



AIDS Clinical Conference

March 27, 2007

14th CROI: Update

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Notable Abstracts: Brief Summaries

- Circumcision:

- Randomized trial of circumcision 4996 men in Uganda: HIV incidence at 24 months 0.66/100 Vs 1.33/100.

- **Circumcision was protective** regardless of GUD:0.63/100 (C+/GUD-), 1.06/100 (C-/GUD-), 1.82/100 (C+/GUD+), 6.32/100 (C-/GUD+). (#155aLB and 155bLB)

- Microbicides:

- Phase III, blinded, PC study of cellulose sulfate (CS) gel to prevent HIV infection.

- Conducted in 3 African and 2 Indian sites: **study was halted** after enrollment of 1333 patients. **35 sero-conversions** occurred (#106LB)

Notable Abstracts: Brief Summaries

- Hepatitis B Vaccine:
 - R, DB, PC trial of CPG-7909 (immunostimulatory oligodeoxynucleotide that activates B cells via TLR9) and DD Enderix-B
 - Given to 38 HIV+ subjects (50% previous NR).
 - Dosed at 0,1,2 months:
 - **Response: 17/18 Vs 10/18 (36 months), 6/8 Vs 3/12 (60 months) (#134)**
- Entecavir and HIV Activity:
 - Demonstrated entecavir **inhibited HIV pseudoviruses** with IC50 of 0.1 to 1.0 nM (below plasma concentrations)
 - **3 HIV+ patients on entecavir alone had decline of HIV RNA of 1 to 3 logs.** One patient developed 184V mutation in 61% and 96% of clones at 4 and 6 months into entecavir therapy. **Strains with 184V mutation were resistant to entecavir.** (#136LB)

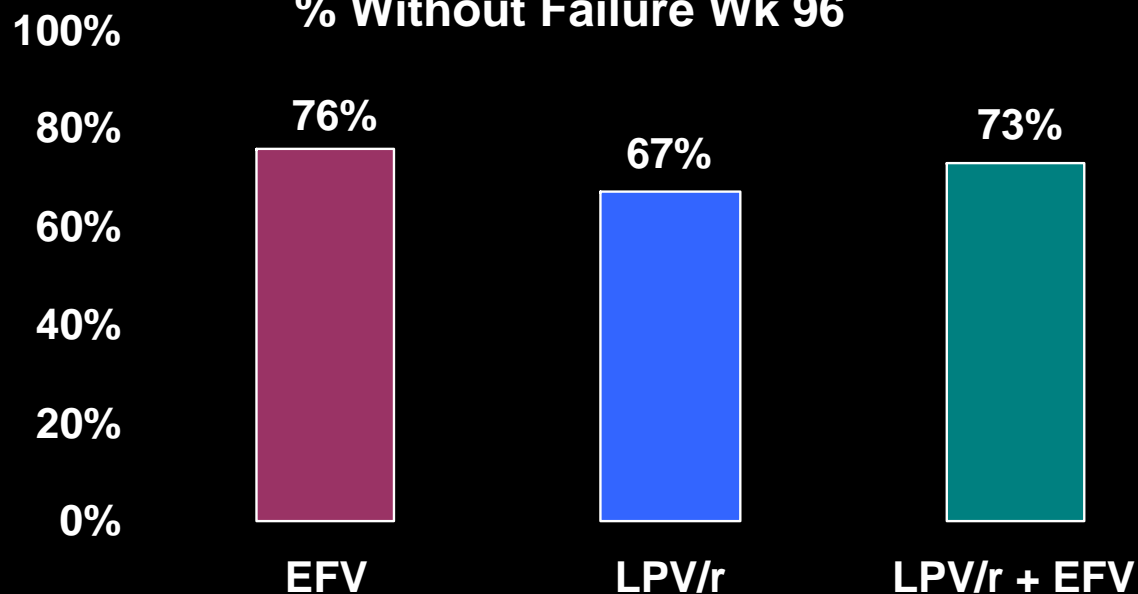
Discussion

Comparison of 1st Line Regimens (A5142)

- Multicenter, open-label, randomized study
- To compare 2 common U.S. 1st line regimens and a NRTI-sparing regimen
- EFV + 2 NRTIs vs LPV/r BID + 2 NRTIs vs LPV/r BID + EFV
- NRTIs:
3TC + either ZDV or d4T XR or TDF
ZDV 42%, d4T XR 24%, TDF 34%
- 753 ARV-Naïve pts, CD4 191, RNA 100K

Comparison of 1st Line Regimens (A5142)

% Without Failure Wk 96



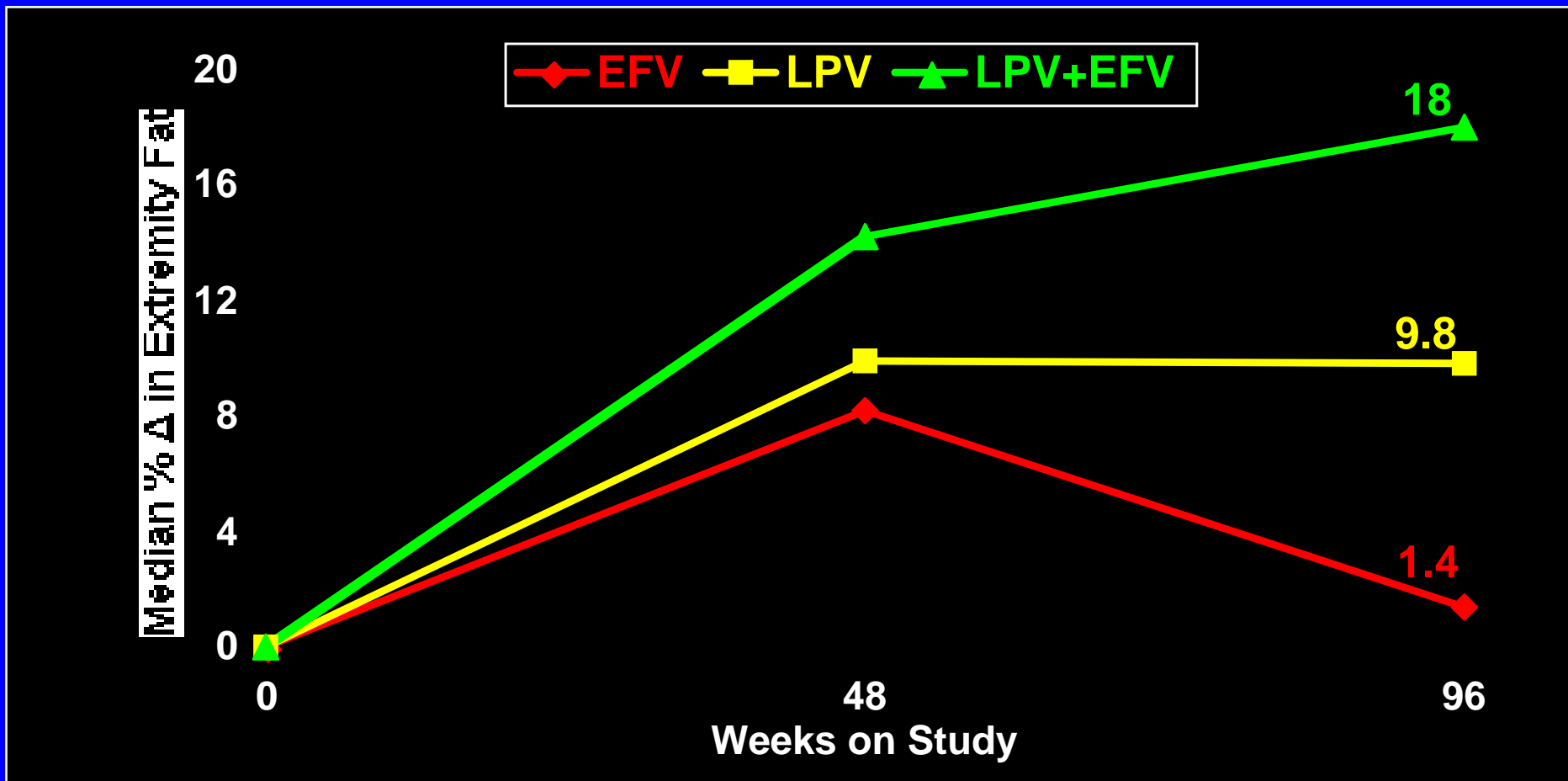
	<u>P</u>
EFV vs LPV/r	0.006
EFV vs LPV/r + EFV	0.5
LPV vs LPV/r + EFV	0.13

- EFV had better viral suppression than LPV/r
- LPV/r + EFV was not different from either of the other regimens

Metabolic Effects of 1st Line Regimens

- Compare:
 - Body composition and lipids
 - DEXA scans (0, 48, 96 wk)
 - Fasting Lipids
- Pt. characteristics similar on 3 arms

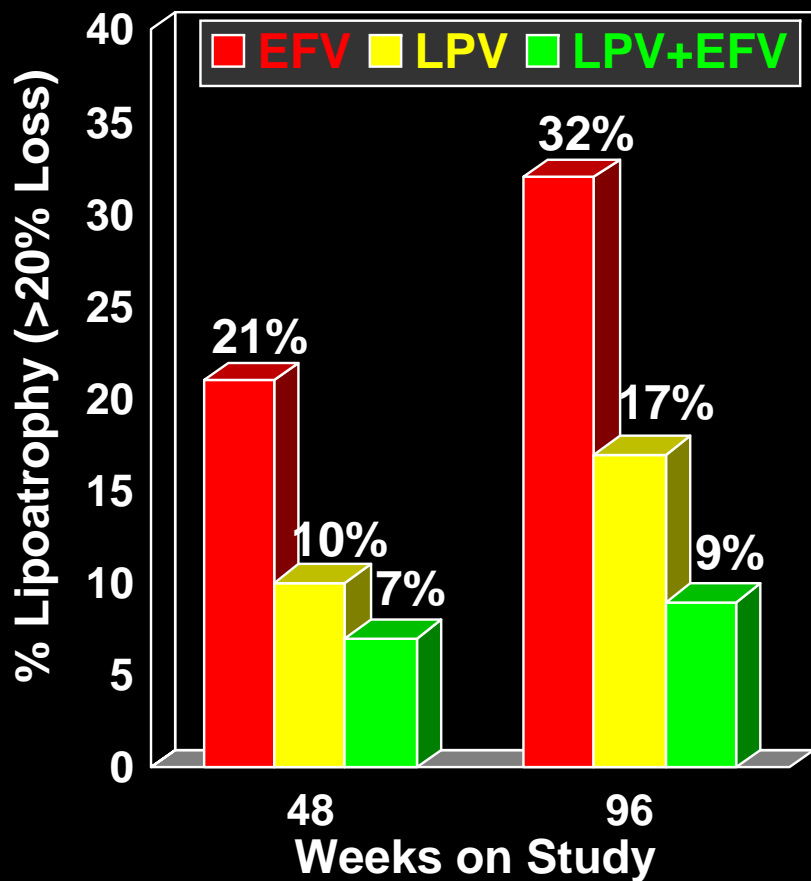
A5142: Effects of 1st Line Regimens on Extremity Fat



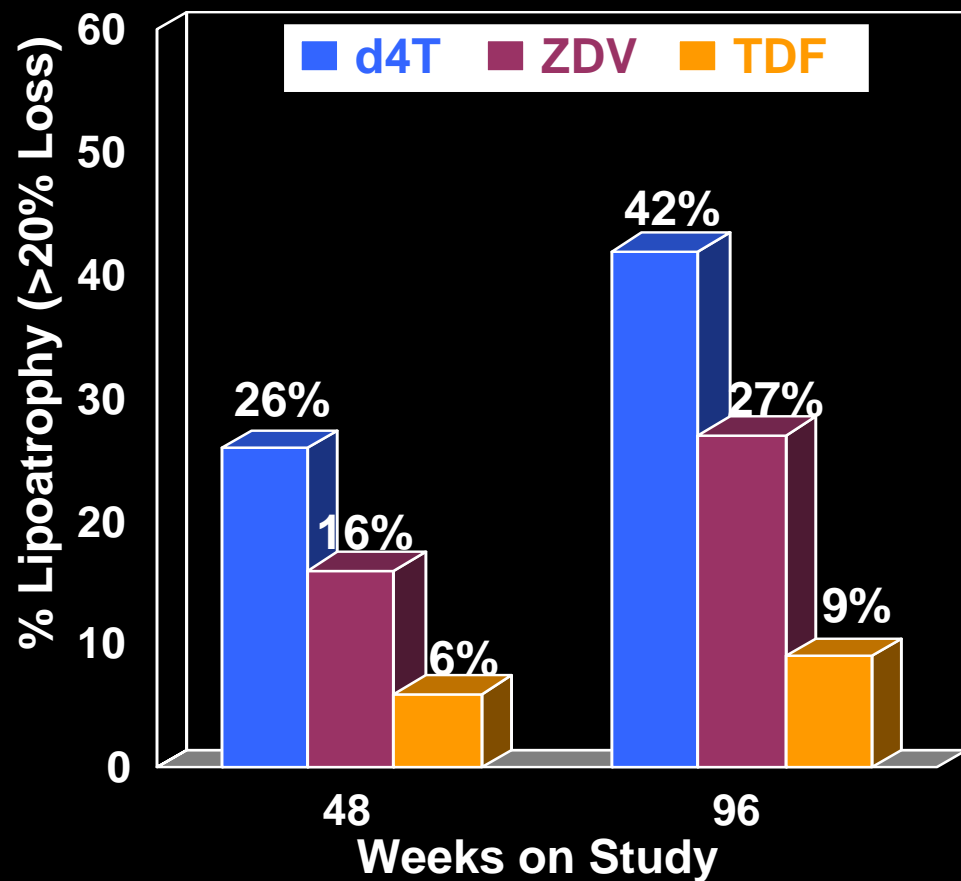
Trunk Fat increased 12-16% and was not different across the arms

A5142: Effects of 1st Line Regimens on Extremity Fat

Lipoatrophy (>20% loss Extremity Fat)



Lipoatrophy (NRTI arms only)



A5142: Effects of 1st Line Regimens on Extremity Fat

- Risk Factors for Lipoatrophy
 - EFV 2.7x higher risk than LPV/r
 - d4T 1.9x higher than ZDV
 - TDF less likely than ZDV
- Greater increases in cholesterol, TG with LPV/r + EFV

A5142: Effects of 1st Line Regimens on Extremity Fat

Feature	Better ← → Worse
Viral Suppression	EFV > LPV/r + EFV > LPV/r
Lipoatrophy	LPV/r + EFV << LPV/r < EFV
Lipids	EFV < LPV/r << LPV/r + EFV

Lipoatrophy and lipids worse with d4T

Illustrates tradeoffs in regimen choices when options are available



Discussion

TMC-278 versus Efavirenz in ARV-Naive STUDY C204

Eligibility (N = 368)

- HIV-infected
- ARV-naïve
- HIV RNA > 5,000 copies/ml
- Randomized, double-blind
- No major NNRTI mutations

Efavirenz (600 mg qd) +
ZDV-3TC or TDF-FTC

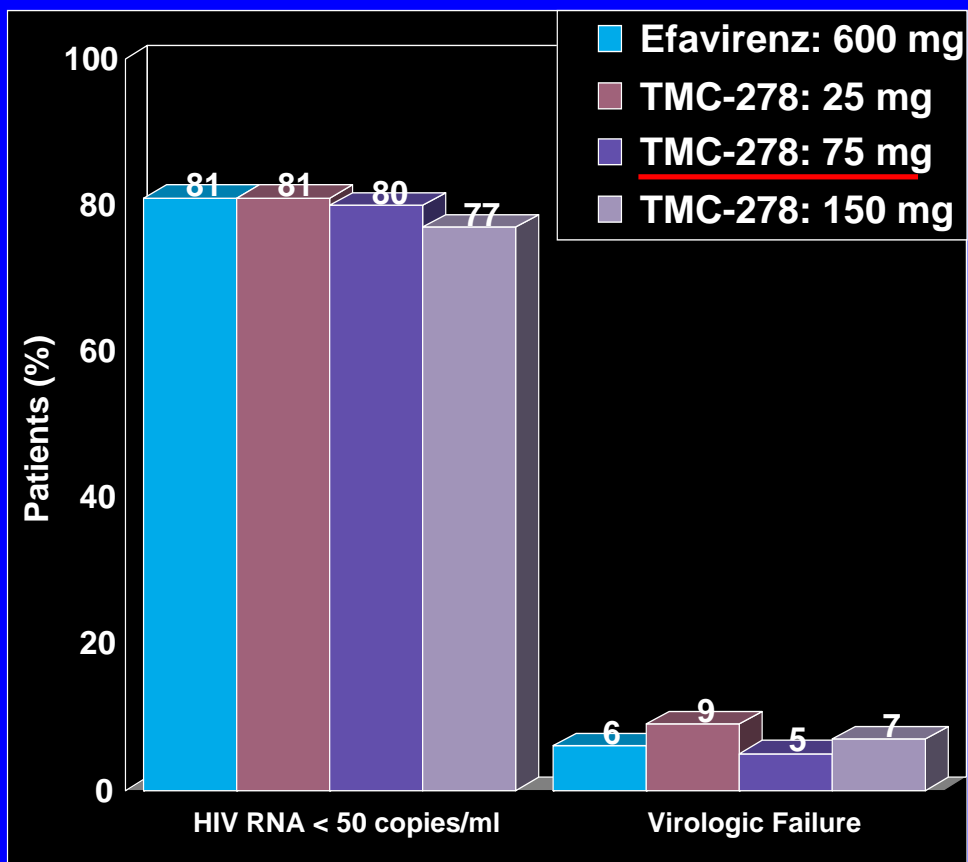
TMC-278 (25 mg qd) +
ZDV-3TC or TDF-FTC

TMC-278 (75 mg qd) +
ZDV-3TC or TDF-FTC

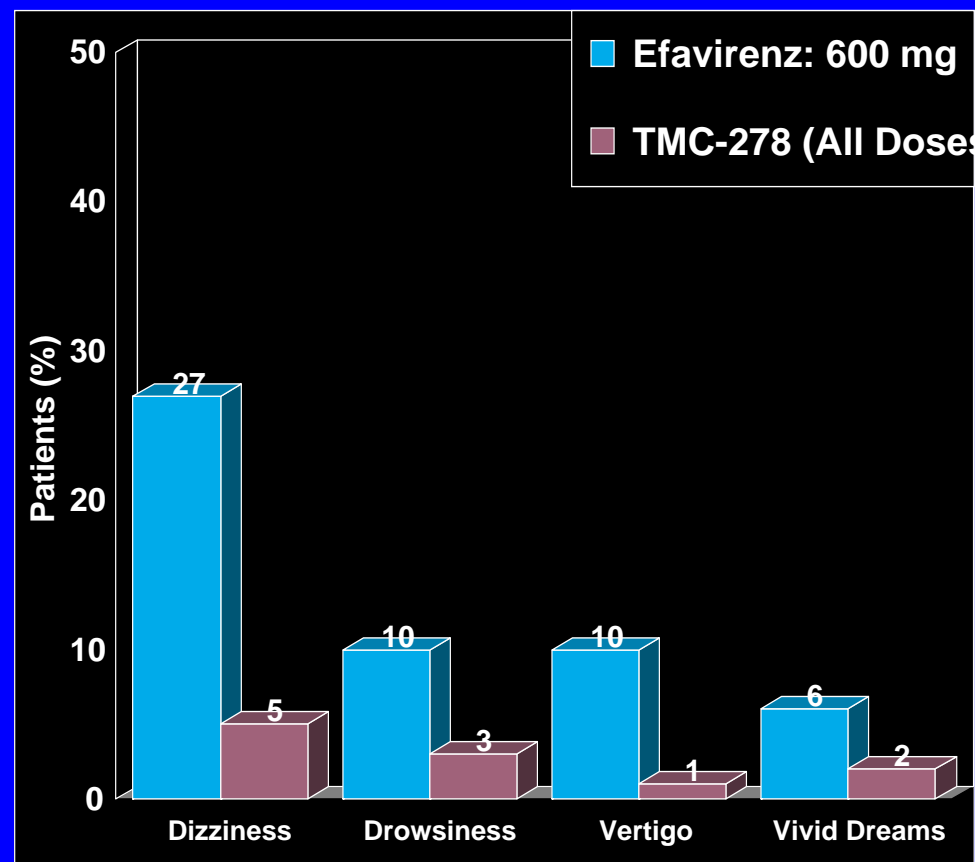
TMC-278 (150 mg qd) +
ZDV-3TC or TDF-FTC

TMC-278 versus Efavirenz in ARV-Naive STUDY C204

48 Week Results (ITT:NC = F)



Central Nervous System AEs



Discussion

Resistance

Transmission of DR HIV, Susan Little (#60)

- Prevalence:
 - TDR in newly infected 11-15%;
 - In newly diagnosed, ARV naïve 7-11%
- Persistence:

14 subjects with TDR identified within 66 d of infection and followed for mean of 110 wks:

 - Time from all DR --> DR/WT (mostly DR): 103 wks
 - Time from all DR --> DR/WT (mostly WT): 142 wks
 - At end of study TDR virus present in 13/14 patients

Resistance

Transmission of DR HIV, Susan Little (#60)

- Natural History (AIEDRP 003, 93-07, N=1555)
 - Baseline VL set point: WT:TDR (p=NS), WT:PI/r 5.0:4.5 (p=NS), WT:NRTI/r 5.0:4.2 (p=.001), WT:NNRTI/r 5.0:5.3 (p=.003)
 - At 1000 days VL set point: WT:TDR (p=NS), WT: 4.5, PI/r 4.5, NRTI/r 3.8, NNRTI/r 4.8
- Response to Rx (AIEDRP 002, 95-06, N=793)
 - N=84 with TDR
 - Overall: no difference in response to Rx TDR vs WT
 - No delay in time to ND: NNRTI/r vs WT
 - Delayed response in patients with PI/r or 215 mutation but these patients received fewer active drugs

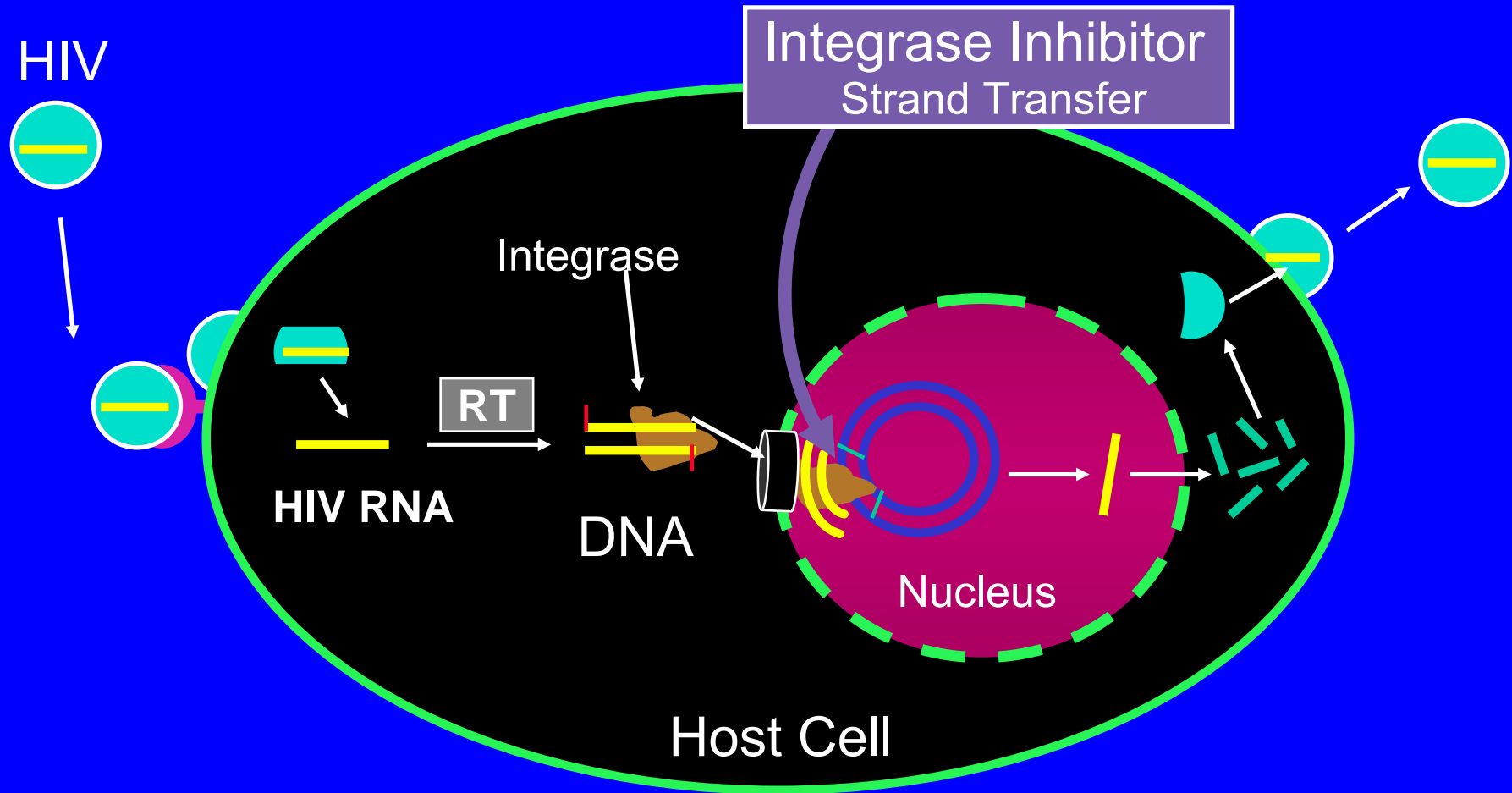
Resistance

Clinical Implications of Low Frequency HIV Variants, Jeff Johnson (#61)

- Developed RT-PCR, point-mutation assay to detect common mutations with sensitivity of 99% for L90M, M41L, K70R, K103N, Y181C, M184V, T215Y, T215F
- Screened recently diagnosed drug naïve patients:
 - *30/205 (15%) classified as WT had mutations*
 - *21/302 (7%) with 1 Mu had R to another class of drug*
- Screened GSK study of naïve patients treated with EFV/3TC + ABC or ZDV
 - *95 patients failed at 48 weeks, 221 did not*
 - *Unmasked 9 patients with mutations at baseline*
 - *7 of these 9 were among the 95 failures at wk 48*

Discussion

HIV: Integrase Inhibitor



Raltegravir in ARV-Experienced Patients

BENCHMARK-1 & 2 Studies

BENCHMARK 1: N = 350 (Europe, Asia, Peru)
BENCHMARK 2: N = 349 (North & South America)

Eligibility

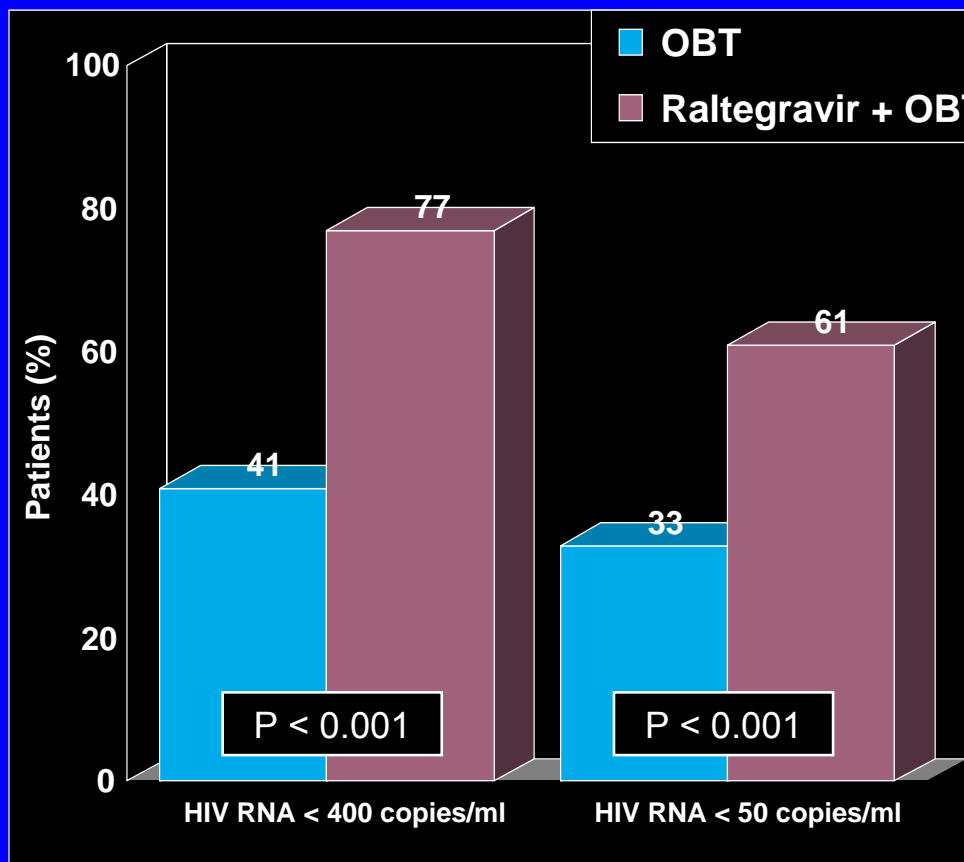
- HIV-infected
- Treatment Experienced
- HIV RNA > 1,000 copies/ml
- Randomized, double-blind
- Resistance to 3 classes of ARV drugs



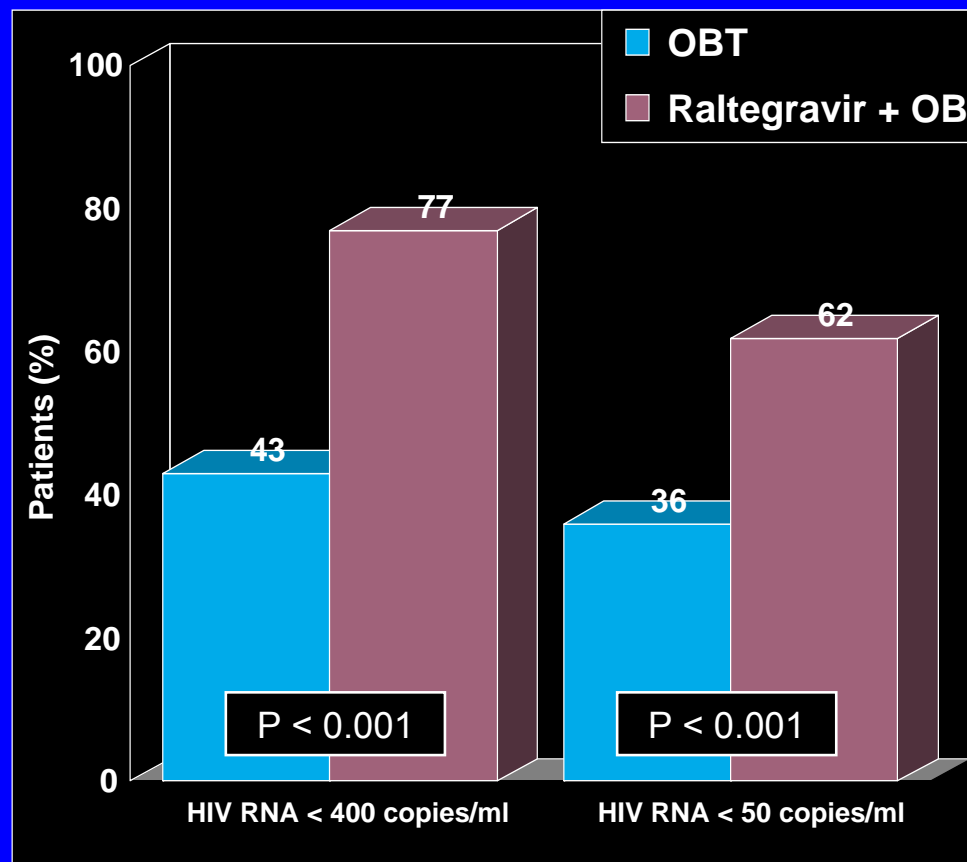
From: Cooper DA, et al. 14th CROI 2007. Abstract 105a-LB.
Steigbigel R, et al. 14th CROI 2007. Abstract 105b-LB.

Raltegravir in ARV-Experienced Patients BENCHMARK-1 & 2 Study

BENCHMARK 1: 16 Week Result



BENCHMARK 2: 16 Week Result

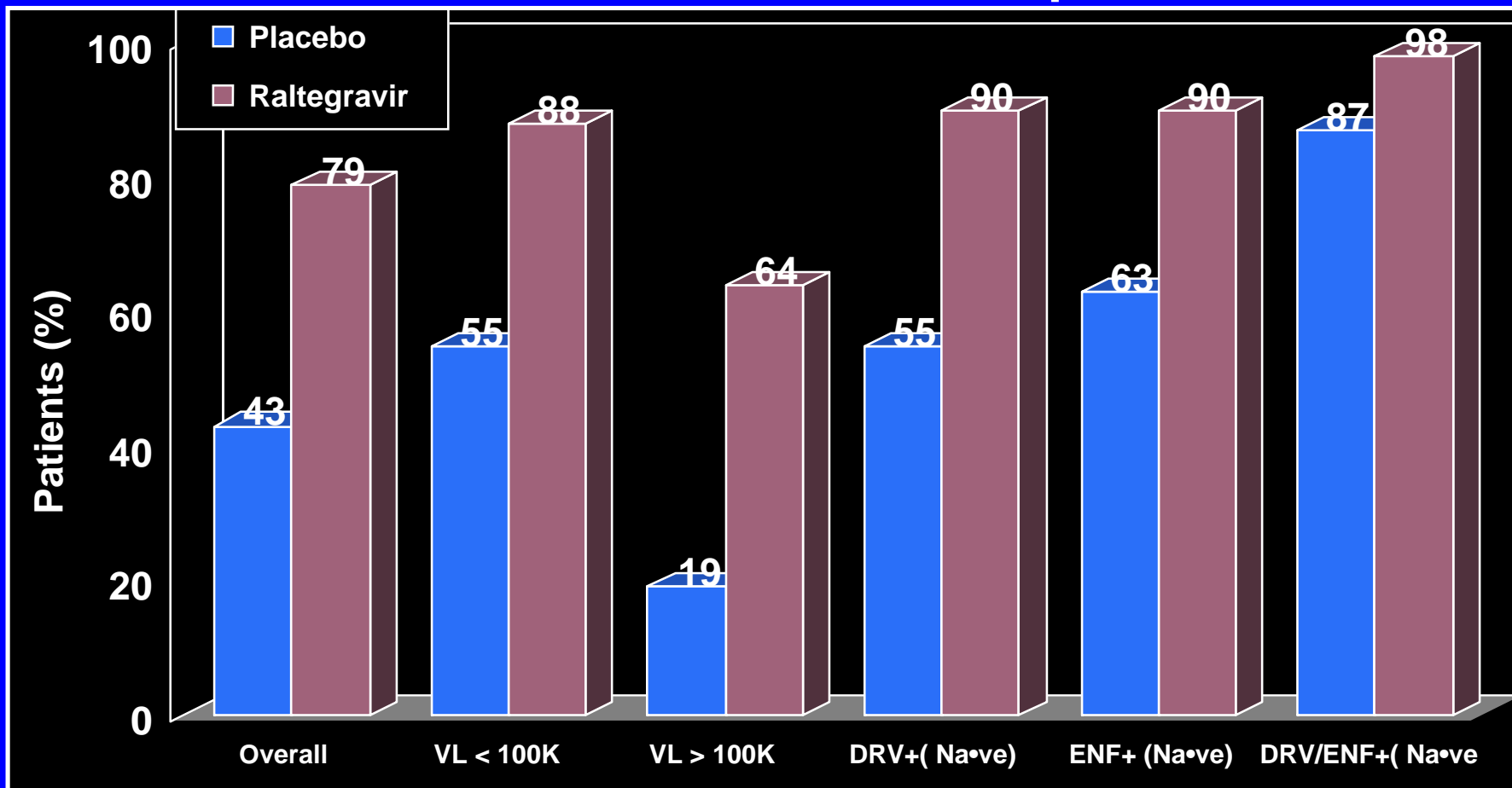


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Raltegravir in ARV-Experienced Patients

BENCHMARK-1 & 2: Combined Data

Week 16: HIV RNA < 400 copies/ml

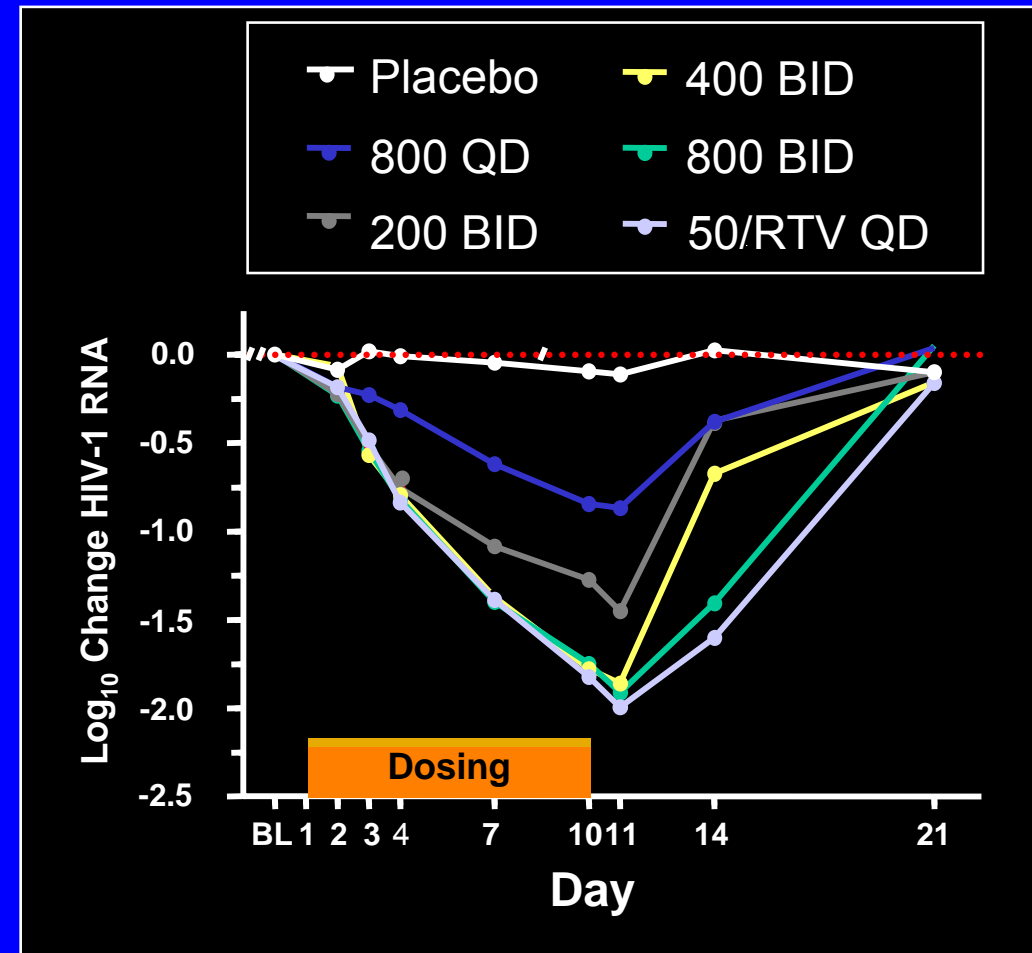


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Discussion

Elvitegravir (GS-9137) Background

- HIV integrase inhibitor
- Blocks strand transfer
- Dihydroquinolone
- IC_{90} 1.2nM
- Cyp P450 3A4 metabolism
- $\frac{1}{2}$ life 9 hrs with RTV
- Previous 10 day monotherapy study



Elvitegravir Phase 2 Study

- Ongoing, randomized, partially-blinded study
- 3 doses + RTV vs Optimized Bckgr with NRTIs ± T20
- 278 experienced pts. with ≥ 1 PI mutation
- Median GSS zero
- 20 mg dose stopped 2° poor activity
- Then allowed PIs (15% took after wk 16)
- No difference in side effects

Elvitegravir Phase 2 Study

	50 mg (N=71)	100 mg (N=73)	Optim Bck (N=63)
Δ RNA (wk 24)	-1.4	-1.7	-1.2
RNA > -2 log	69%	76%	51%
% RNA <50	38%	40%	30%
Δ CD4/mm ³	+52	61	+28

Sustained response with GSS >1
Elvitegravir active, Phase III planned

Discussion

AIDS Pathogenesis

- Humans infected with HIV have high plasma viral loads, gradual CD4 depletion and develop AIDS
- Sooty Mangabeys (SM) and African Green Monkeys (AGM) infected with SIV have high plasma viral loads, no CD4 depletion and no disease

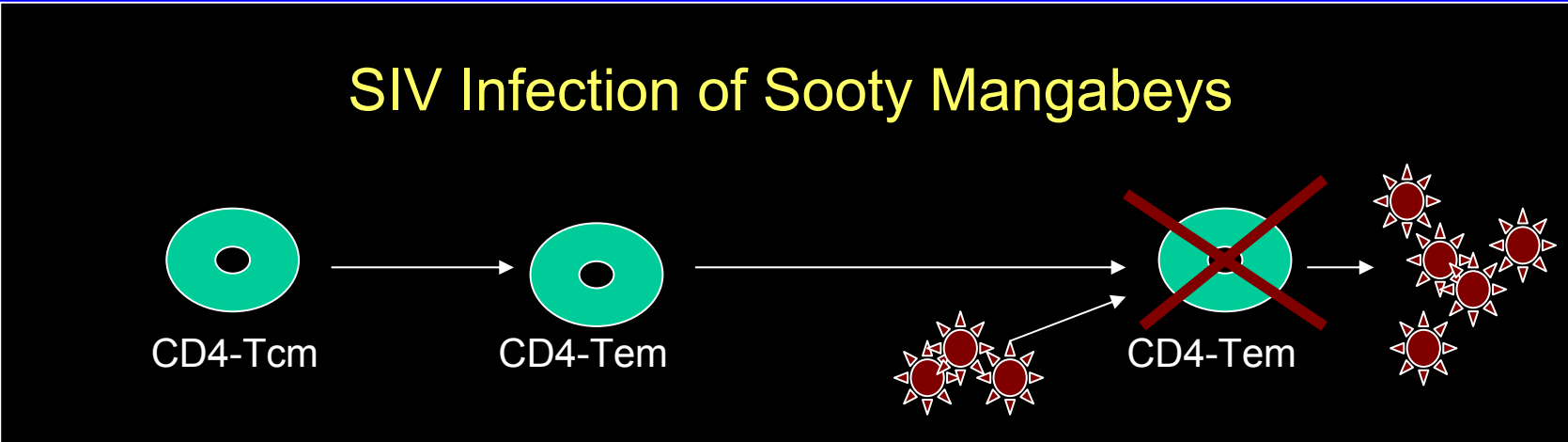
AIDS Pathogenesis

- *Slow* repopulation of CD4+ T-cells in SM occurs after depletion with an anti-CD4 monoclonal antibody – suggesting SM do not have an intrinsically high rate of CD4 production. (#316, Engram)
- SIV infection of AGM leads to massive depletion of GALT CD4+ T-cells and persistent high plasma VL but no increase in mucosal translocation as measured by LPS (#315, Pande)
- SIV infected SM experience high plasma VL, rapid depletion of GI and lung CD4+ T-cells but only a temporary increase in plasma LPS and immune activation (2/5 animals) (#69, Gordon)
- Increased plasma LPS is associated with progressive HIV disease. HAART only partially reduces plasma LPS. LPS in SM is very low. (#65, Brenchley)

AIDS Pathogenesis

Viral replication and disease: Non-human primates versus Humans;
Louis Picker, (Plenary #8)

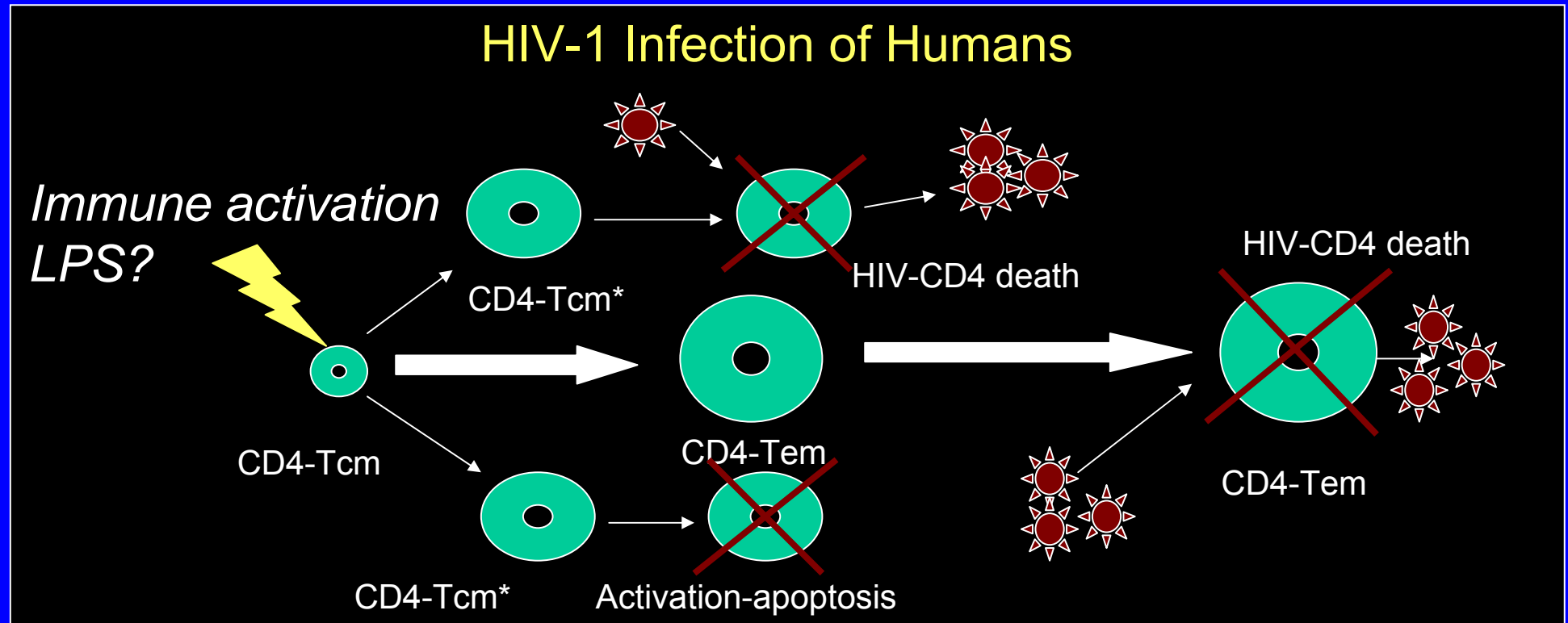
SIV infection of a natural host



AIDS Pathogenesis

Viral replication and disease: Non-human primates versus Humans;
Louis Picker, (Plenary #8)

AIDS is a disease of Immune Activation leading to Depletion of CD4-Tcm cells



Discussion

TH9507 for Fat Redistribution

- Synthetic 1-44 Growth Hormone (GH) Releasing Factor analogue
- GH secretion is ↓ in pts. with fat redistribution and GH has trunkal fat
- Double-blind, randomized, placebo-controlled 6 months study of 2mg/d SC
- 412 pts. with abdominal fat accumulation on ART
Men: Waist >95, WHR>0.94
Women: Waist >94, WHR>0.88
Fasting glucose <150

TH9507 for Fat Redistribution

	TH9502 N=211	Placebo N=137
VAT	-15%	+5%
SAT	<1%	+3%
Trunk fat	-1 kg	0.4 kg
Limb fat	0 kg	+0.2 kg
TG	-50 mg/dL	+8 mg/dL

No change in glucose or insulin

No change in RNA or CD4 cells

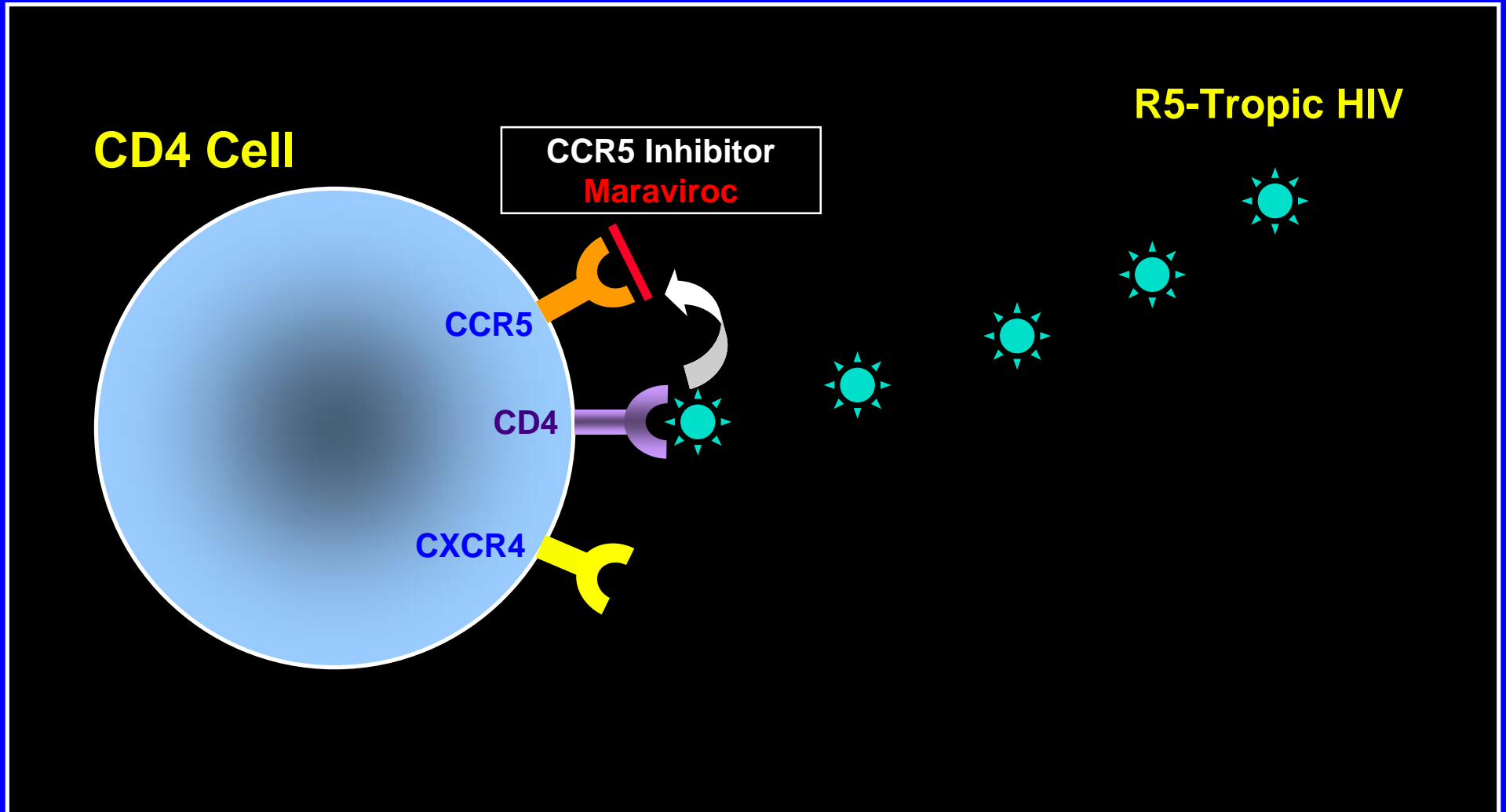
More edema, myalgias, rash with TH9502

Hypersensitivity in 2% (no SAEs)

TH9502 decreases VAT and improves lipids

Discussion

Inhibitors of HIV Cell Binding and Entry

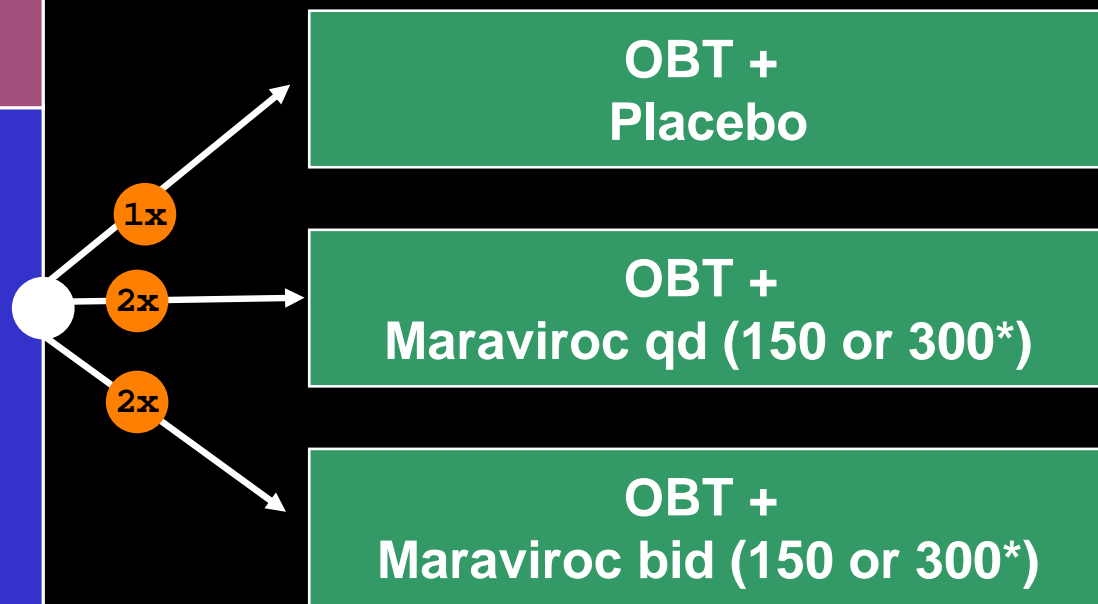


Maraviroc in ARV-Experienced Patients MOTIVATE-1& 2 Study

Motivate 1: N = 601 (Canada, US)
Motivate 2: N = 475 (Europe, Australia, US)

Eligibility

- HIV-infected: R5-tropic
- Treatment Experienced
- HIV RNA > 5,000 copies/ml
- Randomized, double-blind
- Resistance to (and/or) > 6 months of 3 classes of ARV drugs

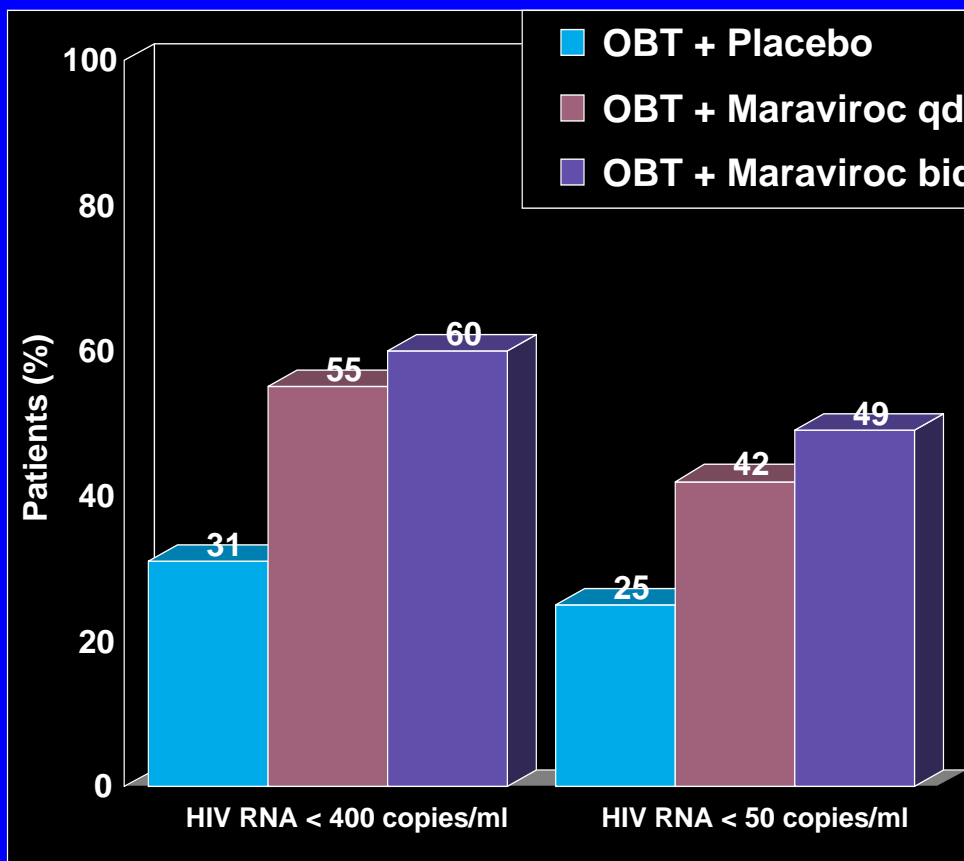


* Maraviroc 300 mg dose reduced to 150 mg in patients receiving RTV (except with Tipranavir)

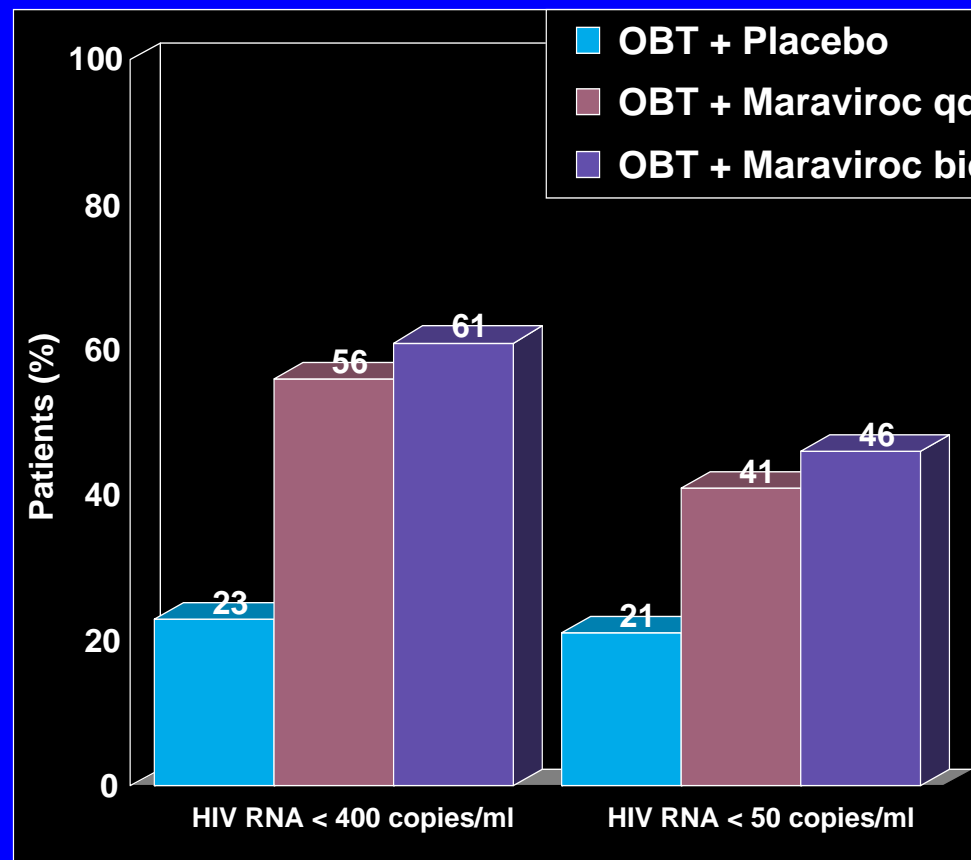
From: Lalezari J, et al. 14th CROI 2007. Abstract 104b-LB.
Nelson M, et al. 14th CROI 2007. Abstract 104a-LB.

Maraviroc in ARV-Experienced Patients MOTIVATE-1 & 2 Studies

Motivate 1: Results: 24 Weeks



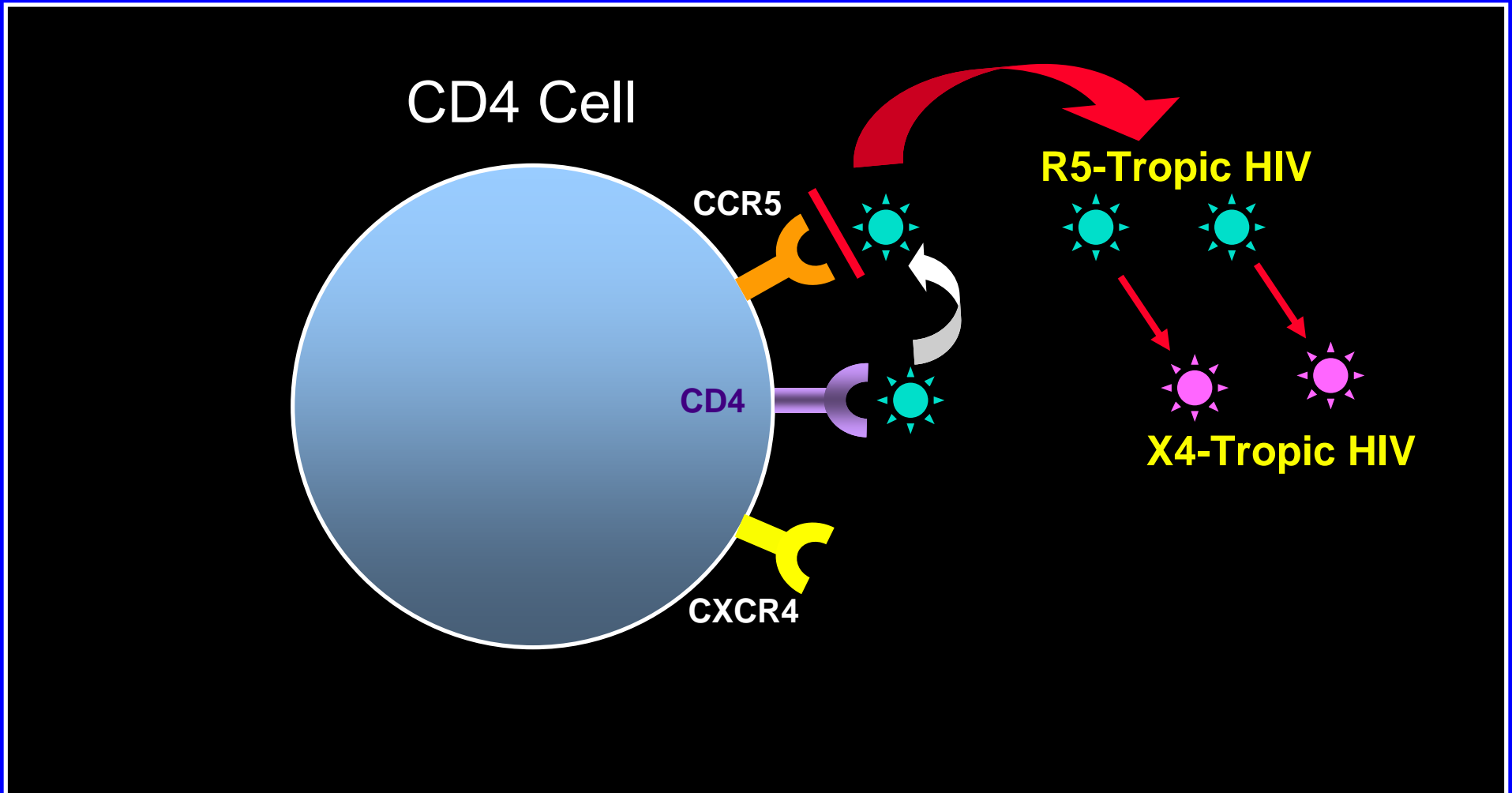
Motivate 2: Results: 24 Weeks



From: Lalezari J, et al. 14th CROI 2007. Abstract 104b-LB.
Nelson M, et al. 14th CROI 2007. Abstract 104a-LB.

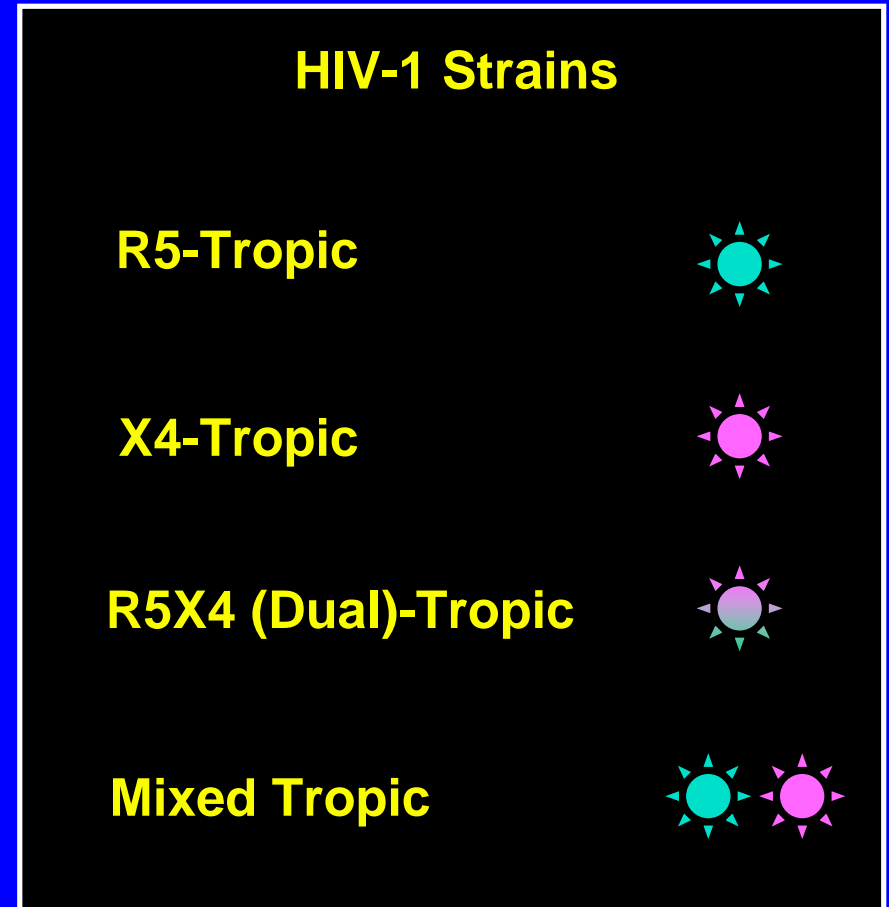
HIV Cell Binding

Potential Shift from R5-Tropic HIV to X4-Tropic HIV

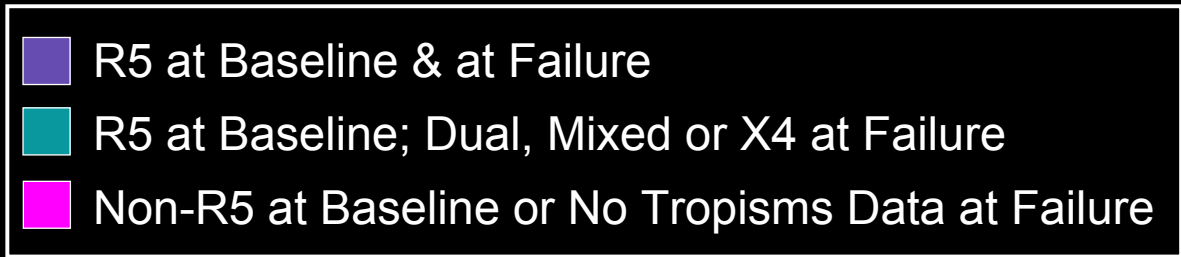


HIV Co-Receptor Tropism Assay

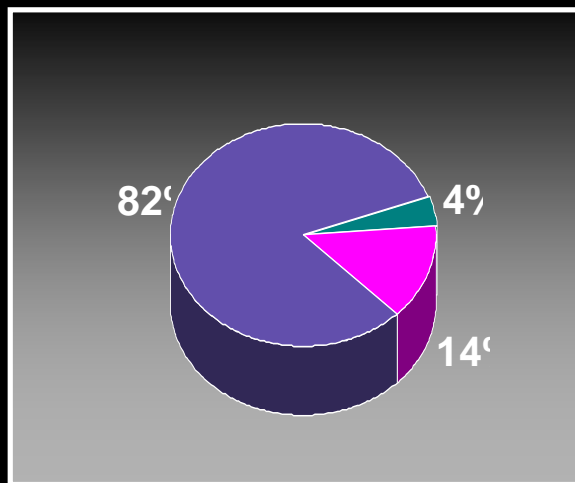
- Assay Measures HIV Tropism
 - R5 Tropic
 - X4 Tropic
 - Dual Tropic
 - Mixed Tropic
- Utilizes Entire Envelope Gene
 - Generates pseudoviruses
- Viral Load
 - Above 1,000 copies/ml
- Detection of Minor Species
 - Reliably detected at 5-10%



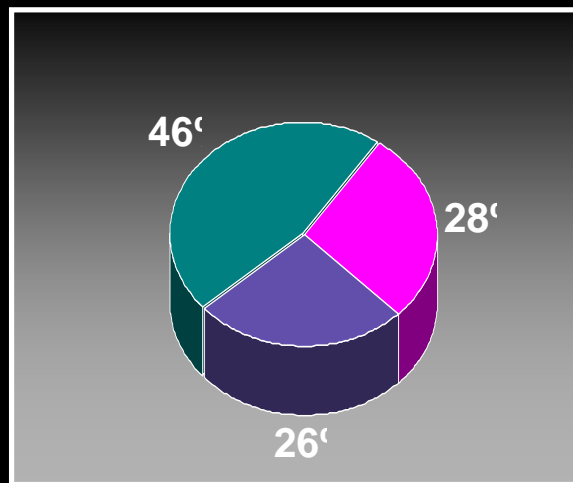
HIV Tropism at Time of Virologic Failure MOTIVATE-1 & 2 Studies



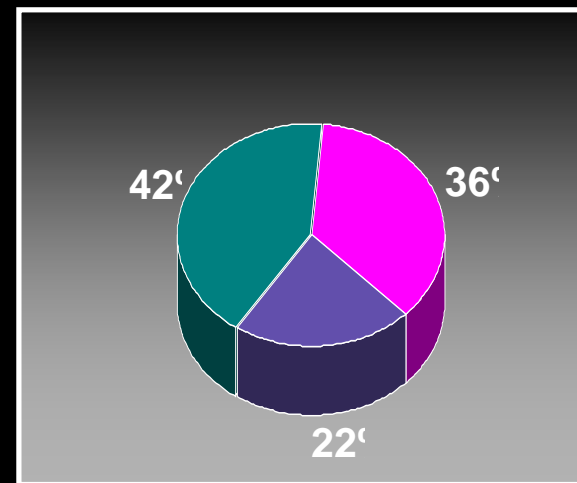
OBT + Placebo



OBT + Maraviroc qd



OBT + Maraviroc bid



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Nelson M, et al. 14th CROI 2007. Abstract 104a-LB.

Discussion

Immune Reconstitution Syndrome

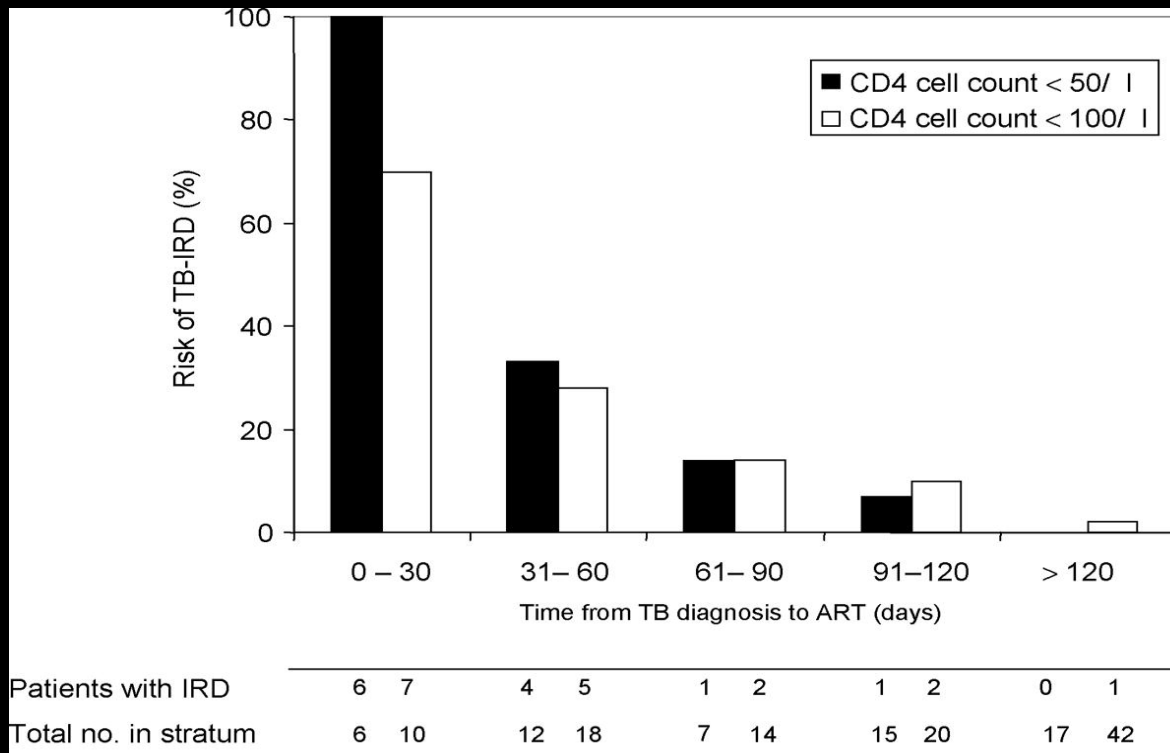
Plenary session by Martyn French (#111)

- **Timing**: Early: < 3 months, either unmasking or paradoxical worsening, mostly live organisms. Late: > 3 months, non-viable pathogens.
- **Incidence**: Unmasking 16-28%, paradoxical 4-50% (cryptococcus), 8-43% (tuberculosis)
- **Pathogenesis**: 1) increase TH-1 IFN producing CD4 and CD8 cells, 2) increase IL-17 producing T-cells (recruit PMNs), 3) decrease regulatory IL-10 T-cells
- **Risks for IRS**: low CD4, recognized disseminated OI and early start of HAART. (Abstract # 859 (Elliot) MTB IRS: OR for IRS if CD4 < 50 = 5.47, if HAART started < 28 days = 21.29)

Immune Reconstitution Syndrome

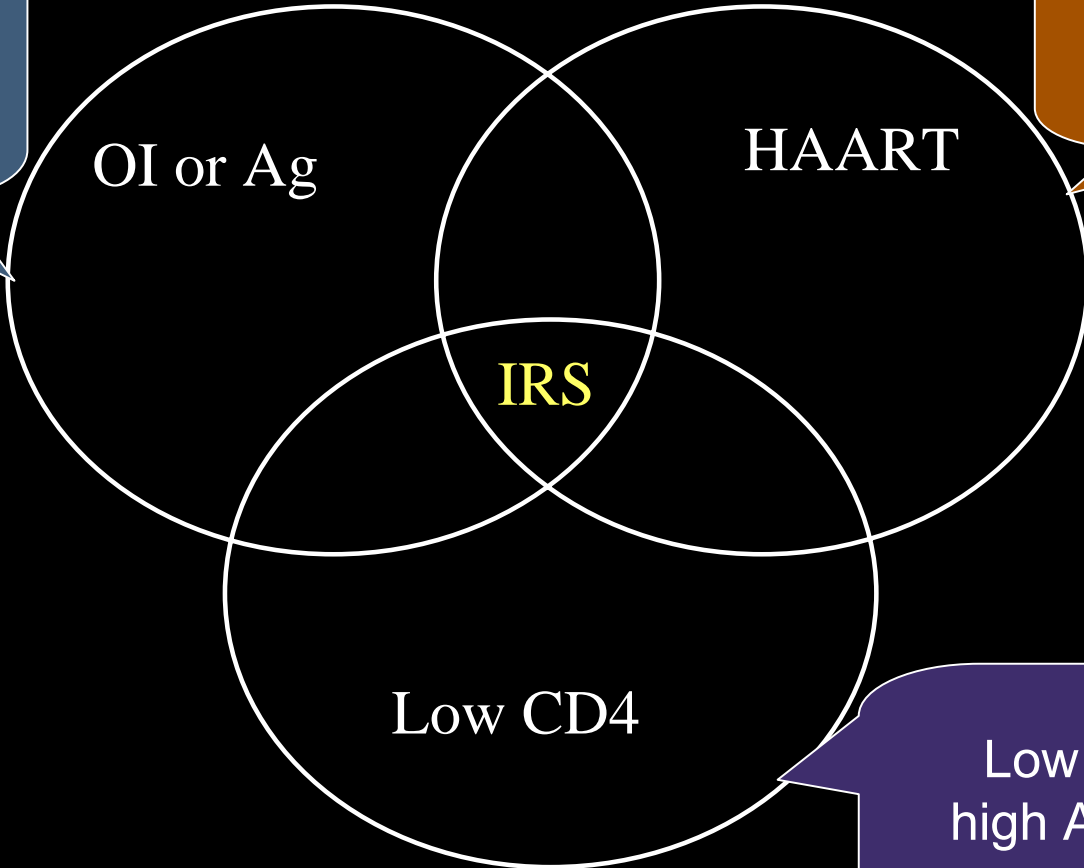
Plenary session by Martyn French (#111)

- Risk for IRS: Early HAART start: Lawn, AIDS, 2007: MTB IRS: OR if HAART start 0-30 days: 69.5



Immune Reconstitution Syndrome

Increased with disseminated infection, high Ag load



Increased if started early

Low CD4 assoc with high Ag load & immune dysregulation

END