



A Randomized, Open Label Factorial Trial Comparing Efavirenz to Lopinavir and Zidovudine + Didanosine + Stavudine + Lamivudine in Treatment-Naïve HIV-Infected Persons with <200 CD4+ cells/mm³ in South Africa

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ABSTRACT

Phidisa II: A Randomized 2 x 2 Factorial Trial Comparing Initial Therapy of Efavirenz with Lopinavir/Ritonavir and Zidovudine + Didanosine with Stavudine + Lamivudine in Treatment-Naïve HIV-Infected Persons with <200 CD4+ cells/mm³ or a Prior AIDS Diagnosis
Background: When the South African Phidisa II study began in 2004, few NRTIs were available and the relative efficacy of lopinavir/ritonavir (LPV/r) and efavirenz (EFV) was not known.
Methods: Phidisa II enrolled antiretroviral naïve HIV-infected members of the South African National Defense Forces or family members at 6 sites. Participants > 13 years old with <200 CD4+ cells/mm³ or prior AIDS diagnosis were randomized to EFV or LPV/r; also to zidovudine + didanosine (ZDV+ddl) or stavudine + lamivudine (d4T+3TC). HIV RNA and CD4+ cell count were centrally determined monthly for 3 months, then every 3 months until March 2008 study closure. The primary endpoint was AIDS or death. Cox models were used to estimate hazard ratios (HRs). All analyses are by intention to treat.
Results: 1771 persons were randomized and followed for 24.7 months (median). At baseline, median HIV RNA level and CD4+ count were 144,000 copies/mL and 106 cells/mm³. 163 persons in the EFV group and 157 on LPV/r reached primary endpoints (HR:1.04; 95% CI 0.84-1.30). Virologic suppression was faster with EFV than LPV (68% vs 58% < 400 copies/mL at 3 months; p<0.001); the difference was negligible by 12 months (66% vs 65%) and through study closure. Persons assigned LPV had greater CD4+ cell responses; CD4+ count was 272 for EFV and 317 for LPV at 36 months (p=0.004). 170 participants in the ZDV+ddl group, 150 on d4T+3TC reached primary endpoints (HR=1.15; 95% CI: 0.93-1.44). HIV RNA was significantly lower over follow-up (by 0.25 log; p=0.001) for d4T+3TC compared to ZDV+ddl. A corresponding greater CD4+ count response was also seen; CD4+ count was 309 for d4T+3TC, 279 for ZDV+ddl at 36 months (p=0.04). Effects of the two treatment factors were additive. Fastest HIV-RNA suppression was with EFV+d4T+3TC (73% < 400 copies/mL at 3 months); greatest CD4+ response with LPV+d4T+3TC (326 cells/mm³ at 36 months). Those assigned EFV+ZDV+ddl had lowest 36 month CD4+ count (251 cells/mm³) and highest rate for the primary endpoints (10.6/100 person-years vs 7.6 to 8.8 for the other groups).
Conclusions: EFV led to more rapid HIV RNA suppression than LPV but CD4+ counts were increased more with LPV than EFV. AIDS/deaths rates were similar for EFV and LPV. A trend towards better clinical outcomes and significant virologic and immunologic improvement favored d4T+3TC over ZDV+ddl. The nucleoside combination of zidovudine with didanosine is not recommended in this setting.

BACKGROUND

Phidisa II is a completed, randomised, open-label, 2 X 2 factorial clinical trial conducted in South Africa that compared the safety and efficacy of different combination antiretroviral therapy regimens in treatment naïve patients with advanced HIV disease and/or CD4+ cell counts < 200 cells/mm³. When the Phidisa II study began in 2004, there was no governmental rollout of antiretrovirals by the South African Department of Health or the South African Military Health Services. In resource limited settings there are few good quality data comparing the relative safety and efficacy of combination antiretroviral therapy (ART) regimens.

STUDY OBJECTIVES

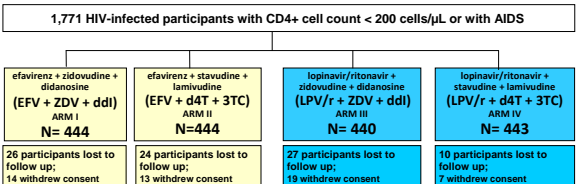
In a 2x2 factorial design:
 To compare efavirenz (EFV) to lopinavir/ritonavir (LPV/r), and zidovudine (ZDV) + didanosine (ddl) to stavudine (d4T) + lamivudine (3TC) for clinical and virologic efficacy and tolerability.

METHODS

- Main Eligibility criteria:**
- Uniformed South African military personnel or family members
 - HIV infected adult patients (>14 years of age)
 - Antiretroviral naïve (defined as ART for < 7 days)
 - CD4+ T lymphocyte cell counts <200 cells/μl or a prior AIDS diagnosis
- Study design and outcome measures:**
- Randomization: Equal allocation to EFV + ZDV + ddl; EFV + d4T + 3TC; LPV/r + ZDV + ddl; LPV/r + d4T + 3TC
 - Primary Endpoint: Death or progression of disease (POD)
 - Secondary Endpoints: HIV RNA, CD4+ cell counts, grade 4 events, treatment discontinuation
 - Power: 80% power to detect 20% difference between main effects with 635 primary events
 - The protocol was approved by the Phidisa (RSA) and NIAID (USA) IRBs
 - All participants on the study signed written informed consent.

RESULTS

Figure 1. Recruitment and disposition



RESULTS

Baseline Characteristics

- 68% Male, 32% Female; Average age 35 years
- Median CD4+ count = 106 cells/mm³; 27% had <50 cells/mm³
- Median HIV RNA = 144,000 RNA copies/mL (5.1 log₁₀/mL)

Table 1. Summary of Primary and Major Secondary Endpoints

Endpoint	EFV (n = 888)	LPV/r (n = 883)	Hazard ratio (95%CI)	P-Value	ZDV + ddl (n = 884)	d4T + 3TC (n = 887)	Hazard ratio (95%CI)	P-Value
AIDS or death	163	157	1.04 (0.84-1.30)	0.71	170	150	1.15 (0.93-1.44)	0.20
Death	106	102	1.05 (0.80-1.37)	0.75	111	97	1.15 (0.88-1.51)	0.31
AIDS	80	69	1.18 (0.85-1.62)	0.32	83	66	1.29 (0.94-1.79)	0.12
Grade 4 events	137	129	1.07 (0.84-1.36)	0.57	142	124	1.16 (0.91-1.48)	0.23

Additional Notes

- 1771 persons were randomized between February 2004 and December 2007 at 6 sites.
- Median follow-up was 24.7 months; one-third of subjects were followed for ≥ 36 months.
- The HR for EFV vs LPV/r was greater for those assigned ZDV + ddl (1.23; 95% CI: 0.91-1.66) than d4T + 3TC (0.87; 95% CI: 0.63-1.20) (p = 0.13 for interaction). The trend for interaction arises from the difference in the rates for the two EFV groups, i.e., the rate per 100 person years for AIDS or death was 10.6 for those assigned EFV + ZDV + ddl and 7.6 for those assigned EFV + d4T + 3TC.
- 171 (53%) of the 320 primary events were due to death.
- 168 (53%) of the 320 primary events occurred in the first 6 months after randomization.
- 108 (52%) of the 208 deaths occurred in the first 6 months.

Table 2. Summary of Primary and Major Secondary Endpoints for the 4 Treatment Arms

	EFV + ZDV+ddl	EFV+ d4T+3TC	LPV/r+ ZDV+ddl	LPV/r+ d4T+3TC	P-Value (ddl)
No. Patients Randomized	444	444	440	443	
AIDS or Death N(Rate/100 person-yrs)	93 (10.6)	70 (7.6)	77 (8.6)	80 (8.8)	0.13
Grade 4 Events N(Rate/100 person-yrs)	73 (8.5)	64 (7.2)	69 (7.7)	60 (6.7)	0.62
CD4+ cell count change at 24-months (cells/μL) (Mean ± SE)	200 ± 11	238 ± 11	249 ± 12	274 ± 12	<0.01
HIV-RNA suppressed at 24-months (% <400 copies/mL)	62.1%	76.5%	67.8%	67.7%	0.009

Table 3a. Viral Load suppression for EFV vs LPV/r at selected Follow-up Visits

Months from randomization	EFV HIV RNA copies/mL	LPV/r HIV RNA copies/mL	Mean Difference (SE)	P-Value
3 months	768	752	-2.80 (-0.22 (0.06))	0.001
6	694	691	-2.78 (-0.14 (0.07))	0.04
12	611	613	-2.70 (-0.04 (0.07))	0.58
24	427	416	-2.80 (0.03 (0.06))	0.67
36	281	257	-2.81 (0.10 (0.10))	0.29

Table 3b. Viral Load suppression for ZDV + ddl vs d4T +3TC at selected Follow-up Visits

Months from randomization	ZDV + ddl HIV RNA copies/mL	d4T + 3TC HIV RNA copies/mL	Mean Difference (SE)	P-Value
3 months	741	776	-2.84 (-0.25 (0.06))	<0.001
6	671	704	-3.05 (-0.41 (0.07))	<0.001
12	606	618	-2.86 (-0.26 (0.07))	0.001
24	409	434	-2.86 (0.17 (0.06))	0.04
36	263	255	-2.81 (0.11 (0.10))	0.27

Table 4a. CD4+ Cell Count Changes for EFV and LPV/r at selected Follow-up Visits

Months from randomization	EFV CD4+ cell count (cells/mm ³)	LPV/r CD4+ cell count (cells/mm ³)	Mean Difference (SE)	P-Value
3 months	766	751	36.5 (-5.8 (4.3))	0.17
6	692	692	119.4 (-2.1 (4.8))	0.25
12	611	612	171.2 (-21.8 (6.6))	<0.001
24	428	414	261.8 (-42.1 (11.4))	<0.001
36	260	271	316.5 (-45.1 (15.8))	0.004

Table 4b. CD4+ Cell Count Changes for ZDV + ddl and d4T + 3TC at selected Follow-up Visits

Months from randomization	ZDV + ddl CD4+ cell count (cells/mm ³)	d4T + 3TC CD4+ cell count (cells/mm ³)	Mean Difference (SE)	P-Value
3 months	741	776	30.9 (-1.0 (4.3))	0.66
6	672	704	119.7 (-2.1 (4.8))	0.23
12	600	618	164.9 (-8.7 (6.7))	0.19
24	406	435	255.2 (-31.2 (11.4))	0.006
36	261	253	309.1 (-32.6 (15.9))	0.04

RESULTS

Figure 2a. Primary Clinical Events: EFV versus LPV/r

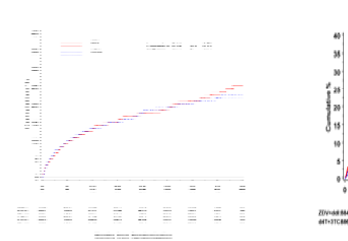


Figure 2b. Primary Clinical Events: ZDV + ddl versus d4T + 3TC

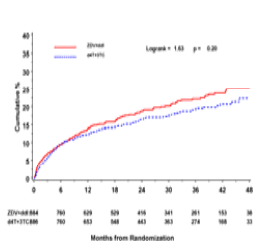


Figure 3a. Kaplan-Meier Plot for Death: EFV versus LPV/r

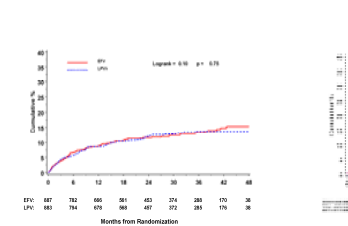
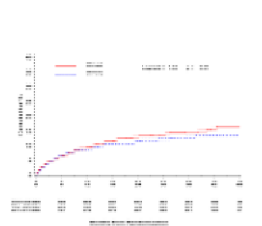


Figure 3b. Kaplan-Meier Plot for Death: ZDV + ddl versus d4T + 3TC



CONCLUSIONS

- Significant morbidity and mortality occurred, especially during the initial 6 months of treatment.
- Rates of POD or death were similar for the EFV and LPV/r groups; the fewer than planned number of events (320 vs. 635) allows us to rule out a 30% difference between groups with 95% confidence.
- Rates of POD or death did not significantly differ for the ZDV + ddl and d4T + 3TC groups. However, there was a trend towards more favorable clinical outcomes, supported by CD4+ counts and viral load, for the d4T + 3TC compared to the ZDV + ddl group.

DISCUSSION

- A large, multicenter randomized clinical trial was conducted in the SANDF with outstanding follow-up.
- Both EFV and LPV/r can be recommended for use in this population. Preference for use should be made on clinical and contextual grounds.
- d4T + 3TC appeared to be an effective combination in this study. Use of ZDV + ddl should be approached cautiously.
- The much higher mortality during the first 6 months of study strongly suggests that treatment with antiretroviral therapy should be started before CD4+ counts drop below 200 cells/mm³ and before AIDS is diagnosed.

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