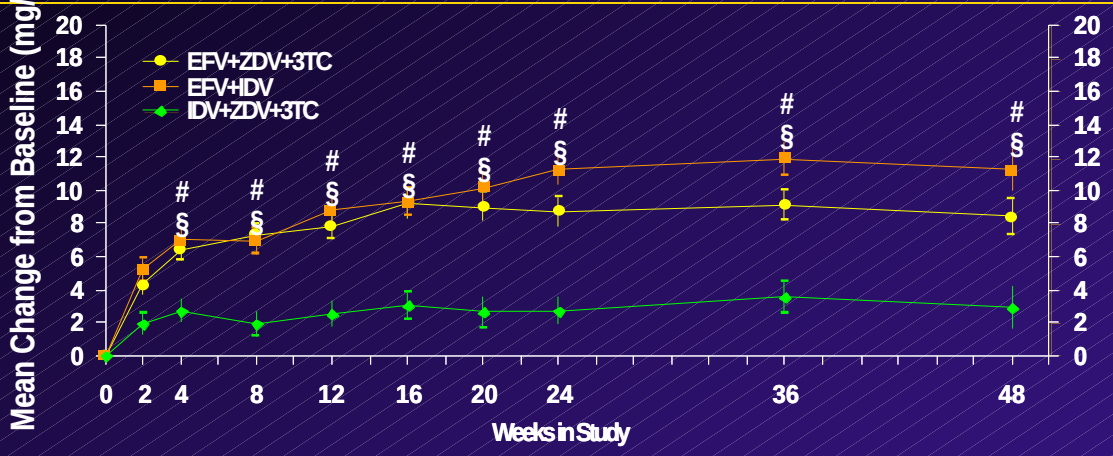
EFV+ZDV+3TC	N=	208	198	197	193	187	185	173	156	108
EFV+IDV	N=	202	201	189	186	187	179	177	139	97
IDV+ZDV+3TC	N=	182	183	178	169	161	158	150	122	92

Statistically significant difference between EFV+ZDV+3TC and IDV+ZDV+3TC, $p \leq 0.05$

§ Statistically significant difference between EFV+IDV and IDV+ZDV+3TC, $p \leq 0.05$

Nonfasting High Density Lipid Levels

Mean Change from Baseline



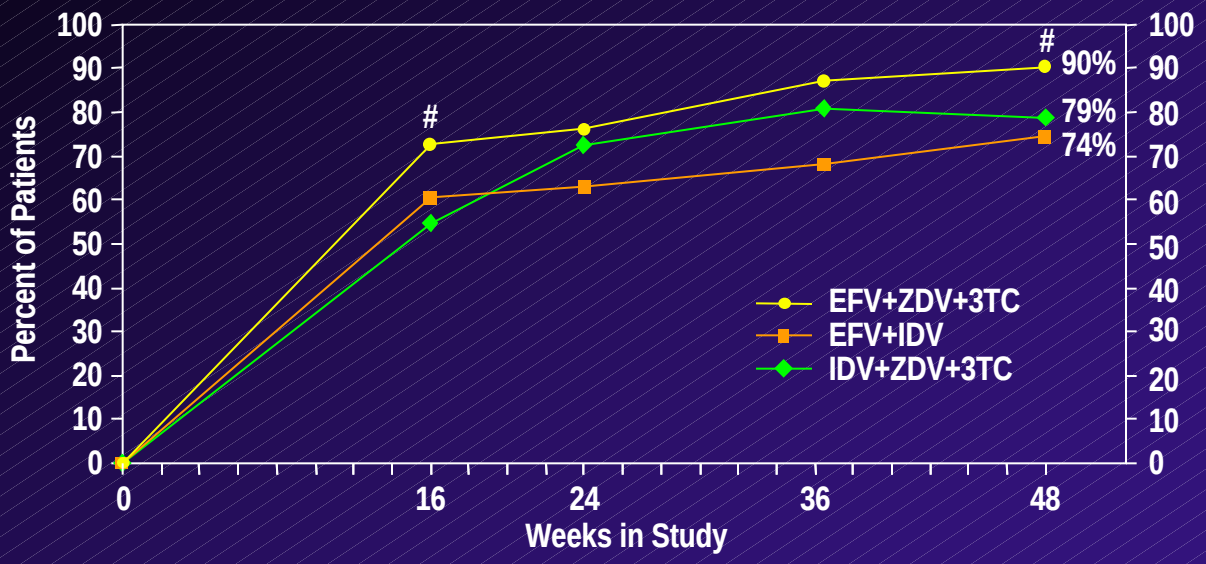
EFV+ZDV+3TC	N= 208	198	197	192	186	184	172	156	107
EFV+IDV	N= 202	200	188	185	188	179	177	138	95
IDV+ZDV+3TC	N= 182	183	178	169	164	158	151	122	89

Statistically significant difference between EFV+ZDV+3TC and IDV+ZDV+3TC, $p \leq 0.05$

§ Statistically significant difference between EFV+IDV and IDV+ZDV+3TC, $p \leq 0.05$

Study 006

Amplicor Plasma HIV RNA: Percent of Patients <50 Copies/mL Observed Data



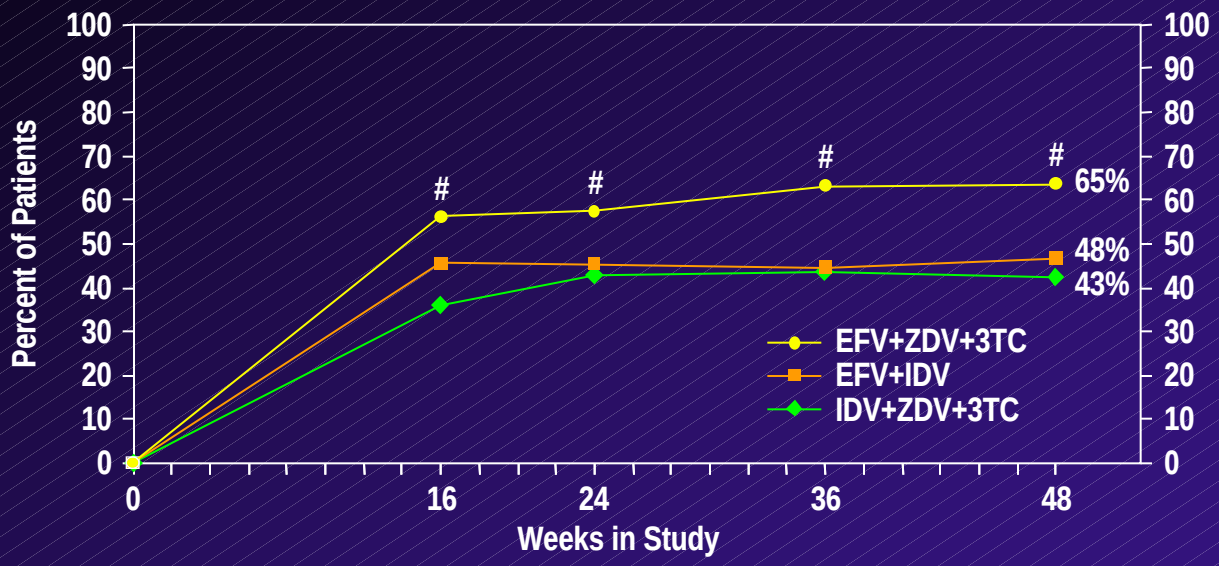
EFV+ZDV+3TC	N=	121	114	108	103
EFV+IDV	N=	114	106	91	89
IDV+ZDV+3TC	N=	99	87	79	80

#: Statistically significant difference from IDV+ZDV+3TC, $p \leq 0.05$

Tashima. *6th CROI*, 1999

Study 006

Ultrasensitive Plasma HIV RNA: Percent of Patients <50 Copies/mL
Intent-to-Treat: Noncompleter = Failure



EFV+ZDV+3TC	N=	154	149	146	144
EFV+IDV	N=	148	145	137	139
IDV+ZDV+3TC	N=	148	145	144	144

#: Statistically significant difference from IDV+ZDV+3TC, p<0.05

Tashima. *6th CROI*, 1999