# HIV Integrase Inhibitors: Current and Future Use

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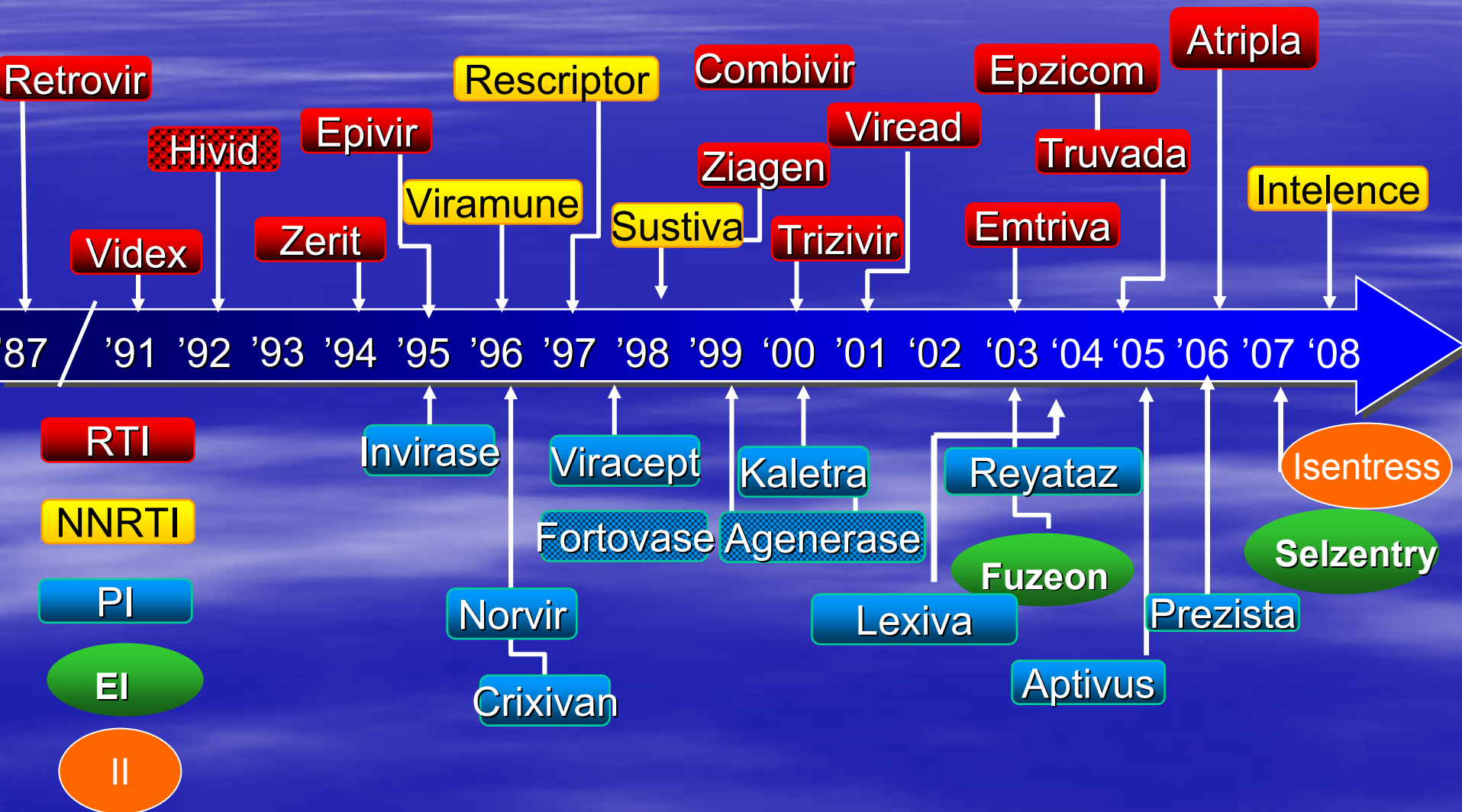
## ¿Which of the following statements about raltegravir is false?

a) Raltegravir is metabolized by cytochrome P450.
b) At 48 weeks of follow-up of raltegravir in treatment-experienced patients, there has been no increased risk of malignancies seen compared to placebo-optimized background treated patients.
c) Raltegravir has a low drug interaction profile.
d) The integrase inhibitor, raltegravir, works against the integrase enzyme by inhibiting strand transfer.
e) Creatine kinase elevations (CK) have been seen in some patients treated with raltegravir.
f) I do not know, I'm coming to learn.

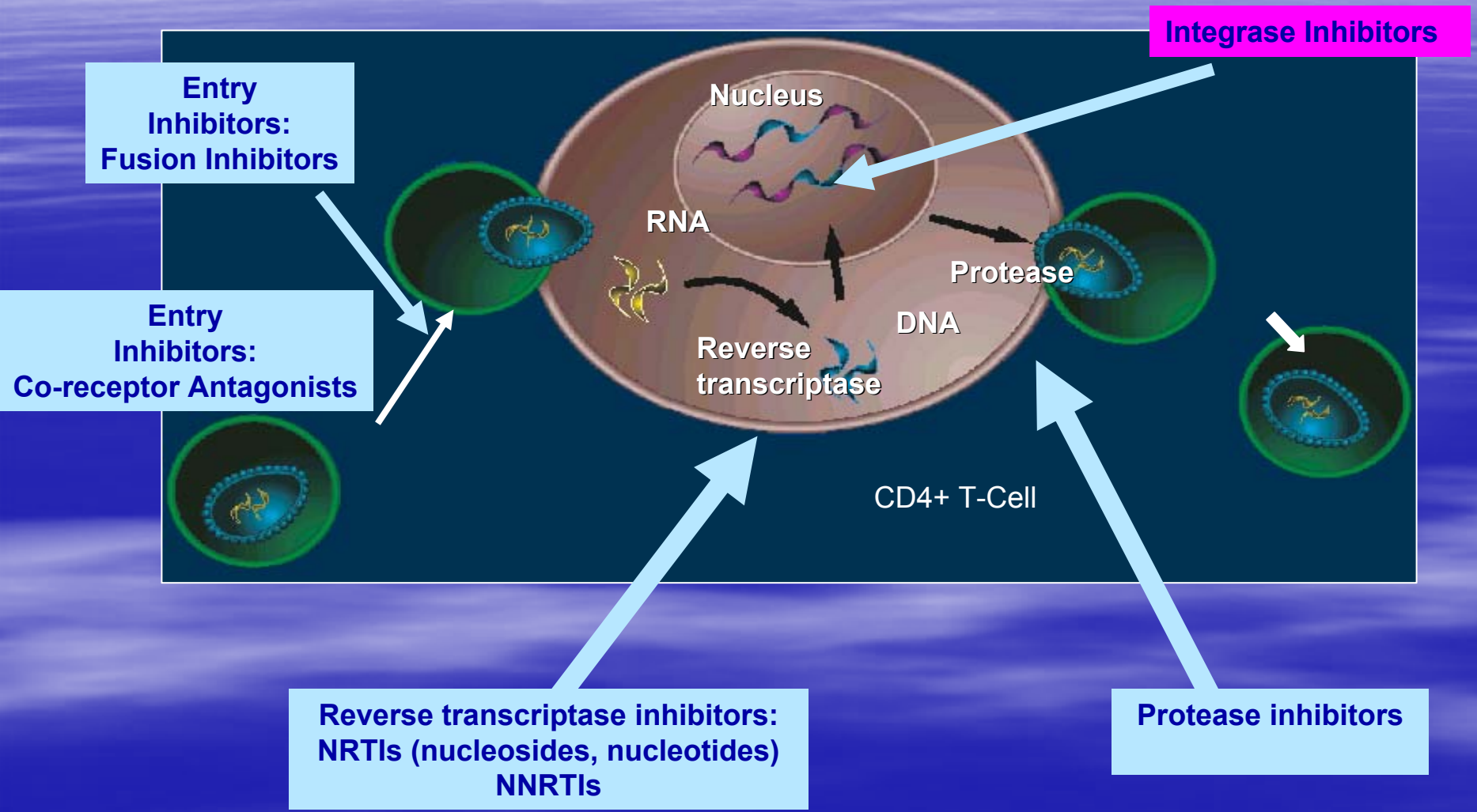
# Approved Antiretrovirals

**Between ’87 and ’94, 4 antiretrovials were launched.**

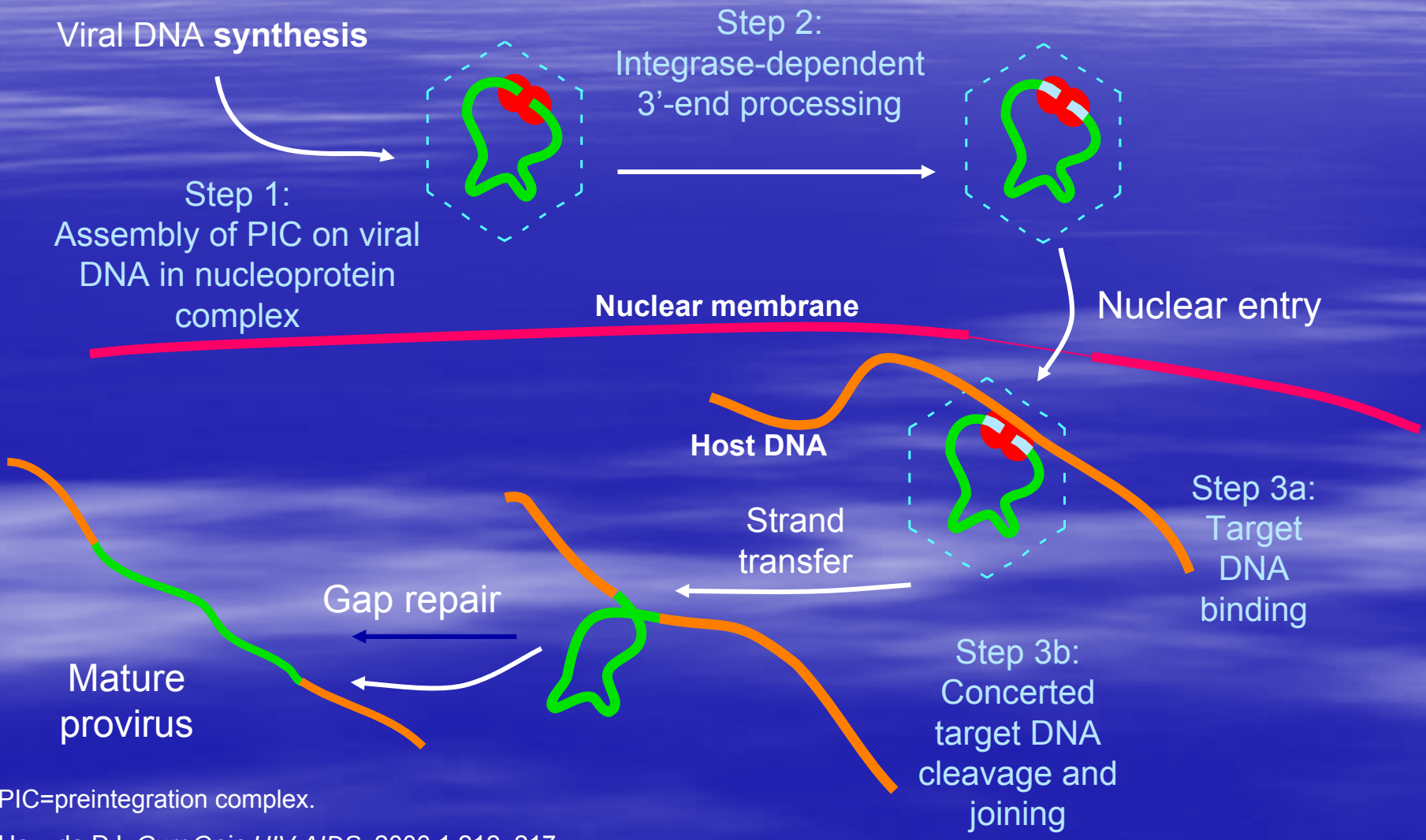
**Since ’95, *26 new products* have been introduced.**



# Targets of HIV Therapy



# Integration Requires Multiple Steps

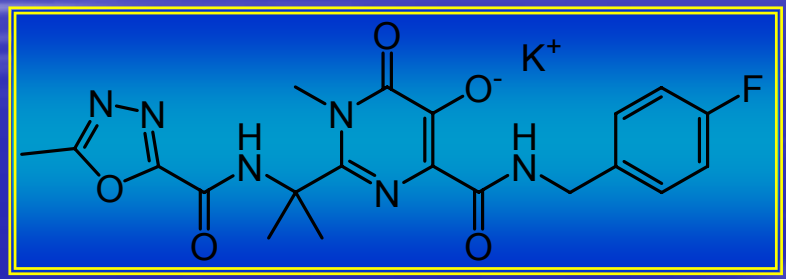



PIC=preintegration complex.

Hazuda DJ. *Curr Opin HIV AIDS*. 2006;1:212–217.

# Raltegravir: A Novel HIV-1 Integrase Inhibitor

- **A new mechanism of action**




- **Potent *in vitro* activity**
  - $IC_{95}$ = 33 nM ± 23 nM in 50% human serum
  - Active against:
    - multi-drug resistant HIV-1
    - CCR5 and CXCR4 HIV-1
  - HIV resistant to raltegravir remains sensitive to other ARTs
  - Synergistic *in vitro* with all ARTs tested

# Blocking Integrase in Treatment- Experienced Patients With a Novel Compound Against HIV: MERCK, MK-0518 (BENCHMRK)

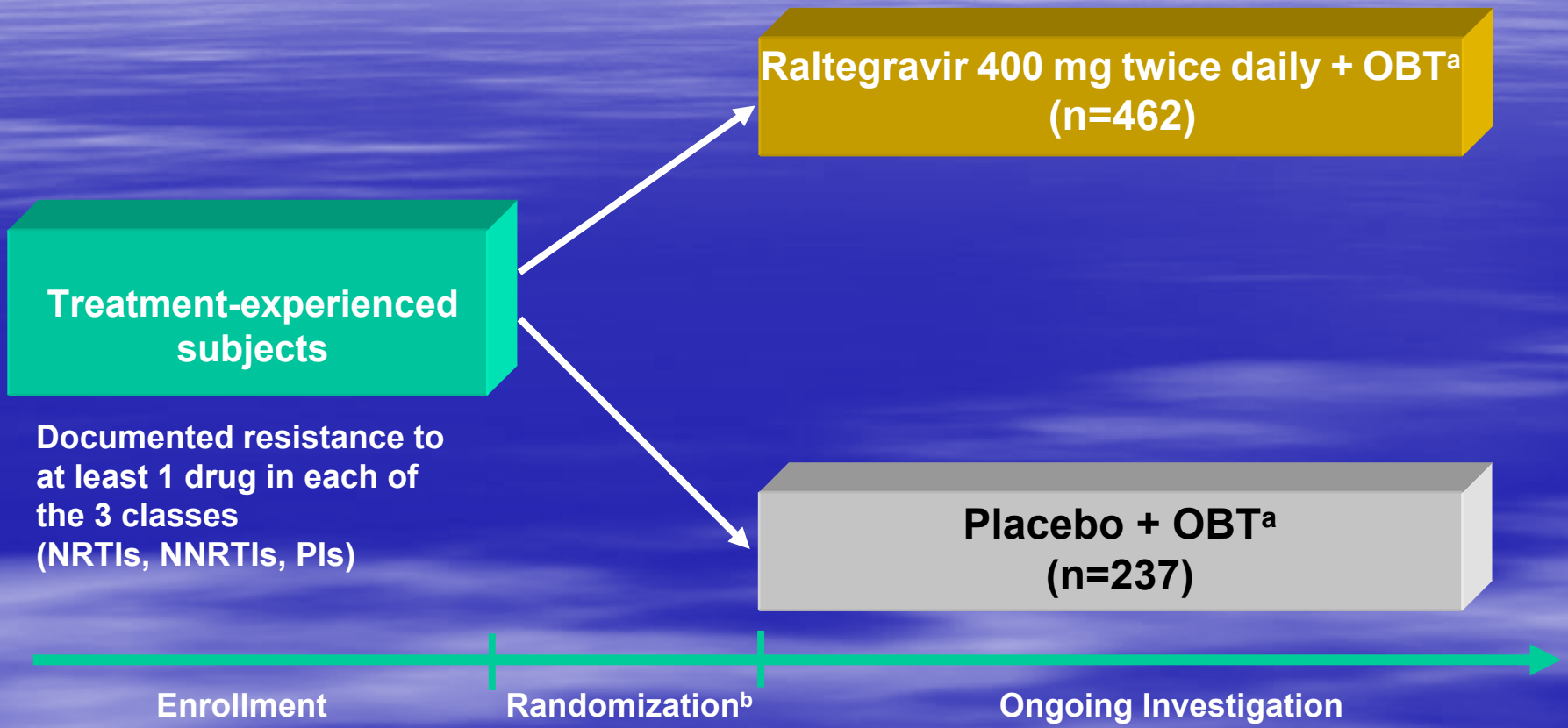
Phase III Studies of Raltegravir

BENCHMRK-1: Europe, Asia/Pacific, Peru

BENCHMRK-2: North and South America

# BENCHMRK-1 and -2

## Study Design




[a]Optimized background therapy (OBT) selected by investigator based on genotypic/phenotypic resistance testing and ART history. [b]Randomization was stratified by the degree of resistance to PI (1 PI vs >1 PI) and use of enfuvirtide in the OBT.

NRTI=nucleoside reverse transcriptase inhibitor; NNRTI=nonnucleoside reverse transcriptase inhibitor; PI=protease inhibitor

# BENCHMRK 1 and 2: Raltegravir in Patients With Triple-Class Resistance

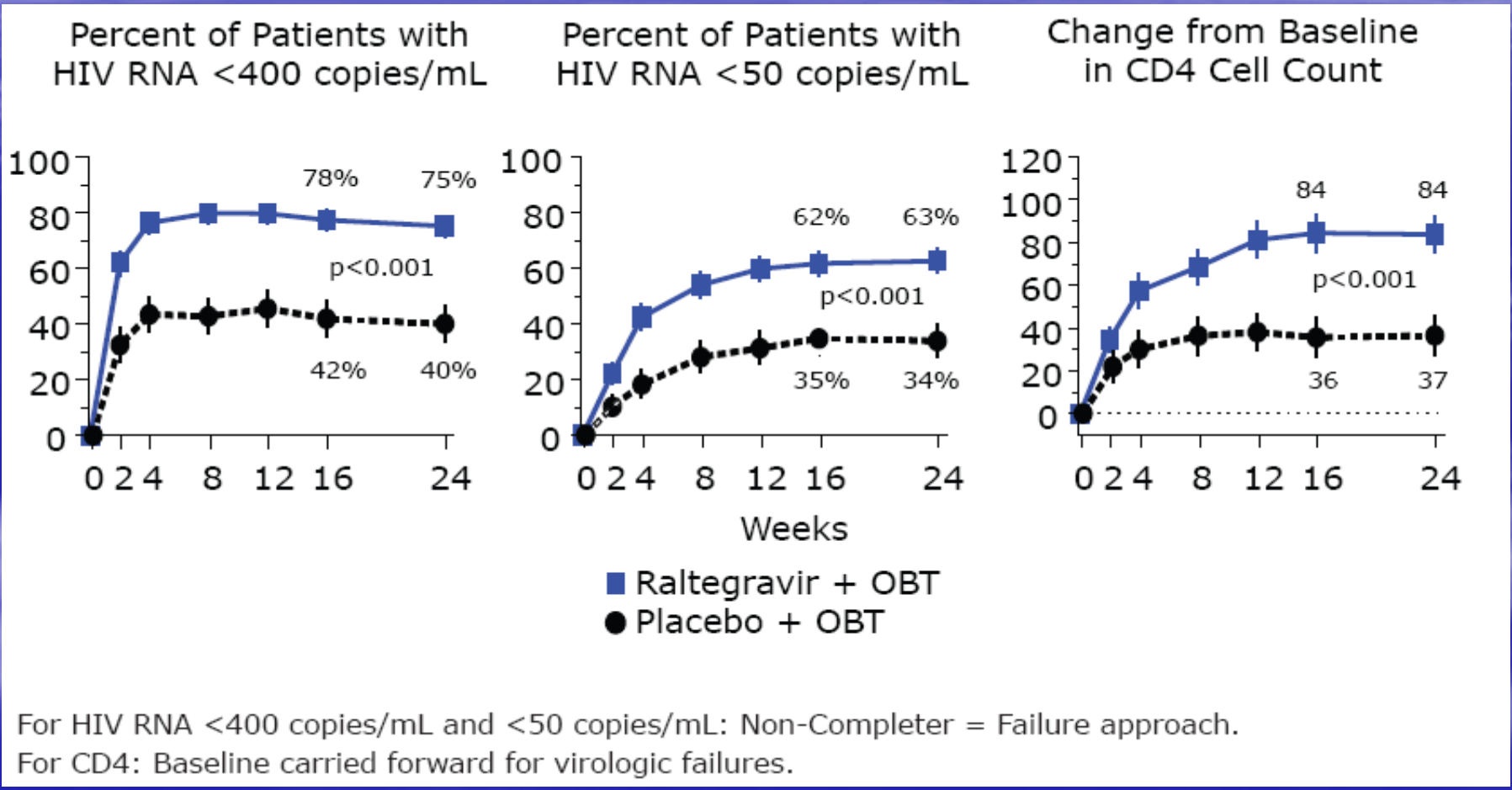
- Phase 3, 156-week trial
  - Treatment-experienced patients with triple-class resistance
  - Stratified by baseline HIV RNA, enfuvirtide and darunavir use in optimized background therapy (OBT), number of active agents in OBT

**BENCHMRK 1/2 Baseline Data**

| | Placebo (n=118/119) | Raltegravir (n=232/230) |
|---|---|---|
| Mean CD4 (cells/$mm^3$) | 105/132 | 140/102 |
| Mean HIV RNA ($log_{10}$ copies/mL) | 4.5/4.7 | 4.6/4.7 |
| AIDS (%) | 89/91 | 94/91 |
| OBT (%) | | |
| New enfuvirtide | 20/20 | 21/19 |
| New darunavir | 25/50 | 27/45 |

Cooper D, et al. 15th CROI. Boston, 2008. Abstract 788.
Steigbigel R, et al. 15th CROI. Boston, 2008. Abstract 789.

# BENCHMRK-1& -2 Combined Efficacy at Week 24

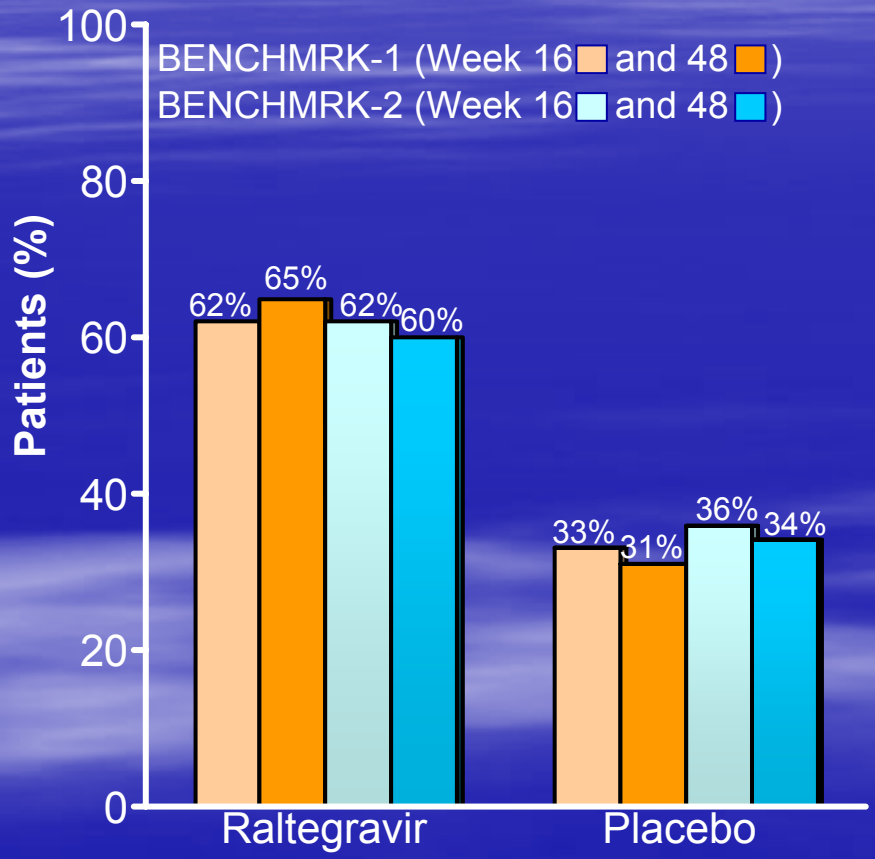



For HIV RNA <400 copies/mL and <50 copies/mL: Non-Completer = Failure approach.
For CD4: Baseline carried forward for virologic failures.

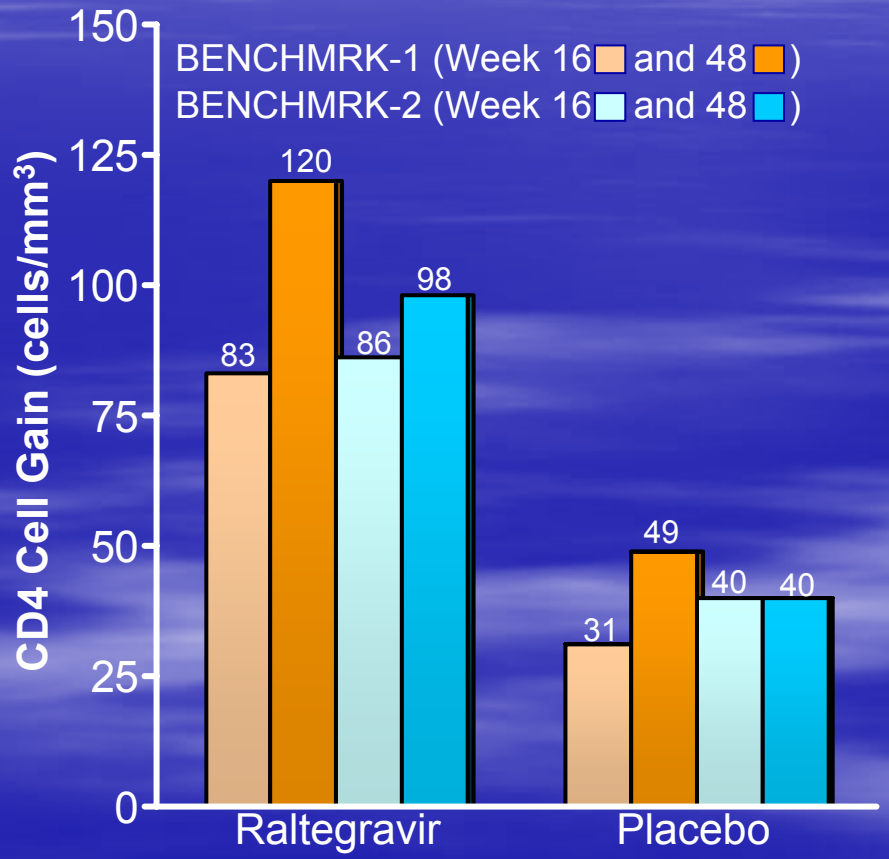
Kumar et al. 11th European AIDS Conference, Madrid, Spain, poster p7.2/06

# BENCHMRK 1 and 2: Virologic and Immunologic Outcomes at Week 48

## HIV RNA <50 Copies/mL




## CD4 Cell Gain

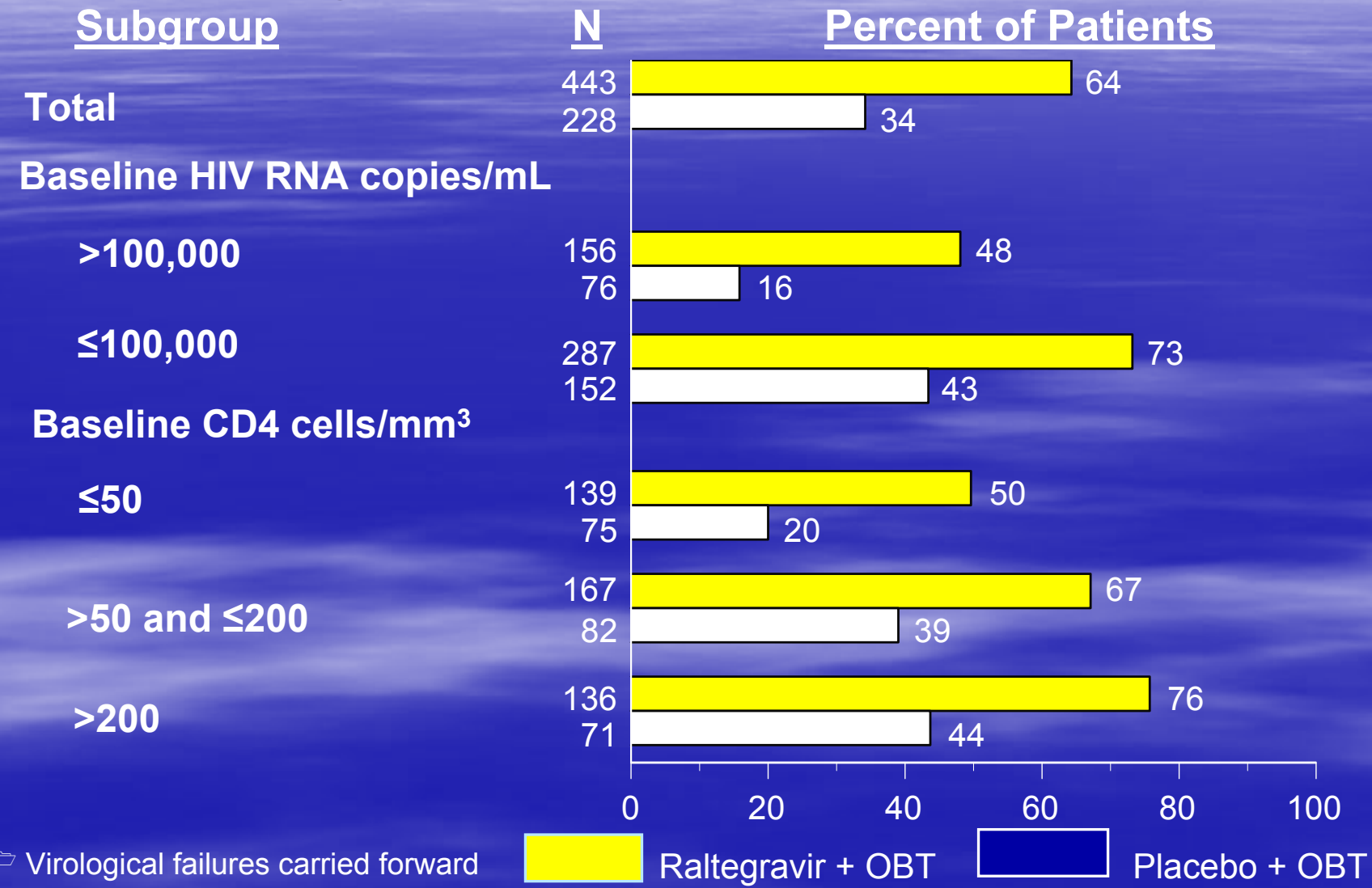



*P*<0.001 for raltegravir versus placebo at weeks 16 and 48 for HIV RNA <50 copies/mL and CD4 cell gain.


Cooper D, et al. 15th CROI. Boston, 2008. Abstract 788.
Steigbigel R, et al. 15th CROI. Boston, 2008. Abstract 789.

# BENCHMRK-1 & 2 Combined Efficacy

## Percent of Patients with HIV RNA <50 copies/mL at Week 48 by Baseline HIV RNA and CD4 Cell Count



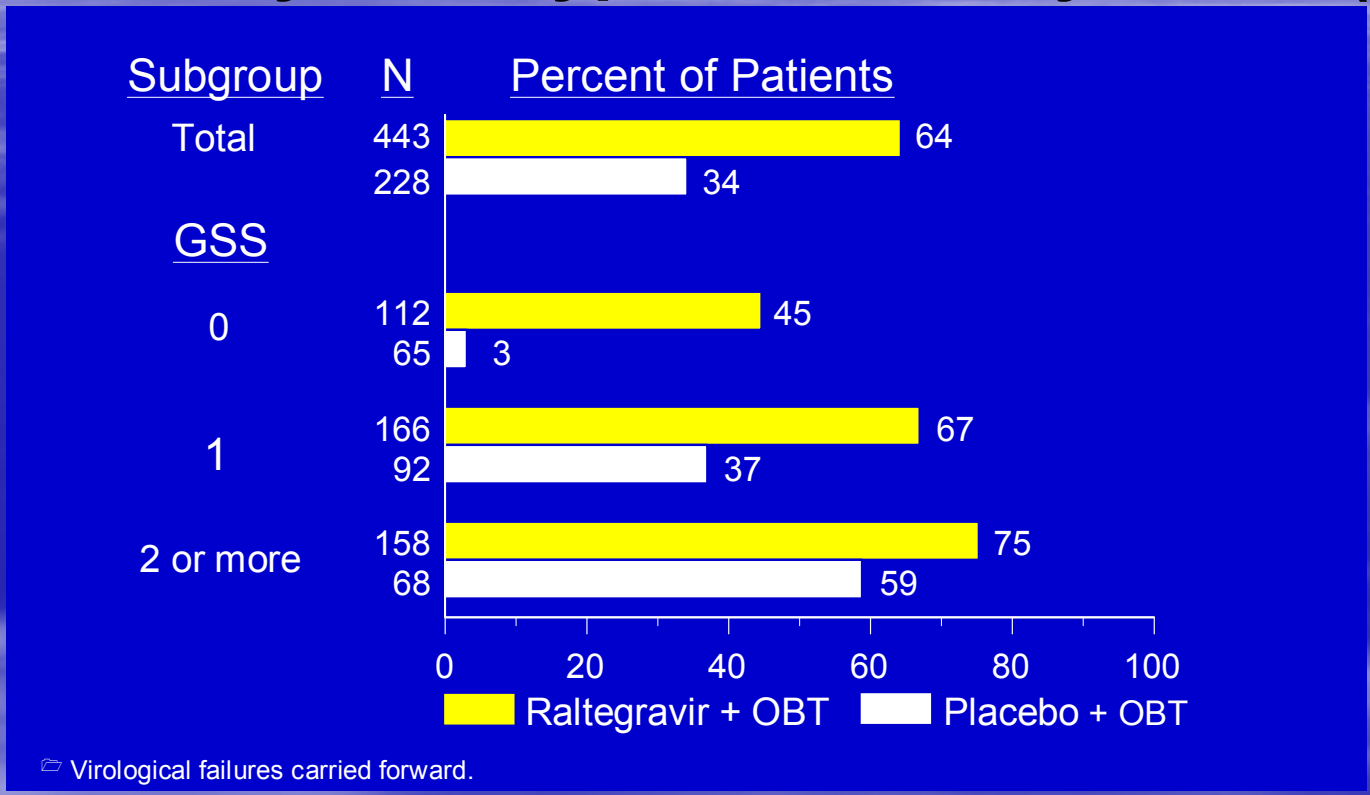

Virological failures carried forward


Cooper D, et al. 15th CROI. Boston, 2008. Abstract 788.
Steigbigel R, et al. 15th CROI. Boston, 2008. Abstract 789.

# Sensitivity Scores

- Genotypic sensitivity score (GSS)
  - Denotes the number of active drugs predicted by the genotype & included in the optimized background, in addition to the study drug
- Phenotypic sensitivity score (PSS)
  - Denotes the number of active drugs predicted by the phenotype & included in the optimized background, in addition to the study drug

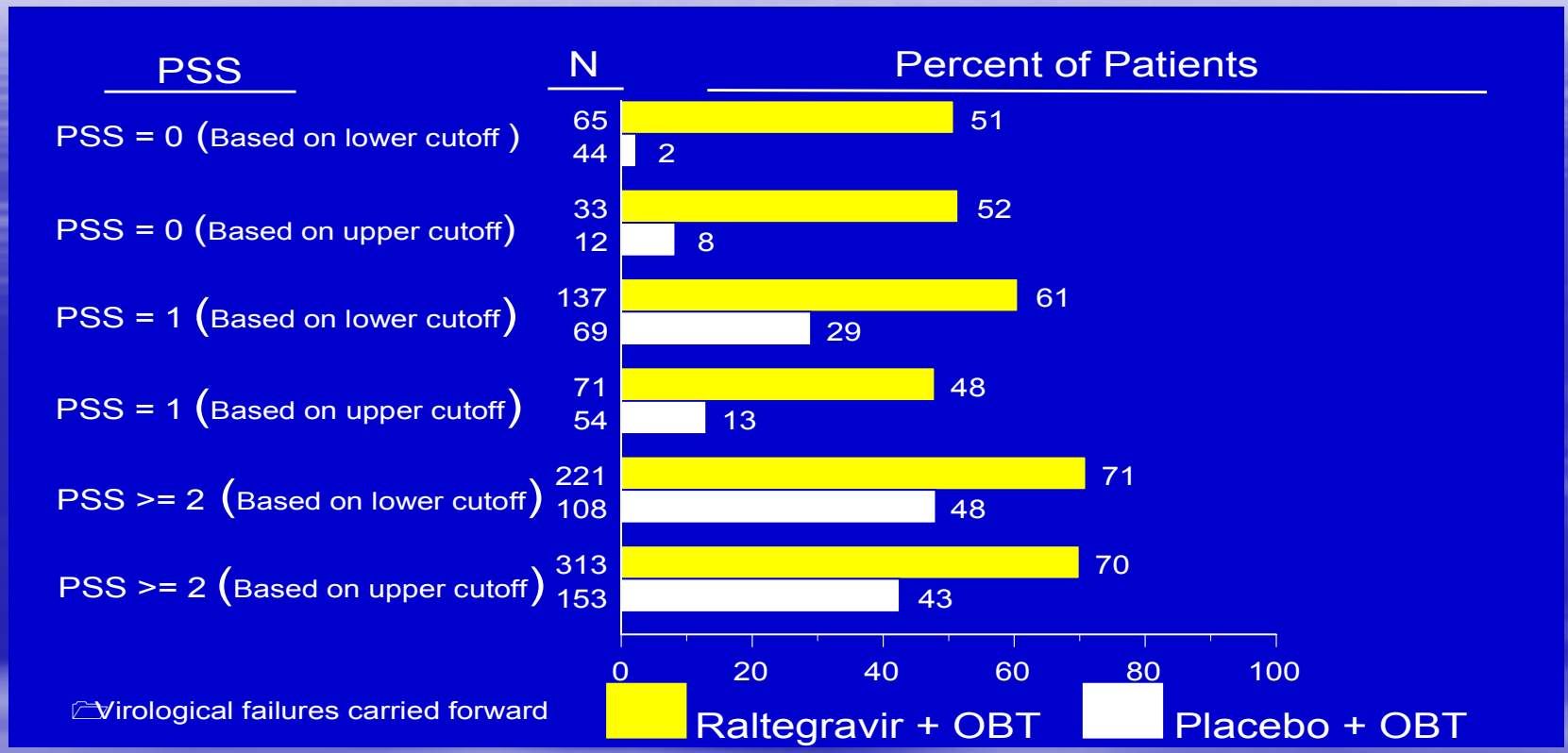
# BENCHMRK-1 & 2 Combined Efficacy† Percent of Patients With HIV RNA<50 copies/mL at Week 48 by Genotypic Sensitivity Score (GSS)




**For patients with GSS=1, 4 ART agents represented at least 80% of the active agents in OBT: darunavir (52%, 52% in raltegravir and placebo groups, respectively), enfuvirtide (8%, 16%), tenofovir (12%, 6%), and tipranavir (11%, 11%).**


Cooper D, et al. 15th CROI. Boston, 2008. Abstract 788.
Steigbigel R, et al. 15th CROI. Boston, 2008. Abstract 789.

# BENCHMRK-1 & 2 Combined Efficacy†
# Percent of Patients HIV RNA<50 copies/mL at Week 48 by PSS




**The analysis by PSS score has been reanalyzed using the upper cutoff to better account for the impact of partial ART activity.**

**Isolates with fold-change IC50 above the lower but below the upper cutoff are now reported as "partially sensitive". The upper cutoff was developed as the lower cutoff may underestimate partial ART activity in a regimen.**

**At the time the BENCHMRK studies were initiated, only the lower cutoff was reported. The efficacy by PSS has been reanalyzed using the upper cutoffs, where available, to better account for the impact of partial ART activity.**

**Conclusion: At all levels of PSS, the results using the upper and lower cutoffs are similar, confirming the contribution of raltegravir in the treatment regimen.**


Cooper D, et al. 15th CROI. Boston, 2008. Abstract 788.
Steigbigel R, et al. 15th CROI. Boston, 2008. Abstract 789.

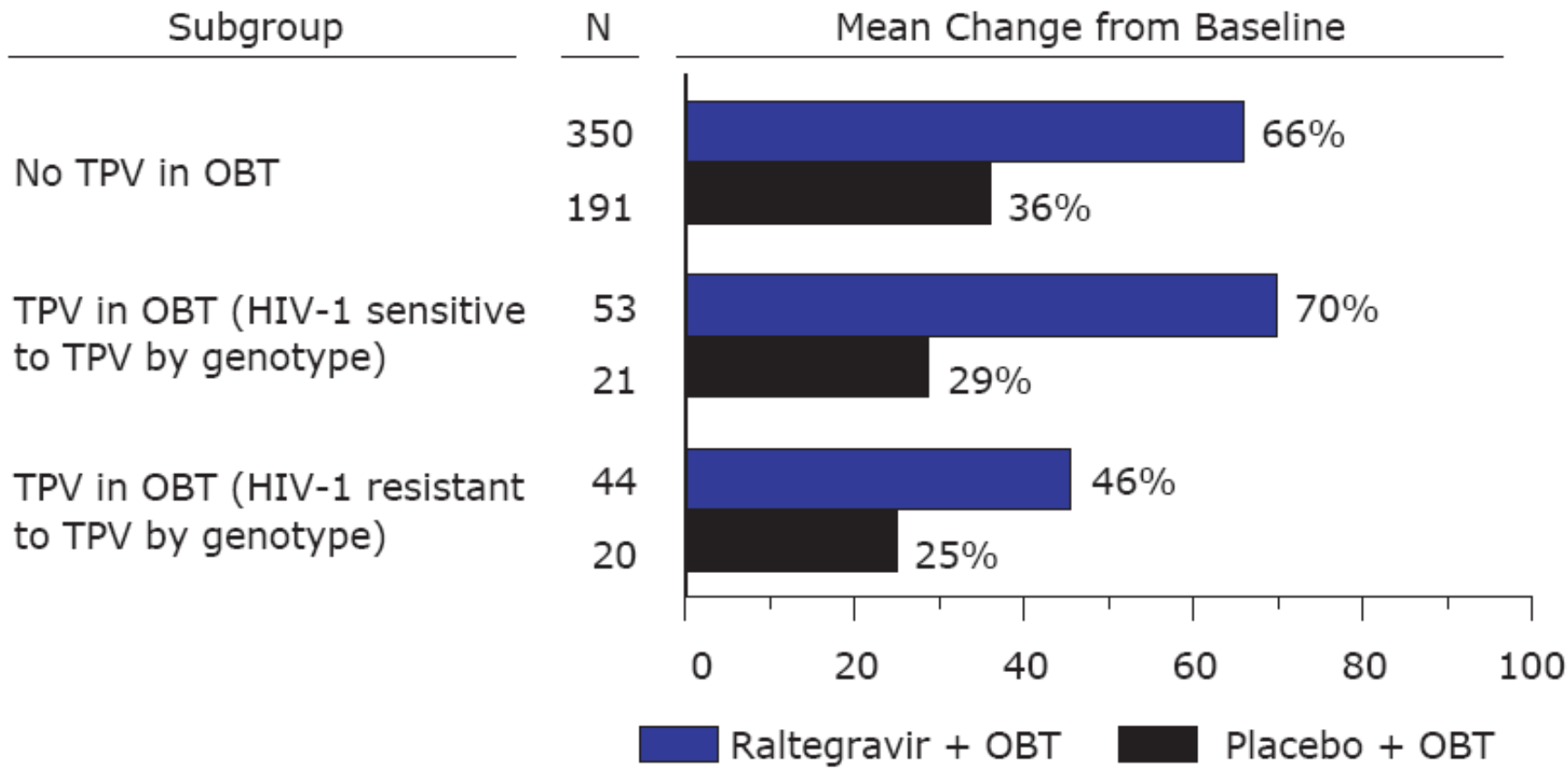
# BENCHMRK 1/2: Combined Virologic Subgroup Analyses at Wk 48

- Fewer virologic failures in the raltegravir + OBT arm compared with the OBT-alone arm
  - 14.6% versus 49.4%
- Raltegravir failure
  - Generally associated with 1 or 2 primary mutations (N155 or Q148) plus at least 1 other mutation

| | | HIV RNA <50 Copies/mL (%) | |
|---|---|---|---|
| | | Placebo | Raltegravir |
| Overall | | 34 | 64 |
| By ARTs in OBT | | | |
| Enfuvirtide | Darunavir | | |
| Yes | Yes | 68 | 89 |
| Yes | No | 57 | 80 |
| No | Yes | 47 | 69 |
| No | No | 20 | 60 |
| Baseline HIV RNA | | | |
| ≤100K | | 43 | 73 |
| >100K | | 16 | 48 |

Cooper D, et al. 15th CROI. Boston, 2008. Abstract 788.
Steigbigel R, et al. 15th CROI. Boston, 2008. Abstract 789.

# Percentage of patients with HIV RNA < 50 copies/mL at Week 24 by Tipranavir (TPV) Use in OBT




†Virological failures carried forward.

Kumar et al. 11th European AIDS Conference, Madrid, Spain, poster p7.2/06

# Most Commonly Reported (>10%) Adverse Reactions of All Intensities[a] and Regardless of Causality Occurring in Treatment-Experienced Adult Subjects

| System Organ Class, Adverse Reaction | Randomized Studies: BENCHMRK-1 and -2; Protocol 005 | |
|---|---|---|
| | Raltegravir 400 mg Twice Daily + OBT (n=507)[b] % | Placebo + OBT (n=282)[b] % |
| **Gastrointestinal disorders** | | |
| Diarrhea | 16.6% | 19.5% |
| Nausea | 9.9% | 14.2% |
| **Nervous system disorders** | | |
| Headache | 9.7% | 11.7% |
| **General disorders and administration site conditions** | | |
| Pyrexia | 4.9% | 10.3% |

[a]Intensities are defined as follows: Mild (awareness of sign or symptom, but easily tolerated); Moderate (discomfort enough to cause interference with usual activity); Severe (incapacitating with inability to work or do usual activity).

[b]n=total number of subjects per treatment group.

# Drug-Related[a] Adverse Reactions of Moderate to Severe Intensity[b] Occurring in ≥2% of Treatment-Experienced Adult Subjects

| System Organ Class, Adverse Reaction | Randomized Studies: BENCHMRK-1 and -2; Protocol 005 | |
|---|---|---|
| | Raltegravir 400 mg Twice Daily + OBT (n=507)[c] % | Placebo + OBT (n=282)[c] % |
| **Gastrointestinal disorders** | | |
| Diarrhea | 3.7% | 4.6% |
| Nausea | 2.2% | 3.2% |
| **Nervous system disorders** | | |
| Headache | 2.4% | 1.4% |

[a]Includes adverse reactions at least possibly, probably, or very likely related to the drug.
[b]Intensities are defined as follows: Moderate (discomfort enough to cause interference with usual activity); Severe (incapacitating with inability to work or do usual activity).
[c]n=total number of subjects per treatment group.

# Selected Grade 2 to 4 Laboratory Abnormalities Reported in Treatment-Experienced Subjects

| | | Randomized Studies: BENCHMRK-1 and -2; Protocol 005 | |
|---|---|---|---|
| Laboratory Parameter Preferred Term (Unit) | Limit | Raltegravir 400 mg twice daily + OBT (n=507) | Placebo + OBT (n=282) |
| **Hematology** | | | |
| **Absolute neutrophil count ($10^3$/µL)** | | | |
| Grade 2 | 0.75–0.999 | 3.7% | 7.4% |
| Grade 3 | 0.50–0.749 | 2.4% | 2.5% |
| Grade 4 | <0.50 | 1.0% | 1.1% |
| **Hemoglobin (g/dL)** | | | |
| Grade 2 | 7.5–8.4 | 1.0% | 2.8% |
| Grade 3 | 6.5–7.4 | 1.0% | 0.4% |
| Grade 4 | <6.5 | 0.0% | 0.0% |
| **Platelet count ($10^3$/µL)** | | | |
| Grade 2 | 50–99.999 | 3.7% | 5.7% |
| Grade 3 | 25–49.999 | 0.4% | 0.4% |
| Grade 4 | <25 | 0.8% | 0.4% |

# Selected Grade 2 to 4 Blood Chemistry Laboratory Abnormalities Reported in Treatment-Experienced Patients (*cont*)

| | | Randomized Studies: BENCHMRK-1 and -2; Protocol 005 | |
|---|---|---|---|
| **Laboratory Parameter Preferred Term (Unit)** | **Limit** | **Raltegravir 400 mg twice daily + OBT (n=507)** | **Placebo + OBT (n=282)** |
| **Blood Chemistry** | | | |
| **Fasting (nonrandom) serum glucose test (mg/dL)** | | | |
| **Grade 2** | 126–250 | 9.3% | 6.8% |
| **Grade 3** | 251–500 | 1.4% | 1.4% |
| **Grade 4** | >500 | 0.0% | 0.0% |
| **Total serum bilirubin** | | | |
| **Grade 2** | 1.6–2.5 x ULN | 5.3% | 6.7% |
| **Grade 3** | 2.6–5.0 x ULN | 3.2% | 2.5% |
| **Grade 4** | >5.0 x ULN | 0.8% | 0.0% |
| **Serum aspartate aminotransferase** | | | |
| **Grade 2** | 2.6–5.0 x ULN | 9.1% | 5.7% |
| **Grade 3** | 5.1–10.0 x ULN | 2.2% | 2.1% |
| **Grade 4** | >10.0 x ULN | 0.4% | 0.7% |

ULN=upper limit of normal range.

# Selected Grade 2 to 4 Laboratory Abnormalities Reported in Treatment-Experienced Subjects (*cont*)

| | | Randomized Studies: BENCHMRK-1 and -2; Protocol 005 | |
|---|---|---|---|
| **Laboratory Parameter Preferred Term (Unit)** | **Limit** | **Raltegravir 400 mg twice daily + OBT (n=507)** | **Placebo + OBT (n=282)** |
| **Serum alanine aminotransferase** | | | |
| **Grade 2** | 2.6–5.0 x ULN | 6.9% | 7.8% |
| **Grade 3** | 5.1–10.0 x ULN | 3.0% | 1.4% |
| **Grade 4** | >10.0 x ULN | 0.6% | 1.1% |
| **Serum alkaline phosphatase** | | | |
| **Grade 2** | 2.6–5.0 x ULN | 2.0% | 0.4% |
| **Grade 3** | 5.1–10.0 x ULN | 0.4% | 1.1% |
| **Grade 4** | >10.0 x ULN | 0.4% | 0.4% |
| **Serum pancreatic amylase test** | | | |
| **Grade 2** | 1.6–2.0 x ULN | 1.4% | 0.7% |
| **Grade 3** | 2.1–5.0 x ULN | 3.6% | 2.1% |
| **Grade 4** | >5.0 x ULN | 0.2% | 0.0% |

ULN=upper limit of normal range.

# Selected Grade 2 to 4 Laboratory Abnormalities Reported in Treatment-Experienced Subjects (*cont*)

| | | Randomized Studies: BENCHMRK-1 and -2; Protocol 005 | |
|---|---|---|---|
| **Laboratory Parameter Preferred Term (Unit)** | **Limit** | **Raltegravir 400 mg twice daily + OBT (n=507)** | **Placebo + OBT (n=282)** |
| **Serum lipase test** | | | |
| **Grade 2** | 1.6–3.0 x ULN | 3.4% | 1.8% |
| **Grade 3** | 3.1–5.0 x ULN | 0.6% | 0.4% |
| **Grade 4** | >5.0 x ULN | 0.2% | 0.0% |
| **Serum creatine kinase** | | | |
| **Grade 2** | 6.0–9.9 x ULN | 2.2% | 1.4% |
| **Grade 3** | 10.0–19.9 x ULN | 2.4% | 1.8% |
| **Grade 4** | ≥20.0 x ULN | 2.2% | 0.7% |

ULN=upper limit of normal range.

# Protocol 005:
# Raltegravir in ARV-Experienced Patients

**Phase II study**

**Multicenter, double-blind, randomized, 2 part study**

Part I: 24 week comparison of RAL (200, 400, 600 mg BID) to placebo (both with OBT)

Part II: After week 24 all patients (including placebo) open-label RAL 400 mg BID

**Enrolled subjects with HIV RNA >5,000 c/mL and resistance to 3 ARV classes**

**RAL (200, 400, 600 mg BID) + OBT (n=133)**

**Placebo + OBT (n=45)**

24 Weeks

**RAL (400 mg BID) + OBT**

Grinsztein B, et al. 47th ICAAC; Chicago, IL; September 17-20, 2007; Abst. H-713.

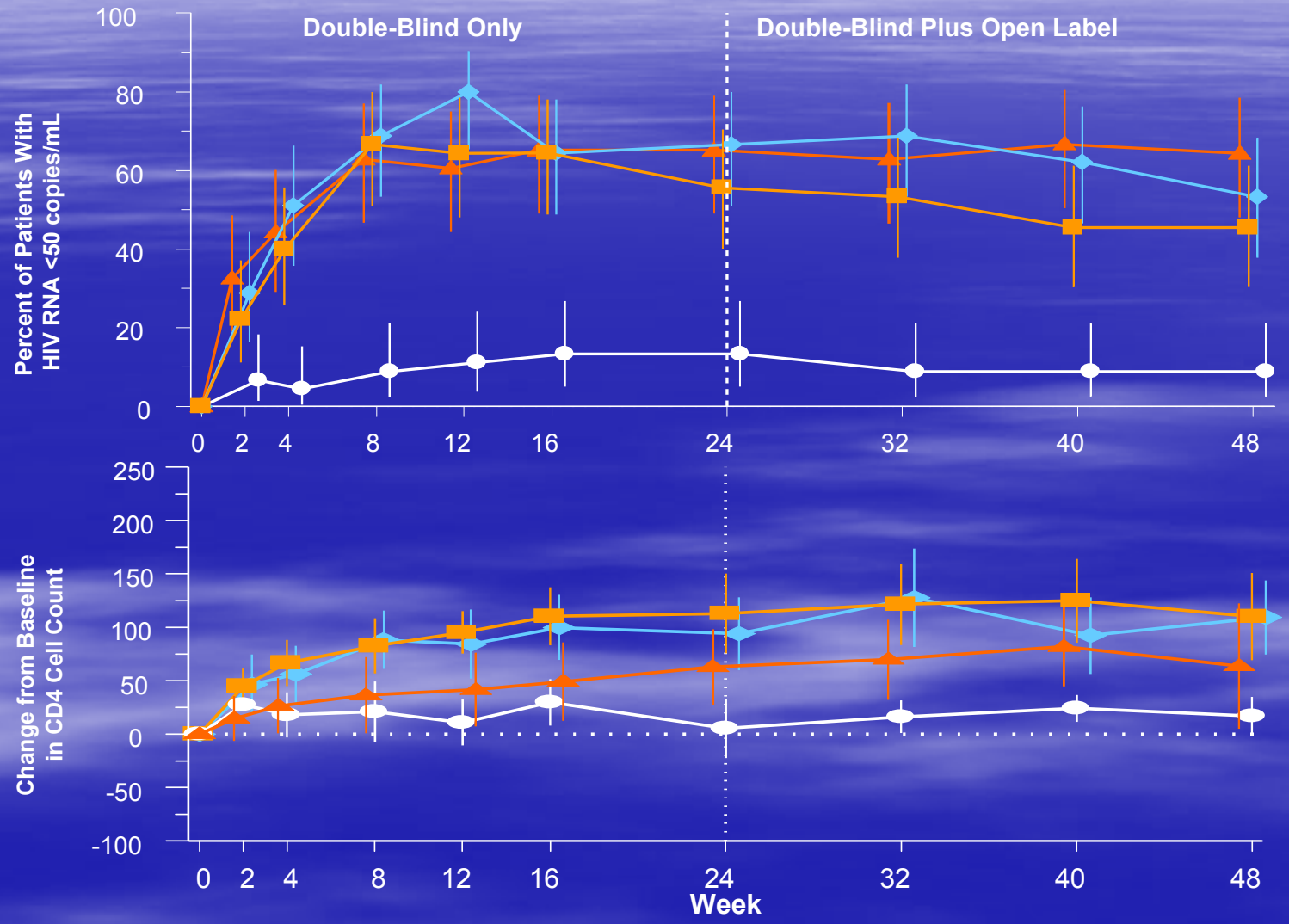
# Protocol 005: Raltegravir Baseline Data

| | Raltegravir | | | Placebo |
|---|---|---|---|---|
| | 200 mg N=43 | 400 mg N=45 | 600 mg N=45 | N=45 |
| Median Age (yrs) | 43 | 43 | 44 | 43 |
| Male | 84% | 89% | 91% | 89% |
| Mean HIV RNA ($log_{10}$copies/mL) | 4.6 | 4.8 | 4.7 | 4.7 |
| Mean CD4 Count (/$mm^3$) | 245 | 221 | 220 | 274 |
| Median Years of Prior ART | 9 | 10 | 9 | 9 |
| OBT: Median # of ARTs | 4 | 4 | 4 | 4 |
| GSS: 0 to all ARTs | 27 (63%) | 38 (84%) | 35 (78%) | 28 (62%) |
| PSS§: 0 to all ARTs | 20 (47%) | 26 (58%) | 22 (49%) | 18 (40%) |
| PSS§: 0 to PI | 42 (98%) | 42 (93%) | 40 (89%) | 39 (87%) |
| # pts with enfuvirtide as new OBT | 12 (28%) | 9 (20%) | 11 (24%) | 10 (22%) |

§PSS: phenotypic susceptibility score on Monogram assay.

Grinsztein B, et al. 47th ICAAC; Chicago, IL; September 17-20, 2007; Abst. H-713.

# Responses at Week 48




Grinsztein B, et al. 47th ICAAC; Chicago, IL; September 17-20, 2007; Abst. H-713.

# Virologic Failure and Resistance

- 29% (n=38/133) had virologic failure on raltegravir during double-blind period
- Factors associated with rebound / resistance:
  - 1) PSS / GSS: 68% of patients with virologic failure had GSS of 0
  - 2) Baseline Viral load > 5 log
- Genotypic resistance data
  - N=35/38 had mutations conferring raltegravir resistance
  - N=34/35 with one of two genetic pathways: N155 or Q148
  - N=31/35 had ≥2 mutations
- No relationship of resistance to dose and/or drug levels

Grinsztein B, et al. 47th ICAAC; Chicago, IL; September 17-20, 2007; Abst. H-713.

# ISENTRESS™ (raltegravir tablets) Dosage and Administration/Contraindications

- Dosage and Administration
  - For the treatment of patients with HIV-1 infection, the dosage of ISENTRESS is 400 mg administered orally, twice daily, with or without food.

- Contraindications
  - None

Isentress package insert 2007

# Drug-Drug Interactions With Raltegravir Use

- Raltegravir is eliminated mainly by metabolism via a uridine diphosphate glucuronsyltransferase UGT1A1-mediated glucuronidation pathway
- Coadministration of raltegravir with drugs that are strong inducers of UGT1A1 may reduce raltegravir plasma concentrations
  - Caution should be used when coadministering raltegravir with rifampin or other strong inducers of UGT1A1
  - The impact of other strong inducers of drug metabolizing enzymes, such as phenytoin and phenobarbital, on UGT1A1 is unknown
- Raltegravir is not a substrate of cytochrome P450 (CYP) enzymes and does not inhibit or induce CYP3A4
  - Raltegravir has a low propensity to alter the pharmacokinetics of agents metabolized by CYP3A4
- Raltegravir is not an inhibitor of UGT1A1, UGT2B7, or P-glycoprotein-mediated transport

Isentress package insert 2007

# ISENTRESS™ (raltegravir tablets)
# Use in Specific Populations

- Patients With Hepatic Impairment
  - There were no clinically important pharmacokinetic differences between subjects with moderate hepatic impairment and healthy subjects.
  - No dose adjustment is necessary for patients with mild to moderate hepatic impairment.
  - The effect of severe hepatic impairment on the pharmacokinetics of raltegravir has not been studied.
- Patients With Renal Impairment
  - There were no clinically important pharmacokinetic differences between subjects with severe renal impairment and healthy subjects.
  - No dosage adjustment is necessary.
  - Because the extent to which ISENTRESS may be dialyzable is unknown, dosing before a dialysis session should be avoided.

Isentress package insert 2007

# ISENTRESS™ (raltegravir tablets) Adverse Reactions

- Adverse Reactions
  - The most common adverse reactions (>10%) of all intensities, reported in subjects in either the ISENTRESS or the placebo treatment group, regardless of causality were: nausea, headache, diarrhea, and pyrexia.
  - Creatine kinase elevations were observed in subjects who received ISENTRESS. Myopathy and rhabdomyolysis were reported; however, the relationship of ISENTRESS to these events is not known. Use with caution in patients at increased risk of myopathy or rhabdomyolysis, such as patients receiving concomitant medications known to cause these conditions.
  - **To report SUSPECTED ADVERSE REACTIONS, contact Merck & Co., Inc. at 1-877-888-4231 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.**

Isentress package insert 2007

# Cancer Events: Relative Risk and Associated 95% CI BENCHMRK-1 & 2 Combined

| | Raltegravir Group | | Control Group | | Relative Risk (95% CI) |
|---|---|---|---|---|---|
| | N | Cases/PYR† (Rate‡) | N | Cases/PYR† (Rate‡) | |
| Total | 462 | 16/460 (3.5) | 237 | 4/178 (2.3) | 1.5 (0.5, 6.3) |
| BENCHMRK-1 | 232 | 8/237 (3.4) | 118 | 1/87 (1.2) | |
| BENCHMRK-2 | 230 | 8/224 (3.6) | 119 | 3/91 (3.3) | |

† Patients-years at risk.
‡ Per 100 person-years (PYR).

For a comprehensive assessment of risk, a similar analysis was done including all double blind data from Phase II and Phase III studies (Protocols 004, 005, and BENCHMRK-1 and 2), which provides a malignancy rate of 2.2 /100PYR for raltegravir and 1.8 /100 PYR for the comparator group, resulting in a relative risk (95% CI) of 1.2 (0.4, 4.1).

Cooper D, et al. 15th CROI. Boston, 2008. Abstract 788.
Steigbigel R, et al. 15th CROI. Boston, 2008. Abstract 789.

# Serious Events
# Regardless of Drug Relationship

- Cancers were reported in treatment-experienced subjects who initiated raltegravir with OBT
  - Several were recurrent

- Types and rates of specific cancers were those expected in a highly immunodeficient population
  - Many had CD4 counts below 50 cells/$mm^3$ and most had prior AIDS diagnoses
  - Cancers included Kaposi's sarcoma, lymphoma, squamous cell carcinoma, hepatocellular carcinoma, and anal cancer

- Most subjects had other risk factors for cancer including tobacco use, papillomavirus, and active hepatitis B virus infection

- It is unknown if these cancer diagnoses were related to raltegravir use

Isentress package insert 2007

# Raltegravir Resistance
## In Vitro and Clinical Trials

- Mutations observed in the HIV-1 integrase coding sequence that contributed to raltegravir resistance generally involved 1 of 2 genetic pathways
  - An amino acid substitution at either Q148 (changed to H, K, or R)

    Or

  - An amino acid substitution at N155 (changed to H)
  - Plus one or more additional substitutions (ie, L74M/R, E92Q, T97A, E138A/K, G140A/S, V151I, G163R, H183P, Y226/D/F/H, S230R, and D232N)
  - Substitution at Y143C/H/R is another pathway to raltegravir resistance

# ISENTRESS™ (raltegravir tablets)
# Use in Specific Populations

- Pregnancy
  - Pregnancy Category C
  - ISENTRESS should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. There are no adequate and well-controlled studies in pregnant women. In addition, there have been no pharmacokinetic studies conducted in pregnant patients.
  - Antiretroviral Pregnancy Registry
  - To monitor maternal-fetal outcomes of pregnant patients exposed to ISENTRESS, an Antiretroviral Pregnancy Registry has been established. Physicians are encouraged to register patients by calling 1-800-258-4263.

Isentress package insert 2007

# Reduction in Proviral RNA

- "More pronounced effect of integrase inhibitor raltegravir on proviral DNA reduction than other antiretroviral drugs in patients achieving undetectable viremia."

  – Arponen S et al. Madrid, Spain.
    - 15th CROI, Boston; Feb. 2008: abstract 796.

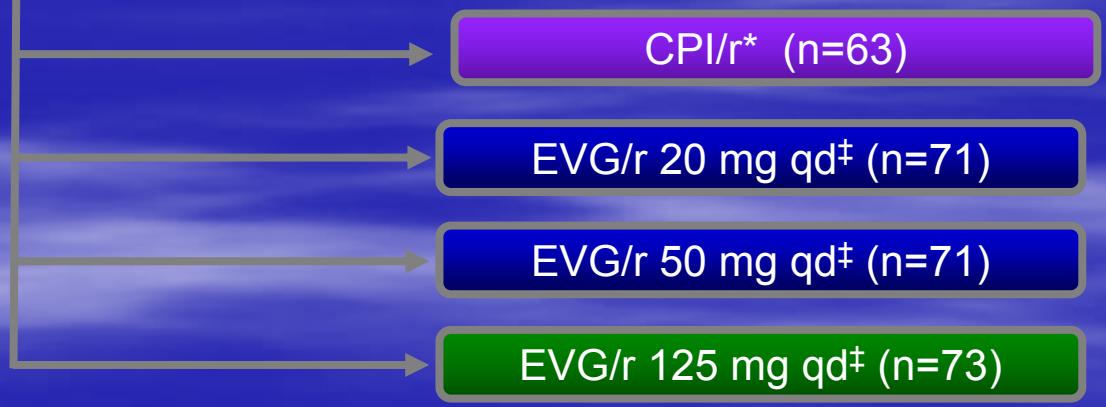
# Enfuvirtide to Raltegravir Switch

- "Outcomes of patients switched from enfuvirtide to raltegravir within a virologically suppressive regimen."
  - 34/35 patients switched from enfuvirtide to raltegravir maintained viral load (VL) < 50 c/mL
    - 1 patient had VL of 60 copies/mL at 5 months
  - Median follow-up of 7 months
    - Harris M et al. Vancouver, Canada
      - 15th CROI, Boston; Feb. 2008: abstract 799.

# Elvitegravir: Phase 2 Study

278 patients
HIV RNA ≥1000 copies/mL
Any CD4 cell count
≥1 protease resistance mutation

OBT = NRTIs +/- ENF
NNRTIs not allowed in OBT
Stratified by ENF use in OBT




*CPI/r included 49% darunavir, 27% tipranavir
‡100mg QD of RTV with all EVG doses

Zolopa A, et al. 47th ICAAC; Chicago, IL; September 17-20, 2007; Abst. H-714.

# Baseline Characteristics

| Baseline Parameters | CPI/r n=63 | EVG/r 125 mg n=73 |
|---|---|---|
| Mean HIV-1 RNA, $log_{10}$c/mL | 4.54 | 4.71 |
| Mean CD4 cells/$mm^3$ | 158 | 157 |
| Genotypic Sensitivity Score (GSS) =0 for all NRTIs in OBT | 32 (51%) | 35 (48%) |
| Median # NRTI Resistance Mutations | 5 | 5 |
| Median # Thymidine Analog Mutations | 3 | 3 |
| Median # PI Resistance Mutations | 11 | 11 |
| First Use of ENF | 12 (19%) | 19 (26%) |
| Median # ARVs in OBT including ENF | 3 | 3 |

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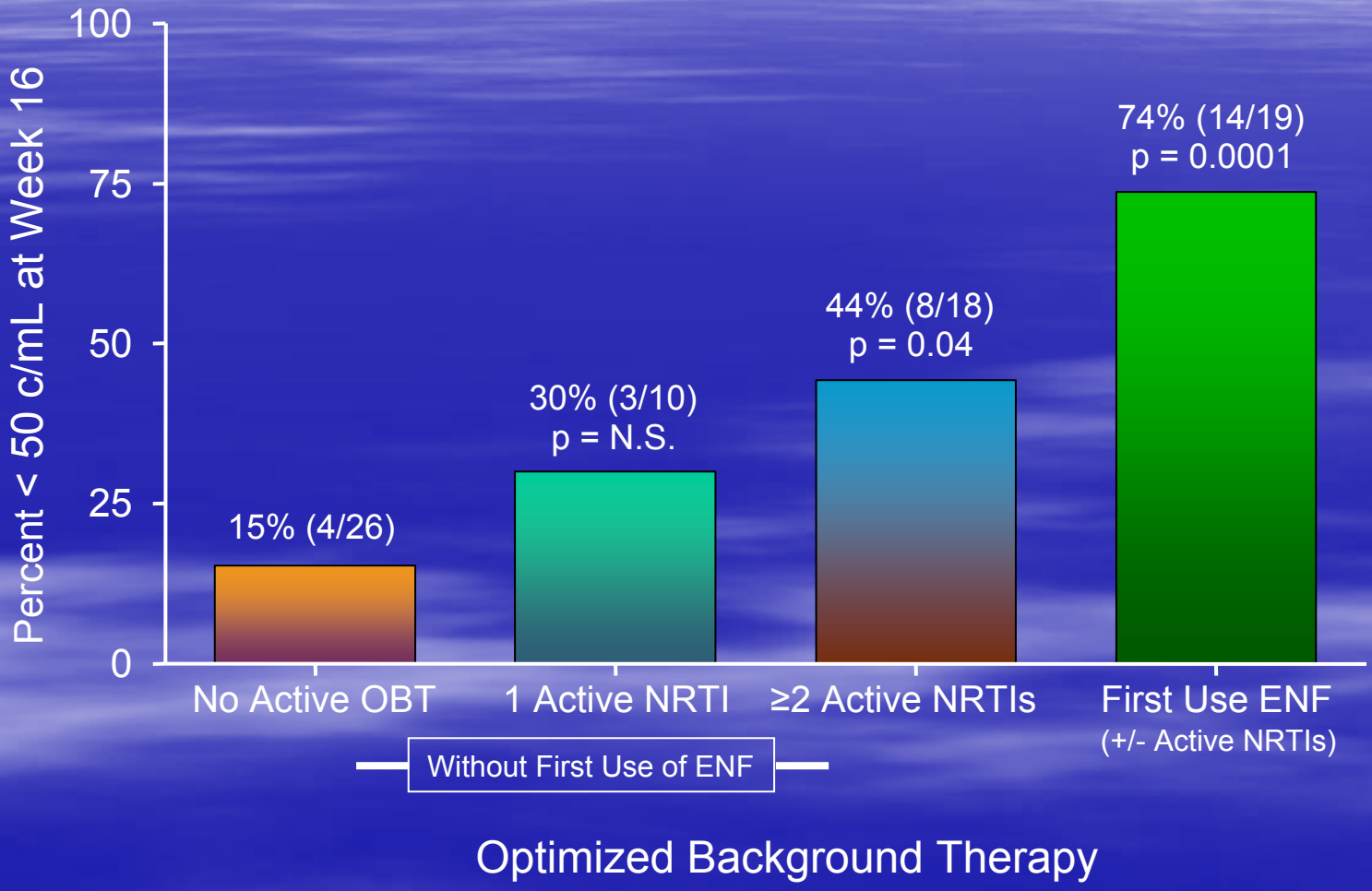
# EVG/r (125/100 mg) Virologic Responses: Effect of OBT




ITT, missing = failure p-values calculated by Fisher's Exact Test vs. No Active OBT

Zolopa A, et al. 47th ICAAC; Chicago, IL; September 17-20, 2007; Abst. H-714.

# Conclusions

- New drug classes will help our treatment-experienced patients
  - A new era in HIV therapy
  - Role in naïve patients currently being studied
- Integrase inhibitor, raltegravir, appears potent, with few drug-drug interaction concerns
- Need at least 2 active agents in any new regimen

## ¿Which of the following statements about raltegravir is false?

a) Raltegravir is metabolized by cytochrome P450.
b) At 48 weeks of follow-up of raltegravir in treatment-experienced patients, there has been no increased risk of malignancies seen compared to placebo-optimized background treated patients.
c) Raltegravir has a low drug interaction profile.
d) The integrase inhibitor, raltegravir, works against the integrase enzyme by inhibiting strand transfer.
e) Creatine kinase elevations (CK) have been seen in some patients treated with raltegravir.
f) I'm sorry, I did not learn.