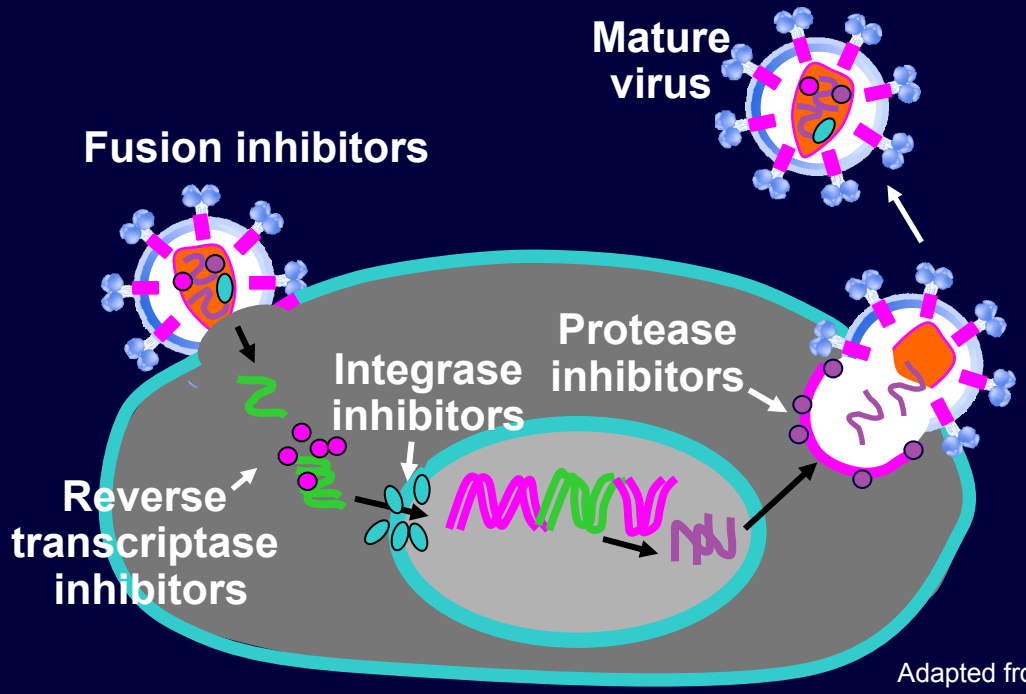
Agenda

- Robert A. Fromtling, PhD
  - Introduction
- Bach-Yen Nguyen, MD
  - Raltegravir Background
  - Clinical Development Program Overview
  - Clinical Trials Results
    - Efficacy
    - Resistance
    - Safety
- Robin Isaacs, MD
  - Drug-Drug Interactions
  - Risk Management Plan
  - Conclusions

Current Antiretroviral Armamentarium



Adapted from clinicaloptions.com/hiv.

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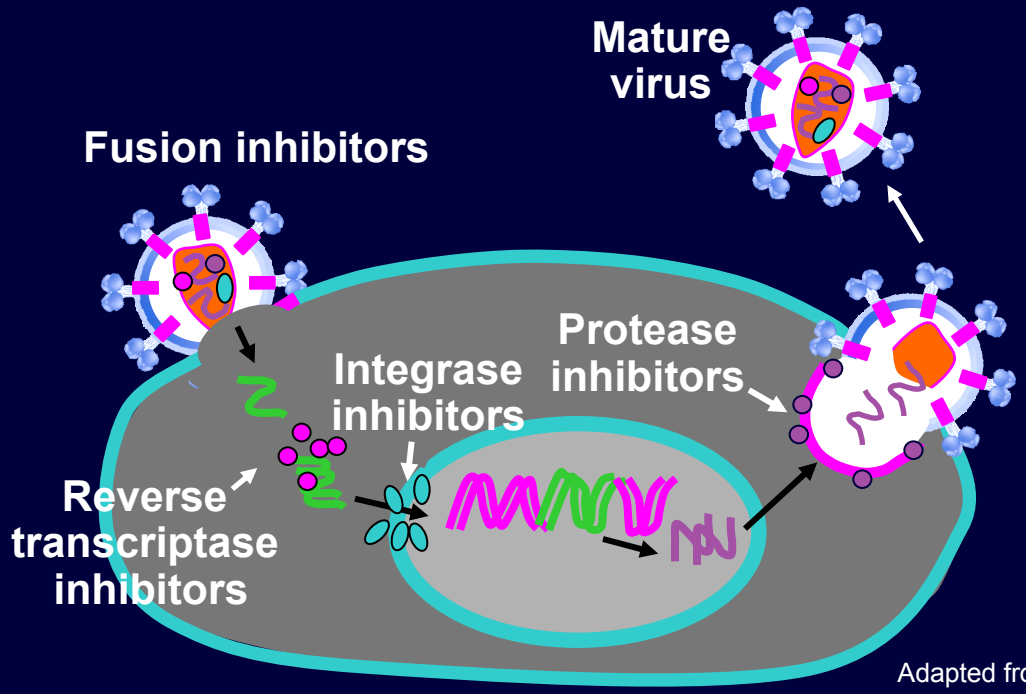

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- Approved antiretroviral therapies belong to 4 classes:

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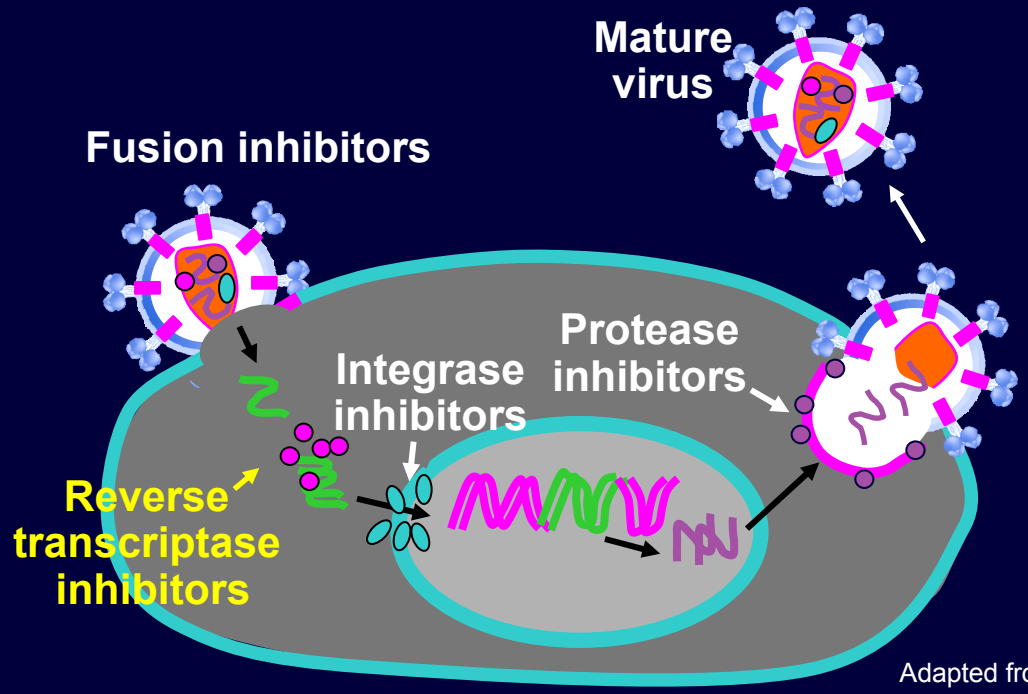

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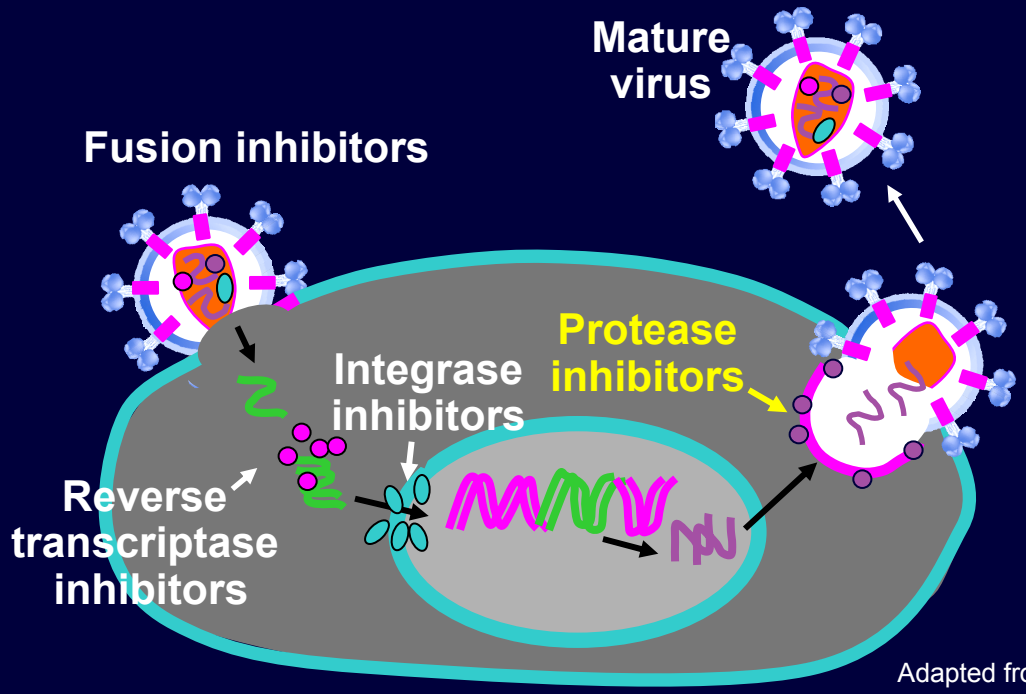
- Approved antiretroviral therapies belong to 4 classes:
  - Nucleoside reverse transcriptase inhibitors (NRTIs)
  - Non-nucleoside reverse transcriptase inhibitors (NNRTIs)

Current Antiretroviral Armamentarium



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- Approved antiretroviral therapies belong to 4 classes:
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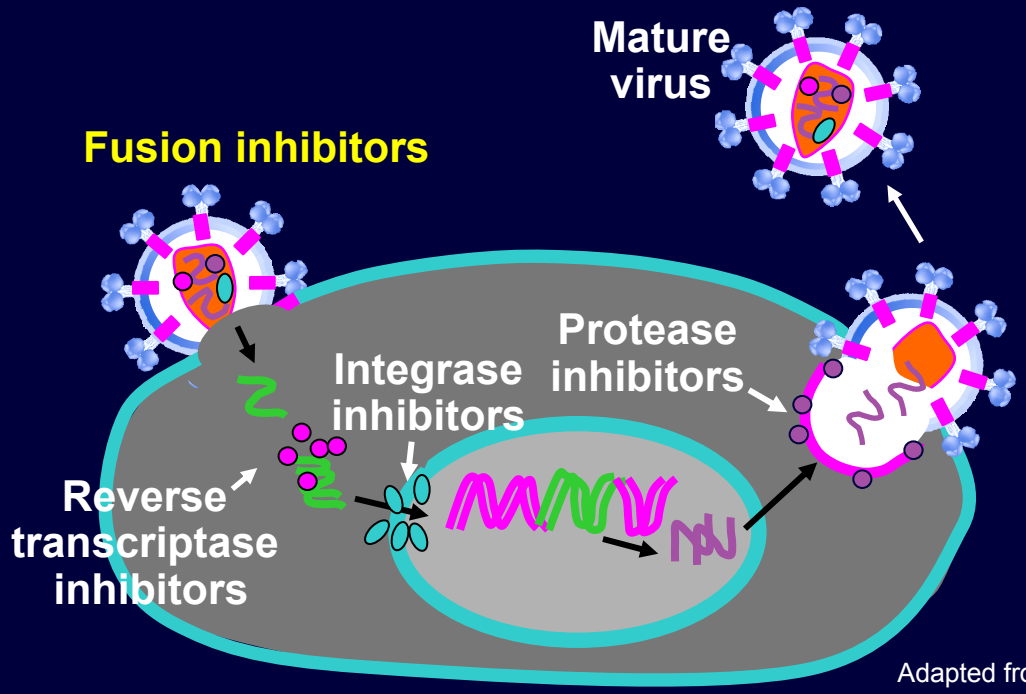
  - Protease inhibitors (PIs)

Current Antiretroviral Armamentarium



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- Approved antiretroviral therapies belong to 4 classes:
  - Nucleoside reverse transcriptase inhibitors (NRTIs)
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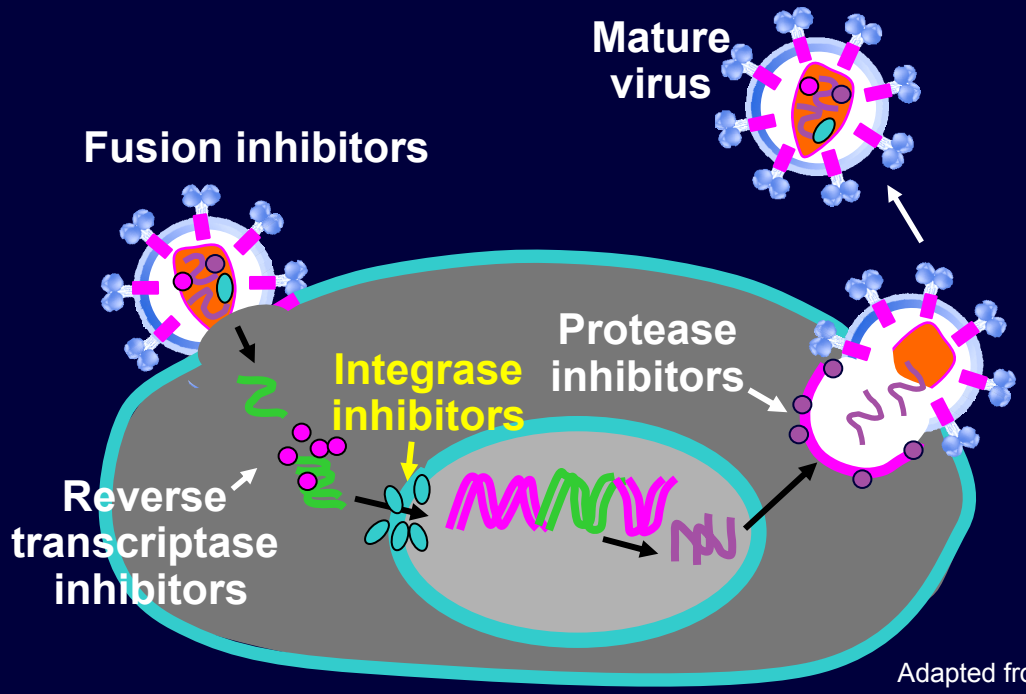
  - Fusion inhibitors

Current Antiretroviral Armamentarium



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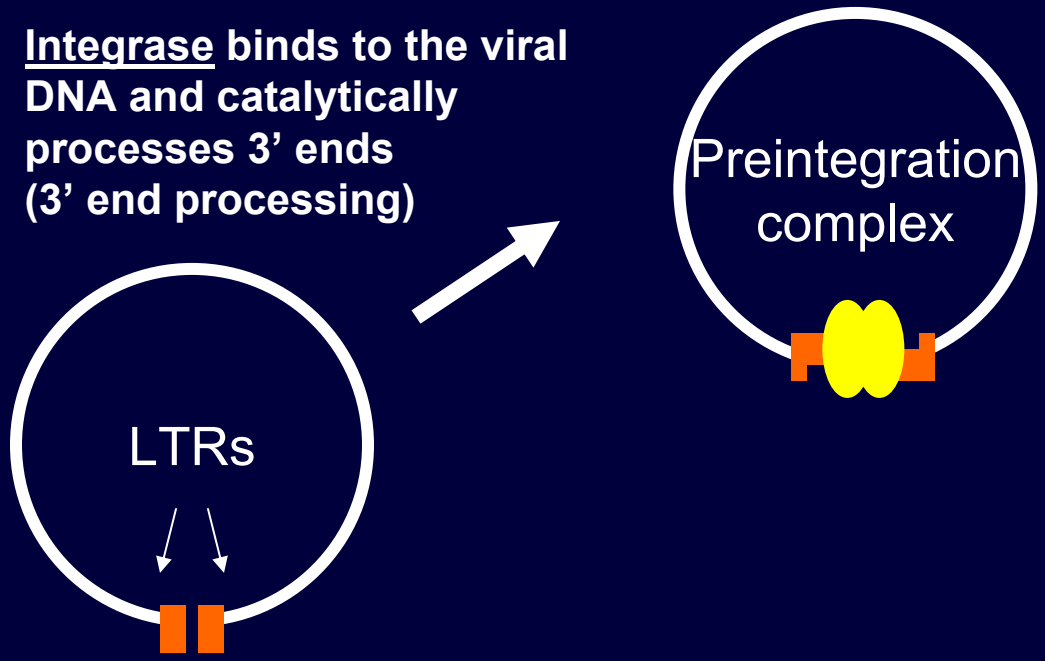
- Approved antiretroviral therapies belong to 4 classes:
  - Nucleoside reverse transcriptase inhibitors (NRTIs)
  - Non-nucleoside reverse transcriptase inhibitors (NNRTIs)
  - Protease inhibitors (PIs)
  - Fusion inhibitors
- HIV integrase enzyme represents a novel target for therapy
  - It catalyzes the integration of viral DNA into host cellular DNA, a critical step for viral replication

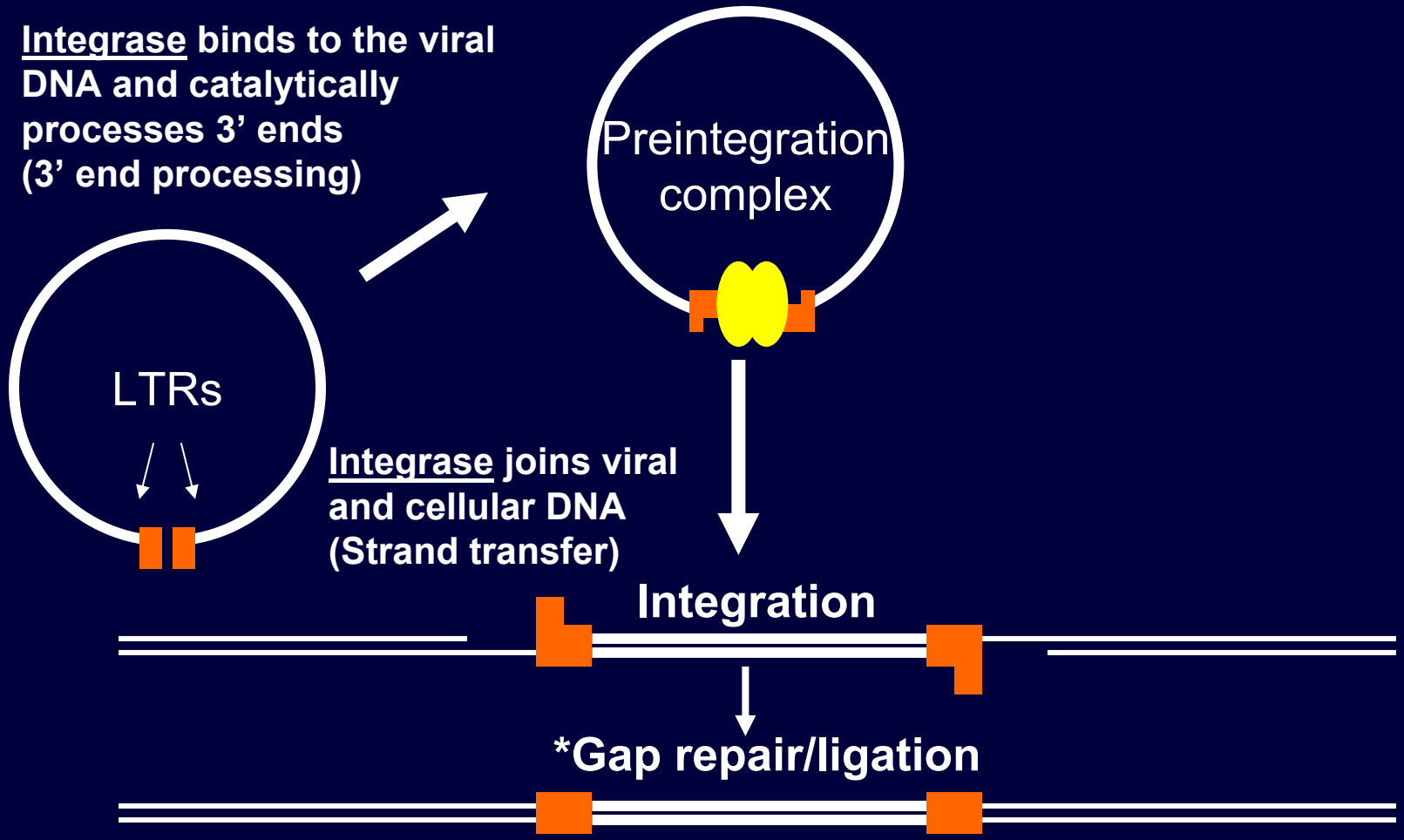
Inhibition of Integrase Strand Transfer Shifts the Fate of HIV-1 DNA Resulting in an Irreversible Block to Infection

<u>Integrase</u> binds to the viral DNA and catalytically processes 3' ends (3' end processing)



LTRs = long terminal repeats.

Inhibition of Integrase Strand Transfer Shifts the Fate of HIV-1 DNA Resulting in an Irreversible Block to Infection



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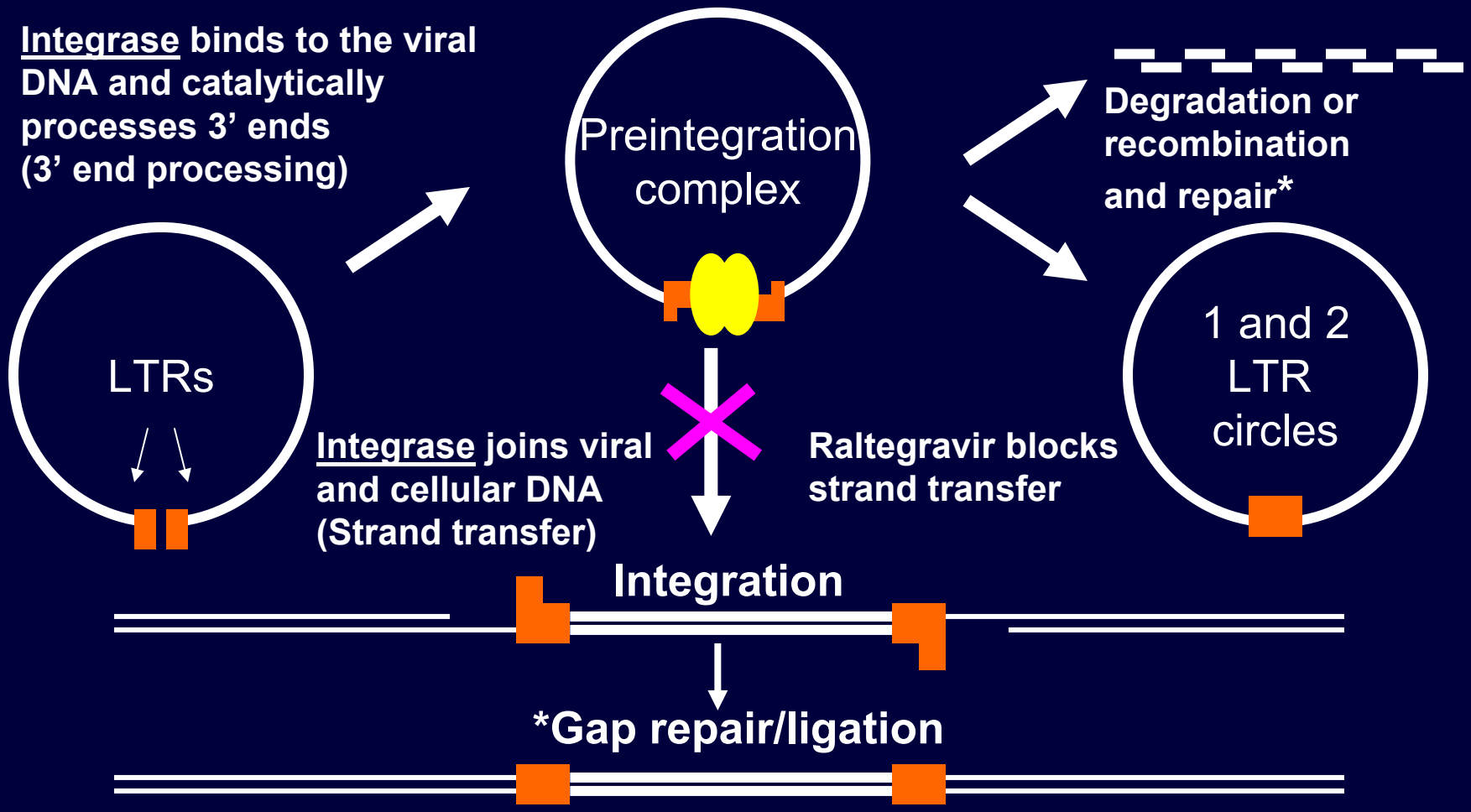
Inhibition of Integrase Strand Transfer Shifts the Fate of HIV-1 DNA Resulting in an Irreversible Block to Infection



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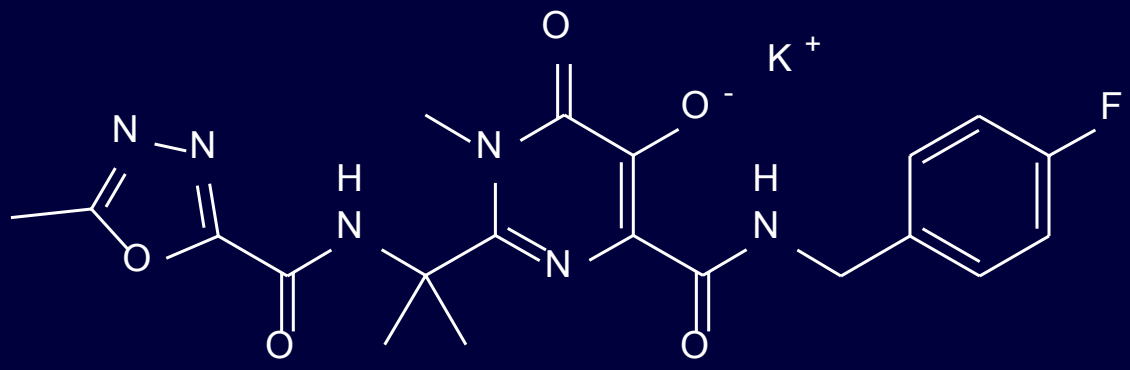
In vitro Activity



- Potent in vitro activity
  - IC_{95} (Mean ± SD) = 31 nM ± 20 nM in 50% NHS
  - Active against:
    - Multi-drug resistant HIV-1
    - CCR5 and CXCR4 HIV-1
  - HIV-1 resistant to raltegravir remain sensitive to other antiretroviral classes
  - Additive/synergistic in vitro with NRTIs, NNRTIs, PIs, and enfuvirtide
- Raltegravir is not genotoxic in in vitro and in vivo assays

Pharmacokinetics

- Raltegravir pharmacokinetics support BID dosing
  - Terminal $t_{½}$ ~9 hours with a shorter α-phase $t_{½}$ ~1 hour
  - Slight degree of accumulation in C_{12hr} with multiple doses
- Considerable variability was observed in the clinical pharmacokinetics of raltegravir
  - For observed C_{12hr} in Phase III
    - CV for inter-subject variability = 212%
    - CV for intra-subject variability = 122%
- In Phase I studies, doses as high as 800 mg p.o. BID were generally well tolerated
  - At 100 mg BID, mean $C_{12hr} > IC_{95}$
  - Pharmacokinetics similar across
    - Gender, race, age (adults), HIV infection status, hepatic function, renal function, and body mass index

Absorption, Metabolism, and Excretion

- Rapidly absorbed: T_{max} ~3 hours
- Food effect
  - Phase II and III studies were conducted with dosing without regard to food
  - Exposure similar in fed (high-fat meal) and fasted states
  - A high-fat meal appeared to slow rate and extend duration of absorption
    - 7.4 hour delay in T_{max}
    - 34% decrease in C_{max}
    - 8.5-fold increase in $C_{12\ hr}$
- Metabolism and excretion
  - Major mechanism of clearance is glucuronidation
    - Mediated by UGT1A1
  - Renal elimination is minor

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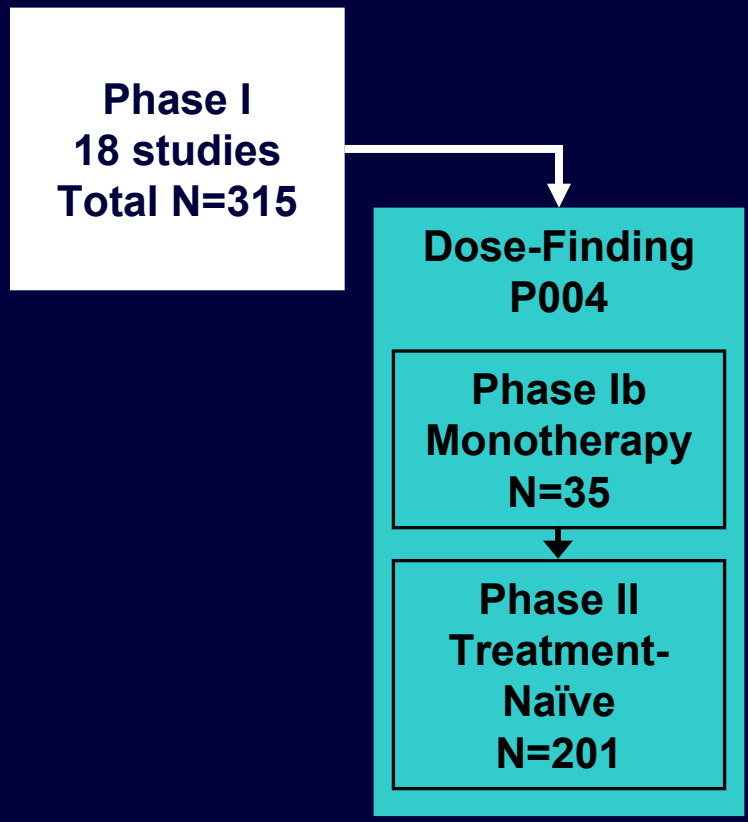
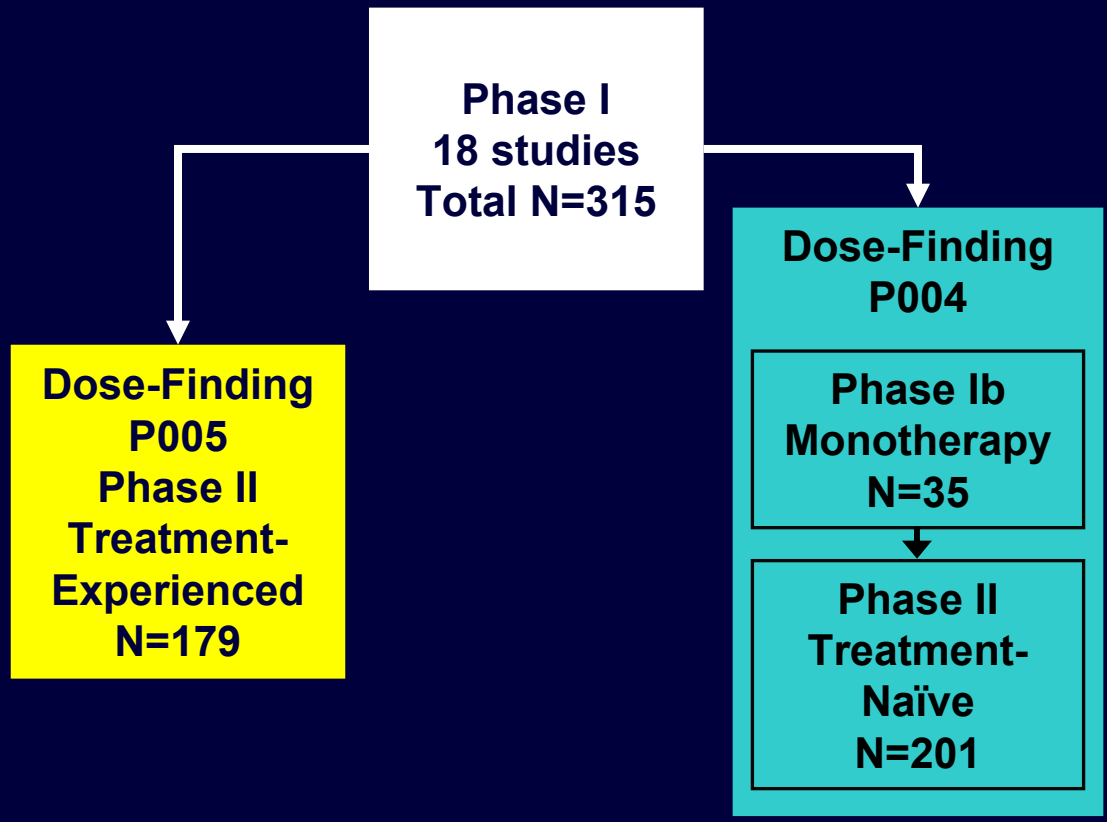
Clinical Development Program

Phase I
18 studies
Total N=315

Clinical Development Program



Clinical Development Program



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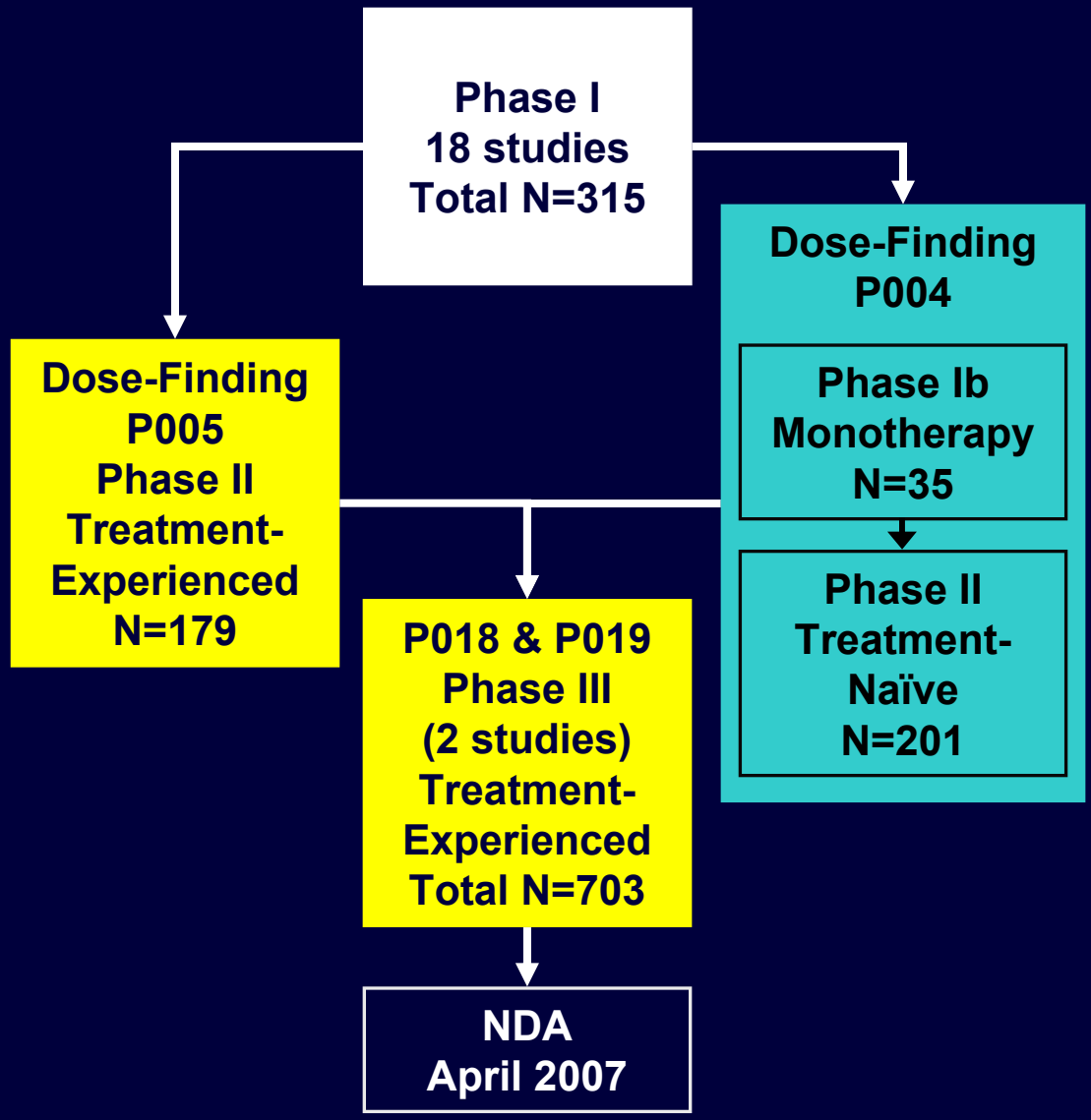
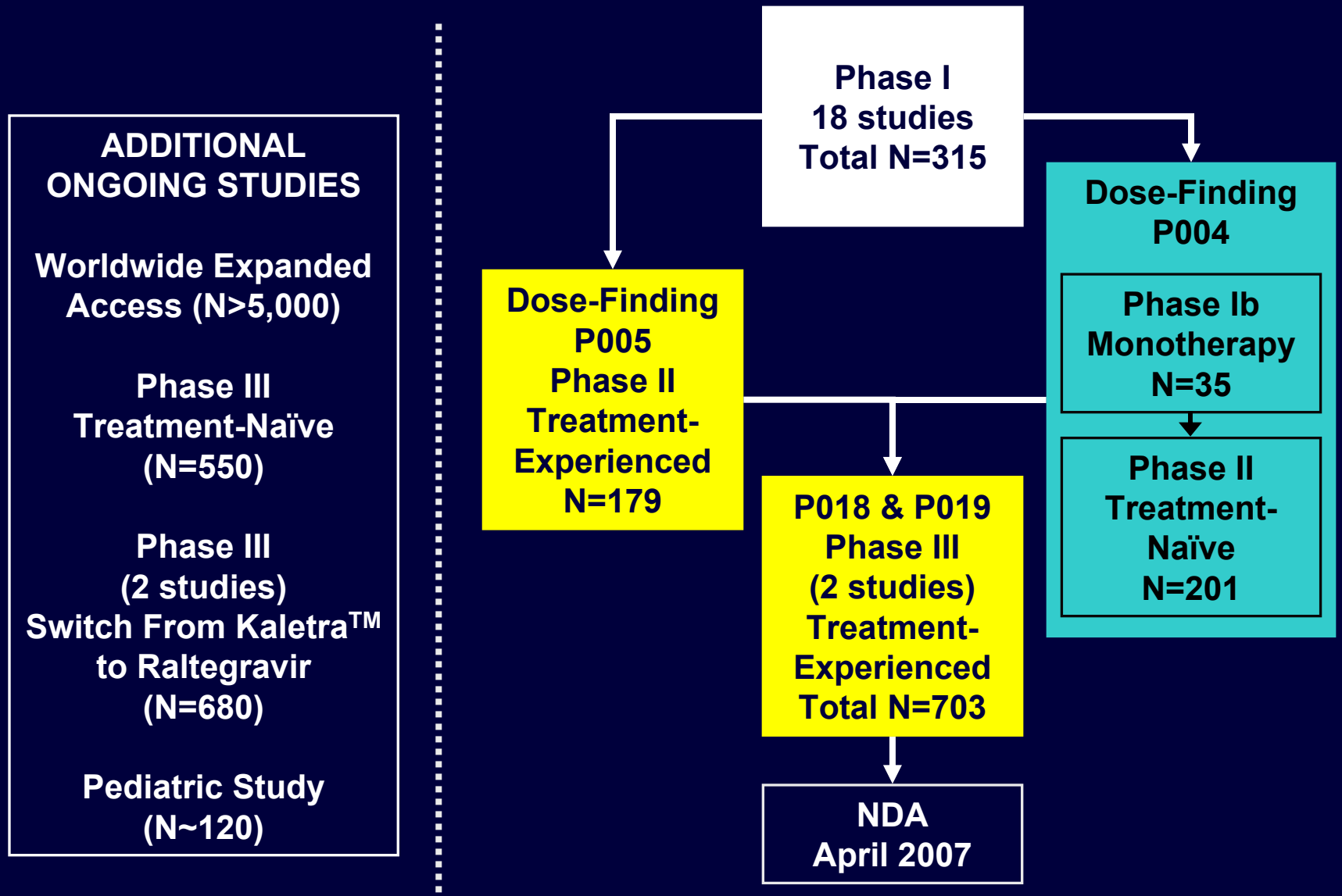


Clinical Development Program



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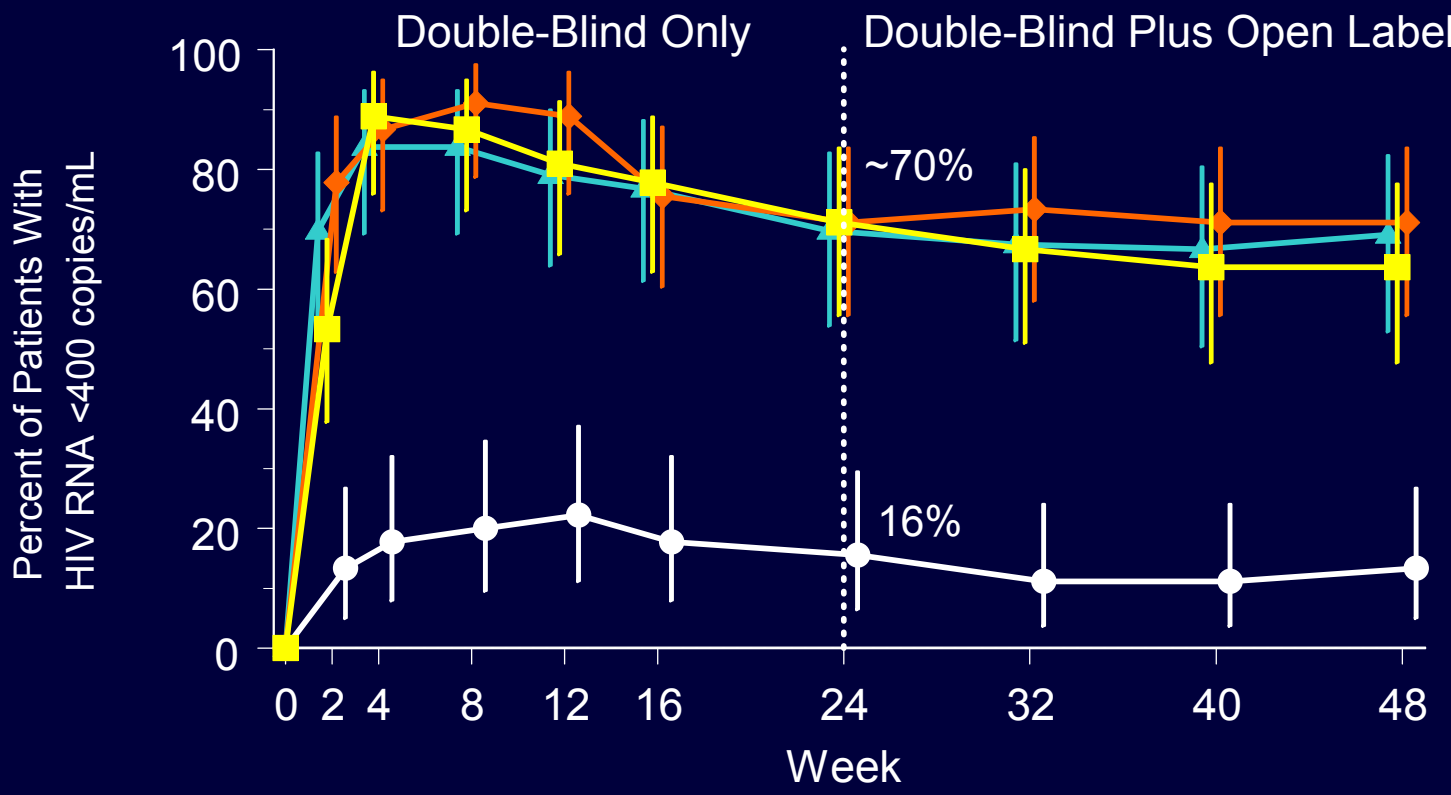
Phase II Dose Finding Studies

- Treatment-naïve (Protocol 004)
  - Doses: 100, 200, 400, and 600 mg BID†
  - Comparator: Efavirenz
  - Regimen: In combination with tenofovir and lamivudine
- Treatment-experienced (Protocol 005)
  - Doses: 200, 400, and 600 mg BID†
  - Comparator: Placebo
  - Regimen: In combination with optimized background therapy (OBT)

    No investigational drugs allowed in OBT

† Twice daily dosing approximately 10-14 hours apart.

Phase II Treatment-Experienced (Protocol 005) Percent of Patients (95% CI) With <400 copies/mL†



Number of contributing patients			
▲ Raltegravir 200 mg BID*	43	43	42
■ Raltegravir 400 mg BID*	45	45	44
◆ Raltegravir 600 mg BID*	45	45	45
● Placebo*	45	45	45

* Plus OBT.
† Non-completer = failure approach.

Selection of Phase III Dosing Regimen

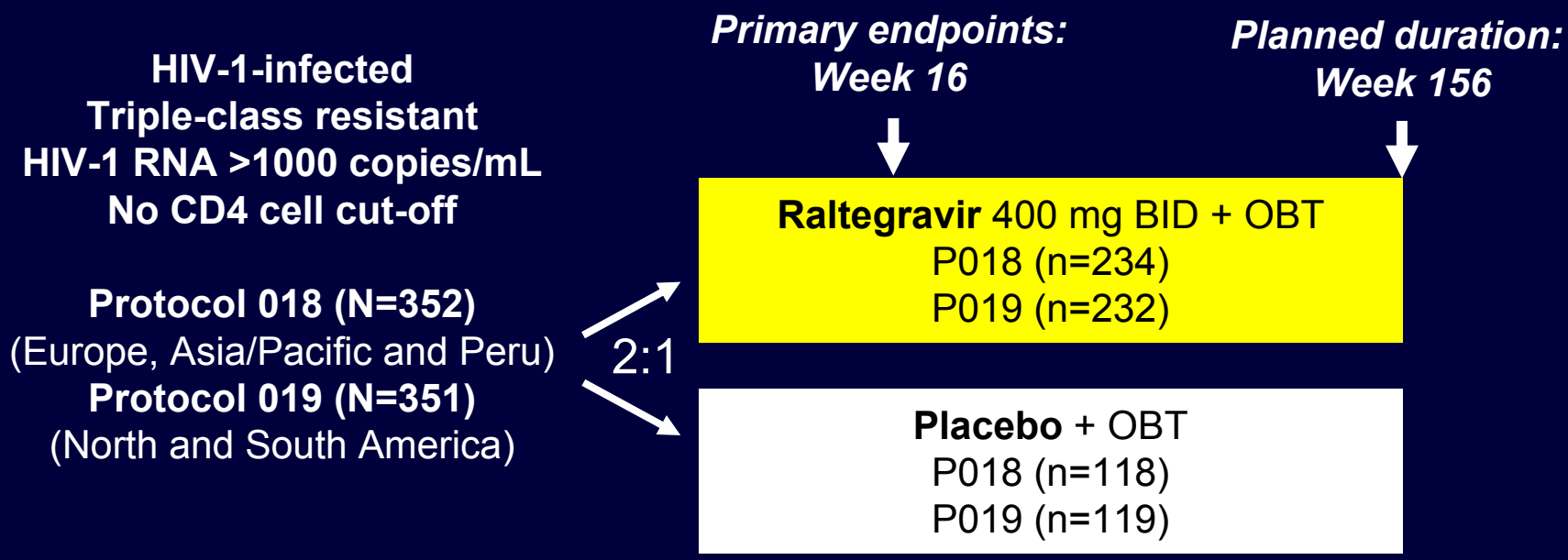
- Results of Phase II dose-ranging studies
  - No differentiation of doses based on efficacy or safety through 48-week
    - All doses studied demonstrated potent and sustained efficacy
    - No dose-limiting or dose-related toxicities
  - Extensive pharmacokinetic/pharmacodynamic analyses did not identify a relationship between raltegravir pharmacokinetics and treatment outcomes
    - Raltegravir doses studied in combination regimens likely on plateau of dose-response curve

400 mg BID selected as Phase III dose

Provides a margin for safety and efficacy when raltegravir is co-administered with drugs that are inhibitors or inducers of UGT1A1

Phase III Study Design (1)

- Randomized, double-blind, placebo-controlled with Data and Safety Monitoring Board
- Primary analysis at Week 16



- Selected investigational antiretrovirals, darunavir and tipranavir, permitted in OBT

Phase III Study Design (2)

- Primary Efficacy Endpoint
  - Percent of patients with HIV-1 RNA <400 copies/mL at Week 16
- Key Secondary Endpoints
  - Percent of patients with HIV-1 RNA <50 copies/mL at Week 16
  - Change from baseline in CD4 cell count at Week 16
- Patients with virologic failure after ≥16 weeks of therapy could enter an open-label post-virologic failure (OLPVF) raltegravir arm

Key Definitions

- Definition of virologic failure
  - Non-responder
    - <1 $\log_{10}$ ↓ HIV RNA from baseline and HIV RNA >400 copies/mL at Week 16
  - Relapse
    - >1 $\log_{10}$ ↑ HIV RNA above nadir

      OR
    - >400 copies/mL after initial response <400 copies/mL
- Genotypic (GSS) and phenotypic (PSS) sensitivity score
  - "Active" drug in the OBT defined by results of PhenosenseGT™ (Monogram Biosciences) testing at baseline
  - For each "active" drug in OBT, +1 added to score
  - For enfuvirtide
    - +1 added to score for use in enfuvirtide-naïve patients
  - For darunavir
    - +1 added to score for use in darunavir-naïve patients

Patient Disposition

	Protocol 018	Protocol 019
Screened	500	512
Randomized	352	351

Patient Disposition

	Protocol 018		Protocol 019	
Screened	500		512	
Randomized	352		351	
	Raltegravir†	Placebo†	Raltegravir†	Placebo†
Randomized	234	118	232	119
Treated	232	118	230	119
Continuing on double-blind therapy	212	68	201	77

† Plus OBT.

Patient Disposition

	Protocol 018		Protocol 019	
Screened	500		512	
Randomized	352		351	
	Raltegravir†	Placebo†	Raltegravir†	Placebo†
Randomized	234	118	232	119
Treated	232	118	230	119
Continuing on double-blind therapy	212	68	201	77
Discontinued therapy	20	50	29	42
Entered OLPVF	15	46	19	39
Discontinued due to AE	4	4	5	1
Discontinued due to other	1	0	5	2

† Plus OBT; OLPVF = open-label post-virologic failure arm; AE = adverse experience.

Baseline Patient Characteristics

	Protocol 018		Protocol 019	
	Raltegravir† N=232	Placebo† N=118	Raltegravir† N=230	Placebo† N=119
Median age, years	46	43	45	46
Male (%)	84	87	91	90
Caucasian (%)	75	81	55	65
Median CD4 count, cells/mm^3	140	105	102	132
GM viral load, copies/mL (log_{10} HIV RNA)	40,519 (4.6)	31,828 (4.5)	48,366 (4.7)	47,789 (4.7)
AIDS (%)	94	90	91	92
Median years of prior ARTs (median # ART)	11 (12)	10 (12)	10 (12)	10 (12)
Hepatitis status				
Hepatitis B (%)	8	4	10	3
Hepatitis C (%)	15	20	3	4

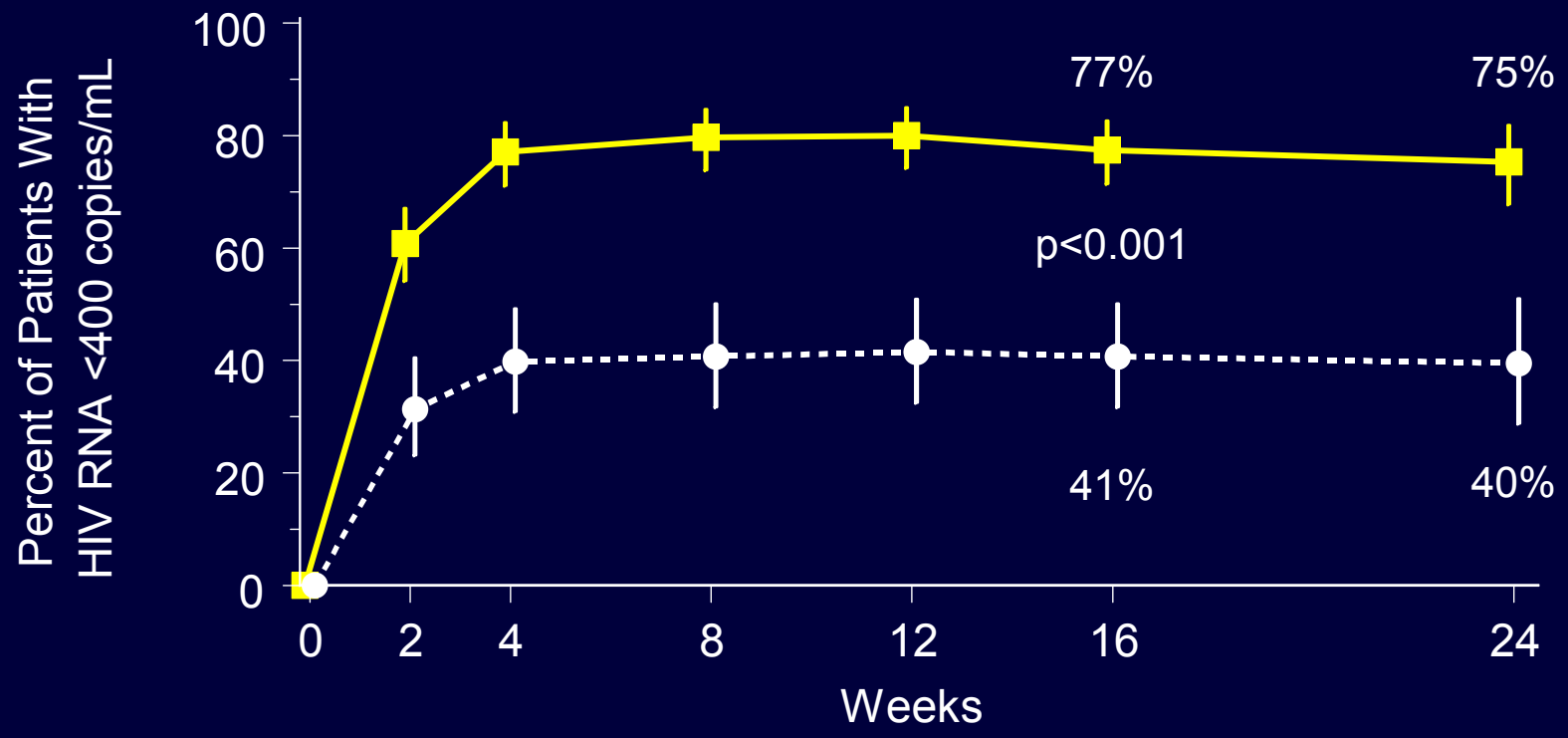
† Plus OBT; GM = geometric mean; ART = antiretroviral therapy.

Characteristics of Optimized Background Therapy

	Protocol 018		Protocol 019	
	Raltegravir† N=232 %	Placebo† N=118 %	Raltegravir† N=230 %	Placebo† N=119 %
GSS				
GSS = 0	30	29	20	26
GSS = 1	33	41	44	40
PSS				
PSS = 0	19	18	10	19
PSS = 1	29	33	34	27
New enfuvirtide in OBT	21	20	19	20
New darunavir in OBT	27	25	45	50

† Plus OBT.
GSS = genotypic sensitivity score; PSS = phenotypic sensitivity score; OBT = optimized background therapy.

Phase III Treatment-Experienced (Protocol 018) Percent of Patients (95% CI) With <400 copies/mL*

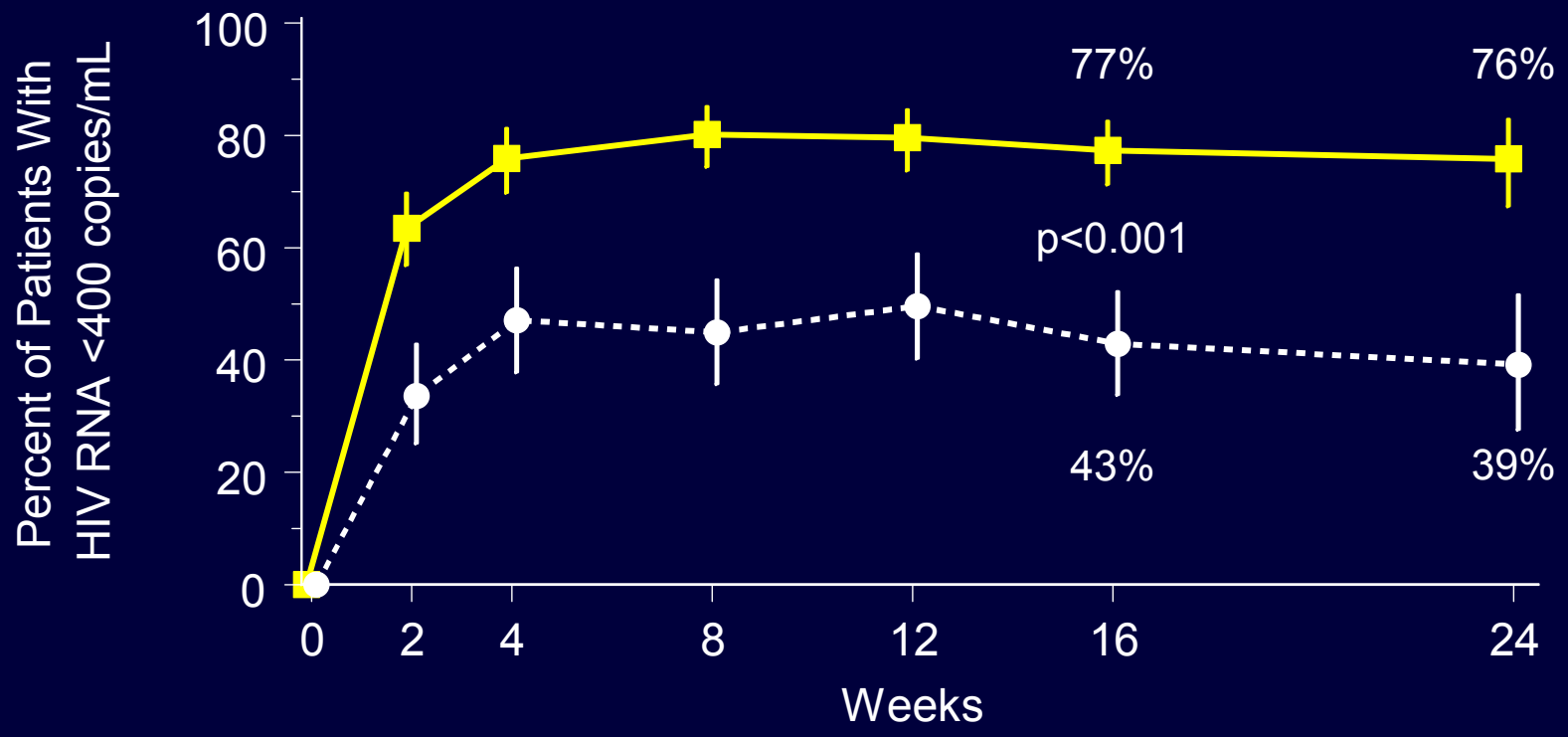


Number of Contributing Patients

■ Raltegravir BID + OBT	232	232	231	231	230	230	158
● Placebo + OBT	118	118	118	118	118	118	81

* Non-completer = failure approach.

Phase III Treatment-Experienced (Protocol 019) Percent of Patients (95% CI) With <400 copies/mL*

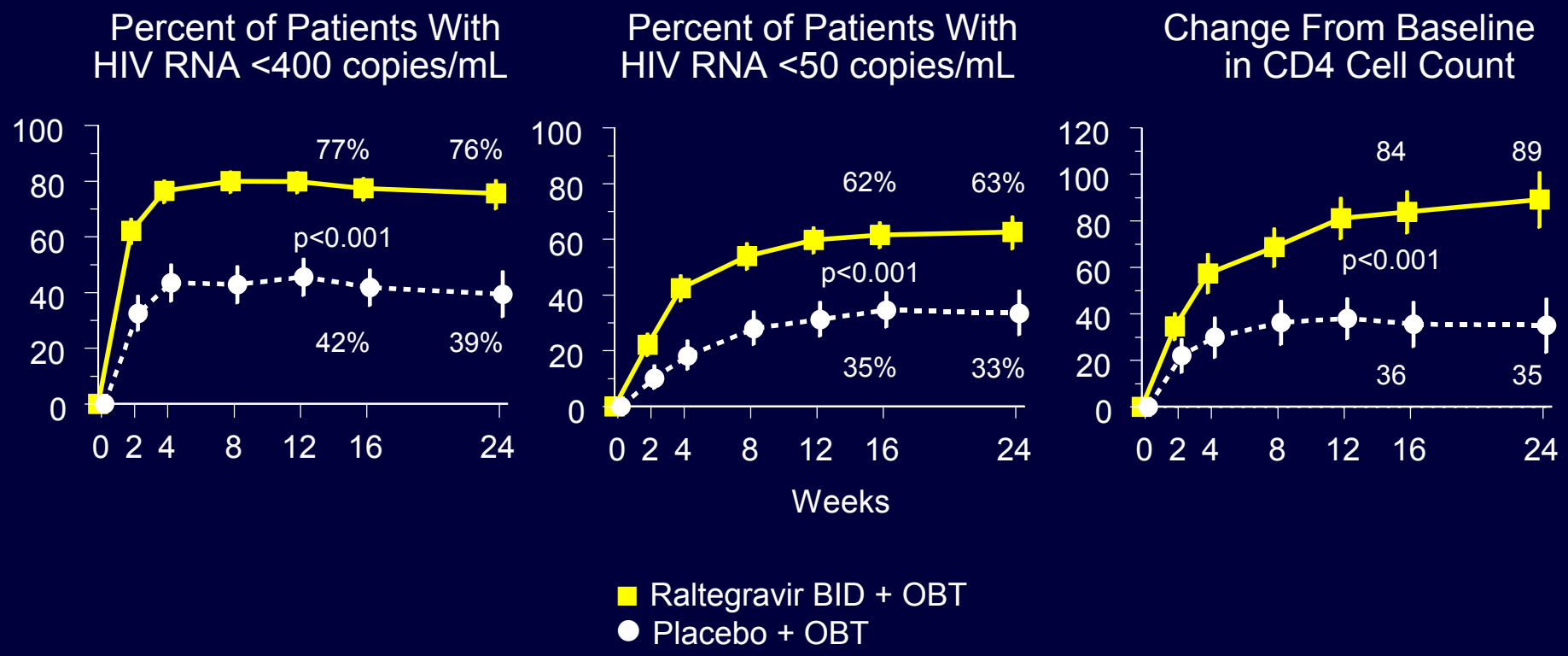


Number of Contributing Patients							
■ Raltegravir BID + OBT	230	230	228	227	230	229	128
● Placebo + OBT	119	119	119	118	119	119	69

* Non-completer = failure approach.

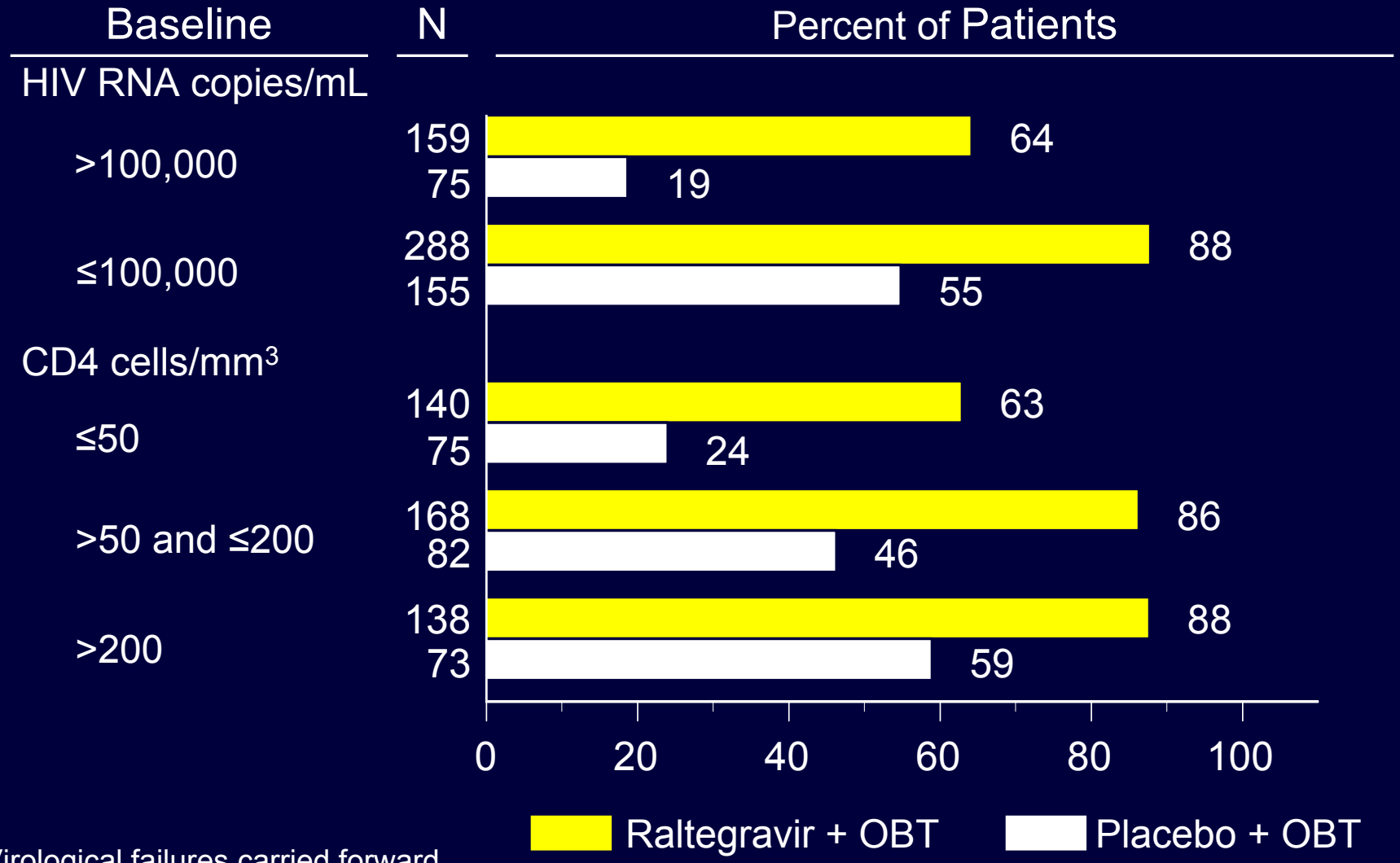
Phase III Treatment-Experienced Protocol 018 and Protocol 019 Integrated Analysis of Efficacy

Treatment-Experienced Patients Integrated Analysis of Efficacy



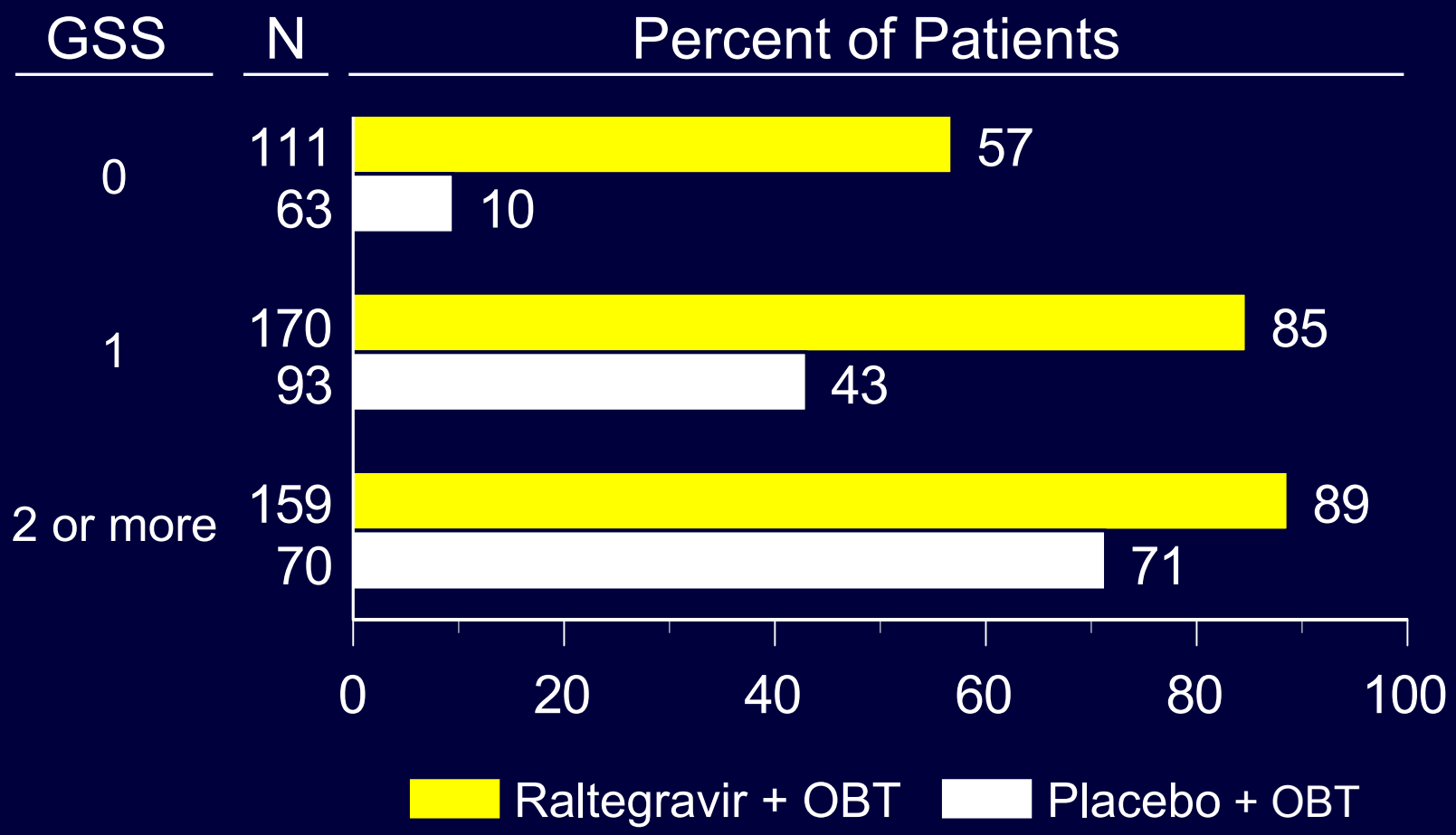
For HIV RNA <400 copies/mL and <50 copies/mL: Non-completer = failure approach.
For CD4: Baseline carried forward for virologic failures.

Protocols 018 and 019 Combined Efficacy† Percent of Patients With HIV RNA <400 copies/mL at Week 16 by Baseline HIV RNA and CD4 Cell Count



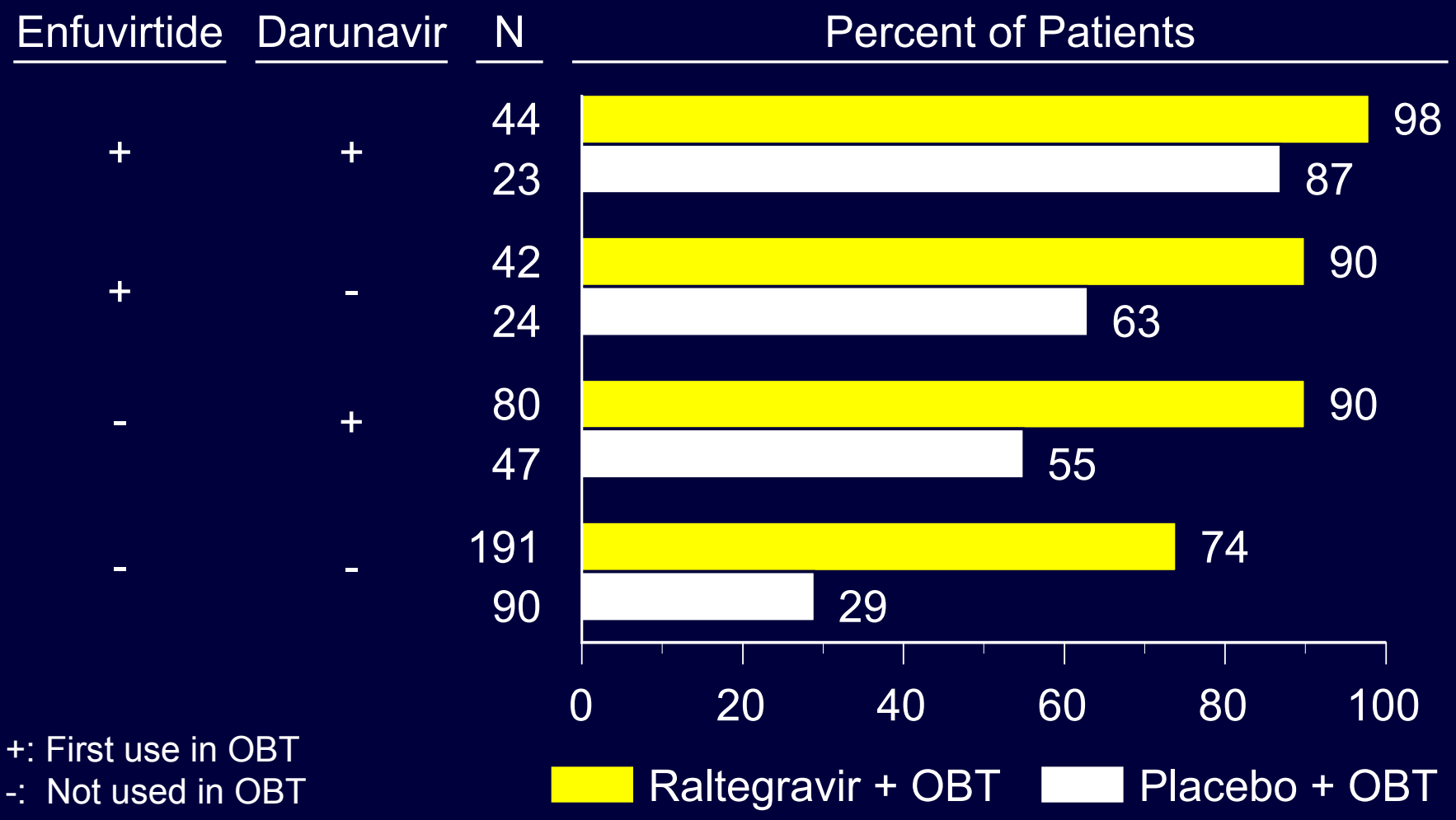
† Virological failures carried forward.

Protocols 018 and 019 Combined Efficacy† Percent of Patients With HIV RNA <400 copies/mL at Week 16 by Genotypic Sensitivity Score (GSS)



† Virological failures carried forward.

Protocols 018 and 019 Combined Efficacy† Percent of Patients With HIV RNA <400 copies/mL at Week 16 by First Use of Selected ARTs in OBT

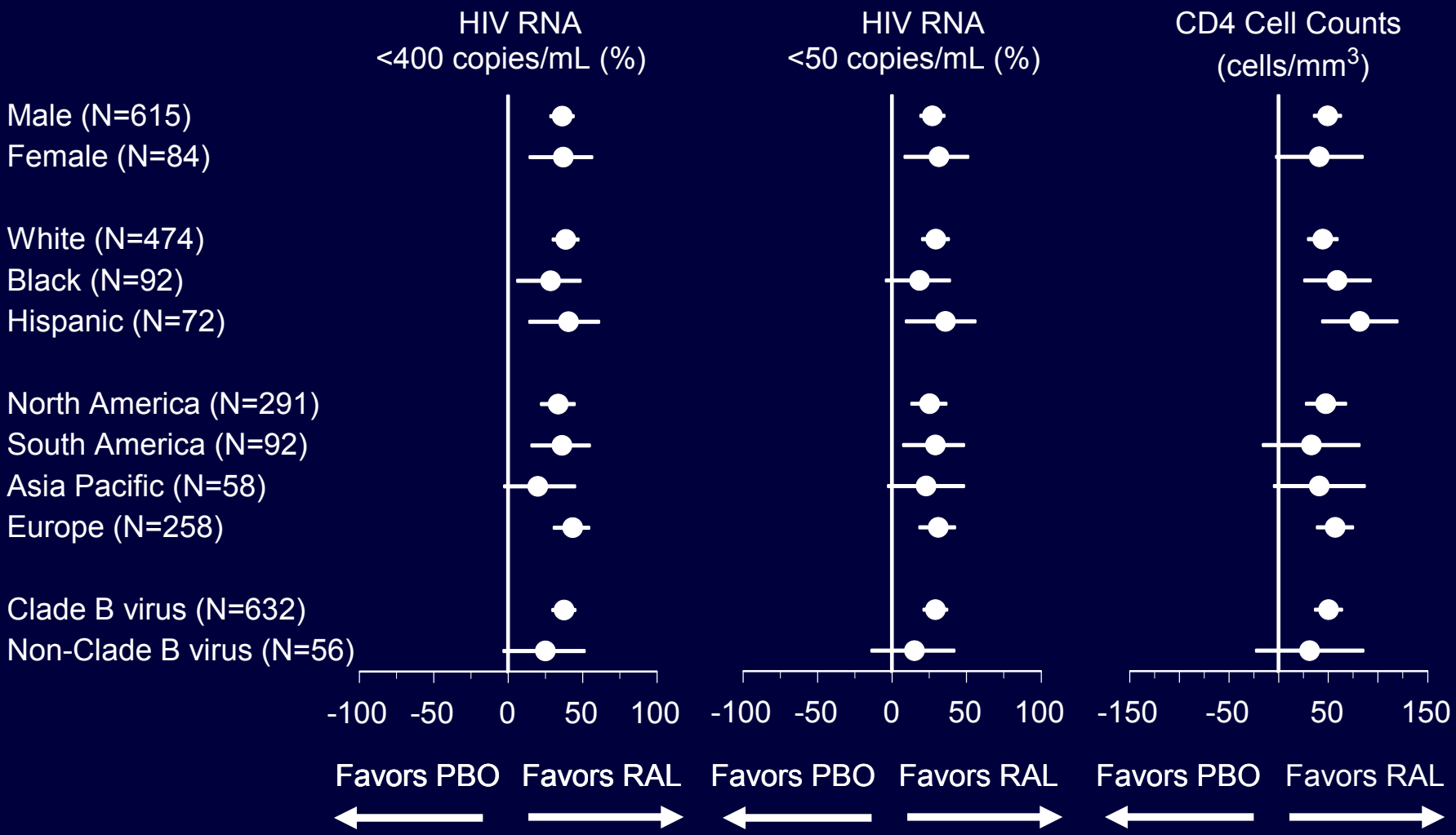


+: First use in OBT
-: Not used in OBT

† Virological failures carried forward.

Consistent Treatment Effect Regardless of Gender, Race, Region, and Viral Sub-type

Treatment Difference (Raltegravir - Placebo) (95% CI) at Week 16



RAL = raltegravir; PBO = placebo.

Efficacy Conclusions

- In HIV-1-infected patients failing antiretroviral therapy with triple-class resistant HIV, raltegravir 400 mg BID plus OBT
  - Has rapid, potent, and superior antiretroviral and immunological efficacy compared to placebo plus OBT
    - In patients receiving new, active antiretroviral therapies in OBT, e.g., enfuvirtide and/or darunavir, ≥90% achieved HIV RNA <400 copies /mL
    - The treatment effect of raltegravir is consistent regardless of baseline viral load, CD4 cell count, GSS, PSS, selected ARTs in OBT, gender, race, geographic region, and viral subtype
  - Has sustained efficacy in patients followed to Week 48 in the Phase II study

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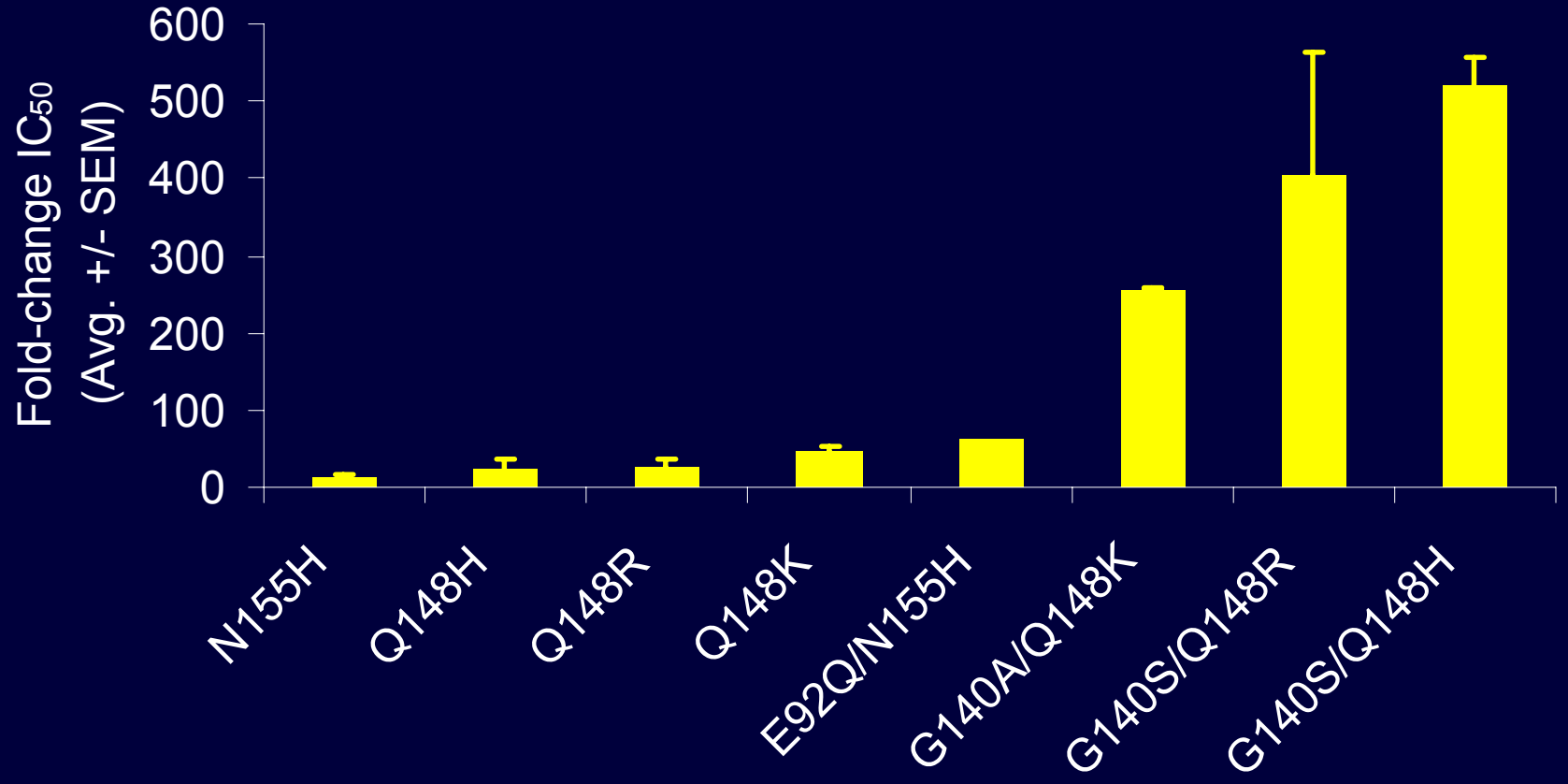
Analysis of Raltegravir Resistance Genotyping Results from Protocols 005, 018, and 019

- In patients with triple-class resistant virus, virologic failure on raltegravir was observed in 38 patients in Protocol 005
- Genotype data available for all 38 failures in Protocol 005:
  - Most patients (35/38) failing raltegravir had integrase mutations conferring raltegravir resistance
  - Integrase mutations were in either of two genetic pathways (N155 or Q148) in 34 of 35 patients
  - Resistance was typically associated with two or more mutations (31 of 35 patients)
    - Q148H/G140S was most common (N=13)
  - No association between dose and/or drug concentration and resistance
- Partial genotype data available for Protocols 018 and 019 showed similar findings

Integrase Mutations Associated With Raltegravir Virologic Failure Confer Raltegravir Resistance



Multiple mutations engender higher-level resistance than single mutation.

Raltegravir Resistance and Clinical Implication

- In patients failing a raltegravir-containing regimen, the HIV isolate often displayed integrase mutations conferring raltegravir resistance
- Signature integrase mutations Q148H/K/R and N155H, as individual mutations, confer reduced susceptibility and viral replication capacity
  - More than 1 mutation is needed to engender high level of resistance
  - No association between dose and/or drug concentration and resistance
- Analysis of longitudinal resistance data is ongoing

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- Signature integrase mutations Q148H/K/R and N155H, as individual mutations, confer reduced susceptibility and viral replication capacity
  - More than 1 mutation is needed to engender high level of resistance
  - No association between dose and/or drug concentration and resistance
- Analysis of longitudinal resistance data is ongoing
- Factors that decrease the development of resistance
  - Lower viral load
  - First use of enfuvirtide/darunavir in OBT
  - PSS > 0
  - GSS > 0
- Raltegravir should be used in combination with other potent active agents to maximize its clinical benefits

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Number of Patients Exposed to Raltegravir ≥400 mg BID Phase II and III Studies

- Entire study period
  - Includes double-blind plus all open-label therapy phases
    - At least 16 weeks: 650 patients
    - At least 24 weeks: 430 patients
    - At least 48 weeks: 134 patients

Phase II and III Safety Database

Patients treated with raltegravir
All doses (100, 200, 400, and 600 mg) – Double-Blind, Open-Label Post-virologic Failure, and Open-Label Extension
N=878 patients

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N=878 patients

Double-Blind Phase

Raltegravir 400 mg
Treatment-experienced patients
P005, P018, P019
507 patients on raltegravir
[261 patient-years of exposure]
282 patients on placebo
[127 patient-years of exposure]

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Raltegravir all doses
All patients
P004, P005, P018, P019
N=758 patients on raltegravir
versus 323 on control

Phase II and III Safety Database

Patients treated with raltegravir
All doses (100, 200, 400, and 600 mg) – Double-Blind, Open-Label Post-virologic Failure, and Open-Label Extension
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Raltegravir all doses
All patients
P004, P005, P018, P019
N=758 patients on raltegravir
versus 323 on control

Open-Label Post-virologic Failure

Raltegravir 400 mg
Treatment-experienced patients
P005, P018, P019
N=114 patients†

Open-Label Extension‡

Raltegravir 400 mg
Treatment-experienced patients
P005
N=6 patients†

† Includes only patients who came from placebo group.
‡ After ≥24 weeks of double-blind treatment, all patients switched to raltegravir 400 mg in an open-label extension.

Phase I and Phase II

- Generally well tolerated in healthy subjects
- In dose-ranging studies in treatment-naïve and treatment-experienced patients
  - Generally well tolerated
    - Clinical and laboratory adverse experience profile similar to control groups
  - No dose-limiting toxicities
  - No dose-related toxicities
- In treatment-naïve patients, in combination with lamivudine and tenofovir
  - No impact on serum cholesterol, LDL-cholesterol, and triglycerides at Week 48

Integrated Summary of Safety

Raltegravir 400 mg BID

Protocol 005, Protocol 018, and Protocol 019

Double-Blind Phase

Clinical Adverse Experiences Double-Blind Phase

	Raltegravir† N=507 %	Placebo† N=282 %
Any adverse experience	81.1	84.4
Drug-related‡ adverse experience	47.7	51.8
Serious adverse experience	10.7	12.8
Serious drug-related‡ adverse experience	1.6	1.8
Death	1.2	1.1
Adverse experience leading to discontinuation	1.6	2.1

† Plus OBT.

‡ Determined by the investigator to be possibly, probably, or definitely related to any drug in the regimen (raltegravir/placebo alone or in combination with OBT, or OBT alone).

Drug-Related† Clinical Adverse Events Any Intensity – Double-Blind Phase Incidence ≥2% in Any Treatment Group

	Raltegravir‡ N=507 %	Placebo‡ N=282 %
Abdominal distension	2.0	2.1
Abdominal pain	2.8	2.1
Diarrhea	8.7	11.0
Flatulence	2.2	1.8
Nausea	6.3	8.2
Vomiting	2.6	4.6
Fatigue	2.8	1.4
Injection site reaction	8.7	9.6
Pyrexia	1.0	2.1
Headache	4.7	5.7

† Determined by the investigator to be possibly, probably, or definitely related to any drug in the regimen (raltegravir/placebo alone or in combination with OBT, or OBT alone).
‡ Plus OBT.

Drug-Related† Clinical Adverse Events Moderate/Severe Intensity - Double-Blind Phase Incidence ≥2% in Any Treatment Group

	Raltegravir‡ N=507 %	Placebo‡ N=282 %
Diarrhea	3.7	3.5
Nausea	2.2	3.2
Headache	2.2	1.4
Injection site reaction	2.4	2.8

† Determined by the investigator to be possibly, probably, or definitely related to any drug in the regimen (raltegravir/placebo alone or in combination with OBT, or OBT alone).
‡ Plus OBT.

Drug-Related† Laboratory Adverse Events Double-Blind Phase Incidence ≥2% in Any Treatment Group

	Raltegravir‡ N=507		Placebo‡ N=282	
	n/m	%	n/m	%
↑ Serum ALT	16/507	3.2	2/282	0.7
↑ Serum AST	13/507	2.6	3/282	1.1
↑ Serum creatinine	7/507	1.4	6/282	2.1
↑ Serum triglycerides	13/507	2.6	3/279	1.1

† Determined by the investigator to be possibly, probably, or definitely related to any drug in the regimen (raltegravir/placebo alone or in combination with OBT, or OBT alone).
‡ Plus OBT.
n/m = number of patients with laboratory adverse experiences / number of patients for whom the laboratory test was recorded postbaseline.

Selected Laboratory Abnormalities Double-Blind Phase

		Raltegravir† N=507 %	Placebo† N=282 %
Total serum bilirubin			
Grade 2	1.6 - 2.5 x ULN	5.5	6.4
Grade 3	2.6 - 5.0 x ULN	3.0	2.5
Grade 4	>5.0 x ULN	0.6	0.0
Serum AST			
Grade 2	2.6 - 5.0 x ULN	8.9	4.6
Grade 3	5.1 - 10.0 x ULN	2.0	2.1
Grade 4	>10.0 x ULN	0.4	0.4
Serum ALT			
Grade 2	2.6 - 5.0 x ULN	6.7	7.8
Grade 3	5.1 - 10.0 x ULN	2.6	1.4
Grade 4	>10.0 x ULN	0.6	0.4
Serum alkaline phosphatase			
Grade 2	2.6 - 5.0 x ULN	1.8	0.4
Grade 3	5.1 - 10.0 x ULN	0.4	1.1
Grade 4	>10.0 x ULN	0.4	0.4

† Plus OBT; ULN = upper limit of normal.

Evaluation of Liver Function Test Results by Hy's Law - Double-Blind Phase

- Key elements of Hy's Law
  - Laboratory criteria
    - AST and/or ALT ≥3x ULN
    - Total bilirubin ≥2x ULN
    - No marked increase in alkaline phosphatase (≤5x ULN)
  - Absence of clinical confounders

No Patients Met Criteria for Hy's Law

- Patients meeting laboratory criteria but had clinical confounders
  - Raltegravir (n=4)
    - Stable Grade 3 ↑ bilirubin due to atazanavir with transient AST/ALT elevation
    - Documented HBV reactivation due to stopping medications
    - Chronic HCV infection with transient flare
    - Complicated patient with multiple confounding factors
      - Concurrent acute thyrotoxicosis and acute respiratory syndrome
      - Fatal bronchopneumonia with septic shock
  - Placebo (n=0)

Safety in Special Groups

- Intrinsic factors
  - Similar safety profile
    - Age (adults ≤65 years)
    - Race
    - Gender
- Extrinsic factors
  - Generally well tolerated with similar safety profile when used in combination with atazanavir and/or tenofovir
  - Hepatitis B and/or C virus infection
    - Safety profile in patients with hepatitis B and/or hepatitis C co-infection was similar to that in patients without co-infection
    - Rates of AST and ALT abnormalities were somewhat higher in the subgroup with hepatitis B and/or hepatitis C co-infection for both the raltegravir and placebo groups

Rare Serious Adverse Experience Malignancies

- Imbalance in number of malignancies in raltegravir group in original application
  - Comprehensive review undertaken in original application
    - Primary population: All patients receiving raltegravir in double-blind period of Phase II and Phase III studies
      - Raltegravir group: N=758; 508 PY
      - Comparator group: N=323; 169 PY
- Updated review through 09 July 2007†
  - Same studies/patient population; same analysis method
  - ~60% greater exposure than original application
    - Raltegravir group: N=758; 820 PY
    - Comparator group: N=323; 261 PY
  - Imbalance in number of malignancies has not been sustained with additional follow-up

PY = patient-years of exposure.
† Data submitted and under review by FDA.

Summary of Malignancy – Double-Blind Phase Phase II and III Studies Original Application

	Raltegravir N=758; 508 PY			Comparator Group N=323; 169 PY		
	n (%)†	Recurrent	Diagnosis ≤3 Months‡	n (%)†	Recurrent	Diagnosis ≤3 Months‡
Patients with malignancy	10 (1.3)	3/10	9/10	1 (0.3)	0/1	0/1
Kaposi's sarcoma	2 (0.3)	1	1	0 (0)	-	-
Non-Hodgkin's lymphoma	3 (0.4)	1	3	0 (0)	-	-
SC carcinoma – anogenital	1 (0.1)	-	1	0 (0)	-	-
SC carcinoma – other	1 (0.1)	-	1	1 (0.3)	-	-
Rectal cancer	1 (0.1)	-	1	0 (0)	-	-
Hepatocellular carcinoma	1 (0.1)	-	1	0 (0)	-	-
Non-melanoma skin cancer	1 (0.1)	1	1	0 (0)	-	-

PY = patient-years of exposure, SC = squamous cell.
† Crude incidence (100×n/N).
‡ Diagnosis of cancer occurred within 3 months of initiating study therapy.
Patients with multiple events may be counted more than once in different terms, but only once in one term.

Summary of Malignancy – Double-Blind Phase Phase II and III Studies Cumulative Update as of 09 July 2007*

	Raltegravir N=758; 820 PY			Comparator Group N=323; 261 PY		
	n (%)†	Recurrent	Diagnosis ≤3 Months‡	n (%)†	Recurrent	Diagnosis ≤3 Months‡
Patients with malignancy	19 (2.5)	8/19	11/19	5 (1.5)	2/5	0/5
Kaposi's sarcoma	4 (0.5)	3	1	0 (0)	-	-
Non-Hodgkin's lymphoma	3 (0.4)	1	3	1 (0.3)	-	-
SC carcinoma – anogenital	5 (0.7)	2	3	2 (0.6)	-	-
SC carcinoma – other	1 (0.1)	-	1	1 (0.3)	-	-
Rectal cancer	1 (0.1)	-	1	0 (0)	-	-
Hepatocellular carcinoma	1 (0.1)	-	1	0 (0)	-	-
Non-melanoma skin cancer	5 (0.7)	2	1	1 (0.3)	1	-
Metastatic neoplasm	0 (0)	-	-	1 (0.3)	1	-

* Data submitted and under review by FDA.
PY = patient-years of exposure, SC = squamous cell.
† Crude incidence (100×n/N).
‡ Diagnosis of cancer occurred within 3 months of initiating study therapy.
Patients with multiple events may be counted more than once in different terms, but only once in one term.

Summary of Malignancy Rates and Relative Risk Double-Blind Phase

Timing	Raltegravir (N=758 Patients)			Comparator Group (N=323 Patients)			Relative Risk (95% CI)
	Cases	PY	Rate‡	Cases	PY	Rate‡	
Original Application	10	508	2.0	1	169	0.6	3.3 (0.5, 144)
09Jul07†	19	820	2.3	5	261	1.9	1.2 (0.4, 4.1)

PY = patient-years of exposure.
‡ Per 100 PY.
† Data submitted and under review by FDA.

Summary of Malignancies

- In original application, imbalance in number of malignancies was noted in raltegravir group
  - No specific cancer risk attributable to raltegravir is apparent
    - Malignancy types are those anticipated in an AIDS population
    - Malignancy rates in the raltegravir group are consistent with those seen in a severely immunodeficient AIDS population
    - Many of the malignancies in the raltegravir group likely present at time of study entry or recurrences of prior diagnosed malignancies
- Based on the most up-to-date analysis†, this imbalance in number of malignancies has not been sustained with additional follow-up
- Further follow-up is proposed in the Risk Management Plan

† Data submitted and under review by FDA.

Raltegravir Safety Conclusions

- In patients with advanced HIV-1 infection, failing antiretroviral therapies with multi-drug-resistant virus, raltegravir in combination with OBT
  - Was generally well tolerated with no dose-limiting toxicities
  - Safety profile comparable to that of placebo with OBT
    - Raltegravir was well tolerated in patients regardless of race, age, and gender and in patients with hepatitis B and/or C co-infection
  - Few adverse experiences leading to discontinuations