

CROI 2005

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TDM: P577: AACTG 5143

Randomized study of twice-daily LPV/r or FPV/r or FPV/LPV/r

- 1 vs 2 PI + TFV + optimal nRTI
- 400/100 vs 700/100 vs 700/400/100 BID
- 56 of planned 214 enrollees
- 24 instead of 48 weeks
- All subjects on 2 PI converted to single

PK Substudy

Kashuba (AIDS 2005;19:145-152)

	LPV	LPV/FPV	FPV
•			
•			
• LPV C _{max}	9800	6300	--
• APV C _{max}	--	2400	5000

	<u>Dual PI</u>	<u>Single PI</u>	<u>P</u>
N	28	28	
Week 24 VR ITT	75%	61%	<i>p</i> = 0.17
Week 24 VR AT	100% (n = 12)	64% (n = 25)	<i>p</i> = 0.02
Week HIV-1 RNA			
< 50 copies ITT	54%	46%	<i>p</i> = 0.37
<50 copies AT	75%	48%	<i>p</i> = 0.14
CD4+ Δ			
ITT	+81	+41	<i>p</i> = 0.4
AT	+114	+43	<i>p</i> = 0.08
Resistance			
≥ 1 mutation	5	10	
≥ 1 PI mutation	2	8	

TDM:P79 Paul Pham et al
(Abbott)

Steady-state PK of APV, LPV,
EFV combination

- N= 12 APV 750 + LPV/r 533/133 BID
- N= 7 APV + LPV/r + EFV 600 QD

PK Parameter	LPV (+APV) Median (IQR range 25, 75)	LPV(+APV+EFV) Median (IQR range 25 to 75)	<i>p</i>
C_{\max} (ng/mL)	11403 (10241, 13007)	10336 (8997, 10965)	.272
T_{\max} (h)	5.16 (5.07, 6.11)	6.38 (3.03, 6.42)	.611
C_{\min} (ng/mL)	4824 (3968, 6806)	5027 (1637, 6130)	.447
AUC (ng·h/mL)	95101 (73281, 121068)	94244 (55061, 96414)	.398
Half-life (h)	8.4 (5.18, 19.51)	5.72 (2.70, 9.54)	.108

PK Parameter	APV (+LPV/r) Median (IQR range 25 to 75)	APV (+LPV/r+ EFV) Median (IQR range 25 to 75)	<i>p</i>
C_{\max} (ng/mL)	3768 (3215, 8063)	2468 (1781, 4721)	.128
T_{\max} (h)	2.1 (1.23, 2.87)	2.4 (2.08, 3.03)	.19
Cmin (ng/mL)	860 (606, 1712)	1053 (704, 1240)	.735
AUC (ng·h/mL)	23129 (16290, 37173)	21145 (11878, 28370)	.176
Half-life (h)	6.68 (5.01, 11.51)	7.61 (5.45, 11.49)	.933

TDM: P80 F van Leth et al

Minimum Plasma NVP and EFV w/r/t VF

- 2NN study
- Conc at d 3, wk 1,2,4,12,24,48
- VF: never <50 copies or 2 >50 copies after control

Nevirapine Virologic Failure

$C_{\min} < 3.1$ mg/L (hazard ratio: 1.34; 95% CI 0.90 to 2.00)

Negative predictive value 78% if >3.1

$C_{\min} < 2.3$ mg/L (hazard ratio: 1.38; 0.79 to 2.41)

Negative predictive value 77% if >2.3

Efavirenz Virologic Failure

$C_{\min} < 1.1$ mg/L (hazard ratio: 1.95; 1.08 to 3.24)

Negative predictive value 88% if >1.1

Sensitivity = 59%

TDM: P639 F Mentre et al.

COPHAR2-ANRS 111

- Prospective trial to evaluate TDM PI with respect to virologic success and tolerance
- PI naïve on IDV/r, LPV/r, or NLF
- TDM at weeks 2, 8 or 16, 24, and 48
- Dose adjustment at week 24
- Failure: 2 consecutive viral loads ≥ 200 copies/mL between weeks 16 and 48, or a PI-related adverse grade 3 or 4 and a grade 2 dose-dependent like diarrhea or renal colic

	Week 2	Week 8/16	Week 24	Week 48
IDV n=42	51% 20/39	69% 22/32	77% 21/27	76% 16/21
LPV n=38	38% 13/34	58% 19/33	59% 17/29	72% 18/25
NFV n=35	44% 15/34	38% 11/29	50% 13/26	56% 9/16

IDV n=30

ITT 70%

OT 87%

LPV n=30

ITT 73%

OT 81%

NFV n=31

ITT 45%

OT 54%

TDM: P642 R Nettles et al.

Frequent PK sampling

- Pilot study, n = 10
- Drug level sampling q M-W-F
- 3-4 months
- Same time each day
- All subjects VL <50 copies

P642 continued

- 713 samples, blips 26 (3.6%)
- PI: $n = 12$, ICV 43%
 - LPV/r: 24%, 33%, 52%, 85%
 - NLF/M8 metabolite 30/44%, 38/52%

nnRTI: $n = 5$, ICV 26%

COMPLICATIONS: RENAL

P818: Riesler et al. (MACS)

- Chronic Kidney Disease and HAART
- 1470 HIV+ and HIV- individuals
- Use of GFR MDRD
- Incorporates race, weight, sCr, age

GFR	HAART	HIV+ no HAART	HIV –
<60 mL/min/1.73 m ² (stages 3-5)	OR 2.5	n/a	1.0
<90	OR 1.7	1	
TFV use Stage 2 (60<GFR<90)	OR 1.7	1	
TFV use Stage 3-5	OR 2.0	1	

No association with pre-HAART CD4 or HIV-1 RNA, or length of time on HAART

COMPLICATIONS:RENAL

P819: S BECKER (GSK)

- CHORUS DATABASE
- Beyond serum Cr: Identification of renal insufficiency using glomerular filtration.
- 1298 enrollees followed prospectively on TDV
- Median duration 16 months
- National Kidney Foundation GFR

sCR: 22 (1.7%) G1 event
1 (<.1%) G4 event

GFR: 128 (9.9%) G3 event
7 (.5%) G4 event

Multivariate analysis: OR

Prior renal disease	4.9
Abn baseline GFR	18.9
Hypertension	1.6
Conc Renal toxic	2.7

COMPLICATIONS: RENAL

P829: J Gallant et al

- Decline in RF associated with TDV compared with nRTI Treatment
- TDV n = 344 vs alternate nRTI n = 314
- Prospective
- Baseline CrCl using Cockcroft-Gault Eq.
- 2 baseline values (within 90 days of start)

	<u>TFV</u>	<u>other nRTI</u>	<u><i>p</i></u>
Baseline Cr/CLR		.8/117.5 ml/min	NS
Δ Cr	+0.15	+0.10	.01
Δ CLR	-13.35	-7.5 ml/min	.005

Multivariate analysis: only associated with TFV use and lower baseline CD4 ($p < .05$)

COMPLICATIONS: BONE

P823: W Powderly (Gilead 903)

- Similar incidence of Osteopenia/porosis in ART-naïve subjects TFV (n=299) vs D4T (n=301)
- 144 week
- Background: 3TC + EFV
- DXA baseline and Q24 weeks
- WHO criteria: OPA (T: -2.5 to -1.0 SD) and OPS (T: ≤ 2.5 SD)

	<u>TFV</u>	<u>d4T</u>
Baseline LS osteopenia	23%	28%
144 weeks no Δ	74%	78%
144 weeks to ≤ -2.5	12%	8%
144 weeks to > -1.0	14%	14%
Baseline LS osteoporosis	3%	4%
144 weeks no Δ	n=5	n=4
144 weeks to -2.5 to -1.0	n=1	n=2
Baseline normal		
144 weeks no Δ	87%	92%
144 weeks to -2.5 to -1.0	13%	8%
144 weeks to ≤ -2.5	n=0	<1%
Fractures (none in ≤ -2.5)	5	11

COMPLICATIONS: BONE

P825: D Jacobson et al.

- Duration of ART and change in bone density over time
- 302 men; 101 women
- DXA, mean time 3.1 years, 903 intervals
- Baseline mean age 42 years; CD4 372; HIV L 2.7 log₁₀

Annualized: -0.0187% per month ($p < 0.0001$)

-0.22% over 1 year (25th -0.86% , 75th 0.41%)

-0.68% over 3 years (25th -2.6% , 75th 1.2%)

Loss associated with:

ddI ($p = 0.0043$)

TDF ($p < 0.0001$)

years known HIV+ ($p = 0.016$)

bilirubin > 2 ($p = 0.01$)

P555: Capravirine

R. Pesano et al. (Pfizer)

- 24-week safety, tolerability, and efficacy
- CPV + NLF + OBT-nRTI in PI-naïve, nnRTI experienced subjects
- Mean age 38.6 years
- 66% male
- 40% white; 49% black

	<u>Placebo</u>	<u>700 mg</u>	<u>1400 mg</u>	<u>p</u>
N	66	65	67	
D/C rates for AE Week 24	8%	12%	7%	.56, .99
<400 copies	43%	46%	59%	.79, .33
< 50 copies	39%	40%	52%	ns
Treatment failures	65	58	47	.62, .15

MTCT:P800

S Eshleman et al. HIVNET 012

- sdNVP
- 9 women and 5 infants
- Plasma collected at baseline at 12-24 months post delivery
- GT ViroSeq
- LigAmp: K103N, lower limit of detection of .08%

K103N	Mothers	Infants
<i>N</i>	9	5
6-8 weeks		
ViroSeq	8	2
LigAmp	8 (mean 14%)	4 (mean 12%)
12-24 months		
ViroSeq	0	0
LigAmp	3 (.8, 1.3, 3.5%)	1 (1.5%)

MTCT: P101

S Palmer et al (NCI)

- sdNVP
- 17 women
- Allele-specific RT-PCR K103N and Y181C
- HIV-1 subtype C

MTCT P101, continued

- Group 1
 - $N = 8$
 - K103N at 6w/6m but not 12m
 - RT-PCR 7/8 (88%)
103N or 181C at 12m
 - Frequency .25%-16%
- Group 2
 - $N = 9$
 - K103N at 6w but not 6m
 - RT-PCR 7/9 (78%)
103N at 6 months
 - Frequency .9%-10%

MTCT P103

N Martinson et al (JH/Soweto)

- sdNVP in 2nd pregnancy
- 13 Clinics in Soweto
- Case:Control (1:2)
- Infection determined by DNA-PCR 6w

		Cases n=106 experienced mothers	Controls n=212 naive mothers	<i>p</i> value
Age at enrollment. (IQR)		28 (23–31)	28.5 (26-32)	0.06
Caesarian section		11.8%	9.7%	<i>ns</i>
CD4 (IQR)	Enroll-ment	410 (273–592)	350 (208-509)	0.113
Viral load (IQR)	Enroll-ment	13,400 (3980–54,400)	22,500 (6630–92,900)	0.121
	6 weeks	22,650 (4390–72,000)	35,550 (6690–121,000)	0.551
Resis-tance	baseline	2/106	0/212	<i>ns</i>
	6 weeks	13/34	34/68	.261
HIV PCR 6 weeks		10.7%	3.8%	OR 2.3 (<i>ns</i>)

VACCINATION: HBV

P937: R Ghandi et al.

- 97 HIV+, HBsAg/HBsAb-
- 44 HBCAb+ (45%)
- 22 HBeAg+ (50%)
- Vaccination at 0, 4w, 24 w
- HBsAb titers at 4w, 8 w, 28w
- Median CD4 518, CD4 nadir 232, 72%
ART

	<u>4 w</u>	<u>8 w</u>	<u>28 w</u>	<u>titer</u>
Over all response (Ab titer >10 IU)	16%	22%	62%	
Anti HBC Ab-	10%		61%	9704
Anti HBC Ab+	24%		63%	116
anti-eAg-	7%			
anti-eAg+	43%			