

Prognosis after HAART

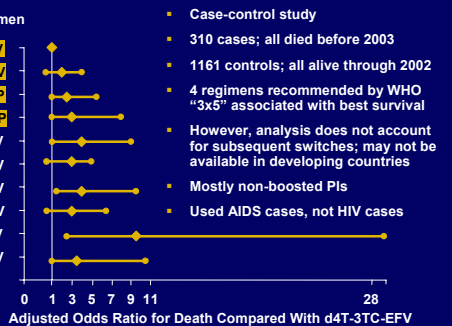
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Association Between WHO "3x5" Regimens and Survival in San Francisco

First-line Regimen

d4T-3TC-EFV
AZT-3TC-EFV
d4T-3TC-NVP
AZT-3TC-NVP
d4T-3TC-NFV
AZT-3TC-NFV
d4T-3TC-IDV
AZT-3TC-IDV
d4T-3TC-SQV
AZT-3TC-SQV



- Case-control study
- 310 cases; all died before 2003
- 1161 controls; all alive through 2002
- 4 regimens recommended by WHO "3x5" associated with best survival
- However, analysis does not account for subsequent switches; may not be available in developing countries
- Mostly non-boosted PIs
- Used AIDS cases, not HIV cases

Chen et al. Abstract MoORC1082.

ART Cohort Collaboration: Prognosis After Initiating HAART

- N = 20,379 patients (12 cohorts) who initiated therapy with 3 drugs; 61,798 person-years of follow-up
- Significant decline in AIDS and death between 1995 and 1998
- No significant change in prognosis between 1998 and 2003
 - Slightly increased death rate in some cohorts
- Increased proportion with undetectable viral load over time
- Progression/death strongly associated with low CD4+; weak association with VL
- Older age, history of IDU, CDC stage C, and low hemoglobin stronger risk factors for death than for progression
- Possible explanations for lack of further improvement in prognosis
 - Aging cohorts; treatment failure in IDUs; comorbidities

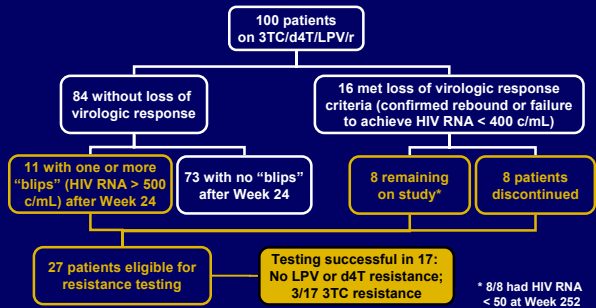
Egger et al. Abstract TuOrC1157.

Regimens Associated With Increased Risk of Viral Rebound in EuroSIDA Study

- N = 1951 pts with VL < 50 copies/mL and no prior HAART failure
- Viral rebound = VL > 400 copies/mL on 2 consecutive occasions
- Among pts naive prior to HAART: overall rate of rebound 4.9/100 PY
 - Lowest rate of rebound with EFV-based regimens: 3.1/100 PY
 - Compared with EFV-based, significantly higher rate with NFV-based (8.0/100 PY; P = .006)
 - ABC-based not significantly different from EFV-based
 - No differences based on NRTI backbones
- Among pts with NRTI experience pre-HAART:
 - Lowest rate of rebound with EFV-based
 - Compared with EFV-based, significantly higher rate with
 - › NFV-based
 - › ABC-based
 - › NVP-based

Phillips et al. Abstract TuPeB4542.

Study 720: No Lopinavir/Ritonavir or Stavudine Resistance During 5 Years



Note also abstract WePeB5701: Abbott study 418 of BID vs QD LPV/r + TDF + FTC
 – Genotypes from 8 patients on QD arm and 7 on BID arm showed 0/15 LPV/r resistance, 0/15 TDF resistance, and 3/15 FTC resistance

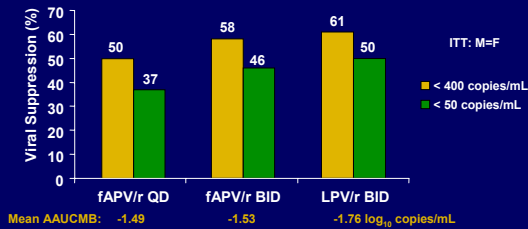
Hicks et al. Abstract WeOrB1291.

Management of Experienced Patients

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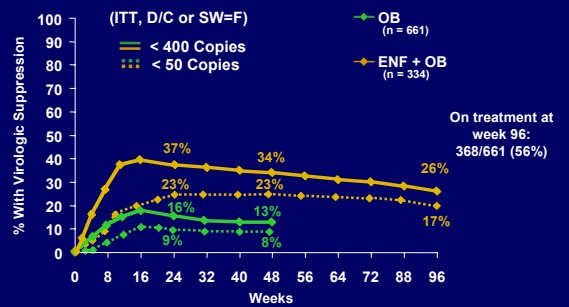
48-Week Results of CONTEXT Study



- Once-daily fAPV/r inferior to the comparator arms
- Twice-daily fAPV/r failed to meet noninferiority endpoint in comparison with LPV/r
 - Study not powered to show differences in suppression
- Modest imbalance in baseline resistance in fAPV/r BID vs LPV/r BID arms:
 - > 2.5-fold resistance to all PIs: 15% vs 9%
 - ≥ 3 TAMs: 38% vs 24%
- Both fAPV/r and LPV/r showed similarly decreased efficacy in presence of baseline mutations: M46I/L (50%), L90M (52-61%), V82A/F/T/S (22-35%), and I84V (17-40%)
 - No change in presence of pre-existing D30N

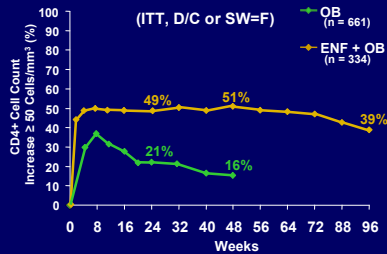
Elston et al. Abstract MoOR1055.

TORO Studies: Viral Suppression Through Week 96



Arastéh et al. Abstract MoOR1058.

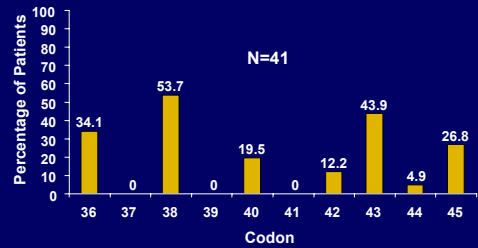
TORO Studies: CD4+ Cell Count Increase ≥ 50 Cells/mm³ Through Week 96



- No increase in incidence of pneumonia during Weeks 48-96
- Rates of ISRs were stable; overall rates of AEs decreased
- No new safety concerns identified

Arastéh et al. Abstract MoOrB1058.

Mutations in gp41 Following Virologic Failure on Enfuvirtide



- Full-length sequencing of pre- and post-failure gp41 in 41 Canadian pts on failing enfuvirtide regimen (incl. TORO pts)
 - Confirms association with mutations at codons 36-45
 - New mutations found at positions 33, 73, 75, 126, 138, and 278
- Loufy et al. Abstract WeOrB1292.

Resistance Mutations Develop Despite Stable Low-Level Viremia

- Retrospective evaluation of 22 patients with at least 2 genotypes while VL 50-1000 copies/mL and no change in regimen
 - 10 on triple NRTI; 8 on PI; 4 on NNRTI
- 15/22 developed new mutations during median 28 months between tests
 - No change in median CD4+ or VL between 1st and 2nd genotypes
- M184V, K65R, and TAMs most common emergent mutations
- By June 2004, 11/15 started new regimen, in 9 cases due to VL increase by > 1 log
- Supports early switching despite stable low-level viremia, when other options exist, to minimize:
 - Accumulation of mutations
 - Subsequent viral rebound
 - Decreased treatment options

Lafeuille et al. Abstract WeOrB1293.

HIV Transmission

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From the Options Study

- Observational cohort in SF of acute and early HIV infections
- 47 partner pairs where HIV transmission occurred; 36 non-transmitting partner pairs with similar high risk exposures¹
 - Frequency of drug resistance in transmitters vs. non-transmitters:
 - NRTI: 19% vs 6% (P=0.1); NNRTI: 15% vs. 8% (P=0.5); PI 13% vs. 17% (P=0.8)
 - Most resistance mutations in source patient were found in the newly infected patient
 - No evidence for selective pressure against the transmission of drug resistance
- Retrospective analysis of 87 subjects who elected to start ARVs within 1 month of study enrollment, achieved undetectable VL and maintained undetectable VL for at least 24 weeks²
 - 7/87 (8%) had routine HIV antibody testing with EIA/WB that would have been interpreted as uninfected
 - No clinical predictors of negative test results
 - Subjects who stopped ARVs all rebounded quickly
 - Newer 3rd generation EIA tests tested positive on all but 1 patient

1. Hecht et al. Abstract WePeB5729.
2. Hare et al. Abstract MoPeB3107.

From the Positive Partners Study

- Prospective cohort of seroconcordant HIV-positive partners in SF who engage in unprotected anal or vaginal intercourse
 - Enrolled if viral genetic tests indicate no evidence of transmission linkage at baseline, or individual with unprotected intercourse with more than 10 HIV-positive individuals within the past year
 - No superinfection among chronically HIV infected partners/individuals after 58 PY of follow-up and 3725 unprotected anal or vaginal exposures to a genetically distinguishable virus
 - One potential case of superinfection among a recent seroconverter still being evaluated

Grant et al. ThPeA6949.

Other Data on Superinfection

- 3 cases of superinfection described in a Southern California cohort of 78 acutely infected patients not on ARVs¹
 - Identified by a change in genotypic resistance
 - Associated with 1.6 log increase in viral load and a mean decrease in CD4 count of 132 cells/mL
- In a high risk population in Tanzania, where clades A, C and D all circulate, 28% of individuals had dual infection with more than one clade over time²
- 12 HIV infections identified among 94 "long-term exposed" individuals³
 - 2/12 remain antibody negative with very low level viremia
 - 6/6 seroconverters analyzed had a genetically different virus from their long-term HIV-positive partner
 - Propose that long-term exposure may elicit protective responses to similar viruses, but not divergent viruses
 - May explain rare superinfection in populations with relatively homogenous virus (like the US) and higher rates of superinfection in areas of more variable virus (like Africa)

1 Smith et al. TuOrB1140.

2 Piyasitip et al. Abstract TuOrA1139.

3 Zhu et al. TuOrA1141.

Resistance With Single-Dose Nevirapine for Prevention of MTCT

Study	Type	Nevirapine Resistance
HIVNET 012 ^{1,2}	NVP alone	25% (70/279) 6 wks PP
HPTN 023 ³	NVP alone	75% (21/28) 2 wks PP
South Africa ⁴	NVP alone	44% 4-10 wks PP; 24% 10-36 wks PP
PACT 316 ⁵	NVP added	15% (14/95) new mutations 6 wks PP
ANRS 1201/2 ⁶	NVP added	21% (21/63) 4 wks PP

1. Eshleman et al. AIDS, 2000.

2. Eshleman et al. JAIDS, 2004.

3. Cantor et al. 13th Resist Wksp, 2003.

4. Martinson et al. 11th CROI, 2004.

5. Cunningham et al. JID, 2002.

6. Chaix et al. 11th CROI, 2004.

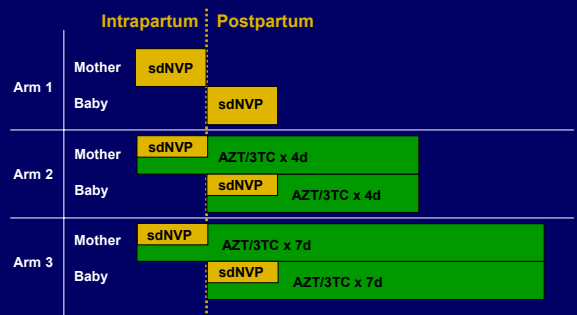
New Studies on Resistance With Peripartum Nevirapine for Prevention of MTCT

- Women enrolled in PHPT-2; received AZT from 28 weeks gestation^[1]
 - 1145 exposed to single-dose NVP
 - 325 exposed to NVP had CD4+ < 250 and started NVP postpartum
 - 134 (41%) had NNRTI resistance mutations 12 days postpartum (range 7-17 days)
- NVP resistance in infants ^[2]
 - Comparison of two regimens for single-dose NVP:
 - 30 infants on a standard regimen (single-dose NVP to both mother & infant)
 - 23 infants on a NVP PEP regimen (single-dose NVP to infant only)
 - Reduced incidence of NVP resistance in PEP infants
 - 11/30 (36%) for standard regimen, 3/23 (13%) for PEP
 - Similar efficacy without risk of NVP resistance to mother

1. Ngo-Giang-Huong et al. Abstract WeOrB1289.

2. Pillay et al. Abstract WeOrB1290.

Treatment Options Preservation Study (TOPS)



McIntyre et al. Abstract LbOrB09.

Interim Results from TOPS

Study Arm	N	Resistance (%)
sdNVP	18	9 (50%)
sdNVP + AZT/3TC x 4d	20	1 (5%)
sdNVP + AZT/3TC x 7d	23	3 (13%)

- Coadministration of 4-7 days of AZT/3TC with single-dose NVP reduced incidence of NVP resistance
 - 9/18 (50%) vs 4/43 (9.3%); $P = .001$
- Transmission (preliminary data; not primary endpoint)
 - 4/68 infants intrauterine transmission
 - 1 peri/postnatal transmission (single-dose NVP without AZT/3TC)

McIntyre et al. Abstract LbOR09.

Pharmacology

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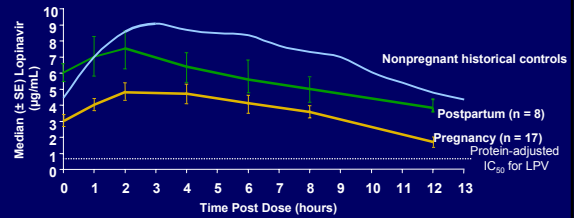


Pharmacogenomics of Nevirapine Hypersensitivity

- Mallal et al. previously identified association between HLA-5701 and ABC hypersensitivity reactions
- HLA-DRB1*0101 and higher CD4+ count strongly associated with hepatitis and/or fever (with or without rash) during NVP
 - Positive predictive value: 40%
 - Negative predictive value: 94%
- NVP rash alone not associated with HLA-DRB1*01
 - Suggests distinct clinical entity
- Data imply cellular mechanism(s) mediate hypersensitivity
 - Potentially abrogated at lower CD4 counts
- Note: HLA typing not a diagnostic test for hypersensitivity

Mallal et al. Abstract LbOrB13.

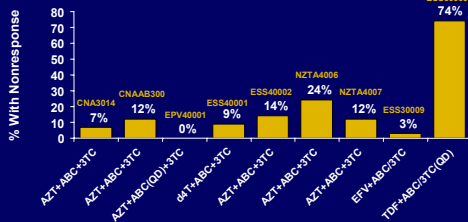
Reduced Lopinavir Plasma Concentrations in Pregnancy



- Note also abstract 4644 – NVP plasma exposure reduced in pregnant vs nonpregnant women
 - But not to clinically significant levels

Stek et al. Abstract LbOrB08.

Response to Abacavir/Lamivudine-based Regimens in Naive Patients With VL > 30,000



- No evidence of high rates of virologic failure with ABC/3TC-based regimens except for TDF + ABC/3TC

Gallant et al. Abstract TuPeB4502.

No Pharmacologic Explanation for Underperformance of ABC/TDF Combinations

Becker et al.^[1]

- Examined peak and trough levels of all drugs among patients in the 30009 trial
- No plasma interaction between TDF + ABC in pts receiving TDF, ABC, 3TC
 - No difference in plasma PK between responders and non-responders in 30009 or compared to historical controls

Hawkins et al.^[2]

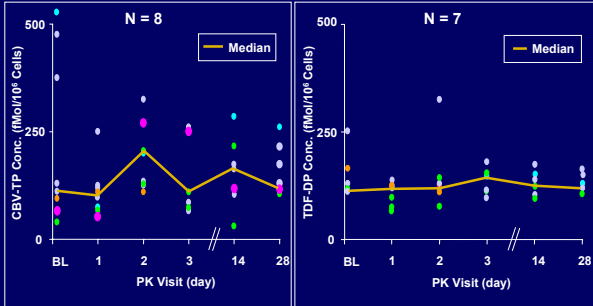
- 15 patients on stable TDF + ABC + 3rd NRTI discontinued either TDF or ABC, replacing with new agent
- Multiple PBMC samples collected at baseline and on days following withdrawal of TDF or ABC
- No difference in IC phosphates – strongly suggests no intracellular interaction

Myrick et al.^[3]

- All 2- and 3-drug combinations of ABC, TDF, ddI, and 3TC were additive to slightly synergistic in primary cells in vitro

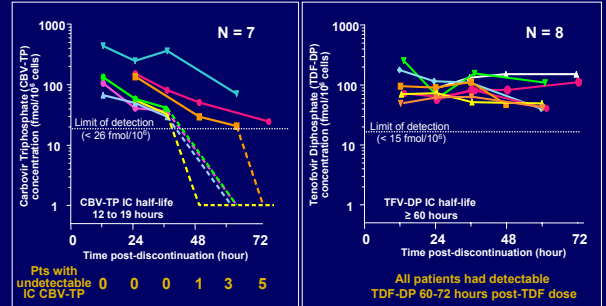
1 Becker et al. Abstract TuPeB4629.
 2 Hawkins et al. Abstract TuPeB4627.
 3 Myrick et al. Abstract WeOrB1237.

CBV-TP and TDF-DP Intracellular Trough Range After Discontinuation of Other Drug



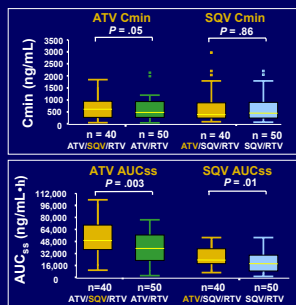
Hawkins et al. Abstract TuPeB4627.

Decay of Intracellular CBV-TP and TDF-DP 12-72 Hours After Discontinuation of Other Drug



Hawkins et al. Abstract TuPeB4627.

Increased SQV and ATV Exposure With ATV/SQV/RTV



Dosing regimens

- ATV/RTV 300/100 mg QD + SQV 1000 mg BID (n = 40)
- ATV/RTV 300/100 mg QD + NRTI BID (n = 50)
- SQV/RTV 1000/100 mg BID + NRTI BID (n = 100)

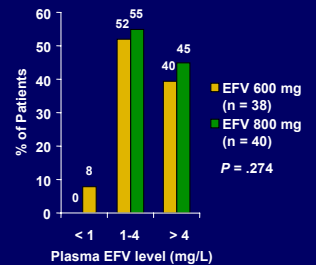
Results

- Addition of saquinavir increased ATV Cmin compared with ATV/RTV
- AUCs of both ATV and SQV increased with double-boosted ATV/SQV/RTV compared with single-boosted PI
- No apparent effect on ATV AUC₀₋₂₄ by sex or coadministered TDF

von Hentig et al. Abstract WeOrB1235.

Efavirenz 600 vs 800 mg in Thai Patients Receiving Concomitant Rifampin

- Randomized controlled trial
- Patients (42 per arm) received RFP for median 8 weeks (range, 4-12) then started EFV 600 or 800 mg/day
- Primary endpoint: EFV levels 12 hours post-dose
- Mean weight = 50 kg
- No difference in outcomes:
 - HIV-1 RNA < 50 copies/mL in all patients
- 600 mg/day appears adequate in these patients
 - Implications unclear for higher-weight patients



Manosuthi et al. Abstract MoOrB1013.

Drug-Drug Interactions

Capravirine

- Increased atorvastatin levels with capravirine, LPV/r, or both^[1]
- No interaction between capravirine and LPV/r ± saquinavir^[2]

Efavirenz + Abacavir + Methadone

- EFV induces MET metabolism; ABC increases MET clearance
- Prospective interaction study of ABC/EFV/3TC added to stable MET^[3]
- Mean 29.5% MET dose increase required to compensate

Nevirapine + Fluconazole

- Addition of FLU (200 mg) to NVP/AZT/3TC/ABC regimen^[4]
- > 2-fold increase in NVP C_{max}, C_{min}, and AUC compared with historical controls
- Increased AEs; 25% serious hepatotoxicity
- No effect of NVP on FLU levels
- Recommendation: use with caution

1. Amantea et al. Abstract TuPeB4630. 2. Raber et al. Abstract TuPeB4631.
3. Kurowski et al. Abstract TuPeB4621. 4. Geel et al. Abstract WeOrB4475.