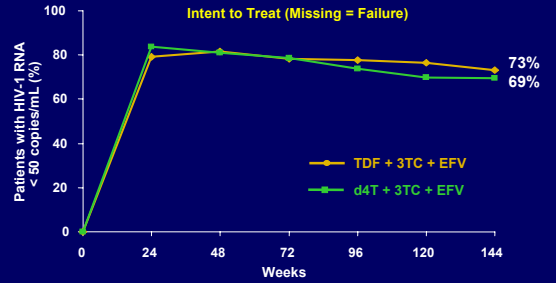


## First-line Antiretroviral Regimens

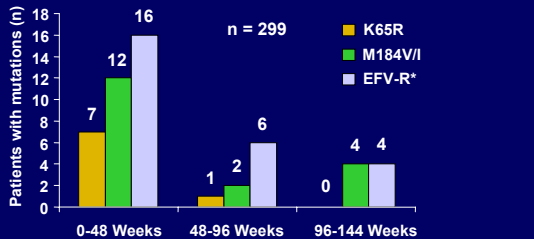
William F. Owen, Jr., M.D.

## GS 903 Study: Week-144 Virologic Outcomes of Tenofovir DF vs Stavudine + 3TC/EFV



Gallant et al. Abstract TuPeB4538.

## GS 903 Study: Development of Resistance Mutations During TDF Treatment



\* K103N, V106M, Y188C/I, G190A/S/E/Q

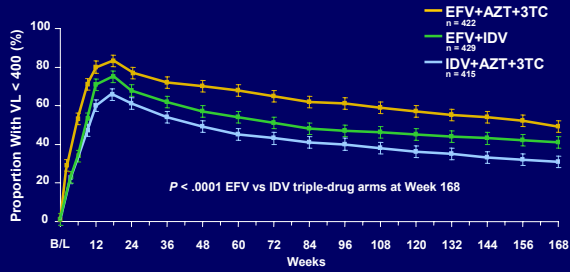
Gallant et al. Abstract TuPeB4538.

## Outcomes of TDF-Treated Patients with K65R (n=8)

Patient Number	Next Regimen	Response (copies/mL)	Follow-up
1	TDF/AZT/LPV/r	<50	W177*
2	TDF/3TC/ddI/LPV/r	<50	W155*
3	ddI/d4T/IDV/r	<50	W151*
4	ddI/IDV	<50	W163*
5	AZT/3TC/SQV/r	<50	D/C W48
6	AZT/ddI/NFV	423	D/C W68
7	AZT/3TC/APV	1905	Non-adherence
8	AZT/3TC/LPV/r	NA	Lost to follow-up

\*Last study visit  
Miller MD. XV Int AIDS Conf, July 2004, Bangkok, #5757

### DP-006 Study: Week 168 Follow-up; Suppression < 400 Copies/mL

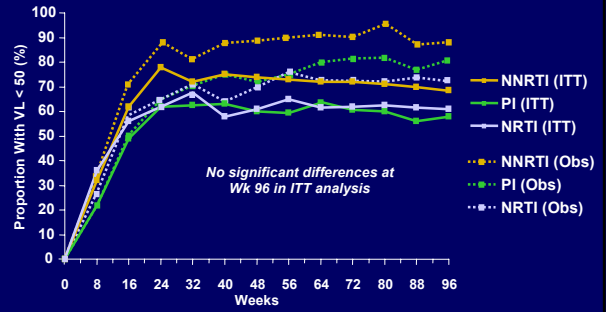


*P* < .0001 EFV vs IDV triple-drug arms at Week 168

ITT, M=F analysis: Proportion of subjects with response according to TLOVR definition of treatment success.

Tashima et al. Abstract TuPeB4547.

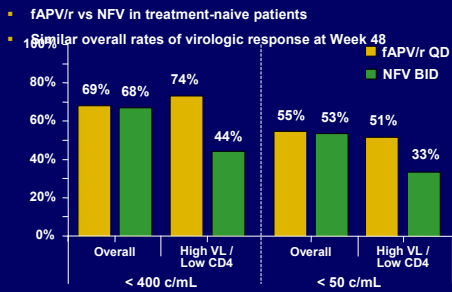
### CLASS Study Final Data: Efavirenz vs Amprenavir/r vs Stavudine (+ 3TC/ABC)



No significant differences at Wk 96 in ITT analysis

Bartlett et al. Abstract TuPeB4544.

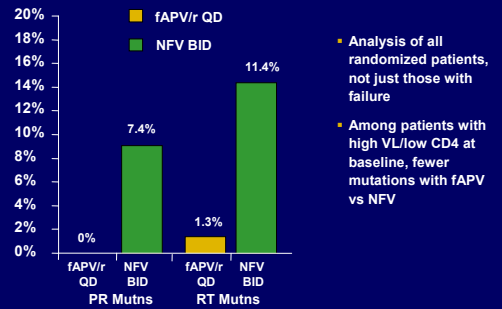
### SOLO Study: Virologic Response at Week 48 by Baseline Viral Load and CD4+ Count



Intent to treat; rebound or discontinuation = failure

DeJesus et al. Abstract TuPeB4503.

### SOLO Study: Resistance Mutations at Week 48



Analysis of all randomized patients, not just those with failure

Among patients with high VL/low CD4 at baseline, fewer mutations with fAPV vs NFV

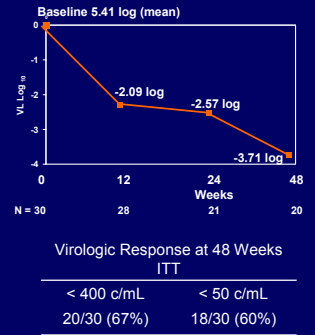
DeJesus et al. Abstract TuPeB4503.

## Investigational Antiretroviral Strategies

William F. Owen, Jr., M.D.

## IMANI 1 Pilot Study of Lopinavir/ritonavir Monotherapy

- 48 week, open label, single inner city clinic (n=30)
- LPV/r dose: <70 kg, 3 caps BID; >70 kg, 4 caps BID
- 10 patients did not complete study
  - GI intolerance (n=2)
  - Virologic failure (n=2)
- Intensification in the absence of LPV resistance
  - (n=1) SQV → TDF/3TC → <50 c/mL
  - (n=1) TDF/3TC → <50 c/mL
- **Single agent therapy should not be part of routine clinical practice**



Gathe J. XV Int AIDS Conf. July 2004, Bangkok, #1057.

## Studies of Lopinavir/Ritonavir Monotherapy

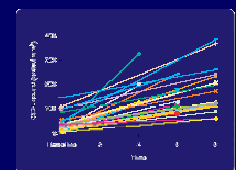
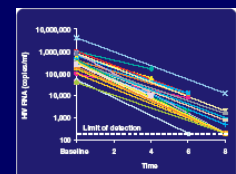
Only *Kaletra* (OK) study: maintenance therapy<sup>[2]</sup>

- 42 pts with VL < 50 copies/mL for > 6 months
  - On LPV/r + 2 NRTIs for > 1 month
  - No history of PI failure
  - Randomized to continue 3-drug HAART or switch to LPV/r monotherapy
- Week 24: 3/21 viral rebound in OK arm, 0/21 in HAART arm
  - No detectable primary PI mutations
  - Pts with rebound had shorter time with VL < 50 than pts without failure
    - 218 vs 1095 days; P = .002

2. Arribas et al. Abstract TuPeB4486.

## Induction with SQV/r in South Africa

- 28 advanced tx-naïve pts
  - CD4 28, VL 5.5 log, Hgb 11.5
- Regimen
  - Induction with SQV/r 600/100 BID x 4-3 wks
  - Switch to 2NRTI + NNRTI
- Results
  - CD4 115, VL 2.5 log, Hgb↑ 4.9%
- Adverse events
  - Bloating, diarrhea, asthenia
- 96 wk outcome (after HAART)
  - 26/28 well, 2 MAI, 1 died



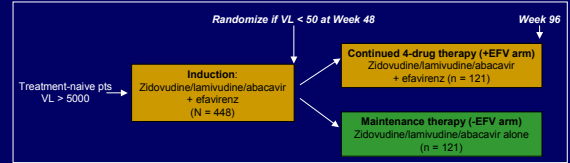
Ebrahim et al. Abstract TuPeB4492

## Induction/Maintenance Therapy

N	Induction (duration)	Maintenance (duration)	Criteria for Maintenance	Results				Ref
				No. evaluable	Sustained Viral Response	Virologic Failure	AEs	
46	AZT-3TC-ABC + LPV/r (20 weeks)	AZT-3TC-ABC	< 50 c/mL	42	26 (62%)	2 (5%) M184V	10 (24%)	1
18	NNRTI-based HAART (> 16 weeks)	LPV/r + NRTI x2 weeks ↓ LPV/r alone (24 weeks)	< 75 c/mL x2	14	13 (93%)	1 (7%) M36I	3 (21%) diarrhea	2
19	HAART (> 9 months)	LPV/r (> 8 weeks)	< 75 c/mL for > 9 months	15	10 (67%)	3 (20%) blips 2 (13%) > 400	1 (7%) abd pain	3

1. van Raalte R, *XV Int AIDS Conf*, July 2004, Bangkok, #4597; 2. Pierone G, *ibid*, #4595; Ruane P, *ibid*, #4577.

## ESS40013: Induction/Maintenance With AZT/3TC/ABC ± EFV

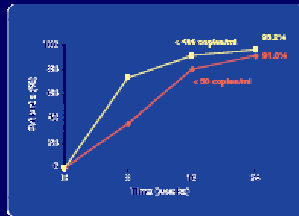


- High drop-out rate prior to randomization
- No difference in proportions with VL < 50 at Week 96 (ITT:M=F)
  - 79% in +EFV, 77% in -EFV
  - More virologic failures in -EFV: n = 16 (7%) vs 8 (3%)
  - More dropouts in +EFV
- 22 mg/dL reduction in fasting cholesterol between Weeks 48 and 96 in -EFV arm
- Trend for improvement in self-reported adherence in -EFV

Markowitz et al. Abstract LbOr14.

## STACCATO: SQV/r QD effective @ 24 wk

- 167 tx naïve pts in Thailand, CD4 265, VL 4.7 log, 86.8% CDC Class A
- SQV<sub>high</sub>/r 1600/100+d4T+ddl
- 15 patients developed new CDC Stage B illnesses
  - None progressed to Stage C
- Adverse events reported in 44%
  - No grade 3 or 4 events
  - Most common events
    - Diarrhea
    - Nausea and vomiting
    - Peripheral neuropathy
  - 9 interrupted/resumed due to AE
  - 2 lost to follow-up
- 16 patients switched d4T/ddI to TDF/3TC (mandated protocol chg)



Ananworanich et al Abstract TuPeB4469

## Trizivir + Tenofovir

- Prospective, observational study<sup>1</sup>
- VL ≤ 10,000 c/mL; M184V ± 1-2 TAMS; switched to TZV+TDF
- Retrospective study from 3 clinics<sup>2</sup>

	Naive (n=25)	Experienced (n=50)*
Baseline VL (log <sub>10</sub> c/mL)	4.74	4.29
CD4 (cells/mm <sup>3</sup> )	331	470
Follow-up (months)	16	13
% < 50 c/mL	72	77
Mean Δ CD4	+266	+61

\* 44% intensification w/ TDF, 56% switched to TZV/TDF

- Tx option in setting of selected mutations and dyslipidemia
- Higher virologic effect in switched vs. intensified patients
- No serious AE

1. Ruane P, et al. *XV Int AIDS Conf*, Bangkok 2004, #4600; 2. Greiger-Zalungo P, et al. *ibid*, #4513

## New Antiretrovirals and Novel Applications of Existing Agents

William F. Owen, Jr., M.D.

## BI 1182.51: Tipranavir in Double-Boosted PI Regimens

Open-label, parallel-group, multicenter study  
N = 315 randomized

N = 296 included in interim analysis



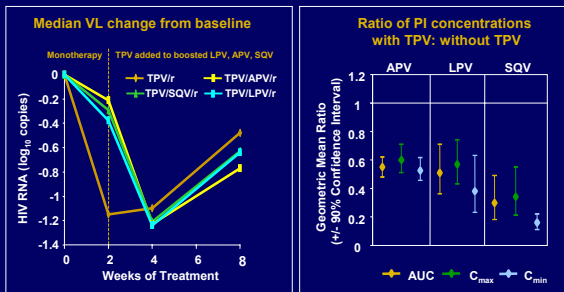
TPV/r 500/100 mg added at 2 weeks  
Final RTV dose 200 mg in all arms

OB = optimized background regimen

- Highly PI-resistant patients, excluded from phase 3 RESIST studies
- ≥ 3 PRAMS at baseline (codons 33, 82, 84, and/or 90)
  - 41- to 350-fold phenotypic resistance to PIs

Walmsley et al. Abstract WeOrB1236.

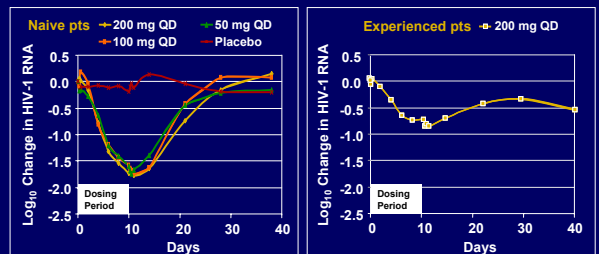
## BI 1182.51: Tipranavir in Double-Boosted PI Regimens



Walmsley et al. Abstract WeOrB1236.

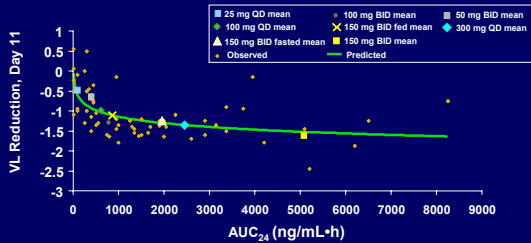
## Activity of D-d4FC (Reverset) in Treatment-Experienced Patients

- Previous data in naive pts: nearly 1.8 log VL reduction at day 10
- New data on 8 experienced pts; mean -0.8 log VL reduction at day 10



Murphy et al. Abstract MoOrB1056.

## Monotherapy With UK-427,857: a Novel CCR5 Inhibitor



- Relationship between AUC and antiviral activity
  - Doses  $\geq$  100 mg QD or BID  $\rightarrow$   $\geq$  1 log VL reduction at day 11
- 50% reduced bioavailability with food, but no  $\downarrow$  in antiviral activity

Fätkenheuer et al. Abstract TuPeB4489.

## Other New Entry Inhibitors

- Novel CCR5 inhibitor: 873140<sup>[1]</sup>
  - Limited interassay variability in different cell lines and viruses
  - Difficulty selecting resistance in serial passage
  - No evidence of switch in coreceptor usage in vitro
- Small molecule fusion inhibitors<sup>[2]</sup>
  - In vitro activity similar to enfuvirtide
  - Potential for oral administration
- Oral CXCR4 inhibitor: KRH-2731-5HC<sup>[3]</sup>
  - Potent activity against X4 HIV-1 in SCID mice
  - Further safety and PK studies ongoing
- Oral CXCR4 inhibitor: AMD070<sup>[4]</sup>
  - PK profiling in seronegative patients

1. Demarest et al. Abstract WeOrA1231. 2. Jiang et al. Abstract WeOrA1232.  
3. Murakami et al. Abstract LbOrA01. 4. Stone et al. Abstract TuPeB4475.

## Novel Applications of Tenofovir

- Oral tenofovir for protection from oral SIV transmission<sup>[1]</sup>
  - Oral tenofovir protected infant macaques against SIV infection by oral exposure
  - Supports studies of TDF prophylaxis against HIV from breast milk
- Tenofovir vaginal gel<sup>[2]</sup>
  - Safety and tolerability in HIV-infected and HIV-uninfected women
- Trials under way exploring oral tenofovir as pre-exposure prophylaxis against sexual transmission

1. Van Rompay et al. Abstract LbOrB10. 2. Mayer et al. ThOrB1373.