Objectives

- To discuss combination antiretroviral drug therapy following feedback from the IAS meeting……..

Outline

- Antiretroviral Therapy
  - Triple nucleoside combinations
    - Abacavir and tenofovir
    - FTC (emtricitabine)
    - Nucleoside sparing regimens
    - Atazanavir and boosted PI regimens
    - Enfuvirtide (T-20)
    - New formulations - nelfinavir, saquinavir
    - Simba study

Triple Nucleosides

- Triple nucleoside combinations
  - Easy to take
    - Fixed dose combinations e.g. Trizivir® Combivir®
    - Future drug combos - abacavir + lamivudine, tenofovir + FTC
  - Minimal drug interactions
  - Preserve other drug classes for future

So just how good are triple nucleosides?

- Concerns re triple nucleosides in VL > 100,000 copies/ml
- Not recommended as first line in BHIVA, IAS or DHHS guidelines

ACTG5095

- Comparison of 3 PI-sparing regimens in naïve patients
  - Interim analysis
  - Randomized trial with HIV+, ART-naïve subjects
  - n=1147 (evaluable)

  - Trizivir® (Combivir® and EFV placebo) 3 nucleosides
  - Combivir® EFV (Trizivir® placebo) Control arm
  - Trizivir® EFV (Combivir® placebo) 4 drug arm

  Double blind + placebo controlled
**Primary Objective**
- compare ability of these 3 regimens to decrease HIV-1 RNA to <200 copies/mL
- To compare the time to virologic failure*

**Virological Failure Definition**
- confirmed HIV-1 RNA ≥200 copies/mL at least 16 weeks after randomisation
- To determine the safety/tolerability of the regimens

**ACTG 5095: Study Subjects**
- N = 1147 subjects enrolled
- 81% men, 19% women
- 40% white, 36% black, 21% latino, 2% other
- 11% with history of IDU

Mean baseline:
- HIV-1 RNA: 4.85 log<sub>10</sub> (71,434) copies/ml
- 57% <100,000 copies/ml
- 42% ≥100,000 copies/ml
- CD4: 238 cells/mm<sup>3</sup>

Median follow-up of 32 weeks (range 0-80)

**ACTG 5095: Proportion of subjects with HIV-1 RNA <200 and <50 cps/ml**

**ACTG 5095: Time to first virologic failure**

**ACTG 5095: CD4 cell responses**

**ACTG 5095: Resistance Results**

Subjects on ZDV/3TC/ABC with virologic failure (n=82)

- At baseline:
  - 78 (95%) wild type
  - 3 (4%) RTI-associated substitutions
  - 1 (1%) sequence not available

- At virologic failure: Trizivir Arm
  - 18 (22%) wild type
  - 28 (34%) M184V alone
  - 9 (11%) M184V + RTI-associated substitutions
  - 2 (2%) RTI-assoc. subs. (without M184V)
  - 22 (27%) seq. not attempted (HIV RNA <500 cps/ml)
  - 3 (4%) could not be sequenced

(Subjects on pooled EFV arms not reported)
What is the conclusion from this study?
• In treatment naïve patients – Trizivir is inferior to EFV containing combinations for both rates and time to virological failure
• Concern over the resistant mutations at failure
• Is this unique to Trizivir?
• Triple nucleoside combinations
• ??? Baseline Viral load?

Abacavir / tenofovir
• Increasingly popular choice of nucleoside backbone in patients on second/third regimen.
• Lamivudine often included in patients on previous multiple Rx
• Easy to take
  – 3 pills daily
• Abacavir once daily NOT licensed

ABC/3TC/TDF in naïve patients
(pilot study demonstrating early virological failure)
• Pilot study to assess efficacy and tolerability of once daily ABC+3TC+TDF in treatment of HIV-infected naïve patients n=19
• Definition of non-responder
  – No reduction in HIV-1 RNA by ≥2log10 by week 8 and/or rebound in viral load after initial suppression
• Baseline Characteristics
  – Mean HIV-1 RNA 147,164 copies/ml
  – Mean CD4 cell count 277 cells/mm³

Results:

<table>
<thead>
<tr>
<th>Virologic Failure (n=19)</th>
<th>Mean HIV RNA Baseline (log10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>11 (58%)</td>
<td>5.098*</td>
</tr>
<tr>
<td>Patient non-compliance</td>
<td>2 (10%)</td>
</tr>
<tr>
<td>Adverse event (ABC HSR)</td>
<td>1 (5%)</td>
</tr>
<tr>
<td>Responders</td>
<td>5 (27%)</td>
</tr>
</tbody>
</table>

Genotypic analysis showed:
• M184V alone in 5 patients 45% of failures (n=11)
• M184V+K65R in 4 patients 36% of failures

Conclusions
• These preliminary results in 19 patients raise concerns about the potency of ABC+3TC+TDF as a regimen administered once daily in HIV-1 treatment naïve patients, particularly in those patients with baseline HIV-1 RNA >100,000 copies/ml

Other studies:
Study ESS30009
  Phase III open label, multicentre, randomised 1:1 (n=345)
  2 arms: A. (ABC+3TC) fixed dose tablet + EFV OD
  B. (ABC+3TC) fixed dose tablet + TDF OD
• Unplanned interim analysis unexpected failures
• Similar results at week 16 to those of Farthing et al.
• Tenofovir arm stopped July 13, 2003
French study (no other details available)
• same design (ABC+3TC+TDF in naives)
• similar results - stopped early July 2003
Possible reasons?

- Absorption?
- Intracellular interaction?
- Resistance development?
- Pharmacokinetics unsuitable for ONCE daily therapy?
- Intracellular studies planned
- QUAD therapy with TZV+TDF........?

And the story continues ......

GlaxoSmithKline – issued a dear Dr letter - 29th July
As a result of recent interim analysis and termination of studies they recommend……

- Do not initiate Abacavir + lamivudine + tenofovir in naïve patients (especially not ONCE daily abacavir)
- Patients on this combination should be closely monitored for early virological failure

What about induction – maintenance?

- Four drugs down to three
  – ESS40013- preliminary results

ESS40013 (TZV+ EFV in naïve patients)
48 week results

Objectives
- To test 4-drug induction and 3-drug maintenance approach to ART.
Subjects received:
  - Induction with Trizivir + EFV (48 week) plasma vRNA <50 copies/ml randomised to either:
    - Maintenance with Trizivir without EFV (48 weeks)
    - Maintenance with Trizivir + EFV (48 weeks)

Baseline Characteristics
- n=448 in Induction phase
  - Mean HIV-1 RNA 5.04 log10 copies/ml (56% 100,000 copies/ml)
  - Mean CD4+ cell count 245 cells/mm3 (48% <200)

Stratified by entry % <50c/ml. Median time to <50c/ml
- <100,000 copies/ml 95% 16 weeks
- 100,000 - 749 999 86% 17 weeks
- ≥750,000 copies/ml 90% 35 weeks

Most common treatment emergent RT mutations were:
- M184V (46%) and K103N (41%)
- Warning bells – similar mutation pattern ACTG 5095, Farthing etc........

ESS40013 (TZV+ EFV in naïve patients)
48 week results

37% discontinued
55 patients (11%) discontinued due to AEs
Drug related AEs >10% incidence
- nausea, fatigue, dreams, diarrhea, rash, sleep disorders, vomiting and headaches
- 33 (7%) consent withdrawal
- 28 (6%) for virological failure
- 7% had abacavir hypersensitivity reaction

Discussion: why such a high drop out?
In patients able to tolerate quad combination did OK
High viral loads took longer to get below undetectable

Markowitz M et al Presentation 9-42

Markowitz M et al Presentation 9-42
Emtricitabine – FTC

- Nucleoside (cytosine) analogue
- One capsule, once daily, without food restrictions
- Long intracellular half-life
- Favorable safety profile
- Proven efficacy in treatment-naive & treatment-experienced patients
- US FDA approval with broad indication, July 2003
- Expected to be available in UK October 2003

FTC

- 301 study: FTC/d4T with ddl/EFV
- ANRS 99: simplification to FTC/ddI/EFV

FTC : 301 study

- FTC similar to 3TC
- Od dosing 200mg capsules
- Slower resistance development
- May be co-formulated with TDF
- Active against HBV
- RCT: d4T vs FTC with ddI/EFV
  - Placebo controlled
  - Median F/U 60w
  - FTC: 301 study
  - FTC similar to 3TC
  - Od dosing 200mg capsules
  - Slower resistance development
  - May be co-formulated with TDF
  - Active against HBV
  - RCT: d4T vs FTC with ddI/EFV
  - Placebo controlled
  - Median F/U 60w

Summary: FTC 301

- Once-daily FTC-containing regimen was statistically superior to twice-daily d4T-containing regimen
  - Significantly lower rate of virologic failure when used with a backbone of once-daily ddl/EFV
  - FTC-containing regimen was better tolerated and had fewer discontinuations than d4T-containing regimen
  - FTC-ddI-EFV is a very potent and safe once-daily combination (ITT: 74% <50cp/ml at 48 weeks)

ALIZE-ANRS 99 Study (FTC/ddI/EFV od versus continued PI-based HAART in HIV infected patients with undetectable HIV-1 RNA)

48 week results

- Prospective, open label, multi-centre, non-inferiority study to assess the efficacy and safety of a once daily regimen of FTC/ddI/EFV in patients controlled with a PI-containing regimen
- NNRTI naïve
- Viral load <400 copies/ml
- Patients (n=350) were randomised to either:
  - continue PI containing regimen (n=177)
  - switch to a once daily regimen FTC/ddI/EFV (n=178) (5 pills taken at bedtime)

Simplification : ANRS 99

- FTC/ddI/EFV (all od) vs continued HAART
- n=350
- NNRTI naïve
- VL <400 copies at baseline
- 48 weeks, ITT

P=0.01
BIKS Study (Bi-therapy Kaletra Sustiva) (lopinavir/ritonavir +efavirenz combination)

24 week results
Pilot, ongoing, multicentre, open label study to evaluate LPV/r + EFV 533mg/133mg bd in HIV infected patients

- NRTI-naive patients
- If PI-experienced - fewer than 5 LPV associated mutations
- To assess NRTI-sparing regimens as alternative HAART

Baseline characteristics
- 86 patients enrolled - 65 ART-naive and 21 experienced (12 PI-naive)
- Mean baseline CD4 = 307 cells/mm³
- Mean baseline VL = 4.84 log₁₀ copies/mL

Ferre V et al and BIKS Study Group
Presentation 9-36

Efficacy results
- % patients with VL <400 copies/mL = 78% (ITT) 93% (AT)
- % patients with VL <50 copies/mL = 64% (ITT) 76% (AT)
- Mean increase in CD4 count (cells/mm³) was 162 at week 24
- Viral rebound occurred in 4 patients
- 2 patients had blips - HIV RNA <400 copies/mL on subsequent control
- 1 patient was non adherent
- 1 patient had confirmed virological failure

Safety and Tolerability results
- grade 3 and 4 clinically relevant adverse events were recorded in 34 patients (40%)
  - hypercholesterolaemia n=29
  - hypertriglyceridaemia n=13
  - asymptomatic hepatic cytolysis n=3

Conclusions
- The dual combination of LPV/r + EFV shows similar virological efficacy to NRTI-based regimens with acceptable tolerability
- Durability of antiviral effect will be assessed at week 48 of follow up
- Complete week 48 results available Q4 2003

Ferre V et al and BIKS Study Group
Presentation 9-36

Boosted PIs vs Unboosted
- Draft BHIVA guidelines recommend boosted PIs are ‘preferred’
So which one is best?
- Od versus bd, pill burden, resistance profile, lipid profile
- Concerns re Kaletra and lipid profiles
- Atazanavir – just how potent is it?
- Saquinavir /ritonavir 1600mg /100mg od – toxicity/tolerability issues

Atazanavir
- Once daily protease inhibitor 400mg od
  - 2 x200mg capsules with food
- Early access programme in UK
  - Current use as unboosted PI
- Caution drug interactions with tenofovir and efavirenz which decrease the atazanavir levels
- Licensed in the USA ‘Reyataz’

Atazanavir: concerns re potency
- Atazanavir = nelfinavir
- Nelfinavir < efavirenz
- Atazanavir = efavirenz ???
- Re-analysis of 034 study ….
Virologic Response* Through Week 48 (ITT) – Primary End Point

TLOVR Response (SE) Through Week 48 (LOQ = 400 c/mL) - Treated Subjects / AI424034

ATV
EFV
N=404
N=401

LLOQ = 400 copies/ml,
5.2 (-1.2, 11.7);

at LOQ = 50 copies/ml,
-4.9 (-11.4, 1.5)

*TLOVR (Time to Loss Of Virologic Response)
AI42-034

Patients (%)

0 20 40 60 80 100

0 4 8 12 16 20 24 28 32 36 40 44 48

Weeks

B/L

ATV-EFV difference estimate (95% CI):

Effect of Using PPT vs EDTA Tubes on Viral Load Measurements

- Duplicated samples were assayed after collection in PPT or EDTA tubes
- 584 subjects (300 on ATV, 284 on EFV) were evaluable
  - 88% of the 661 subjects treated for 48 weeks
  - 73% of all 805 patients treated in the main study

<table>
<thead>
<tr>
<th>LOQ &lt;400 copies/mL</th>
<th>LOQ &lt;50 copies/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>EDTA</td>
<td>PPT</td>
</tr>
<tr>
<td>ATV</td>
<td>93%</td>
</tr>
<tr>
<td>EFV</td>
<td>96%</td>
</tr>
</tbody>
</table>

BMS-043

Study Design

Screening: prior PI failure
1:1 randomization (N = 300)

Group I
Group II

ATV 400 mg qd
LPV/RTV 400/100 mg
+ 2 NRTIs
+ 2 NRTIs

Treated: 144
146

Efficacy cohort*: 144
115

*BMS-043

HIV RNA Mean Change—Co-Primary End Point 1

Efficacy Cohort

HIV RNA Mean Change (SE) (log10 copies/mL)

ATV (N = 114)
LPV/RTV (N = 115)

-2.5
-2.0
-1.5
-1.0
-0.5
0.0

Weeks

B/L

4 8 12 16
20 24

*P <0.0001
†P <0.05

Lipids in Study 043

Mean % Change From Baseline at Week 24

TC
LDL-C
HDL-C
TG

ATV
LPV/RTV

ATV
LPV/RTV

Mean % Change

-30
-20
-10
0
10
20
30

Presentation 23- 117

Presentation 23- 117

BMS-045-24 week results

Study Design

Subjects who failed ≥2 regimens & ≥1 ARV from each class
1:1:1 randomization (N = 358)

Weeks 1-2: maintain NRTIs & replace PI/NNRTI

ATV 300 mg qd
RTV 100 mg qd

Weeks 2-48: replace NRTIs with tenofovir 300 mg qd + 1 NRTI

Randomized 120
115
123

Presentation 23- 117

Presentation 23- 117
Antidiarrhoeal and (≥ CD4 HIV RNA Mean Change (SE)

<table>
<thead>
<tr>
<th></th>
<th>ATV 300/RTV</th>
<th>ATV 400/SQV</th>
<th>LPV/RTV</th>
</tr>
</thead>
<tbody>
<tr>
<td>5% Incidence</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>of 100</td>
<td>-2.5</td>
<td>-2</td>
<td>-1.5</td>
</tr>
<tr>
<td>of 120</td>
<td>-2.0</td>
<td>-1.0</td>
<td>-0.5</td>
</tr>
<tr>
<td>of 140</td>
<td>-1.5</td>
<td>-1.0</td>
<td>0.0</td>
</tr>
<tr>
<td>of 160</td>
<td>-1.0</td>
<td>-0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>of 180</td>
<td>-0.5</td>
<td>0.0</td>
<td>1.0</td>
</tr>
<tr>
<td>of 200</td>
<td>0.0</td>
<td>0.5</td>
<td>1.5</td>
</tr>
<tr>
<td>of 220</td>
<td>0.5</td>
<td>1.0</td>
<td>2.0</td>
</tr>
<tr>
<td>of 240</td>
<td>1.0</td>
<td>1.5</td>
<td>2.5</td>
</tr>
<tr>
<td>of 260</td>
<td>1.5</td>
<td>2.0</td>
<td>3.0</td>
</tr>
<tr>
<td>of 280</td>
<td>2.0</td>
<td>2.5</td>
<td>3.5</td>
</tr>
<tr>
<td>of 300</td>
<td>2.5</td>
<td>3.0</td>
<td>4.0</td>
</tr>
</tbody>
</table>

Virologic Efficacy in Randomized Subjects

<table>
<thead>
<tr>
<th></th>
<th>ATV 300/RTV</th>
<th>ATV 400/SQV</th>
<th>LPV/RTV</th>
</tr>
</thead>
<tbody>
<tr>
<td>% Responders (ITT: TLOVR*)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ATV 300/RTV n=120</td>
<td>64</td>
<td>44</td>
<td>62</td>
</tr>
<tr>
<td>ATV 400/SQV n=115</td>
<td>39</td>
<td>23</td>
<td>42</td>
</tr>
</tbody>
</table>

* TLOVR: Time to Loss of Virologic Response

**Dose reductions, N (%): 9 (8) in ATV 300/RTV arm. No treatment discontinuations

BMS-045
HIV RNA Mean Change From Baseline Through Week 24
Antiviral Efficacy in Randomized Subjects

CD4 Cell Mean Change From Baseline Through Week 24

Patients, N (%)

<table>
<thead>
<tr>
<th></th>
<th>ATV 300/RTV N=110</th>
<th>ATV 400/SQV N=110</th>
<th>LPV/RTV N=118</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total bilirubin*</td>
<td>54 (45)</td>
<td>20 (19)</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>AST/SGOT</td>
<td>4 (3)</td>
<td>4 (4)</td>
<td>1 (&lt;1)</td>
</tr>
</tbody>
</table>
| *Dose reductions, N (%): 9 (8) in ATV 300RTV arm. No treatment discontinuations

Antidiarrhoeal Medication

<table>
<thead>
<tr>
<th></th>
<th>ATV 300/RTV N=110</th>
<th>ATV 400/SQV N=110</th>
<th>LPV/RTV N=118</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loperamide</td>
<td>3 (3)</td>
<td>6 (5)</td>
<td>18 (15)</td>
</tr>
</tbody>
</table>

Patients, N (%)

<table>
<thead>
<tr>
<th></th>
<th>ATV 300/RTV N=110</th>
<th>ATV 400/SQV N=110</th>
<th>LPV/RTV N=118</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>26 (22)</td>
<td>29 (26)</td>
<td>26 (22)</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>3 (3)</td>
<td>5 (5)</td>
<td>13 (15)</td>
</tr>
<tr>
<td>Jaundice</td>
<td>7 (6)</td>
<td>2 (2)</td>
<td>0</td>
</tr>
<tr>
<td>Nausea</td>
<td>2 (2)</td>
<td>8 (7)</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>0</td>
<td>4 (4)</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>Scleral icterus</td>
<td>4 (3)</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
**Both ATV regimens vs LPV/RTV: P-value <0.0001**

Lipids: Mean % Change From Baseline at Week 24

- TC: -8, -10, -7, -2, -9, -11, -1, -14, 3
- LDL-C: -4
- HDL-C: 31
- TG: 0, -30

\* Stratification according to HIV-1 RNA ≥ 400 c/ml and region

MaxCMin 2: Design

Clinical indication for a ritonavir-boosted PI treatment

- PI naive
- PI failure
- PI intolerance

Randomisation 1:1

- Lopinavir / ritonavir 400 / 100 mg bid
- Saquinavir soft gel / ritonavir 1000 / 100 mg bid

\* Risk of virological failure – ITT/e

Primary efficacy analysis of protocol

- Virological failure - ITT

**MaxCMin2 48 week data**

Phase IV randomised open label trial comparing safety and efficacy of Lopinavir/rtv (400/100mg BID) compared with Saquinavir/rtv (1000/100mg BID)

- Concomitant use of ≥ 2NRTI/NNRTI agreed prior to randomisation
- Patients were 79% male, 45% homosexual, 52% were PI experienced and 33% ART naive

MAXCIM2 Trial 48 week data

Clinical toxicity profile similar in both arms

- ATV 300 mg boosted with RTV 100 mg once daily demonstrated efficacy similar to a standard of care (LPV/RTV) in the highly treatment-experienced patients through Week 24
- ATV 400/SQV was less effective than LPV/RTV
- ATV boosted with RTV was associated with a more favorable lipid profile than LPV/RTV
- ATV 300/RTV was safe and well tolerated
  - Diarrhoea was more common on LPV/RTV
  - Total bilirubin increases were not clinically significant, did not lead to treatment discontinuations, and was not associated with hepatotoxicity
MaxCMin2 48 week data

- Virological failure:
  - Higher in r/SAQ arm (p=0.0006)
- Treatment discontinuation:
  - Higher in r/SAQ arm (p=0.0001)
  - Fortovase formulation
  - GI intolerance?

Enfuvirtide (T-20)

- Recently licensed
- Injectable
- New class of antiretroviral
- 48 week results of TORO studies
- Predictors of 24 week success

TORO 1 & TORO 2: Protocol study design

- Randomized 2:1, then start ENF+OB or OB
- Screening period

<table>
<thead>
<tr>
<th>Sample</th>
<th>Status</th>
<th>ENF+OB</th>
<th>OB</th>
</tr>
</thead>
<tbody>
<tr>
<td>-5</td>
<td>blank</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-4</td>
<td>blank</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Switch permitted at virological failure** or at week 48</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

** GT = Genotypic Testing; PT = Phenotypic Testing
** Criteria for virological failure based on 2 consecutive values:
1. >0.5 log₁₀ decrease from baseline starting at week 6 and 8
2. <1.0 log₁₀ decrease from baseline starting at week 10 and 16
3. 2 or more responses and 1 log rebound at any time

Data following virological failure not included in primary efficacy analyses

Katlama LB2:

TORO 1 & TORO 2: BL characteristics and prior ARV experience

<table>
<thead>
<tr>
<th></th>
<th>ENF+OB (N=661)</th>
<th>OB (N=334)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BL RNA</td>
<td>5.2</td>
<td>5.1</td>
</tr>
<tr>
<td>BL CD4⁺ cell count</td>
<td>88</td>
<td>97</td>
</tr>
<tr>
<td>Number of prior ARVs (median)</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td>Years since initiating ARVs (median)</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>Prior NRTI (median, years)</td>
<td>6.3</td>
<td>6.3</td>
</tr>
<tr>
<td>Prior NNRTI (median, years)</td>
<td>1.4</td>
<td>1.5</td>
</tr>
<tr>
<td>Prior PI (median, years)</td>
<td>3.8</td>
<td>4.0</td>
</tr>
</tbody>
</table>

Katlama

The treatment benefit seen at week 24 is maintained at week 48:
Percent responders at week 24 and week 48 (ITT, DC+VF=F)

<table>
<thead>
<tr>
<th></th>
<th>ENF+OB</th>
<th>OB</th>
</tr>
</thead>
<tbody>
<tr>
<td>% of patients</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ENF+OB</td>
<td>47.2</td>
<td>37.4</td>
</tr>
<tr>
<td>OB</td>
<td>51.1</td>
<td>41.7</td>
</tr>
</tbody>
</table>

All comparisons ENF+OB vs. OB P=0.0001

Katlama

CD4⁺ cell count adjusted means change from baseline – intent-to-treat population (LOCF) TORO 1 & TORO 2

<table>
<thead>
<tr>
<th>Study week</th>
<th>ENF+OB</th>
<th>OB</th>
</tr>
</thead>
<tbody>
<tr>
<td>24</td>
<td>71</td>
<td>35</td>
</tr>
<tr>
<td>P&lt;0.0001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>48</td>
<td>91</td>
<td>45</td>
</tr>
<tr>
<td>P&lt;0.0001</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Katlama
The time to virological failure* was longer on ENF+OB compared to OB

![Graph showing the time to virological failure](image)

* Protocol defined

Incidence of injection site reactions (ISRs)*

![Graph showing the incidence of ISRs](image)

* based on pain or discomfort.

% of patients remaining on study

48 Week combined TORO 1 & TORO 2 exposure adjusted AEs

![Graph showing the incidence of bacterial pneumonia](image)

* Boshini et al. Clin Inf Dis, 1996; 23, 107

Hirschtick et al. NEJM, 1995; 333, 845


Caiaffa et al. Am J Resp Crit Care Med, 1994; 150, 1493

Wallace et al. Am Rev Resp Dis, 1993; 148, 1523

Multiple logistic regression for all patients:

HIV-1 RNA <400 copies/mL at week 24

![Table showing multiple logistic regression results](image)

Simplified model for patients initiating enfuvirtide treatment*

![Table showing simplified model results](image)

* HIV RNA<400 copies/mL at week 24
% of patients with viral load <400 copies/ml at week 24 by number of positive prognostic factors by simplified model

- ENF + OB vs OB
- * p<0.05

T-20 Conclusions (Montaner et al)
- ENF added to an OB provided significant benefit across all studied sub-groups of triple-class experienced patients in TORO 1 and TORO 2
- Greatest benefit associated with ENF:
  - CD4 ≥100 cells/mm$^3$
  - Viral load <100,000 copies/ml
  - Up to 10 prior ARVs
  - Two or more active ARVs in background
- Patients with all 4 positive prognostic factors achieved 80% <400 copies/ml at week 24

Saquinavir 500mg tablet
- Bioavailability study
- Healthy volunteers
- 500mg bio equivalent to 200mg hard gel capsules when dosed with ritonavir
- 1000mg /100mg bd with food
- Reduction in pill
- No data on tolerability

Nelfinavir 625mg
- 2 tablets bd instead of 5 bd
- No patients reported severe diarrhoea.
- After 4 weeks
  - 8.1% moderate to severe diarrhoea on 250mg
  - 1.6% on 625mg

Reducing risk of transmission from mother to child transmission through breastfeeding: SIMBA study
- Breastfeeding benefits mother and infant
  - social, cultural, financial and health aspects
- Risk of postnatal transmission though breastfeeding
  - estimated between 10%-15%
  - accounts for 40% of all MTCT

Reducing risk of transmission from mother to child transmission through breastfeeding: SIMBA study
- Design:
  - HIV+ women on AZT/DDI (n=405)
  - 36 weeks gestation to 1 week postpartum
  - infants (randomised 1:1)
    - n= 199 3TC syrup daily
    - n= 198 NVP syrup daily
  - duration of breastfeeding
    - 3TC 106 days (IQR 87-158)
    - NVP 100 days (IQR 87-148)
## Reducing risk of transmission from mother to child transmission through breastfeeding: SIMBA study

### Conclusions
- Combination of prophylactic ART given to breastfed infants from HIV+ mothers and breastfeeding counselling reduces postnatal transmission from 15% to 1% in first month of life
- Effective and affordable
- HIV+ mothers can safely breastfeed and not run the risk of her baby starving in resource-poor settings
- Strategy could reduce stigma in these settings

### SIMBA study
Infant HIV transmission and safety

<table>
<thead>
<tr>
<th>Results</th>
<th>3TC (n=199)</th>
<th>NVP (n=198)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV+</td>
<td>17 (8.5%)</td>
<td>13 (6.5%)</td>
</tr>
<tr>
<td>deaths (HIV+)</td>
<td>5 (2.5%)</td>
<td>8 (4.1%)</td>
</tr>
<tr>
<td>HIV diagnosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intrauterine</td>
<td>13 (6%)</td>
<td>11 (5.5%)</td>
</tr>
<tr>
<td>early postnatal (&lt;4 weeks)</td>
<td>2 (1%)</td>
<td>1 (0.5%)</td>
</tr>
<tr>
<td>late postnatal (&gt;4 weeks)</td>
<td>1 (1%)</td>
<td>1 (0.5%)</td>
</tr>
<tr>
<td>Total SAEs (grade 3-4)</td>
<td>30 (15.1%)</td>
<td>43 (21.7%)</td>
</tr>
</tbody>
</table>

Vyankandondera J, et al. Presentation: 06.8 - LJN