REPORT FROM

13th Conference on Retroviruses and Opportunistic Infections (CROI)

February 5–8, 2006
Denver, CO
Tipranavir Significantly Reduces Concentrations of Other ARVs

[Leith et al. 5th IWPCHT 2004, #5.1; Scholler et al. #583, CROI 2006; Sabo et al. 7th IWPCHT 2006, #41]
Dosing PIs with Tipranavir

- TDM study (n=20):
  a) TPV 500/LPV 533/rtv 233 mg BID
     - 74% achieved therapeutic LPV C\text{trough}
  b) TPV 500/FPV 1400/rtv 200 mg BID
     - 67% achieved therapeutic APV C\text{trough}

TDM recommended!

- 2 dosing strategies studied in 13 pts on stable LPV/r,
  VL<50
- LPV levels generally ↑ vs 400/100 mg BID alone but
  variability also ↑↑

[Harris et al. #584; Peytavin et al. #591, CROI 2006]
Atazanavir/PI Combinations

ATV 300 mg QD + LPV 400/100 mg BID
- ATV Cmin slightly > vs. ATV 300 mg/100 mg QD

ATV 200/SQV 1500 mg BID
- SQV levels << vs. SQV/r, 75% > 100 ng/mL
- ATV levels ≈ ATV 400 mg QD

ATV 400 mg/FPV 1400 mg QD
- APV AUC ↑ 78%, C_{24} ↑ 283% vs. FPV 1400 mg QD (~FPV 1400 mg BID)
- ATV AUC ↓ 33%, C_{24} ↓ 57% vs. ATV 400 mg QD

[Pham et al. #585; King et al. #586; Clay et al. #587, CROI 2006]
Rosuvastatin + Lopinavir/rtv in HIV-infected subjects (n=22)

- Pts stable on LPV/r (VL<400) with TC>6.2 mmol/L treated with rosvastatin 10 mg for 12 weeks
- ROS dose ↑ at wks 4, 8 if target lipids not achieved

![Graph showing median Rosuvastatin Ctrough](image)

**Study**

- 10 mg (n=13)
- 20 mg (n=14)
- 40 mg (n=10)

**Historical**

- ↑ ROS Ctrough compared to historical controls
- ROS is Pgp substrate?

[van der Lee et al. CROI 2006, #388]
No Effect of Ranitidine or Omeprazole on Kinetics of QD or BID Lopinavir/r Tablets

LPV/r BID + OMP 40 mg QD x 5/7

LPV/r QD + RAN 150 mg QD

[Klein et al. CROI 2006, #578]
Negative Dual Interaction between Efavirenz & Carbamazepine

- Co-administration of EFV 600 mg QD with CBZ 400 mg QD in healthy subjects:
  - ↓ AUC 36%, Cmax 21%, Cmin 47% of EFV
  - ↓ AUC 27%, Cmax 20%, Cmin 35% of CBZ
  - kinetics of active CBZE metabolite unchanged

- Recommendations on dose adjustment not available; use alternate anticonvulsant

[Kaul et al. CROI 2006, #575a]
Low Antiretroviral Exposures in Pregnancy

• Nelfinavir
  – 45% had NFV Cmin <1 mg/L (n=40); 1500 mg BID, 2/8 still low

• Lopinavir
  – Cohort 1) regular dose throughout preg., adequate Ctrough
  – Cohort 2) low LPV in 2nd trimester; used 533/133 mg BID in 3rd trimester
  – Difference in weight of women between 2 groups?

• Tenofovir 600 mg at onset of labour:
  – maternal AUC, Cmax < non-pregnant
  – Cord blood:maternal ratio 0.65, low infant TDF
  – phase 2: mother 900 mg x 1; infant 4 mg/kg ASAP after birth

[Rodman et al. #708; Khuong-Josses et al. #707; Lyons et al. #709; Mirochnick et al. #710, CROI 2006]
Female Genital Tract Exposure
(percent of blood plasma)

- SQV (ND)
- EFV (0.6%)
- d4T (4%)
- RTV (20%)
- DLV (20%)
- ATV (30%)
- LPV (30%)
- ABC (40%)
- APV (50%)
- NVP (80%)
- ddi (100%)
- IDV (200%)
- ZDV (200%)
- 3TC (400%)
- TDF (400%)
- FTC (600%)
PK/PD analyses of TMC114

- PK from POWER I and POWER II
  - Blood sampling in 468 subjects randomized to TMC114 arms
  - IQ = Baseline TMC114 EC50

- Found significant relationship between TMC114 PK and efficacy
  - IQ was strongest predictor of virologic response

Virologic response at Week 24 by TMC114 IQ C0h

- Virologic response (<1 log10 drop)
- TLOVR at week 24 (%)

Protein binding adjusted IQ

- <7
- 7–21
- 21–72
- >72

Sekar V, et al. 13th CROI, Denver 2006, #639b
Etravirine (TMC-125)

- NNRTI
- 200 mg BID
  - food ↑ absorption 51%
- Metabolized by CYP and GT, CYP3A4 inducer
- Sildenafil:
  - 57% ↓ sildenafil AUC

Etravirine Interactions

- Avoid combining with SQV, IDV, TPV, EFV, NVP

[Harris et al. #575b; Boffito et al. #575c; Scholler et al. #583; CROI 2006; Scholler-Gyure et al. 7th IWCPHT 2006, #45]
Vicriviroc Can Be Added to Boosted PI Regimens

[Vicriviroc Can Be Added to Boosted PI Regimens][Sansone et al. #582, CROI 2006]
**Adherence: Boosted PIs are more forgiving of suboptimal performance than non-boosted PIs or NNRTIs**

- HOMER Cohort study of 1634 patients (1996–2003) with 2 VL <500 c/mL followed until VL failure (VL >1000 c/mL; median follow-up 29 months)
  - ART: 46% PI, 39% NNRTI, 15% boosted PI
  - Adherence calculated and stratified >95% or <95% based on pharmacy scripts filled
- 606 pts (37%) experienced breakthrough viremia
- <95% adherence most strongly associated with breakthrough for PI and NNRTI, but not boosted PI

**Conclusion:** Unboosted PIs and NNRTIs associated with viremia at <95% adherence, but not boosted PIs

**Hazard ratios**

- Boosted PI
- NNRTI
- PI

Gross R, et al. 13\textsuperscript{th} CROI, Denver 2006, #533
Transmission & Pathogenesis
Male circumcision for prevention of HIV transmission

- Prevalence of male circumcision (MC) varies by country and region:
  - US prevalence 55%, Europe lower

- On population basis, MC rates associated with HIV prevalence:
  - African countries with <20% MC have significantly higher prevalence than countries with >80% MC
  - Multiple cohort studies support long-term effect of risk reduction in those with MC

- Biologically plausible mechanisms for protection by MC include: 9-fold fewer HIV targets in stratified epithelium vs mucosal inner foreskin; infection studies

- 3 randomized, controlled trials of MC vs control accrued:
  - First study of 3520 subjects in S Africa stopped by DSMB; RR of infection 0.4 with MC; 4% adverse events

- WHO concludes that MC should be made available, but awaits 2 ongoing studies for firm recommendation

Quinn T, et al. 13th CROI; Denver 2006, #120
Repeated single-dose NVP in subsequent pregnancies

- Two cohorts studied:
  - Retrospective: pts from HIVNET-012 with previous ZDV ($n=41$) or NVP ($n=57$) use
  - Prospective: pts who were NVP-naïve ($n=63$) or received prior NVP ($n=30$)
- No significant differences in rate of infected infants in both cohorts
- Consistent results presented from separate cohorts (Soweto, $n=76$; Abidjan, $n=35$)
- Results are still not conclusive (lack of resistance, HIV RNA, CD4+ data, possible drop-out of infants because of death in the retrospective cohorts)

Treatment interruptions

**TIME-BASED**

**Staccato (wk on/wk off)**
- Stopped for failure

**Trivacan**
- 2 months off/4 months on
- Ongoing

**Windows**
- 8 weeks on/8 weeks off
- Completed

**ISS / PART**
- 1, 2, 3 months off
- Completed

**CD4-GUIDED**

**Staccato**
- 350 on/off
- Completed 96 weeks

**Trivacan**
- 250 on/350 off
- Stopped early

**SMART**
- 250 on/350 off
- Stopped early

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SMART Study

• Study design:
  – Eligibility: CD4+ >350 cells/mm³

• Randomization:
  – Viral suppression (VS) arm: Continuous ARV
  – Drug conservation (DC) arm: No ARV until CD4+ <250 cells/mm³, then treat until CD4+ >350 cells/mm³ (verified), then stop

• 5472 patients enrolled; stopped early by DSMB

• Primary endpoint: Clinical events / death

• 3.7 (DC) vs 1.5 (VS) events / 100 pt-yrs
  – Relative Risk 2.5; p<0.0001

• Consistent results for all subgroups; eg, by baseline and nadir CD4+ counts

Conclusion

• This strategy cannot be recommended

# SMART Study: Primary endpoint and components

<table>
<thead>
<tr>
<th>Endpoints</th>
<th># Pts with events</th>
<th>Relative Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Progression of disease or death</td>
<td>164</td>
<td>2.5</td>
</tr>
<tr>
<td>Death</td>
<td>84</td>
<td>1.9</td>
</tr>
<tr>
<td>Serious HIV events</td>
<td>21</td>
<td>6.1</td>
</tr>
<tr>
<td>Severe complications*</td>
<td>114</td>
<td>1.5</td>
</tr>
<tr>
<td>*CVD, renal, hepatic events (fatal/nonfatal)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Trivacan Study

- Patients on suppressive HAART with CD4 >350 cells/mm³ and VL <300 c/mL in Côte D’Ivoire randomized to:
  - Continuous therapy (n=110)
  - CD4+ guided therapy (On at 250 cells/mm³, Off at 350 cells/mm³) (n=216)
  - 2 months Off, 4 months On therapy (n=325)

- End-points: Death or serious morbidity

- CD4-guided arm 2.6-fold higher event rate over continuous therapy strategy (95% CI 1.3 – 5.6; p=0.001)

- Consistent with SMART results

- Time-based arm was is ongoing

Danel C, et al. 13th CROI, #105LB
Staccato: STI with higher CD4+ thresholds

- Eligibility: ARV naïve; treated with 2 NRTI/boosted PI
  - HIV RNA <50 c/mL, CD4+ >350 cells/mm³
- Randomized to:
  - Continuous ARV (n=154)
  - Stop ARV >350 cells/mm³, restart <350 cells/mm³ (n=299)
  - In interruption arm after 96 weeks all patients restarted therapy
- Primary endpoint: Progression to AIDS/death (no difference) and proportion of CD4 >350 cells/mm³ at end of randomization (higher in continuous arm) and after resuming ARV (no difference)

<table>
<thead>
<tr>
<th></th>
<th>CD4-guided arm</th>
<th>Continuous arm</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>AIDS events</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Deaths</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>% &lt;50 c/mL</td>
<td>91%</td>
<td>92%</td>
<td></td>
</tr>
<tr>
<td>Time on ARV</td>
<td>37.5%</td>
<td>99%</td>
<td></td>
</tr>
<tr>
<td>Oral candidiasis</td>
<td>3.5%</td>
<td>0%</td>
<td>0.04</td>
</tr>
<tr>
<td>Neuropathy</td>
<td>1.9%</td>
<td>4.6%</td>
<td>0.03</td>
</tr>
</tbody>
</table>
“Time-based” STIs
Window Study

- Continuous ART (n=203) vs STI (n=200) with 8 weeks on/8 weeks off (96-week study)
- Eligible: CD4+ >450 cells/mm$^3$ and HIV RNA <200 c/mL for > 6 months
  - Exclude: CD4+ nadir <100 cells/mm$^3$, ABC or NVP in regimen, HBV infection
- Primary endpoint: confirmed CD4+ <300 cells/mm$^3$
  - n=403; 362/403 complete 96 weeks
  - Overall baseline CD4+ = 744 cells/mm$^3$
- ITT failures: 7 on STI arm, 3 on continuous arm (p=NS)
  - STI arm: 52% time on ART (vs 100% in continuous arm)
  - % <400 c/mL*: 81% (STI arm) vs 90% (continuous); p=0.02
  - No AIDS events
  - Thrombocytopenia: STI arm (n=9), continuous arm (n=2)

*After 8 weeks on therapy

Marchou B, et al. 13th CROI, Denver 2006, #104
## Comparison of CD4-Guided Treatment Interruption Studies

<table>
<thead>
<tr>
<th></th>
<th>Staccato</th>
<th>Trivacan</th>
<th>SMART</th>
</tr>
</thead>
<tbody>
<tr>
<td># of pts</td>
<td>430</td>
<td>326</td>
<td>5472</td>
</tr>
<tr>
<td>PY FU (in STI arm)</td>
<td>490</td>
<td>?</td>
<td>3062</td>
</tr>
<tr>
<td>CD4 at Stop</td>
<td>350</td>
<td>350</td>
<td>350</td>
</tr>
<tr>
<td>CD4 at Start</td>
<td>350</td>
<td>250</td>
<td>250</td>
</tr>
<tr>
<td>Median age (years)</td>
<td>35</td>
<td>34</td>
<td>46</td>
</tr>
<tr>
<td>AIDS, death/100PY</td>
<td>STI</td>
<td>CT</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.2</td>
<td>0.4</td>
<td></td>
</tr>
<tr>
<td></td>
<td>17.6</td>
<td>6.7</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3.1</td>
<td>1.4</td>
<td></td>
</tr>
<tr>
<td>Time on ARV before study (months)</td>
<td>15</td>
<td>7</td>
<td>72</td>
</tr>
</tbody>
</table>
ARV Therapy – Current
Clinical outcomes related to timing of initiation of ART

- Timing of initiation of ART in naïve subjects (n=10,885) in the ART Cohort Collaboration (ART-CC)
  - Median follow-up 2.7 years
- Hazard ratio for progression to AIDS or death by CD4+ cells at initiation of ART
  - <200 vs 201–350 cells/mm³
    HR 2.93 (95% CI: 2.41, 3.57)
  - 201–350 vs 351–500 cells/mm³
    HR 1.26 (95% CI: 0.94, 1.68)
- Trend favoring outcomes for ART initiation at >350/mm³ CD4+ T-cells

Cumulative probability of AIDS/death according to CD4+ count at initiation of HAART

Sterne J, et al. 13th CROI, Denver 2006, #525 (courtesy of ART Cohort Collaboration)
Toxicity in relationship to the timing of initiation of ART

- HIV Outpatient Study (HOPS) cohort prospectively followed >8000 patients
- Assessed relationship between timing of ART and development of select toxicities
- CD4+ >200 cells/mm³ associated with decreased risk of toxicity

<table>
<thead>
<tr>
<th>Factor</th>
<th>Renal</th>
<th>PN</th>
<th>LipA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cases/Total</td>
<td>113/2156</td>
<td>301/2222</td>
<td>176/361</td>
</tr>
</tbody>
</table>

Pre-HAART CD4+ cells/mm³
Adjusted OR (95% CI) vs <200 cells/mm³

<table>
<thead>
<tr>
<th>CD4+ cells/mm³</th>
<th>Renal</th>
<th>PN</th>
<th>LipA</th>
</tr>
</thead>
<tbody>
<tr>
<td>200–349</td>
<td>0.5 (0.3, 0.8)</td>
<td>0.6 (0.5, 0.9)</td>
<td>0.4 (0.2, 0.8)</td>
</tr>
<tr>
<td>350–499</td>
<td>0.7 (0.4, 1.2)</td>
<td>0.6 (0.4, 0.9)</td>
<td>0.3 (0.2, 0.6)</td>
</tr>
<tr>
<td>≥500</td>
<td>0.3 (0.2, 0.6)</td>
<td>0.7 (0.5, 0.9)</td>
<td>0.5 (0.3, 0.9)</td>
</tr>
</tbody>
</table>

PN = peripheral neuropathy
LipA = lipoatrophy

Lichtenstein K, et al. 13th CROI, Denver 2006, #769
Long-term CD4+ response to ART

Dutch ATHENA cohort (n=840)\(^1\)

- ART started 1/97–6/98 (7 yr follow-up)
- Annual increase in CD4+ declined with longer follow-up (p<0.0001)
- Smaller annual increase with:
  - Older age
  - Time with HIV RNA >500 c/ml

JHU HIV clinical cohort (5-yr follow-up)\(^2\)

- >1 year follow-up after initiation of ART
- Persistent HIV RNA <400 c/mL during ART
- Multivariate analysis of risk for reduced CD4+ response
  - IDU
  - Gender, race, type of ART are NOT associated with CD4+ change

HIV encephalopathy in the HAART era

- 7948 seroconverters in EU, Australia, Canada (CASCADE)
- Among non-IDUs, risk of HIV encephalopathy (HIV-E) fell substantially:
  - Pre-1997 vs 1997–99; RR: 0.08, 95% CI 0.02–0.27
  - Pre-1997 vs 2000–04; RR: 0.11, 95% CI 0.04–0.32
- Estimated incidence of HIV-E in 2000–04 ↑ at lower CD4+ among those with previous AIDS diagnosis and IDUs
- ↓ in HIV-E incidence at the same CD4+ levels in the HAART ERA suggests a direct effect of HAART on the pathology of HIV-E

Mussini C, et al. 13th CROI, Denver 2006, #351
Antiretroviral effectiveness in the CNS

- HIV+ subjects in CHARTER study (n=833)
  - Paired plasma & CSF samples
- “Penetration-Effectiveness [P-E] Score” determined by:
  - Pharmacokinetics
  - Pharmacodynamics
  - Drug characteristics
- Higher P-E score correlated with lower CSF viral load (p<0.0001)
  - Independent of plasma VL
  - P-E Score <1.5 nearly doubled odds of having detectable VL in CSF
- Relationship between P-E score and risk of CNS disease uncertain

Letendre S, et al. 13th CROI, Denver 2006, #74
**BMS-089: RTV-boosted vs unboosted ATV in ART-naïve patients**

- 3TC + d4T XR + ATV + RTV vs ATV

<table>
<thead>
<tr>
<th></th>
<th>ATV 300 + RTV (n=95) n (%)</th>
<th>ATV 400 (n=105) n (%)</th>
<th>ATV + RTV</th>
<th>ATV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treated</td>
<td>95 (100)</td>
<td>104 (99)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>D/C before Wk 48</td>
<td>11 (12)</td>
<td>10 (10)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adverse event</td>
<td>8 (8)</td>
<td>1 (&lt;1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>0 (0)</td>
<td>1 (&lt;1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>3 (3)</td>
<td>8 (8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Virologic failure</td>
<td>3 (3)</td>
<td>10 (10)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never suppressed but on study at Wk 48</td>
<td>0 (0)</td>
<td>2 (2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rebound</td>
<td>3 (3)</td>
<td>6 (6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>D/C due to poor virologic response</td>
<td>0 (0)</td>
<td>2 (2)</td>
<td></td>
<td></td>
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### 48-week results

<table>
<thead>
<tr>
<th></th>
<th>ATV + RTV</th>
<th>ATV</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV RNA:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;400 c/mL</td>
<td>86%</td>
<td>85%</td>
</tr>
<tr>
<td>&lt;50 c/mL</td>
<td>75%</td>
<td>70%</td>
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### Resistance mutations

<table>
<thead>
<tr>
<th></th>
<th>ATV + RTV</th>
<th>ATV</th>
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</thead>
<tbody>
<tr>
<td>I50L</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>I50I/L +/- G73G/S</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>M184M/V, M184V</td>
<td>1</td>
<td>7</td>
</tr>
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</table>

### Lipids

<table>
<thead>
<tr>
<th></th>
<th>ATV + RTV</th>
<th>ATV</th>
</tr>
</thead>
<tbody>
<tr>
<td>TC</td>
<td>+15%</td>
<td>+6%</td>
</tr>
<tr>
<td>LDL</td>
<td>+23%</td>
<td>+16%</td>
</tr>
<tr>
<td>HDL</td>
<td>+30%</td>
<td>+29%</td>
</tr>
<tr>
<td>TG</td>
<td>+26%</td>
<td>−3%</td>
</tr>
</tbody>
</table>

- Total bilirubin elevation (>2.5 x ULN): 59% (ATV + RTV), 20% (ATV)

- ATV + RTV non-inferior to ATV

Malan N, et al. 13th CROI, Denver 2006, #107LB
ACTG 5201: Boosted ATV alone for maintenance

Inclusion criteria:
- CD4+ $\geq 250$ cells/mm$^3$
- HIV RNA $< 50$ c/mL for $\geq 48$ weeks, no history of virologic failure ($n=36$)

8 semen samples: all $<150$ c/mL

Virologic failures ($n=3$)
- No PI mutations in any failures
- No ATV plasma levels in 2/3

Week -6
- ATV + RTV + 2 NRTIs

Week -3
- ATV + RTV

Baseline
- Wk 0

Primary Endpoint
- Wk 24

Week 48
- Continued F/U

Confirmed HIV RNA $< 50$ c/mL

D/C NRTIs ($n=34$)

91% without virologic failure by Wk 24 (lower 90% CI= 85%)