

ART Treatment

- Naïve
- Experienced
- Strategies
- ARV in pregnancy

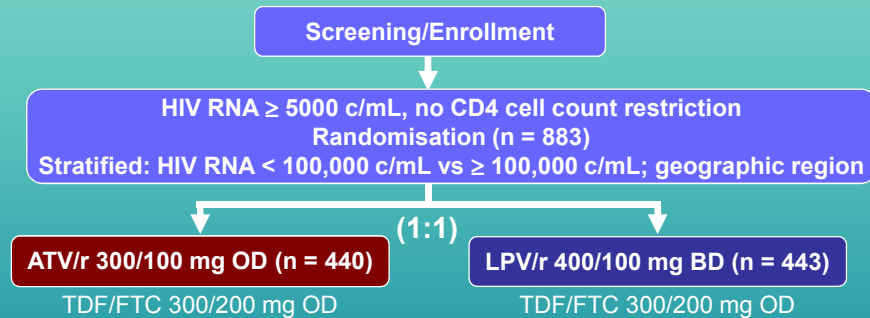
ART Treatment

Naïve studies:

| | |
|----------------|---|
| Abstract 37 | Atazanavir/r vs Lopinavir/r: Castle study |
| Abstract 774 | Kivexa vs Truvada: HEAT study |
| Abstract 775 | Lopinavir/r od vs bd : M05-730 study |
| Abstract 40 LB | Maraviroc : MERIT study |

CASTLE: Study Design (Abs 37)

International, multicentre, open-label, randomised, 96-week study to determine the comparative clinical efficacy and safety of ATV/r and LPV/r in treatment-naïve HIV-1 infected subjects



Molina et al., Oral presentation 37 CROI Feb 2008, Boston, USA

Castle study: Study Objectives

Primary end point:

- Proportion of subjects with HIV RNA < 50 c/mL at week 48
 - Principal analysis: ITT-Confirmed Virologic Response (CVR) - (NC = F)
 - Supportive analyses:
 - ITT-TLOVR
 - On-treatment-Virologic Response - Observed Cases (OT-VROC)

Primary objective:

- Demonstrate non-inferiority of ATV/r once daily vs LPV/r twice daily based on primary end point
 - Δ -10%, ATV/r – LPV/r

Secondary end points:

- Immunologic response
- Resistance
- Safety and tolerability
- Changes in fasting lipids

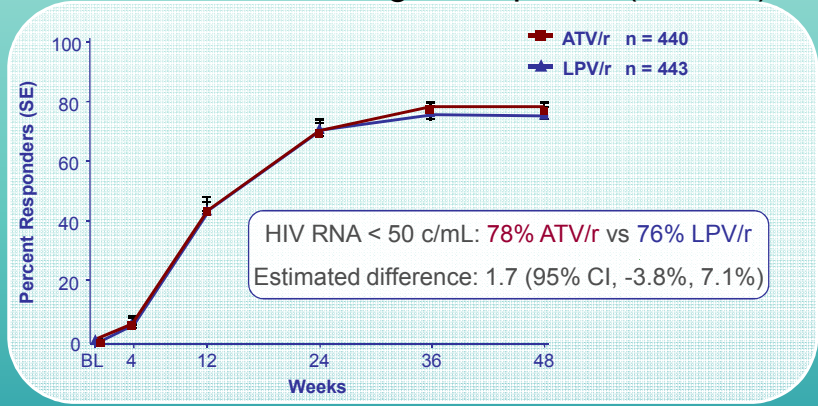
Castle Study: Baseline Characteristics

| | ATV/r n = 440 | LPV/r n = 443 |
|--|------------------|------------------|
| Age, median (min-max) | 34 (19-72) | 36 (19-71) |
| Female, n (%) | 138 (31) | 139 (31) |
| CDC Class C AIDS, n (%) | 19 (4) | 24 (5) |
| HIV RNA log ₁₀ c/mL, median (min-max) | 5.01 (2.60-5.88) | 4.96 (3.32-5.88) |
| HIV RNA ≥ 100,000 c/mL, n (%) | 225 (51) | 208 (47) |
| CD4 cells/mm ³ , median (min-max) | 205 (2-794) | 204 (4-810) |
| CD4 < 50 cells/mm ³ , n (%) | 58 (13) | 48 (11) |
| Hepatitis B and/or C co-infection, n (%) | 61 (14) | 51 (12) |

Castle study: Patient Disposition

| | ATV/r n = 440 n (%) | LPV/r n = 443 n (%) |
|--|---------------------------|---------------------------|
| Randomized | 440 | 443 |
| Treated | 438 (99) | 440 (99) |
| Discontinued before week 48 | 39 (9) | 58 (13) |
| AEs | 10 (2) | 14 (3) |
| Death | 4 (< 1) | 4 (< 1) |
| Lack of efficacy | 5 (1) | 8 (2) |
| Lost to follow-up | 6 (1) | 6 (1) |
| Poor/noncompliance | 6 (1) | 9 (2) |
| Withdrew consent | 4 (< 1) | 13 (3) |
| Other (pregnancy, no longer meets study criteria, other) | 4 (< 1) | 4 (< 1) |

Castle Study: Primary Efficacy End Point ITT-Confirmed Virologic Response (NC = F)

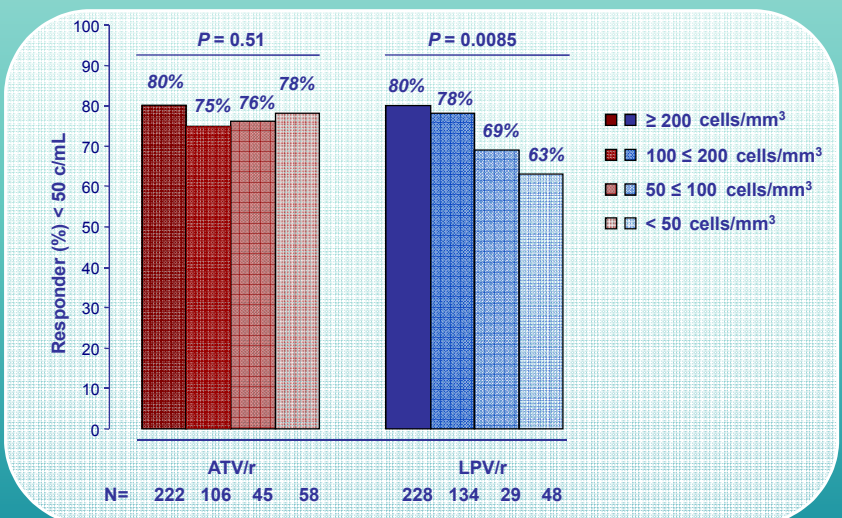


ATV/r has non-inferior antiviral efficacy compared with LPV/r

Supporting Analyses:
 ITT-TLOVR: HIV RNA < 50 c/mL: ATV/r 78%, LPV/r 76%; 1.9 (-3.6, 7.4)
 OT-VROC: HIV RNA < 50 c/mL: ATV/r 84%, LPV/r 87%; -3.5 (-8.7, 1.8)

Castle Study: Response Rate by Baseline CD4 Cell Count

Post Hoc Analysis



P-values are from Cochran-Armitage trend test

Castle Study: Adverse Events Summary

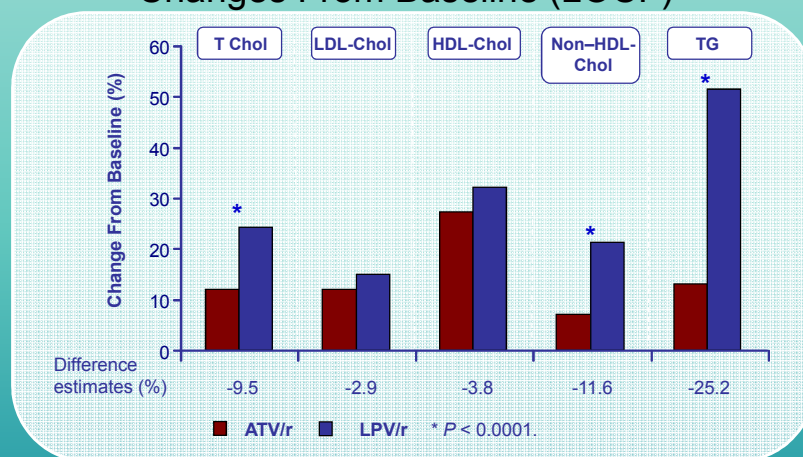
| | | ATV/r n = 441 n (%) | LPV/r n = 437 n (%) |
|---|------------------|---------------------------|---------------------------|
| Serious Adverse Events (SAEs) | | 51 (12) | 42 (10) |
| All grade 2-4 treatment-related AEs^a | | 115 (26) | 129 (30) |
| Grade 2-4 treatment-related AEs \geq 3%^{a,b} | Jaundice | 16 (4) | 0 |
| | Nausea | 17 (4) | 33 (8) |
| | Diarrhoea | 10 (2) | 50 (11) |
| | Rash | 14 (3) | 9 (2) |

- **Renal all grade AEs: 2% in both arms**

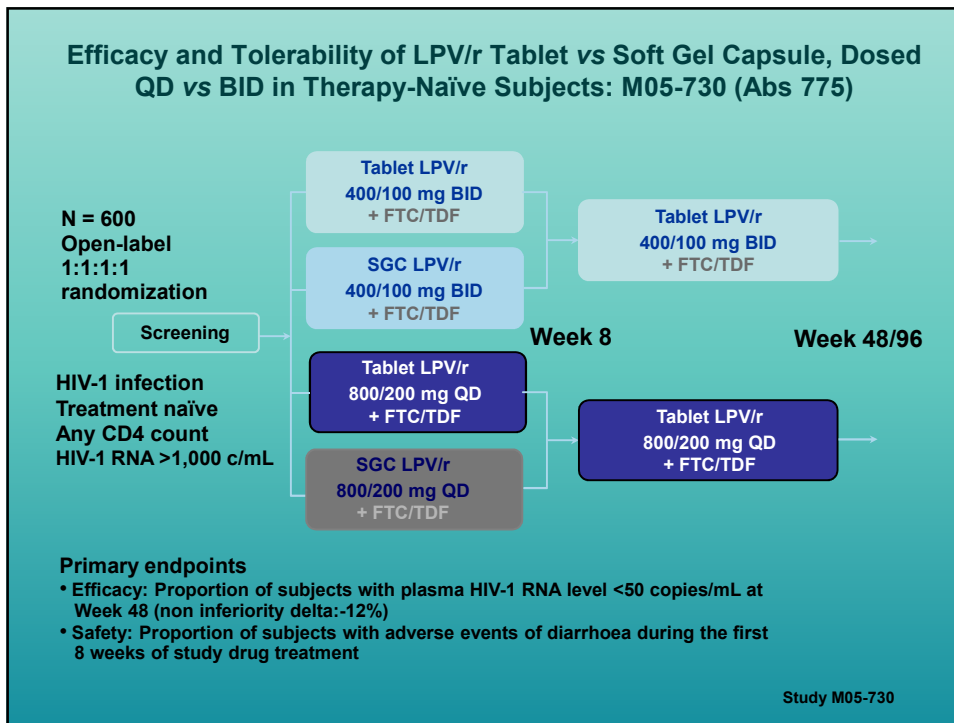
^a Through 48 weeks.

^b Excluding laboratory abnormalities reported as AEs.

Castle study: Fasting Lipids Mean Percent Changes From Baseline (LOCF)



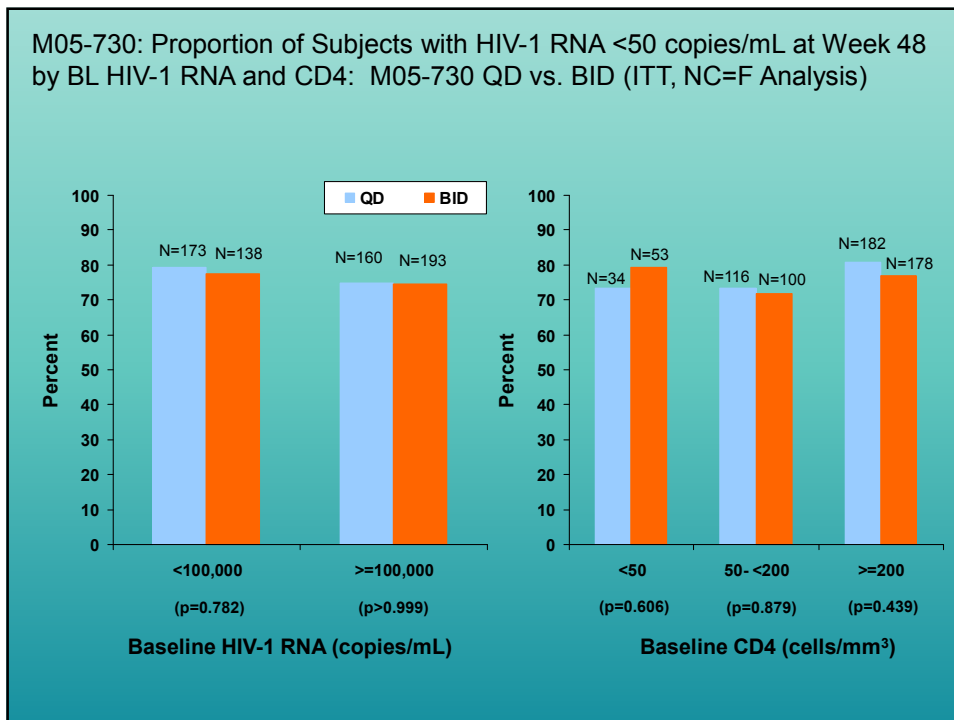
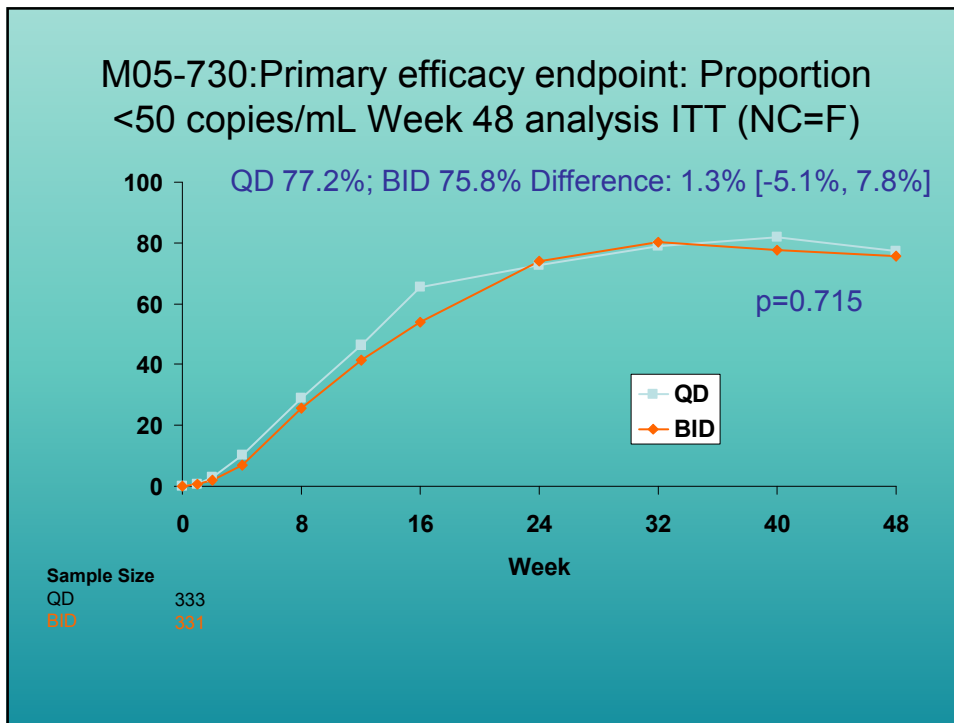
- **2% of ATV/r vs 7% of LPV/r subjects initiated lipid-lowering therapy during the study**



Study M05-730: Disposition through Week 48

| | LPV/r 800/200 mg QD (n=333) | LPV/r 400/100 mg BID (n=331) |
|------------------------------|-----------------------------|------------------------------|
| Subjects discontinued | 49 (14.7%) | 55 (16.6%) |
| Adverse event | 16 (4.8%) | 10 (3%) |
| Death | 2 (0.6%) | 1 (0.3%) |
| Virologic Failure | 2 (0.6%) | 5 (1.5%) |
| Lost to follow-up | 10 (3%) | 17 (5.1%) |
| Withdrew consent | 16 (4.8%) | 13 (3.9%) |
| Nonadherence | 5 (1.5%) | 9 (2.7%) |
| Other | 9 (2.7%) | 8 (2.4%) |

Investigators may have provided more than one reason for a subject's discontinuation



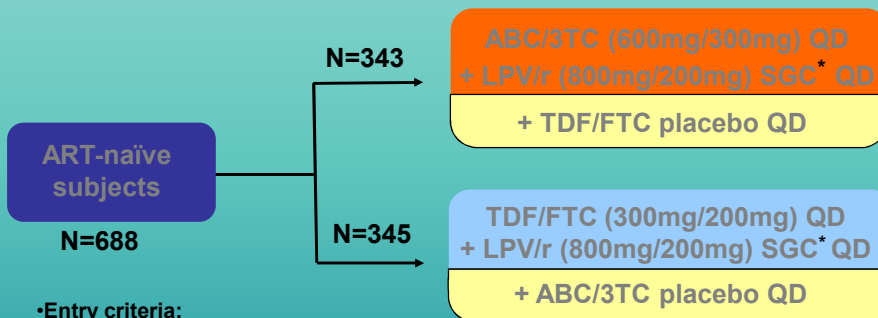
M05-730: Table 4: Most Common Moderate/Severe Related Adverse Events and Grade 3/4 Laboratory Abnormalities

| Moderate or severe LPV/r-related adverse events or Grade 3/4 lab abnormality* | QD (N=333) | BID (N=331) | p-value@ |
|---|------------|-------------|----------|
| Diarrhea | 17% | 15% | 0.671 |
| Nausea | 7% | 5% | 0.426 |
| Vomiting | 3% | 4% | 0.684 |
| Hypertriglyceridemia | 2% | 2% | 0.801 |
| SGOT/AST (>5 x ULN) | 1% | 2% | 0.380 |
| Cholesterol (>300 mg/dL) | 4% | 3% | 0.672 |
| Triglycerides (>750 mg/dL) | 3% | 6% | 0.063 |
| CrCL (<50 ml/min) | 2% | 2% | 0.800 |

* Includes all events occurring in at least 2% of subjects in either group
 @ P-value based on Fisher's exact test

HEAT Study Design (Abs 774)

Randomized (1:1), double-blind, placebo-controlled, multicentre study conducted at 78 sites in the US over 96 weeks



- Entry criteria:
HIV-1 RNA ≥ 1000 c/mL No CD4 cell count restrictions
- Stratified by entry HIV-1 RNA <100,000 or $\geq 100,000$ c/mL
- Primary endpoint: VL <50 at 48 weeks,
- Non inferiority delta: -12% (ITT-E, M=F, switch included)

* All subjects switched to LPV/r tablets at Week 48

Smith K 15th CROI Abs 774

Heat Study: Virologic Non-Response

Protocol-Defined Virologic Failure

- Virologic failure was any one of the following:

By Week 24:

- No confirmed HIV-1 RNA < 200 c/mL
- Confirmed reduction of HIV-1 RNA to <50 c/mL with confirmed rebound in HIV-1 RNA to \geq 200 c/mL

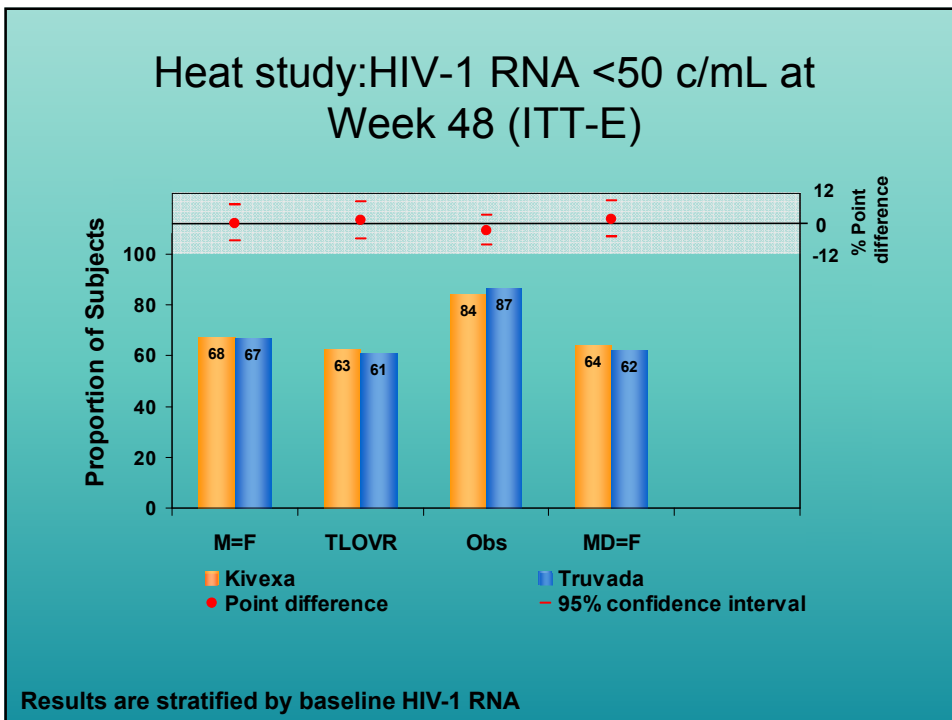
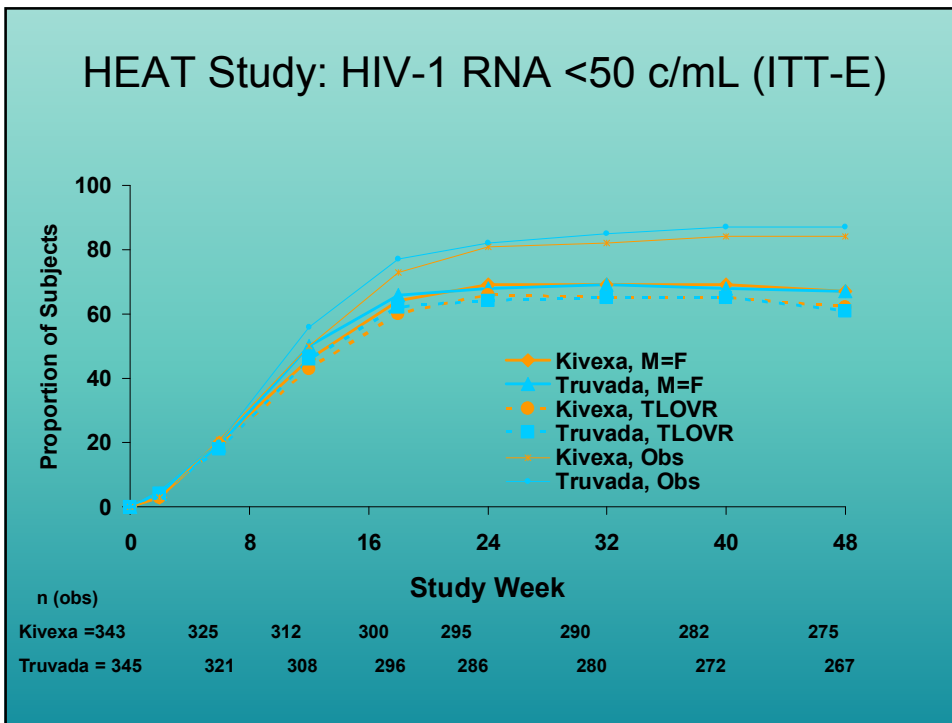
After Week 24:

- Confirmed HIV-1 RNA \geq 200 c/mL

Heat Study: Subject Disposition by Week 48

| | Kivexa | | Truvada | | Total | |
|------------------------------------|--------|-------|---------|-------|-------|-------|
| | 343 | | 345 | | 688 | |
| Completed 48 weeks | 275 | (80%) | 262 | (76%) | 537 | (78%) |
| Prematurely withdrawn | 68 | (20%) | 83 | (24%) | 151 | (22%) |
| Primary Reason for withdrawal | 68 | | 83 | | 151 | |
| Adverse event | 13 | (4%) | 20 | (6%) | 33 | (5%) |
| Protocol violation | 2 | (1%) | 0 | (0%) | 2 | (0%) |
| Protocol-defined virologic failure | 4 | (1%) | 4 | (1%) | 8 | (1%) |
| Lost to follow-up | 27 | (8%) | 30 | (9%) | 57 | (8%) |
| Subject decision | 9 | (3%) | 14 | (4%) | 23 | (3%) |
| Noncompliance | 7 | (2%) | 9 | (3%) | 16 | (2%) |
| Other | 6 | (2%) | 6 | (2%) | 12 | (2%) |

* 7 deaths occurred in the study: 1 (<1%) KVXA and 6 (2%) TVDA



Heat study: Protocol-allowable Toxicity Switches

| | Kivexa (n=343) | Truvada (n=345) |
|------------------------------------|-------------------|--------------------|
| Suspected HSR | 14 (4%) | 3 (1%) |
| Proximal renal tubule dysfunction* | 0 | 3 (1%) |
| Total | 14 (4%) | 6 (2%) |

*PRTD was defined as confirmed rise in Scr of ≥ 0.5 mg/dL from BL AND serum phosphate < 2 mg/dL or either of the former accompanied by any two of the following (proteinuria, glycosuria, low serum potassium or low serum bicarbonate)

Heat Study: Virologic Failures by Week 48 (ITT-E)

| | Kivexa (N=343) | Truvada (N=345) | Total (N=688) |
|---|-------------------|--------------------|------------------|
| Virologic failures (protocol-defined) | 41 (12%) | 44 (13%) | 85 (12%) |
| Confirmed rebound to ≥ 200 c/mL | 19 (6%) | 15 (4%) | 34 (5%) |
| Failure to achieve confirmed < 200 c/mL by Week 24 | 21 (6%) | 24 (7%) | 45 (7%) |
| Unconfirmed rebound at last visit (Suspected virologic failures) | 1 ($< 1\%$) | 5 (2%) | 6 (1%) |

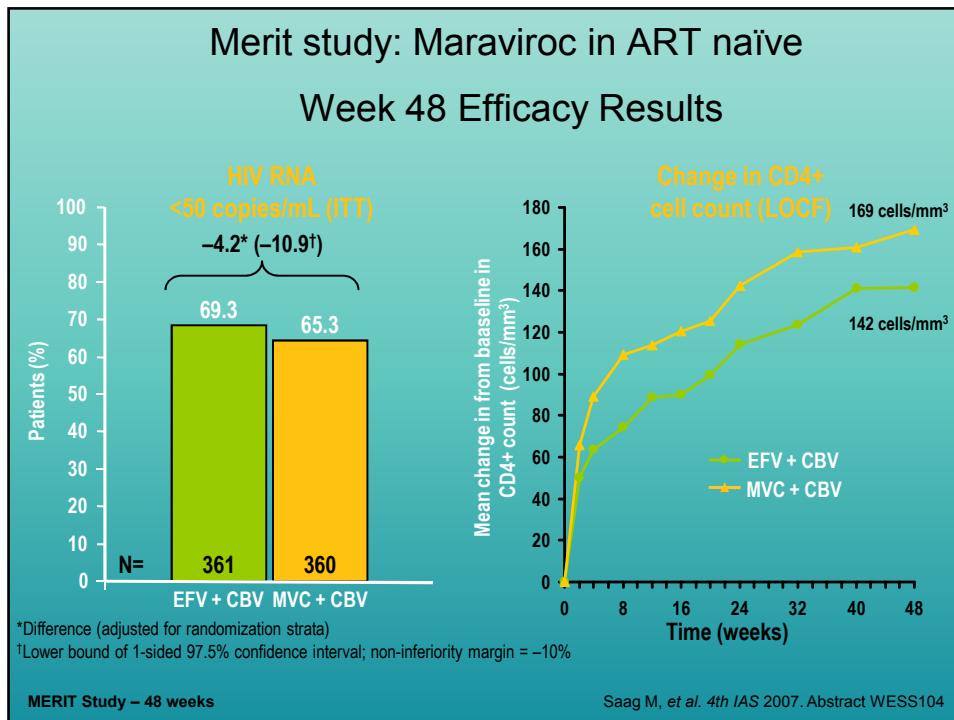
Heat Study: Resistance Through 48 Weeks

| | Kivexa | Truvada |
|-------------------------------------|----------|----------|
| Protocol Defined virologic failures | 41 | 44 |
| With GART data at both BL and VF | 35 | 32 |
| No treatment-emergent mutations | 23 (66%) | 15 (47%) |
| Treatment-emergent mutations | 12 (34%) | 17 (53%) |

Heat Study: Summary of Treatment-Related Adverse Events (AEs)

| | Kivexa (N=343) | Truvada (N=345) |
|------------------------------------|-------------------|--------------------|
| Grade 2-4 AEs | 154 (45%) | 152 (44%) |
| Severe or Grade 3-4 AEs | 43 (13%) | 46 (13%) |
| Serious AEs | 17 (5%) | 9 (3%) |
| Suspected HSR | 14 (4%) | 3 (1%) |
| Proximal renal tubule dysfunction* | 0 | 3 (1%) |

*PRTD was defined as confirmed rise in Scr of ≥ 0.5 mg/dL from BL AND serum phosphate < 2 mg/dL or either of the former accompanied by any two of the following (proteinuria, glycosuria, low serum potassium or low serum bicarbonate)



Merit study: Maraviroc v EFV in ART naïve Analysis of possible reasons for inferior outcome (Abs 40LB)

- **13 patients (3.8%) receiving MVC had a change in tropism result from R5 to D/M between screening and baseline**
 - The response to MVC was significantly reduced in this subgroup
 - Tropism changes were 50% less frequent in patients with Clade C HIV-1 than in patients with Clade B or other Clades
- For subjects with R5 virus at baseline, no appreciable difference in treatment response was seen between the MVC and EFV treatment groups
- **CXCR4-using virus was detected at failure in 10/32 (31.3%) MVC-treated (300mg BID) subjects with R5 virus at baseline**
- **Resistance to MVC in patients failing with R5 virus was uncommon**
 - 2/12 patients studied
- Viral load rebound in patients failing the MVC arm was more commonly associated with BLQ plasma levels at the time of failure

Heera J 15th CROI Abs 40 LB

ART Treatment

Experienced:

- Raltegravir:
- Etravirine:
- Maraviroc:

Treatment Experienced:48 Week Data

| | VL<50 24 Weeks(%) | VL<50 48 Weeks(%) | VL<50 PSS: 2or> | Discont from AEs (%) |
|--------------------------------|---------------------------------|---------------------------------|----------------------------------|---------------------------------|
| Benchmark⁽¹⁾ | | | | |
| Ralt +OBT | 62 | 65 | 70 | 1.7 |
| OBT | 33 | 31 | 43 | 4.3 |
| DUET⁽²⁾ | | | | |
| Etrav+OBT | 61 | 61 | 78 | 7 |
| OBT | 41 | 40 | 67 | 7 |
| Motivate⁽³⁾ | | | | |
| MVC bd + OBT | 42.2 | 43.2 | - | 5.8 |
| OBT | 24.6 | 16.7 | - | 5.3 |

- 1. Benchmark 1+ 2 studies Abs 788,789 (24 ,48 week VL data from Benchmark1)
- 2. DUET 1+2 studies Abs 790,791
- 3. Motivate 1+2 studies Abs 792

Treatment experienced

Benchmark studies

- 67% of 49 patients experiencing VL failure developed raltegravir associated resistance mutations
- No difference in risk of malignancy: Ralt + OBT v OBT: OR 1.5 (95%CI 0.5 -6.3)

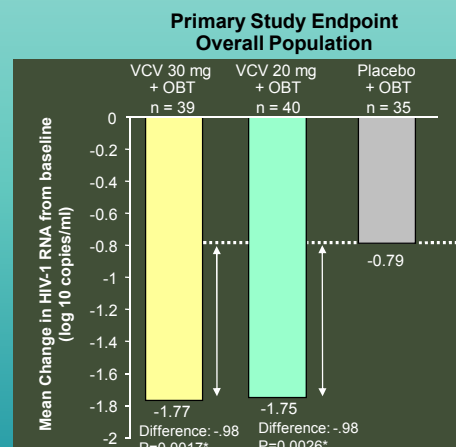
Motivate Studies

- No difference in incidence of malignancy (HIV and non HIV cancers): MVC +OBT: 5.4% v OBT: 7.3%
- No difference in grade 3 or 4 increase in ALT: MVC bd +OBT: 2.7% v OBT: 3.4%

Vicriviroc: Victor-EI study phase IIb

- Triple class experienced
- Primary end point: mean VL decrease at 48 weeks (ITT)
- Higher doses of Vicriviroc evaluated than in previous trials
- 30mg dose chosen for phase III trials
- No grade 3 or 4 ALT increase with Vicriviroc

• Abs 39Lb,795



Zingman 15th CROI Abs 39LB

ART treatment

Strategies:

- PI dual therapy:
 - ANRS 127 pilot study in ART naïve: Abs 779
 - Atv/Saq/r v Fosamp/Atv/r
 - suboptimal response at week 24
 - no difference between arms
 - VL <50: 42%; VL 51- 400: 33%
- Treatment interruption: Final SMART analysis Abs 36
- ART post OI: ACTG 5164, Abs 142
 - Immediate v Deferred initiation of ART during an acute OI or serious bacterial infection
 - Excluded: Tb
 - Unable to take oral medications
 - Prior ART

ACTG 5164: Study outcomes

| Outcome | Total | Immediate: 12 days (9-13) | Deferred: 45 days (41-55) | P value OR (99%CI) |
|-------------------------------|-------------|------------------------------|---------------------------------|-----------------------------------|
| Time to start (median IQR) | | | | |
| No endpoint | 36 (12.8%) | 18 (12.8%) | 18 (12.8%) | - |
| Primary | | | | |
| Death or AIDS | 54 (19.1%) | 20 (14.2%) | 34 (24.1%) | - |
| VL >50, no progression | 98 (34.8%) | 54 (38.3%) | 44 (31.25) | - |
| VL <50, no progression | 130 (46.1%) | 67 (47.5%) | 63 (44.7%) | P=0.215 |
| Secondary | | | | |
| Death/AIDS | 54 (19.1%) | 20 (14.2%) | 34 (24.1%) | P=0.035 OR=0.51(0.23- 1.15) |

ACTG 5164: secondary outcomes

| Time to: (Weeks) | Immediate | Deferred | HR (995CI) P value |
|-------------------------------------|-----------------------|------------------------|-------------------------------------|
| AIDS/ Death | | | 0.53 (0.25-1.09) P=0.023 |
| CD4 >100 (median,IQR) | 4.3 (4.0-23.6) | 12.1 (8.6-28.1) | P=<0.001 |
| Outcomes | | | |
| VL<50 at Wk 48 (ITT) | 71 (50%) | 72 (51%) | ns |
| ART adherent at wk 48 | 95% | 93% | ns |
| ART Changes | 42% | 35% | 0.19 |
| IRIS confirmed | 8 (5.7%) | 12 (8.5%) | ns |

Summary

- Atazanavir/r non inferior to Lopinavir/r in ART naïve patients, with less diarrhoea and better lipid profile
- Lopinavir/r tablets od non inferior to Lopinavir/r tablets bd with similar tolerability profile.
- Kivexa non inferior to Truvada in ART naïve patients in combination with Lopinavir/r allowing for toxicity switches
- Non inferiority of Maraviroc v Efavirenz in ART naïve partially explained by switch in tropism at baseline and at failure. Resistance to Maraviroc in failures uncommon
- Raltegravir, Maraviroc and Etravirine maintain similar efficacy at 48 weeks compared to 24 weeks in triple class experienced patients
- Early initiation of ART in patients with Acute OI or severe Bacterial sepsis results in lower clinical progression by 48 weeks and earlier increase in CD4 count