Clinical Update MSD

Raltegravir in treatment naïve and treatment experienced patients

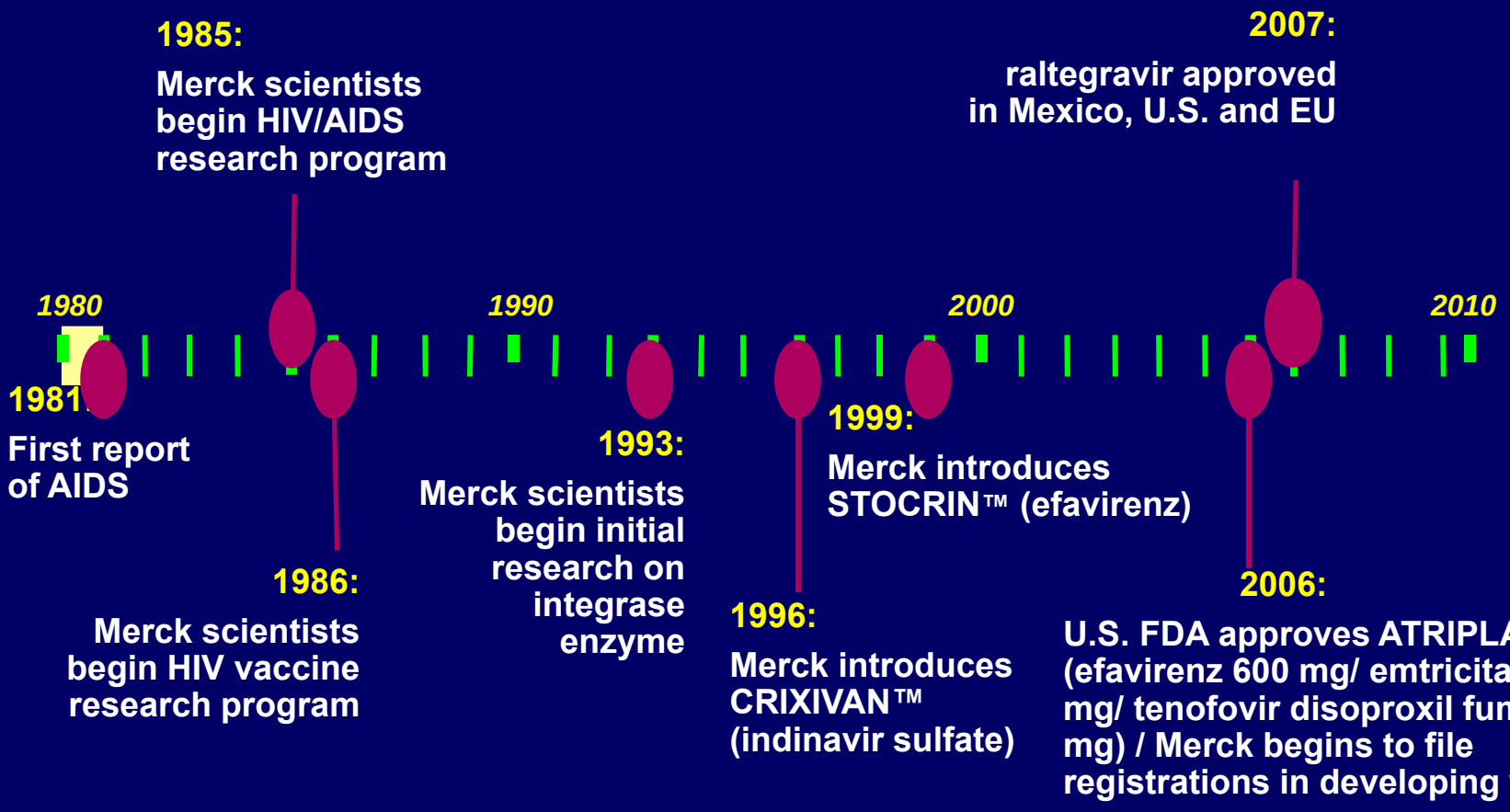
Dr. Armin Schuster PhD
Regional Director Medical Affairs HIV
MSD

Merck Research Laboratories
Antiinfective Drug Development *

1939	*sulfamerzine* (CREMOMERZINE)
1939	*sulfamethazine* (MERMETH)
1942	*succinylsulfathiazole* (SULFASUXIDINE)
1942	*potassium penicillin G* (PENALEV)
1946	*streptomycin* (MERSTREP)
1946	*phthalylsulfathiazole* (SULFATHALIDINE)
1948	*dihydrostreptomycin* (DYSTREP)
1956	*novobiocin* (CATHOMYCIN)
1978	*cefoxitin* (MEFOXIN)
1983	*norfloxacin* (NOROXIN)
1985	*imipenem/cilastatin sodium* (PRIMAXIN/TIENAM)
1987	*ivermectin* (MECTIZAN)
1996	*indinavir sulfate* (CRIXIVAN)
1999	*efavirenz* (STOCRIN)
2001	*caspofungin acetate* (CANCIDAS)
2002	*ertapenem sodium* (INVANZ)
2007	*raltegravir*
2011	*boceprevir*

* Year is date of first launch in any country

Merck/MSD's Corporate History in HIV/AIDS



CRIXIVAN (indinavir) is a trademark of Merck & Co., Inc, Whitehouse Station, NJ, USA
STOCRIN (efavirenz) is a trademark of Merck & Co., Inc, Whitehouse Station, NJ, USA

HIV Replication Cycle and Current Drug Targets

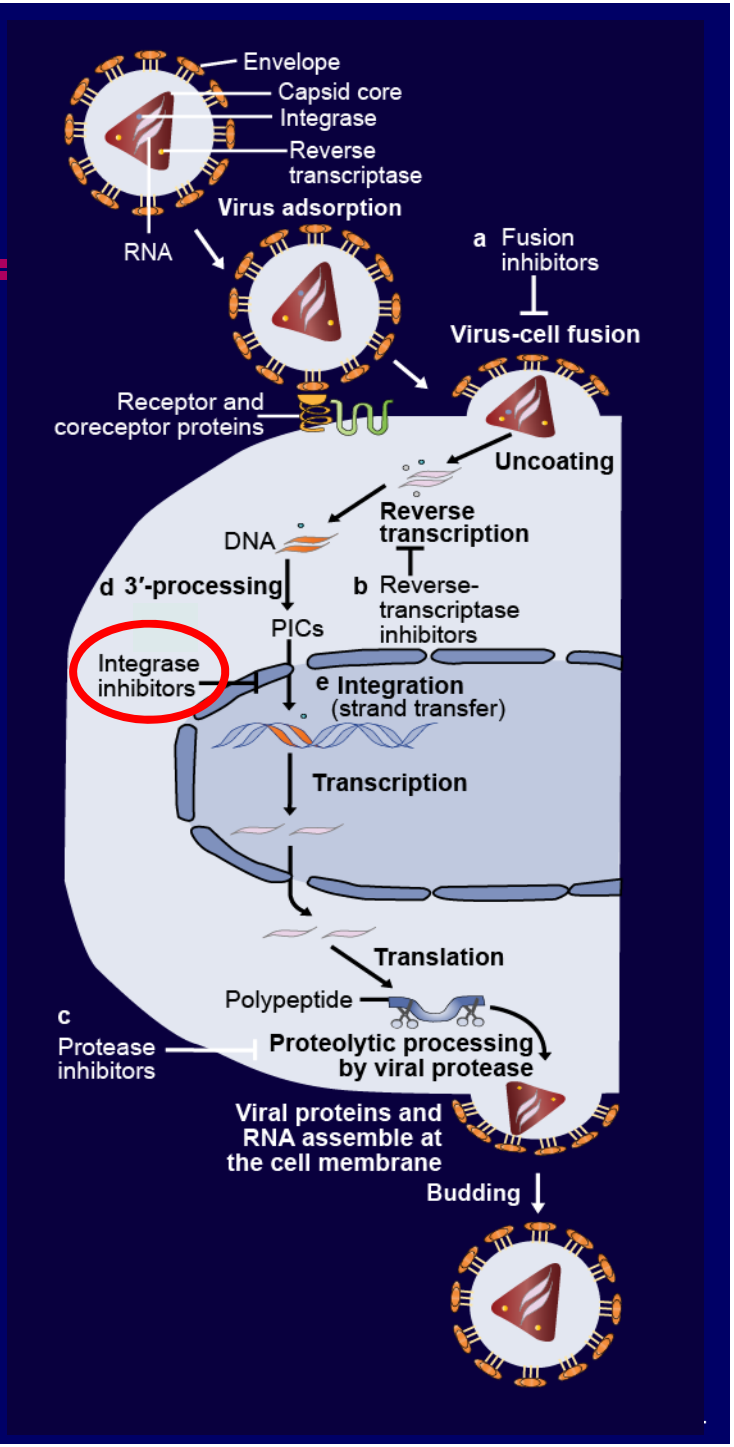
a. Entry
   - Fusion inhibitors
   - CCR5 antagonists

b. Reverse transcriptase
   - NRTIs
   - NNRTIs

c. Protease
   - PIs

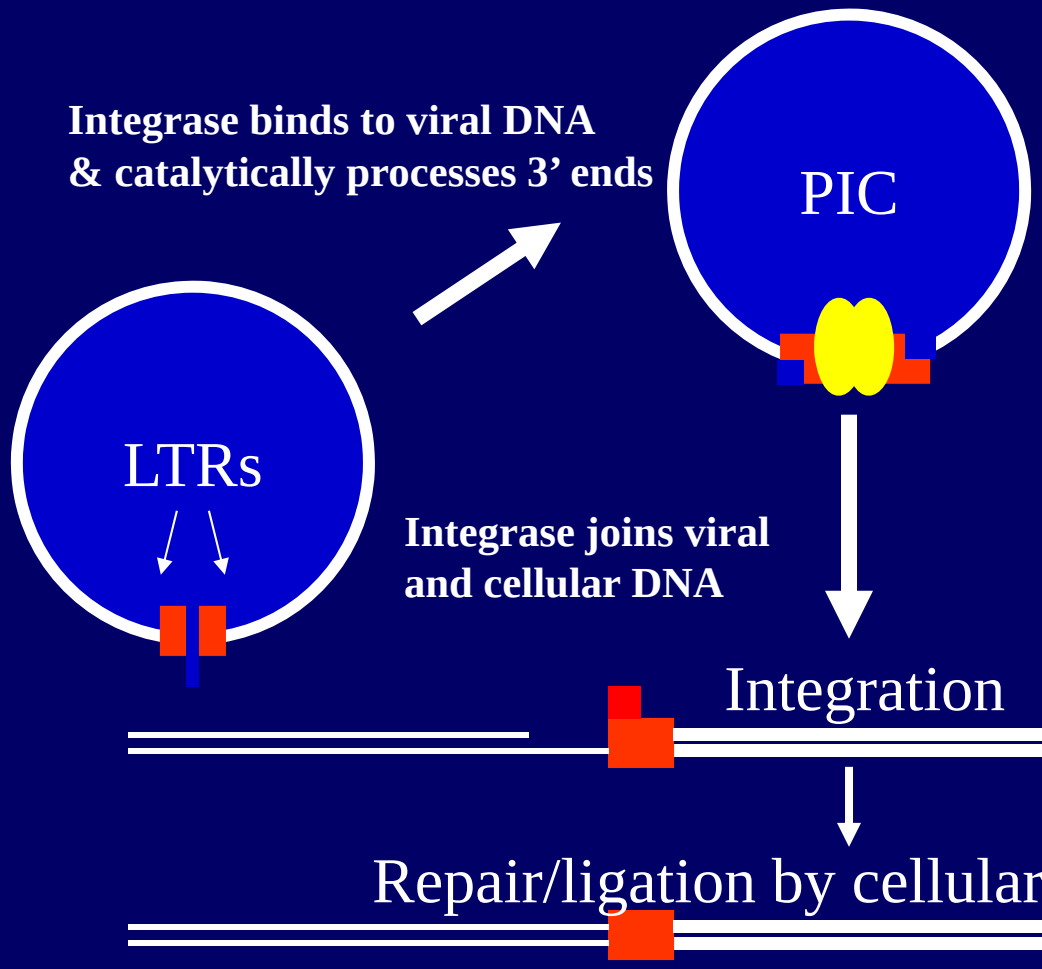
d. Integrase
   - InSTIs

In 2007, first new oral classes in more than a decade: CCR5 (Maraviroc) and Integrase (Raltegravir)



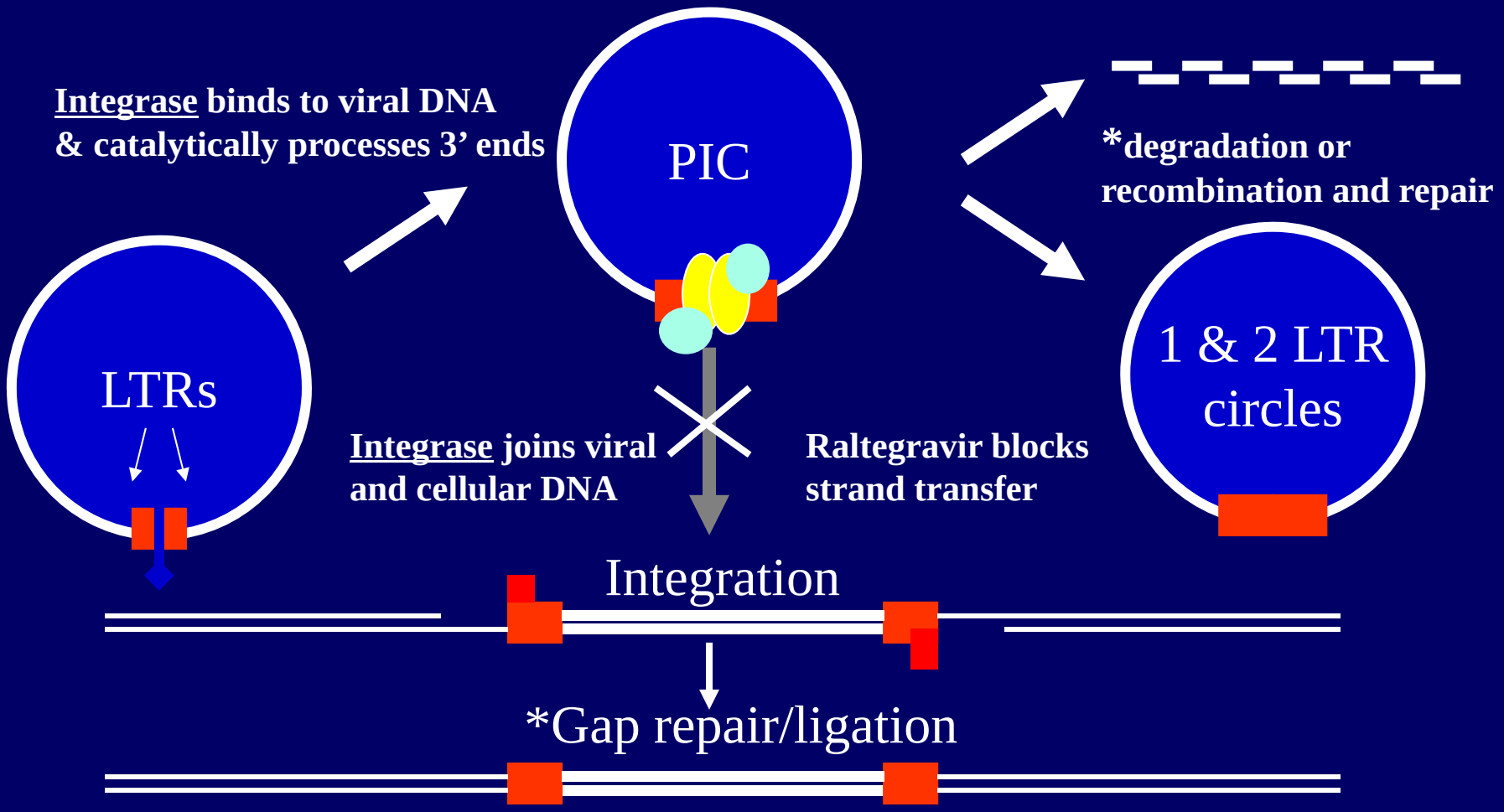
Pommier Y, et al. Nat Rev Drug Discov. 2005;4:236-248.

Integrase Presents Multiple Potential Targets for Intervention



- Recombinant integrase will form stable complexes with LTR DNAs in vitro.

Inhibition of Strand Transfer Shifts the Metabolic Fate of HIV-1 DNA



Note: *cellular functions

Raltegravir Pharmacokinetics

- Steady state achieved rapidly (within ~2 days)
- Little to no accumulation in AUC and C_{max} and slight accumulation in C_{12hr}
- Recommended dose:
  - RAL 400 mg q12hr
  - C_{12hr} = 142 nM; AUC = 14.3 μM•hr
  - In vitro IC_{95} = 31 nM

Raltegravir Pharmacokinetics

- Demographic factors
  - No clinically meaningful effect on RAL PK
    - Gender
    - Age
    - Race
    - Body mass index
    - Hepatic insufficiency
    - Renal insufficiency
  - UGT1A1 polymorphism
    - There is no evidence that UGT1A1 polymorphism alters RAL PK
    - 27 subjects *28/*28 and 30 subjects wild type
      - GMR (90% CI) AUC = 1.41 (0.96, 2.09)

GMR = geometric mean ratio.

Raltegravir Drug-Drug Interactions

Mean effect on other agents

	AUC[a]	C_{max}	C_{trough}[b]
TFV	↓ 10%	↓ 33%	↓ 13%
Midazolam	↓ 8%	↑ 3%	—
TMC125	↑ 10%	↑ 4%	↑ 17%
Ethinyl Estradiol	↓ 2%	↑ 6%	—
Norelgestromin	↑ 14%	↑ 29%	—

[a] $AUC_{0-\infty}$ for midazolam; AUC_{0-24hr} for TFV, EE, and NGMN; AUC_{0-12hr} for TMC125.

[b] C_{24hr} for TFV; C_{12hr} for TMC125.

Raltegravir Drug-Drug Interactions

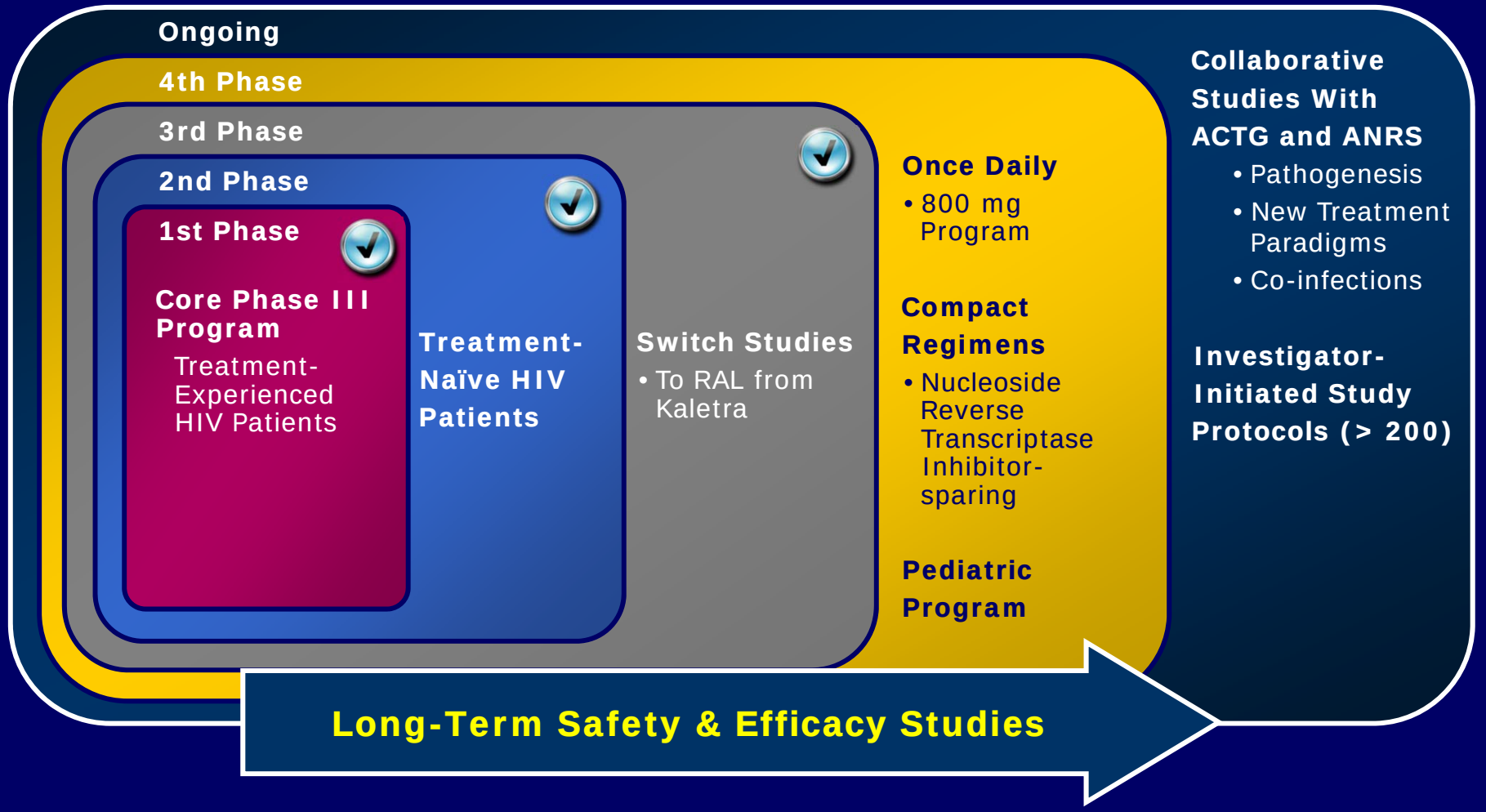
Mean effect on raltegravir

	C_{12hr}	AUC[a]	C_{max}	
Atazanavir/RTV[b]	↑ 77%	↑ 41%	↑ 24%	Likely mechanism: inhibition of UGT1A1
Atazanavir[c]	↑ 95%	↑ 72%	↑ 53%	
Ritonavir (RTV)[c]	↓ 1%	↓ 16%	↓ 24%	
Efavirenz[c]	↓ 21%	↓ 36%	↓ 36%	
Tipranavir/RTV[b]	↓ 55%	↓ 24%	↓ 18%	Likely mechanism: induction of UGT1A1
Rifampin[c]	↓ 61%	↓ 40%	↓ 38%	
TMC125[b]	↓ 34%	↓ 10%	↓ 11%	
TFV[b]	↑ 3%	↑ 49%	↑ 64%	

- Based on collective efficacy and safety data, RAL may be coadministered with all of the antiretroviral agents above without dose adjustment
- Caution is advised regarding the coadministration of RAL with rifampin

[a]$AUC_{0-\infty}$ for single dose of RAL; AUC_{0-12hr} for multiple doses of RAL.
[b]Multiple doses of concomitant medication plus multiple doses of RAL.
[c]Multiple doses of concomitant medication plus single dose of RAL.

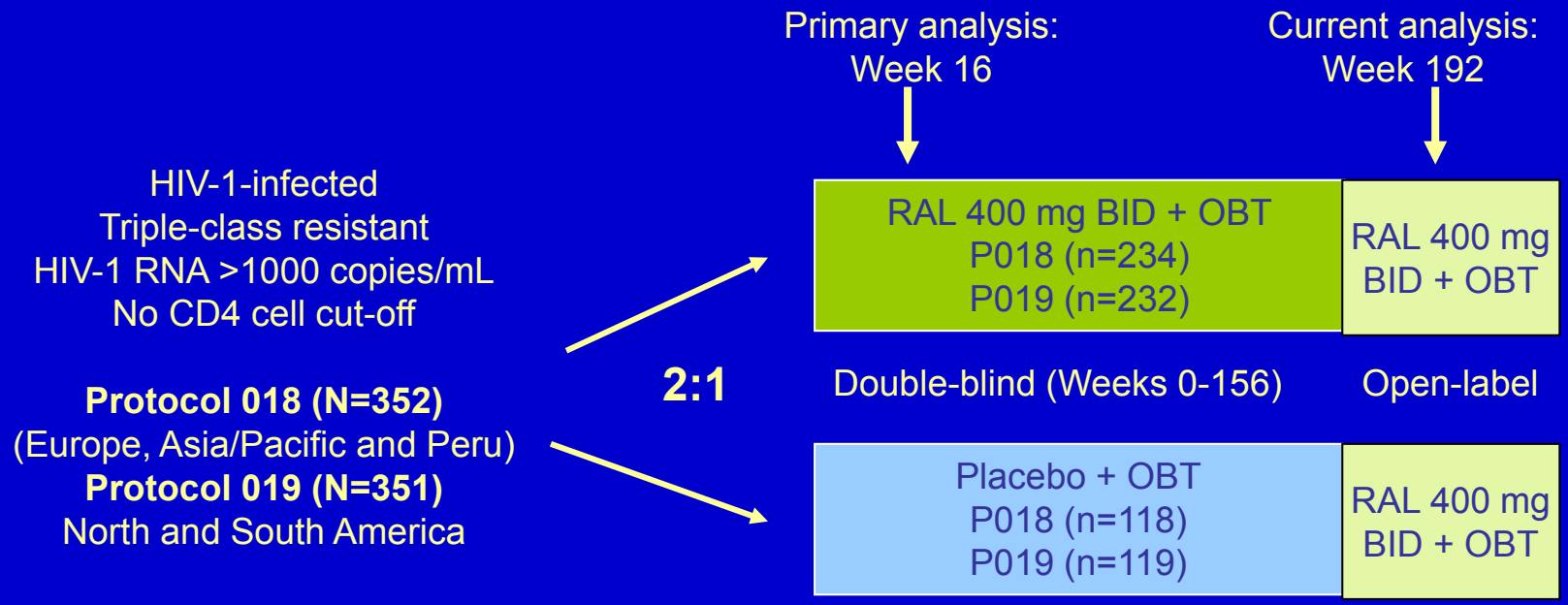
Raltegravir Clinical Development



ACTG = Aids Clinical Trials Group; ANRS = Agence Nationale de Recherche sur le SIDA et les Hepatites Virales

Study Design: BENCHMRK 1 and 2

- Randomized, double-blind, placebo-controlled with DSMB.
- Total study duration of 240 weeks.
- Double-blind phase completed at Week 156; all patients offered open-label RAL until Week 240.



- At Week 156, 50% of RAL group vs 22% of placebo group had HIV RNA < 50 copies/mL (NC=F approach).

Statistical Methods, Overall Analysis

Efficacy

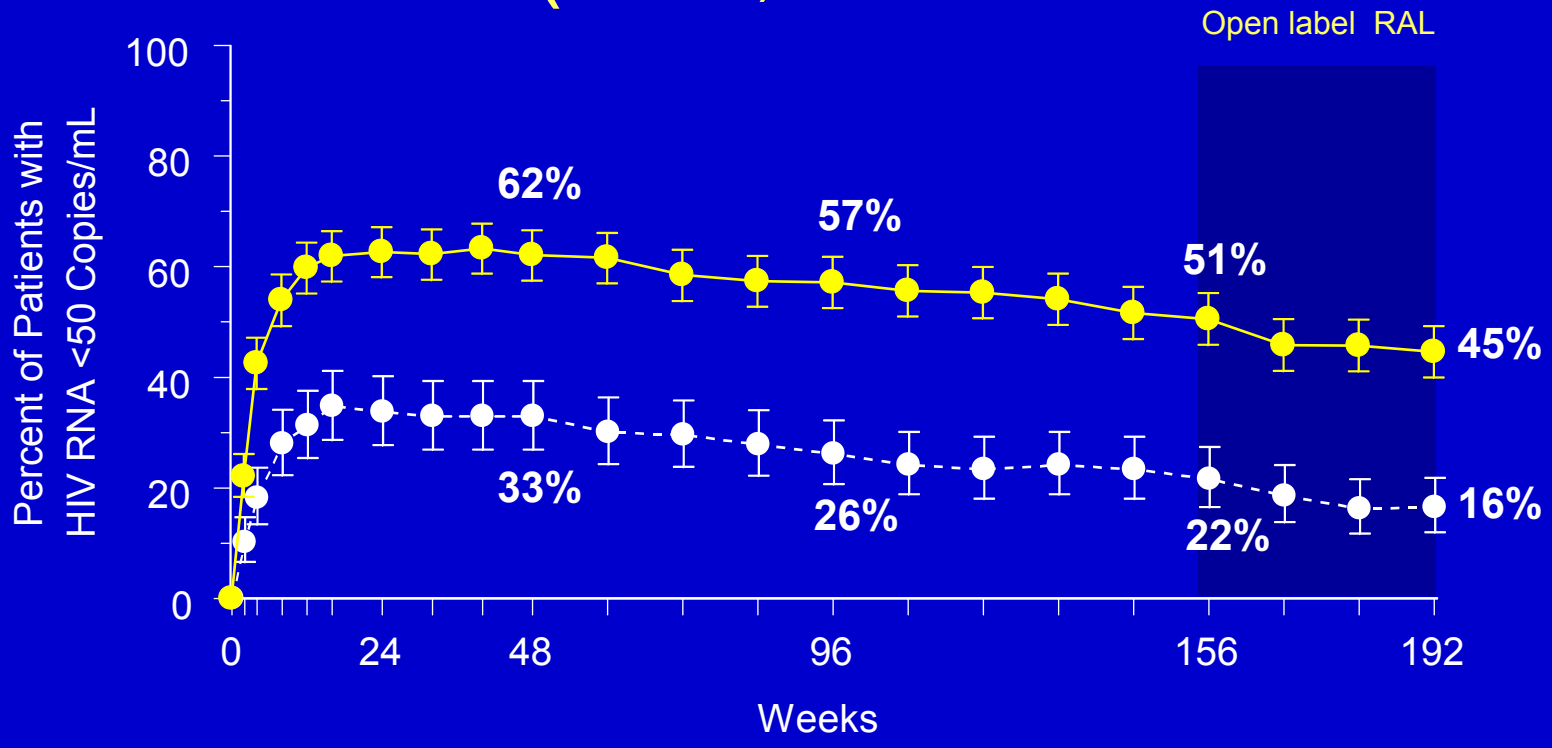
- Pre-defined endpoints examined at Week 192:
  - HIV RNA <50, <400 copies/mL
    - Non-Completer = Failure (NC=F) approach
  - Change from baseline in CD4 cell count
    - Observed Failure (OF) approach, baseline value carried forward for discontinuation due to lack of efficacy

Safety

- Clinical & laboratory adverse events: displayed in 2 ways due to greater exposure for RAL/RAL vs Pbo/RAL (mean 139 vs 78 weeks)
  - percent of patients (n/N) with event
  - exposure-adjusted event rates: number of patients with event /100 person-years (PYR) exposure

IAS 2011: Abstract # MOPE225

Patients Achieving HIV RNA <50 copies/mL (NC=F†)



Number of Contributing Patients

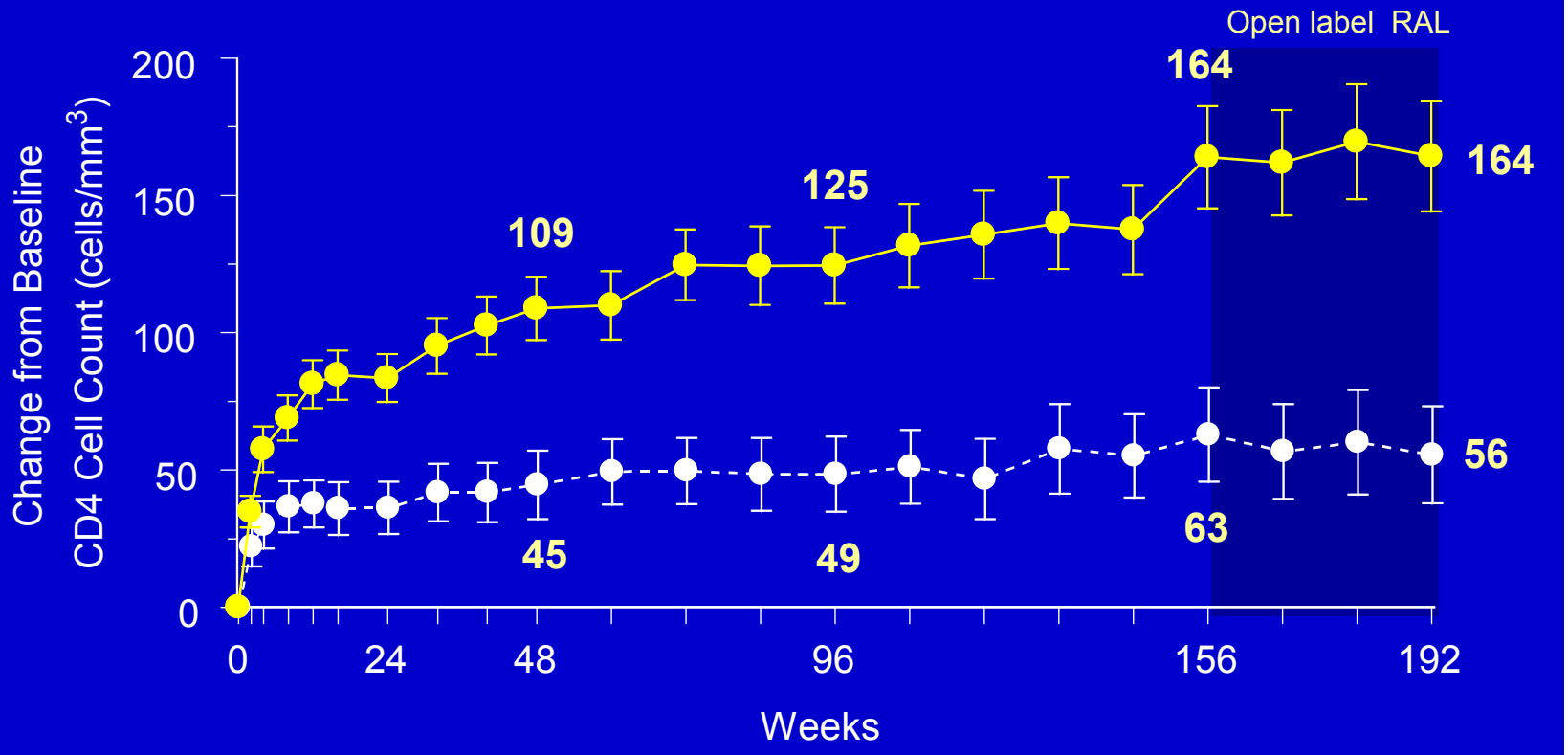
● Raltegravir + OBT	462	461	459	460	461	462
○ Placebo + OBT	237	237	237	237	236	237

Open label RAL

† Non-completer=failure approach; error bars indicate 95% confidence interval.

IAS 2011: Abstract # MOPE225

Change From Baseline in CD4 Cell Count (OF†)



Number of Contributing Patients

● Raltegravir + OBT	462	435	439	418	397	382
● Placebo + OBT	237	230	228	219	208	194
					Open label	RAL

† Observed Failure Approach: only discontinuations for lack of efficacy are counted as failures.

IAS 2011: Abstract # MOPE225

Table 3. Summary of Adverse Events (Week 192)

	RAL / RAL§ (N = 462)		Pbo / RAL§ (N = 237)	
Person-years (PYR) at risk	1232		356	
	%	(rate†)	%	(rate†)
Clinical Adverse Events	94.8	(35.6)	89.9	(59.8)
Drug-related ‡	60.2	(22.6)	60.8	(40.4)
Serious	31.8	(11.9)	24.1	(16.0)
Serious & drug-related	3.5	(1.3)	3.8	(2.5)
Deaths	3.9	(1.5)	3.8	(2.5)
Patient discontinued	4.5	(1.7)	5.9	(3.9)
Laboratory Adverse Events	35.7	(13.4)	28.3	(18.8)
Drug-related ‡	19.5	(7.3)	16.5	(11.0)
Serious	0.9	(0.3)	0.4	(0.3)
Serious & drug-related	0.2	(0.1)	0.0	(0.0)
Patient discontinued	0.2	(0.1)	0.0	(0.0)

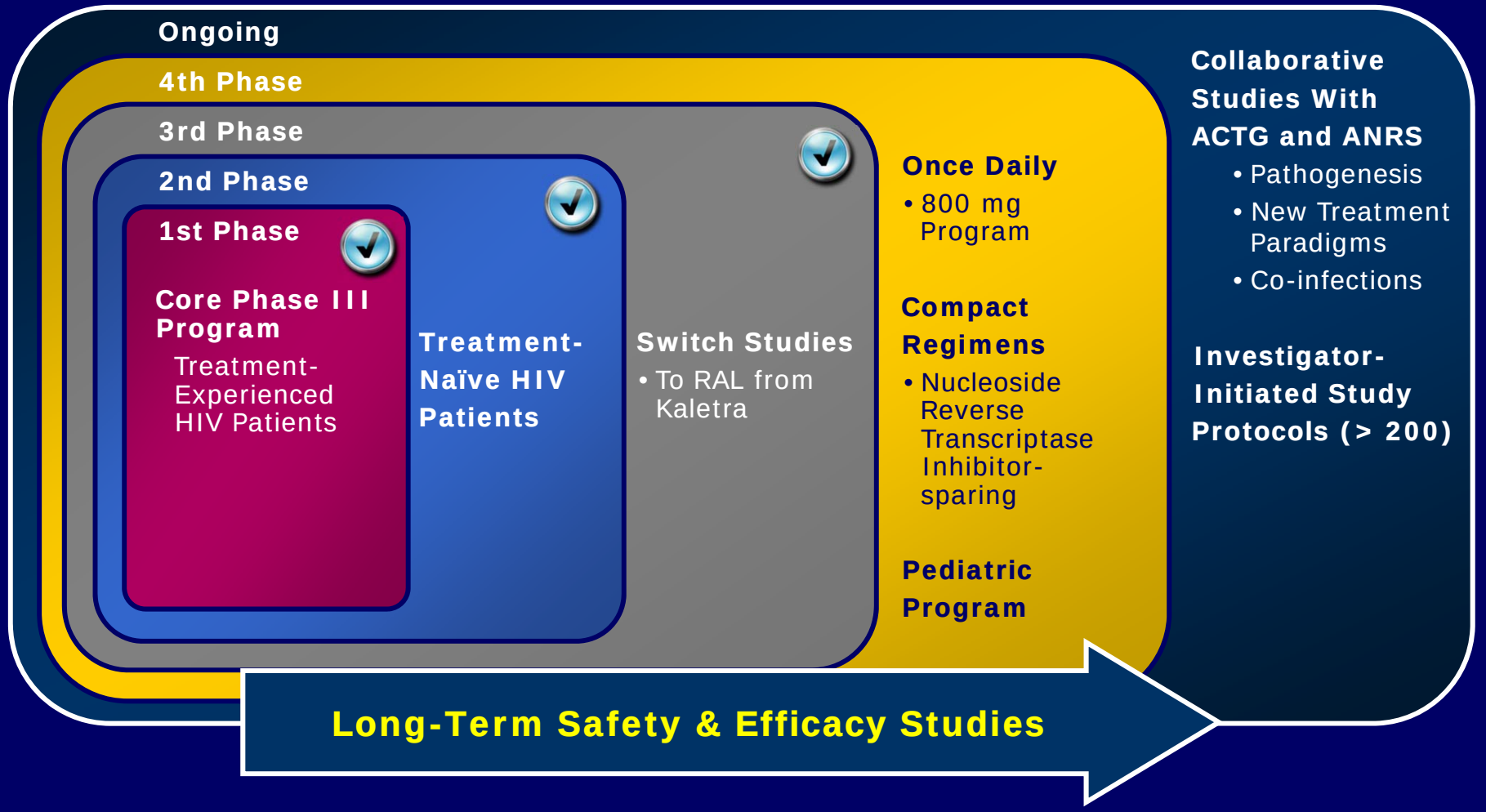
§ All patients also received optimized background therapy (OBT).
† per 100 person-years (PYR); for Pbo/RAL group, PYR includes 3 yrs on Pbo + 1 yr on RAL.
‡ Determined by site investigator to be possibly, probably, or definitely related to raltegravir or placebo (alone or in combination with OBT).

CONCLUSIONS

In HIV-infected, treatment-experienced patients failing ART with triple-class resistance:

- RAL 400 mg b.i.d. plus OBT had durable antiretroviral and immunological efficacy sustained through Week 192.
  - 45% in RAL group sustained vRNA < 50 cp/mL
- RAL 400 mg b.i.d. plus OBT was generally well tolerated.
  - Few discontinuations due to adverse events

Raltegravir Clinical Development



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IDSA 2011, Abstract 30623, Poster H.405

Raltegravir (RAL)-based Therapy Demonstrates Superior Virologic Suppression and Immunologic Response Compared with Efavirenz (EFV)-based Therapy, with a Favorable Metabolic Profile, Through 4 Years in Treatment-naïve Patients: 192 Week Results from STARTMRK

E. DeJesus[1], J. Rockstroh[2], J. Lennox[3], M. Saag[4], A. Lazzarin[5], H. Wan[6], A. Rodgers[6], K. Strohmaier[6], H. Teppler[6], B-Y. Nguyen[6], R. Leavitt[6], P. Sklar[6] and the STARTMRK Study Team

[1]Orlando Immunology Center, Orlando, FL; [2]University of Bonn, Bonn, Germany; [3]Emory University School of Medicine, Atlanta, GA; [4]University of Alabama, Birmingham, AL; [5]Universita Vita-Salute San Raffaele, Milan, Italy; [6]Merck, Whitehouse Station, NJ

Methods

- STARTMRK Study Design
  - Multicenter, double-blind, randomized (1:1), active-controlled study
    - RAL 400mg BID vs. EFV 600mg qhs
    - Both given with co-formulated TDF / FTC
  - Key inclusion criteria
    - Susceptible to EFV, TDF, FTC at entry
    - No prior antiretroviral therapy
    - HIV RNA >5000 c/mL

Methods

- Main Objectives
  - RAL + TDF/FTC will have non-inferior efficacy compared to EFV + TDF/FTC
    - Primary hypothesis time point: 48 weeks
    - Secondary hypothesis time point: 96 weeks
    - Long term follow-up through 5 years; study remains double-blind; efficacy analyses beyond 96 weeks are exploratory
    - Efficacy endpoints: vRNA <50 copies/mL, CD4 change from baseline
  - RAL + TDF/FTC will be generally safe and well tolerated
    - Safety endpoints: Lipid changes from baseline, other selected laboratory abnormalities, clinical adverse events (AEs)

Methods

- Statistical Methodology
  - 3 pre-specified analytic approaches to missing data for efficacy analyses
    - Observed Failure (OF): Patients who discontinued tx due to lack of efficacy were considered as failures thereafter
    - Tx-Related Discontinuation=Failure (TRD=F): Patients who discontinued tx due to lack of efficacy or AE were considered as failures thereafter
    - Non-Completer=Failure (NC=F): Patients who discontinued tx regardless of reason were considered as failures thereafter

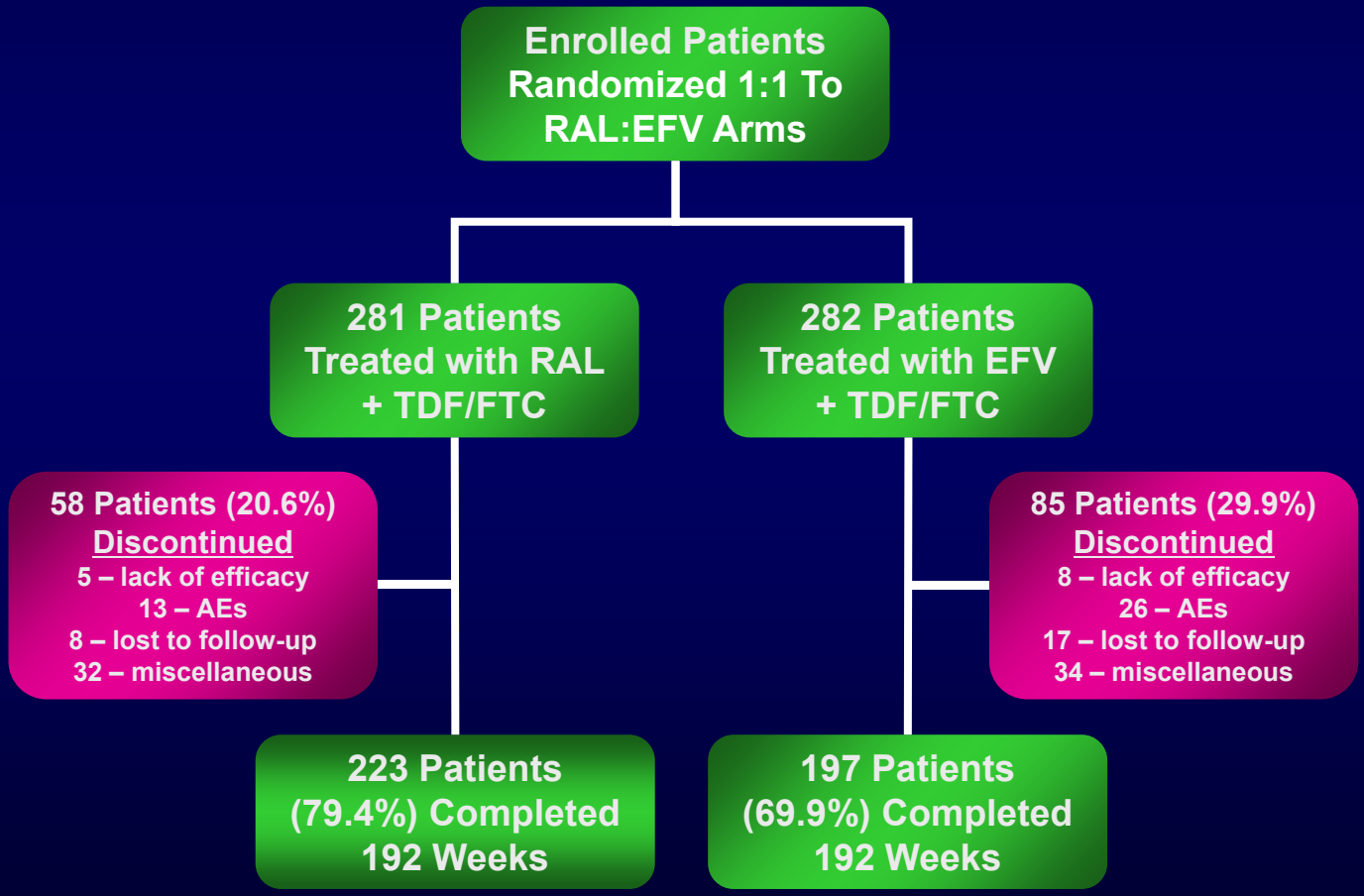
Methods

- Primary efficacy analysis: vRNA level <50 c/mL using NC = F approach for missing data
  - RAL is considered non-inferior to EFV if the lower bound of the two-sided 95% CI for the difference in response proportions (RAL-EFV) remains above -12 percentage points
  - Due to the principles of closed testing, it can be further concluded that RAL is superior to EFV if the lower confidence bound exceeds zero
- Secondary efficacy analysis: Change in CD4 count from baseline using OF approach
  - Baseline values carried forward for virologic failures

Methods

- Virologic Failure was defined as
  1) Non-responder for those with
     a) HIV RNA >50 copies/mL at the time of discontinuation for patients who prematurely discontinue study therapy or
     b) HIV RNA >50 copies/mL at Week 24; or
  2) Virologic rebound for those with HIV RNA >50 copies/mL (on 2 consecutive measurements at least 1 week apart or discontinuation after one measurement >50 copies/mL) after initial response with HIV RNA <50 copies/mL
- Safety analyses: treatment-emergent AEs and laboratory abnormalities were tabulated; data are cumulative through Week 192

Patient Disposition at Week 192



Baseline Characteristics (1)

	All Treated Patients	
	Raltegravir Group (N = 281)	Efavirenz Group (N = 282)
Gender, n (%)		
Male	227 (80.8)	231 (81.9)
Female	54 (19.2)	51 (18.1)
Race, n (%)		
White	116 (41.3)	123 (43.6)
Black	33 (11.7)	23 (8.2)
Asian	36 (12.8)	32 (11.3)
Hispanic	60 (21.4)	67 (23.8)
Other	36 (12.8)	37 (13.1)
Region, n (%)		
Latin America	99 (35.2)	97 (34.4)
Southeast Asia	34 (12.1)	29 (10.3)
North America	82 (29.2)	90 (31.9)
EU/Australia	66 (23.5)	66 (23.4)
Age (years)		
Mean (SD)	37.6 (9.0)	36.9 (10.0)
Median (min, max)	37 (19 to 67)	36 (19 to 71)

Baseline Characteristics (2)

	All Treated Patients	
	Raltegravir Group (N = 281)	Efavirenz Group (N = 282)
Hepatitis B or C Positive†, n (%)		
yes	18 (6.4)	16 (5.7)
CD4 Cell Count (cells/microL)		
Mean (SD)	218.9 (124.2)	217.4 (133.6)
Median (min, max)	212.0 (1 to 620)	204.0 (4 to 807)
≤ 50 cells/μL, n (%)	27 (9.6)	31 (11.0)
> 50 but ≤ 200 cells/μL, n (%)	104 (37.0)	105 (37.2)
> 200 cells/μL, n (%)	150 (53.4)	145 (51.4)
Plasma HIV RNA (copies/mL)		
Geometric Mean	103205	106215
Median (min, max)	114000 (400 to 750000)	104000 (4410 to 750000)
≤ 100,000 copies/mL, n(%)	127 (45.2)	139 (49.3)
> 100,000 copies/mL, n (%)	154 (54.8)	143 (50.7)
Viral Subtype n (%)		
Clade B	219 (77.9)	230 (81.6)
Non-Clade B	59 (21.0)	47 (16.7)
missing	3 (1.1)	5 (1.8)

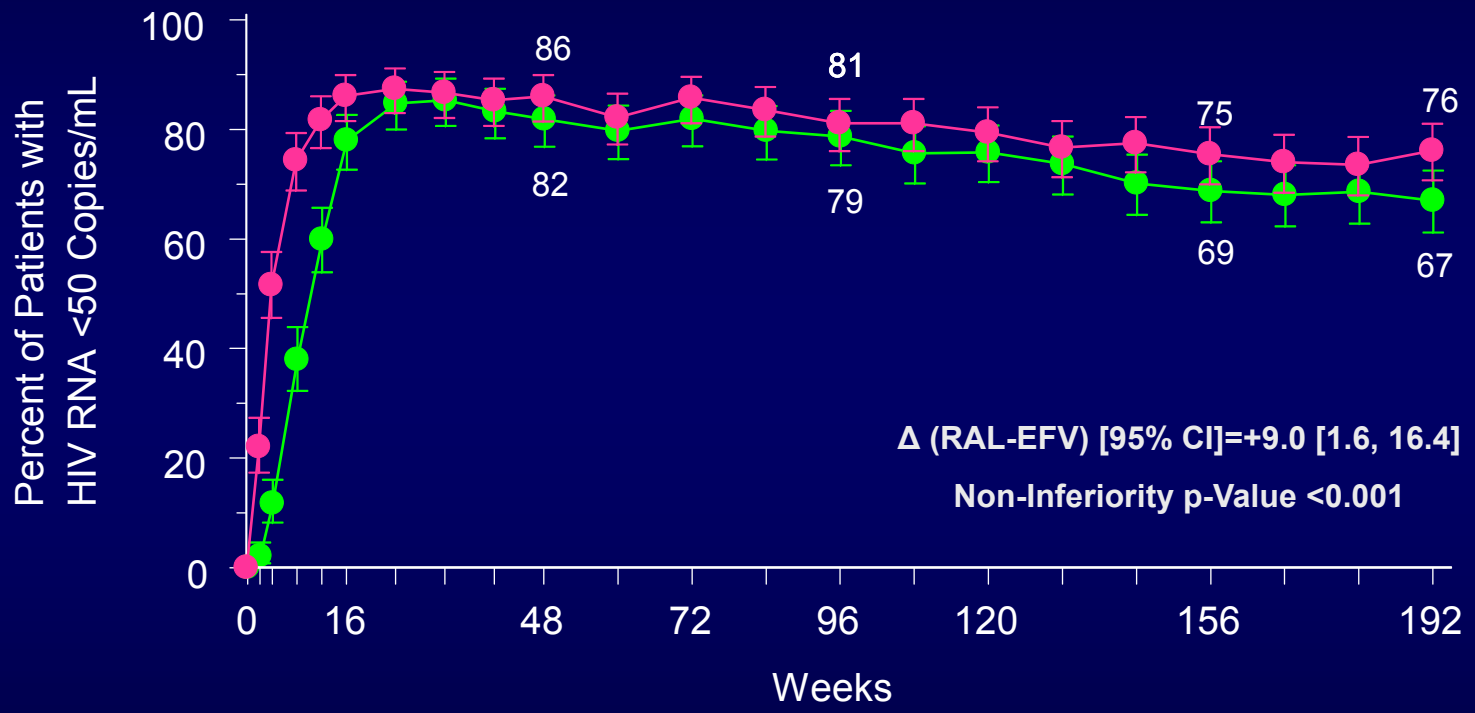
† Evidence of hepatitis B surface antigen or evidence of HCV RNA by polymerase chain reaction (PCR) quantitative test for hepatitis C Virus.

Proportion of Patients with HIV RNA < 50 copies/mL (NC=F)

	Raltegravir	Efavirenz	Treatment Difference‡
	n/N (%)	n/N (%)	% (95% CI)
Week 48	241/280 (86.1)	230/281 (81.9)	4.2 (-1.9, 10.3)
Week 96	228/281 (81.1)	222/282 (78.7)	2.4 (-4.3, 9.0)
Week 144	217/280 (77.5)	197/281 (70.1)	7.3 (0.0, 14.5)
Week 192	214/281 (76.2)	189/282 (67.0)	9.0 (1.6, 16.4)

‡ 95% CIs and p-values for non-inferiority for treatment differences in percent response were calculated using Miettinen and Nurminen's method with weights proportional to the size of each stratum (screen HIV RNA>50,000 copies/mL or ≤ 50,000 copies/mL). Raltegravir is considered non-inferior to Efavirenz if the lower bound of the 95% CI for the difference in percent response is above -12 percentage points. It can be further concluded that Raltegravir is superior to Efavirenz if the lower bound exceeds zero.

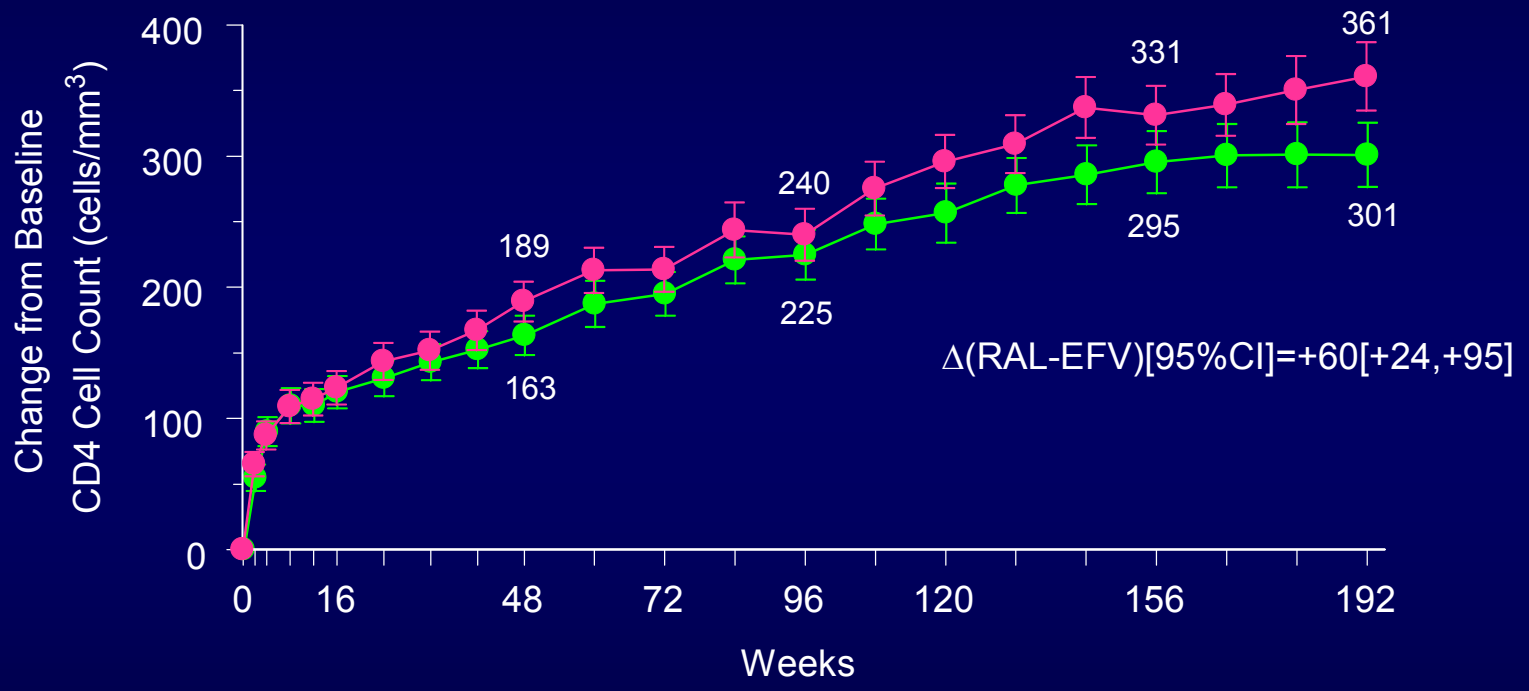
Proportion (%) of Patients (95% CI) with HIV RNA < 50 copies/mL (Non-Completer = Failure)



Number of Contributing Patients

Raltegravir group	281	281	280	281	281	277	281	281
Efavirenz group	282	281	281	282	282	281	282	282

Change from Baseline in CD4 Cell Count (Observed Failure Approach)



Number of Contributing Patients

Raltegravir group	281	270	258	255	250	240	237	235
Efavirenz group	281	269	251	252	243	234	228	219

Summary of Efficacy at Week 192

	Proportion of Patients (%, n/N) with HIV RNA < 50 copies/mL			CD4 Cell Count, Change from BL (cells/mm^3)
	NC=F	TRD=F	OF	OF‡
RAL (N=281)	76.2 (214/281)	86.3 (214/248)	91.1 (214/235)	360.7
EFV (N=282)	67.0 (189/282)	76.2 (189/248)	85.1 (189/222)	300.9
RAL - EFV†, §	9.0* (1.6, 16.4)	10.1* (3.3, 17.0)	6.0* (0.1, 12.2)	59.8 (24.1, 95.4)

† Difference between RAL and EFV (95%CI)
* p-value for non-inferiority <0.001
§ RAL is considered non-inferior to EFV if the lower bound of the 95% CI for the difference in % response was above -12%, and superior to EFV if the lower bound exceeds 0.
‡ BL values carried forward for virologic failures.

Cumulative Resistance at Week 192

Raltegravir group (N=281)	FTC Sensitive (12)	FTC Resistant (6)	TDF Sensitive (18)	TDF Resistant (0)	RT not amplified (3)
RAL Sensitive (12)	9	1	10	0	2
RAL Resistant (4)#	0	3*	3	0	1
IN not amplified (5)	3	2	5	0	0

#4/281 (1.4%) developed proven IN resistance
***3/281 (1.1%) developed proven dual IN/RTI resistance**

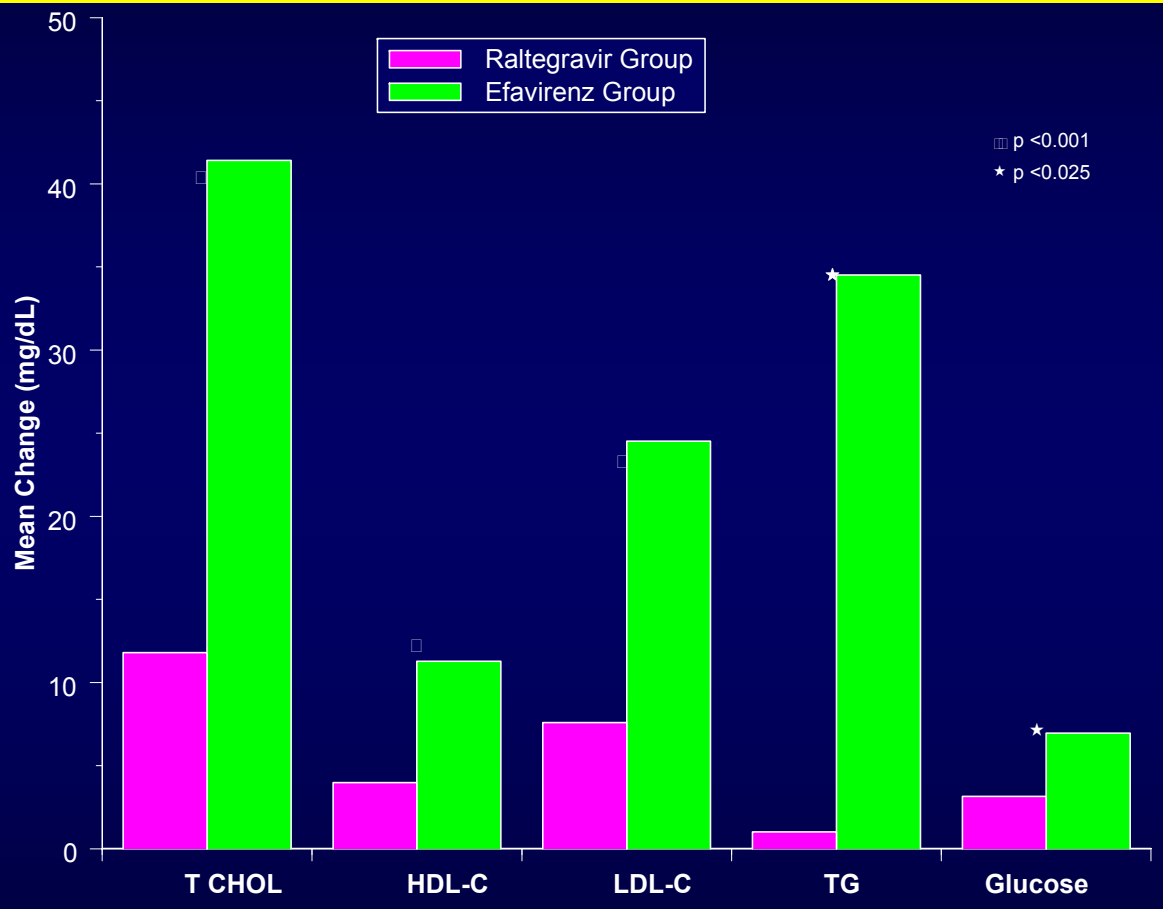
Efavirenz group (N=282)	FTC Sensitive (9)	FTC Resistant (5)	TDF Sensitive (13)	TDF Resistant (1)	RT not amplified (3)
EFV Sensitive (7)	5	2	7	0	0
EFV Resistant (7) #	4	3*	6	1*	0
RT not amplified (3)	0	0	0	0	3

#7/282 (2.5%) developed proven NNRTI resistance
***3/282 (1.1%) developed proven dual NNRTI/RTI resistance**

Interval Resistance Data from Week 156 to Week 192

- Between Weeks 156 and 192, there were 4 new patients (3 in the RAL group and 1 in the EFV group) who met the protocol definition of virologic failure
  - 1/4 patients (1 in the RAL group and 0 in the EFV group) had vRNA >400c/mL and evaluable resistance data
- 0/1 patients with evaluable data in the RAL group had detectable resistance to any of the drugs in their regimen
- No patient in the RAL group has failed with detectable resistance to RAL since Week 96
- 2 patients in the EFV group have failed with detectable resistance to EFV since Week 96

Mean Change from Baseline† in Metabolic Parameters at Week 192



- The change from baseline in the Total CHOL:HDL-C ratio was -0.17 for the RAL group and 0.02 for EFV group (p=0.177).

† Last Observation Carried Forward approach. If patients initiated lipid-lowering therapy, last available lipid values prior to the use of lipid-lowering therapy were used in the analysis.

Number (%) of Patients with Selected Laboratory Abnormalities at Week 192 (1)

Laboratory Test	PDLC Criteria	Grade	Number (%) with PDLC	
			RAL 400 mg BID (N=281) n/m (%)	EFV 600 mg qhs (N=282) n/m (%)
blood chemistry test				
Fasting LDL-C (mg/dL)	160 – 189	Grade 2	21/271 (7.7)	32/262 (12.2)
	≥190	Grade 3	5/271 (1.8)	25/262 (9.5)
Fasting Cholesterol (mg/dL)	240 – 300	Grade 2	27/276 (9.8)	47/267 (17.6)
	>300	Grade 3	0/276 (0)	17/267 (6.4)
Fasting Triglycerides (mg/dL)	500 – 750	Grade 2	3/276 (1.1)	12/267 (4.5)
	751-1200	Grade 3	1/276 (0.4)	4/267 (1.5)
	>1200	Grade 4	0/276 (0.0)	4/267 (1.5)
Fasting Glucose (mg/dL)	126 – 250	Grade 2	13/274 (4.7)	15/266 (5.6)
	251 – 500	Grade 3	5/274 (1.8)	2/266 (0.8)
	>500	Grade 4	0/274 (0.0)	0/266 (0.0)
Total Bilirubin (mg/dL)	1.6 – 2.5 × ULN	Grade 2	13/281 (4.6)	0/279 (0.0)
	2.6 – 5.0 × ULN	Grade 3	2/281 (0.7)	0/279 (0.0)

Only patients with a worsened grade from baseline were included in this analysis. ULN, upper limit of normal. No Grade 4 events were reported for fasting LDL-C, fasting cholesterol, or total bilirubin.

Number (%) of Patients with Selected Laboratory Abnormalities at Week 192 (2)

Laboratory Test	PDLC Criteria	Grade	Number (%) with PDLC	
			RAL 400 mg BID (N=281) n/m (%)	EFV 600 mg qhs (N=282) n/m (%)
blood chemistry test				
Creatinine (mg/dL)	1.4 – 1.8 x ULN	Grade 2	2/281 (0.7)	2/279 (0.7)
	1.9 – 3.4 x ULN	Grade 3	0/281 (0.0)	1/279 (0.4)
	≥3.5 x ULN	Grade 4	0/281 (0.0)	0/279 (0.0)
Aspartate aminotransferase (IU/L)	2.6 – 5.0 x ULN	Grade 2	16/281 (5.7)	23/279 (8.2)
	5.1 – 10.0 x ULN	Grade 3	12/281 (4.3)	8/279 (2.9)
	>10.0 x ULN	Grade 4	3/281 (1.1)	1/279 (0.4)
Alanine aminotransferase (IU/L)	2.6 – 5.0 x ULN	Grade 2	29/281 (10.3)	31/279 (11.1)
	5.1 – 10.0 x ULN	Grade 3	4/281 (1.4)	5/279 (1.8)
	>10.0 x ULN	Grade 4	4/281 (1.4)	2/279 (0.7)
Alkaline phosphatase (IU/L)	2.6 – 5.0 x ULN	Grade 2	3/281 (1.1)	9/279 (3.2)
	5.1 – 10.0 x ULN	Grade 3	0/281 (0.0)	1/279 (0.4)
	>10.0 x ULN	Grade 4	1/281 (0.4)	1/279 (0.4)

Only patients with a worsened grade from baseline were included in this analysis. ULN, upper limit of normal.

Clinical Adverse Events

- Overall clinical AEs:
  - RAL 269 (95.7%) vs. EFV 276 (97.9%), p=0.160
- Drug-related clinical AEs:
  - RAL 141 (50.2%) vs. EFV 226 (80.1%), p<0.001
- Patients discontinued due to clinical AE:
  - RAL 14 (5.0%) vs. EFV 23 (8.2%), p=0.173

Serious Clinical Adverse Events

- RAL 50 (17.8%) vs. EFV 52 (18.4%), p=0.913
  - Deaths (cumulative): RAL 5 (1.8%) vs. EFV 2 (0.7%)
    - Cause of death: Kaposi's sarcoma, lung CA (x2), drug toxicity/alcohol poisoning, and cerebral hemorrhage in RAL group; sepsis and unknown (not reported) in EFV group
    - 3 patients died since Week 156: 1 in RAL group (lung CA) and 2 in EFV group (sepsis and cause unknown)
    - None of the deaths were considered drug related
  - 14 new serious clinical AEs between Week 156 and 192
    - 7 in RAL group: migraine (x2), depression, meningitis, basal cell carcinoma, Kaposi's sarcoma, back pain
    - 7 in EFV group: lymphoma, endometritis, death, pancreatitis, anemia, mononucleosis, tuberculosis
    - One new SAE (pancreatitis) was considered possibly related to EFV (alone or in combination with TDF/FTC)

Most Common Drug-Related† Clinical AEs

	RAL 400 mg BID (N = 281) n (%)	EFV 600 mg qhs (N = 282) n (%)
Diarrhea	14 (5.0)	27 (9.6)
Nausea	25 (8.9)	29 (10.3)
Fatigue	12 (4.3)	25 (8.9)
Dizziness	18 (6.4)	99 (35.1)
Headache	26 (9.3)	40 (14.2)
Abnormal dreams	19 (6.8)	37 (13.1)
Insomnia	19 (6.8)	23 (8.2)
Nightmares	8 (2.8)	15 (5.3)
Rash	3 (1.1)	23 (8.2)

† determined by investigator to be possibly, probably, or definitely related to RAL or EFV alone or in combination with TDF/FTC; incidence >5% in either treatment group.

Conclusions

- After 4 years of treatment, RAL + TDF/FTC is associated with superior antiretroviral efficacy and CD4 responses vs EFV + TDF/FTC in treatment-naïve patients
  - HIV suppression <50 copies/mL maintained in 76.2% of RAL group vs 67.0% of EFV group [tx difference, 9.0% (95% CI, 1.6 - 16.4)]
  - Mean change from baseline in CD4 count was 361 for RAL group and 301 for EFV group [tx difference, 60 (95% CI, 24 - 95)]
- The long-term tolerability and metabolic profile of RAL + TDF/FTC remain favorable
  - Drug-related clinical AEs occurred less often with RAL than EFV
  - RAL was generally well tolerated with few discontinuations due to clinical AEs
  - At week 192, RAL had less impact on fasting lipids than EFV

Long-term Efficacy of Raltegravir or Efavirenz Combined with TDF/FTC in Treatment-naïve HIV-1-infected Patients: *Week-192 Subgroup Analyses from STARTMRK*

J. K. Rockstroh, A. Lazzarin, J. Zhao,
A. Rodgers, M. J. DiNubile, B-Y. Nguyen,
R. Leavitt, H. Teppler, and P. Sklar
for the STARTMRK Study Team

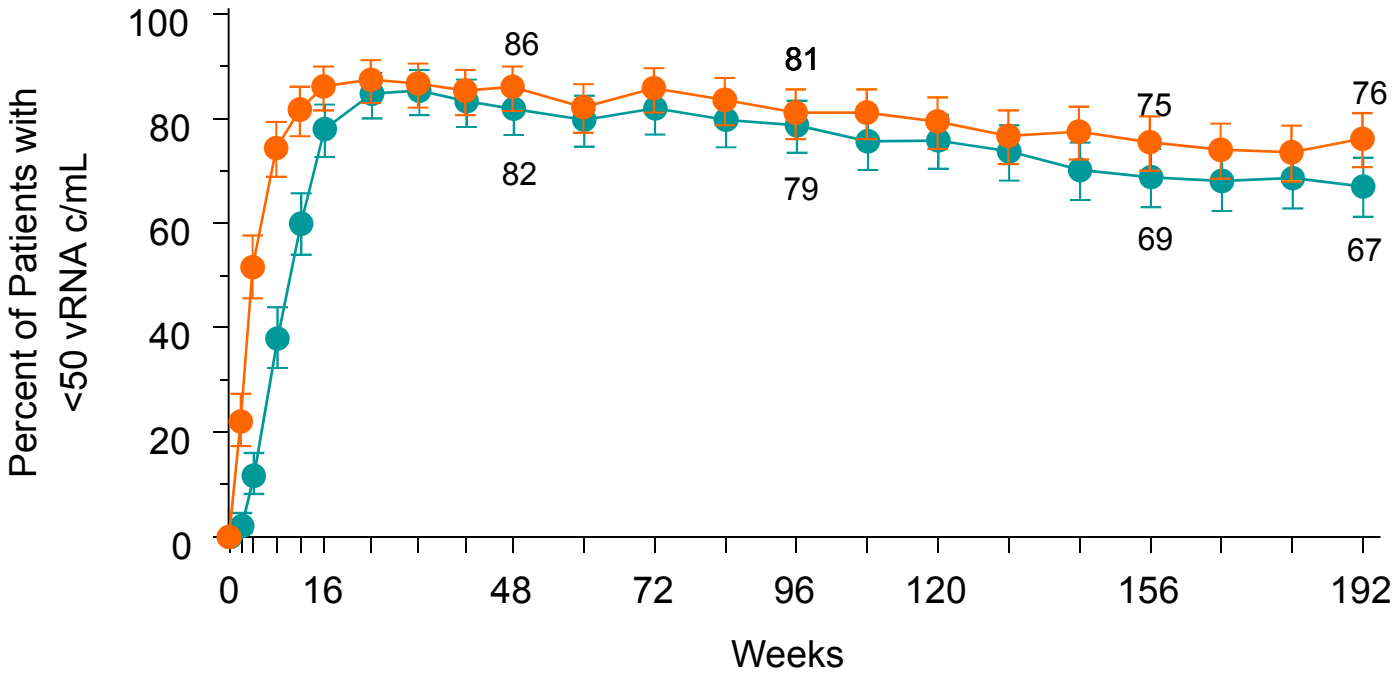
Data Analysis Plan: Efficacy

- Efficacy hypothesis
  - RAL would have non-inferior efficacy compared to EFV
    - Efficacy defined as proportion of patients with vRNA <50 c/mL
    - Between-group differences calculated as the response rate in the RAL group minus the response rate in the EFV group
- Primary (and secondary) analyses
  - Wk 48 (and Wk 96)
  - Non-Completer = Failure approach to missing data
  - 12% non-inferiority margin
- Prespecified exploratory analyses
  - To be performed yearly at Wks 156, 192, and 240
  - Includes subgroup analyses using Observed-Failure (OF) approach
    - Emphasizes virologic effect
    - D/C due to lack of efficacy considered as a failure
      - Patients with D/Cs other than for lack of efficacy excluded

Objectives of Subgroup Analyses

- **To assess the consistency of virologic and immunologic effects of RAL relative to EFV at Week 192 across pre-specified subgroups based on demographic and prognostic factors at baseline, including:**
  - **Demographics**
  - **HIV subtype (clade B *vs* non-B clades)**
  - **Viral load**
  - **CD4 cell count**
  - **Hepatitis B and/or C co-infection**

Proportion of Patients with <50 vRNA c/mL Over Time (Primary NC=F Approach)

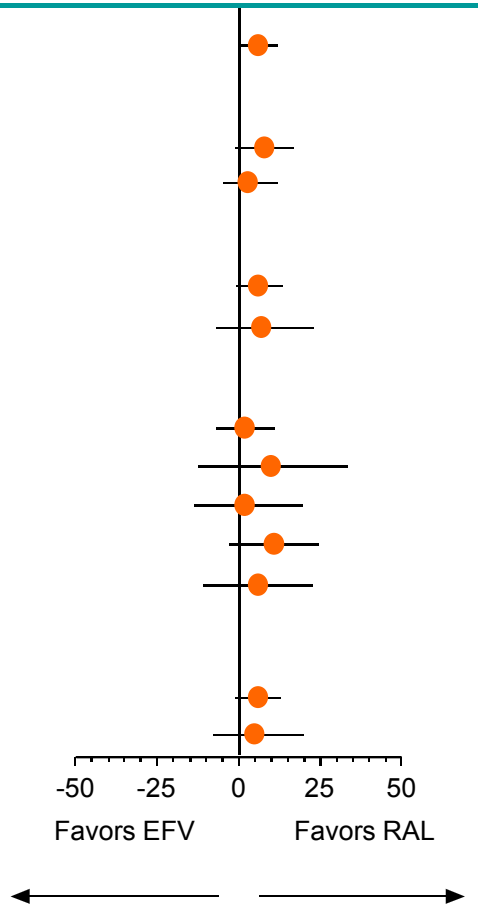


Number of Contributing Patients

Raltegravir group	281	281	280	281	281	277	281	281
Efavirenz group	282	281	281	282	282	281	282	282

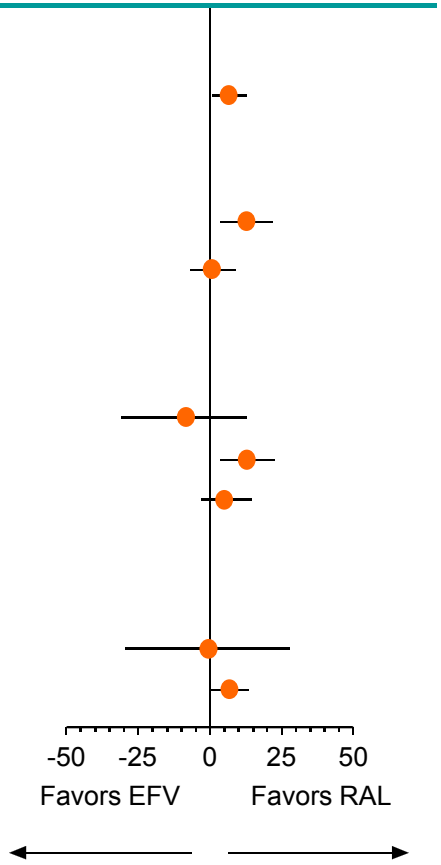
Proportion of Patients with <50 vRNA c/mL at Wk 192 by Demographic Factors (OF Approach)

	RAL Group n/N (%)	EFV Group n/N (%)
Total	214/235 (91)	189/222 (85)
Age (years)		
≤Median	109/122 (89)	105/129 (81)
>Median	105/113 (93)	84/93 (90)
Gender		
Male	173/191 (91)	157/185 (85)
Female	41/44 (93)	32/37 (86)
Race		
White	86/93 (92)	75/83 (90)
Black	21/24 (88)	17/22 (77)
Asian	31/34 (91)	25/28 (89)
Hispanic	47/53 (89)	44/57 (77)
Multiracial	28/30 (93)	28/32 (88)
Viral Subtype		
Clade B	164/181 (91)	149/177 (84)
Non-Clade B	47/51 (92)	35/40 (88)



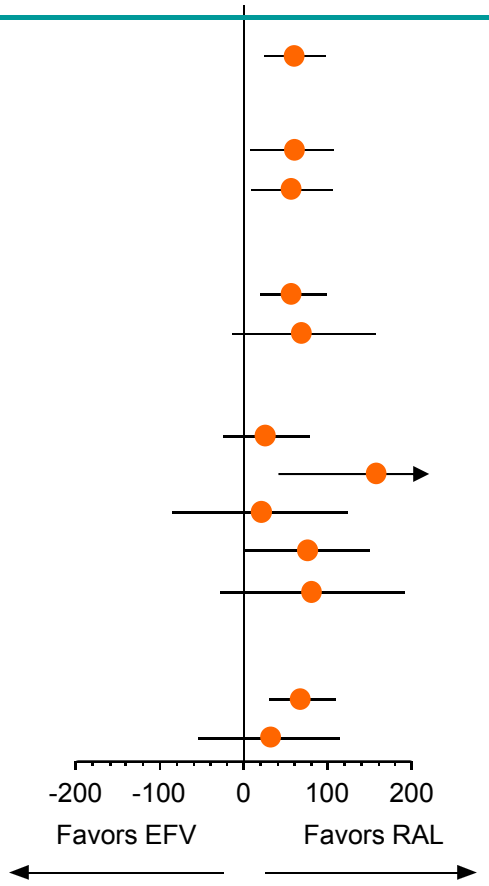
Proportion of Patients with <50 vRNA c/mL at Wk 192 by Baseline Prognostic Factors (OF Approach)

	RALGroup n/N (%)	EFV Group n/N (%)	Difference in Response Rates % (95% CI)
Total	214/235 (91)	189/222 (85)	
Baseline Plasma HIV RNA (c/mL)			
≤100,000	98/105 (93)	86/106 (81)	
>100,000	116/130 (89)	103/116 (89)	
Baseline CD4 Counts (cells/mm^3)			
≤50	17/22 (77)	25/29 (86)	
>50 and ≤200	84/88 (95)	71/85 (84)	
>200	113/125 (90)	93/108 (86)	
Hepatitis Status			
Hepatitis B or C Positive	11/12 (92)	12/13 (92)	
Both Hepatitis B and C Negative	203/223 (91)	177/209 (85)	



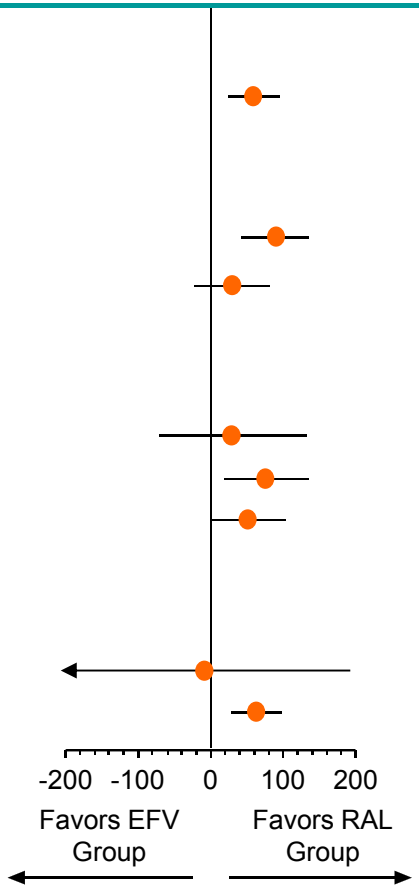
Change from Baseline in CD4-cells/mm^3 at Wk 192 by Demographic Factors (OF Approach)

	RAL Group Mean (95% CI)	EFV Group Mean (95% CI)
Total	361 (335, 387)	301 (277, 325)
Age (years)		
≤Median	358 (320, 396)	297 (262, 333)
>Median	364 (327, 400)	306 (273, 338)
Gender		
Male	362 (332, 392)	304 (278, 330)
Female	355 (300, 410)	285 (217, 354)
Race		
White	362 (325, 399)	335 (297, 372)
Black	366 (278, 455)	206 (120, 292)
Asian	337 (267, 407)	316 (233, 398)
Hispanic	356 (301, 412)	281 (231, 330)
Multiracial	387 (286, 489)	305 (248, 361)
Viral Subtype		
Clade B	366 (336, 396)	297 (271, 323)
Non-Clade B	340 (284, 395)	307 (239, 374)



Change from Baseline in CD4-cells/mm^3 at Wk 192 by Baseline Prognostic Factors (OF Approach)

	RAL Group Mean (95% CI)	EFV Group Mean (95% CI)
Total	361 (335, 387)	301 (277, 325)
Baseline Plasma HIV RNA (c/mL)		
≤100,000	351 (317, 386)	262 (228, 295)
>100,000	368 (330, 407)	337 (303, 372)
Baseline CD4 Counts (cells/mm^3)		
≤50	309 (217, 401)	279 (220, 339)
>50 and ≤ 200	398 (353, 443)	321 (283, 359)
>200	343 (310, 377)	291 (253, 329)
Hepatitis Status		
Hepatitis B or C Positive	375 (206, 544)	382 (249, 515)
Both Hepatitis B and C Negative	360 (334, 386)	296 (271, 321)



Conclusions

- In the STARTMRK trial of previously untreated patients, RAL/TDF/FTC demonstrated consistent virologic and immunologic efficacy relative to EFV/TDF/FTC across prespecified demographic and baseline prognostic factors, including:
  - Demographic subpopulations (including age, gender, region, race, hepatitis co-infection)
  - Baseline plasma vRNA level >100,000 copies/mL
  - Baseline CD4 count ≤200 cells/mm^3
  - Viral subtypes (comparing non-clade B vs clade B)
- The non-stratified nature of the subgroup analyses, especially for subgroups with small numbers, precludes definitive conclusions

ICAAC 2011, Abstract #2564, Poster H2-789

Safety, Tolerability, and Efficacy of Raltegravir (RAL) in a Diverse Cohort of HIV-Infected Patients (pts): 48-week Results from the REALMRK Study

K. SQUIRES[1], L-G. BEKKER[2], J. ERON[3], B. CHENG[4], J. ROCKSTROH[5], F. MARQUEZ[6], P. KUMAR[7], M. THOMPSON[8], R. CAMPO[9], K. MOUNZER[10], C. LU[11], A. RODGERS[11], B. JACKSON[11], M. ROBERTSON[11], B-Y. NGUYEN[11], P. SKLAR[11] and the REALMRK Investigators

[1]Jefferson Medical College, Philadelphia, PA; [2]Univ of Capetown, Capetown, South Africa; [3]Univ of North Carolina, Chapel Hill, NC; [4]Intl HIV Partners, Lake Forest Park, WA; [5]Univ of Bonn, Bonn-Venusburg, Germany; [6]Palm Springs Research Inst, Hialeah, FL; [7]Georgetown Univ, Washington DC; [8]AIDS Research Consortium, Atlanta, GA; [9]Univ of Miami, Miami, FL; [10]Philadelphia FIGHT, Philadelphia, PA; [11]Merck Research Labs, North Wales, PA

Background

- Raltegravir 400 mg BID is approved for the treatment of HIV-1 infection in treatment-naïve and treatment-experienced patients
- HIV-infected patients include increasing numbers of women and individuals from diverse racial and ethnic backgrounds
- <20% of patients in Phase III clinical trials of raltegravir were female, and <15% were black
- Additional efficacy and safety data for raltegravir are needed in these diverse patient populations and were specifically requested by US FDA

Study Design

- Multicenter, open-label, single-arm study
  - Conducted in North America (USA), South America (Brazil, Dominican Republic, Jamaica) and Southern Africa (South Africa)
  - Raltegravir 400 mg given BID for up to 48 weeks
    - In combination with additional ART, selected at baseline & limited to approved and licensed agents
- Categories of treatment experience
  - Treatment-experienced, failing current therapy
  - Treatment-experienced, intolerant to current therapy
  - Treatment-naïve (limited to ≤20% of total*)
- Enrollment targets
  - at least 25% female
  - at least 50% African-American (US black patients)

* as requested by FDA; raltegravir not yet approved for use in treatment-naïve patients at time of REALMRK study start.

Patient Recruitment & Retention

To ensure that the study met the goal of enrolling a diverse patient population, the following measures were taken:

Recruitment strategies

- Identify study sites with access to diverse patient populations
  - Potential sites were queried as to their ability to enroll ≥2 women and ≥4 black patients
- Limit enrollment of male and non-black patients
  - Accomplished through managed enrollment in the IVRS system
- Provide sufficient time for patient enrollment
  - Two year enrollment period was planned
  - First patient entered Oct 2008; last patient entered March 2010 (7 months ahead of schedule)

Patient Recruitment & Retention

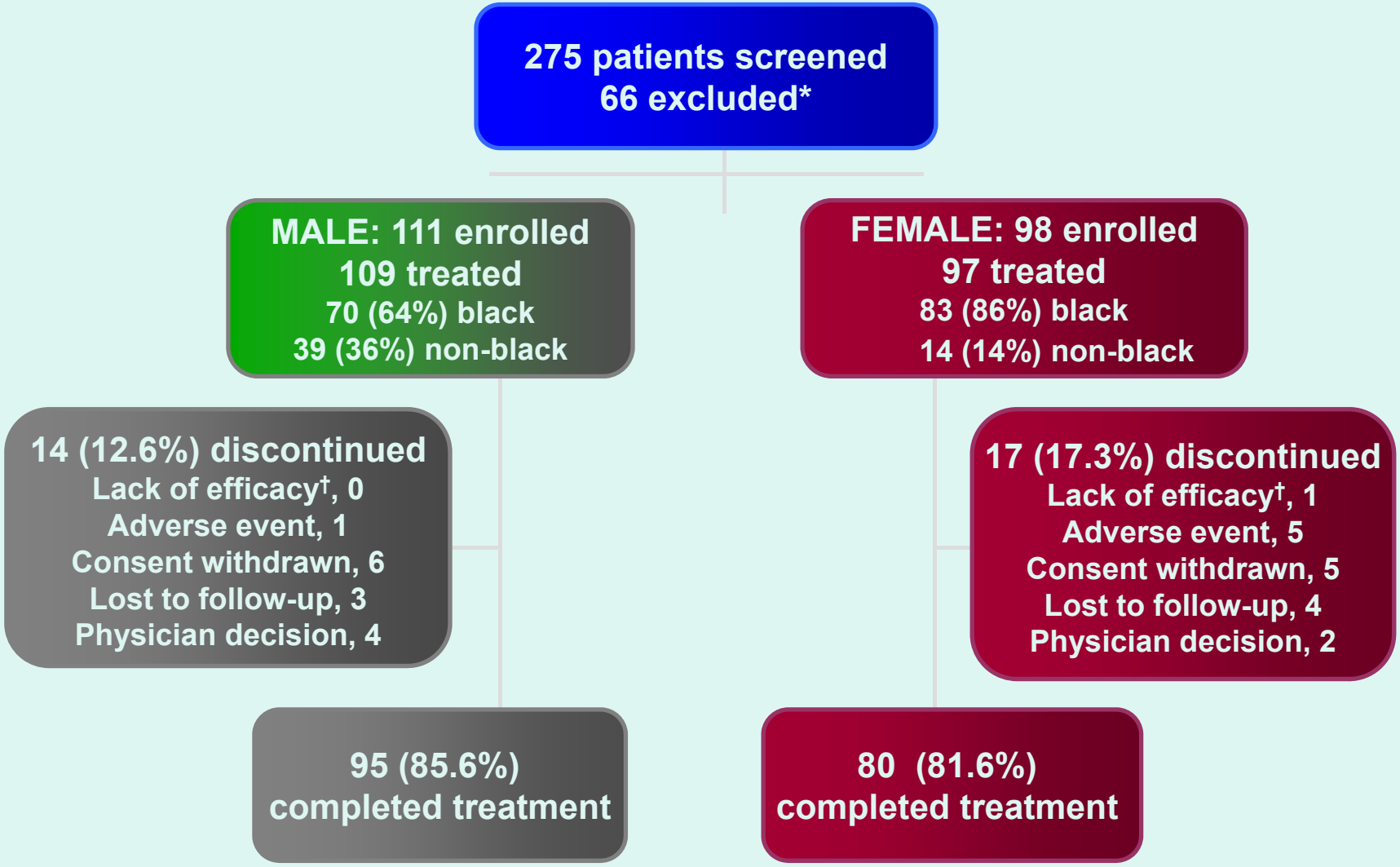
Retention strategies

- Select appropriate candidates for the study
  - Can they meet the time commitment for participation?
- Patient engagement & support
  - Educational programs/events
  - Follow-up phone calls between visits
  - Reimbursement for travel, childcare expenses
  - "Carry-all bags" for study medications
  - Provided with "Guide to Living with HIV Infection" (developed at Johns Hopkins AIDS Clinic)

Efficacy Analysis

- Full analysis set (FAS) population
- Time point of interest = 48 weeks
- Endpoints:
  - Proportion with HIV RNA < 50 copies/mL
    - Treatment-Related Discontinuation = Failure (TRD=F) approach: patients who discontinued due to lack of efficacy or adverse events were considered failures thereafter
    - Patients who discontinued before Week 48 for reasons other than lack of efficacy or adverse events were excluded from Week 48 analysis
  - Change from baseline in CD4 cell counts
    - Observed Failure (OF) approach: baseline value was carried forward for patients who discontinued due to lack of efficacy
    - Patients who discontinued before Week 48 for reasons other than lack of efficacy were excluded from Week 48 analysis

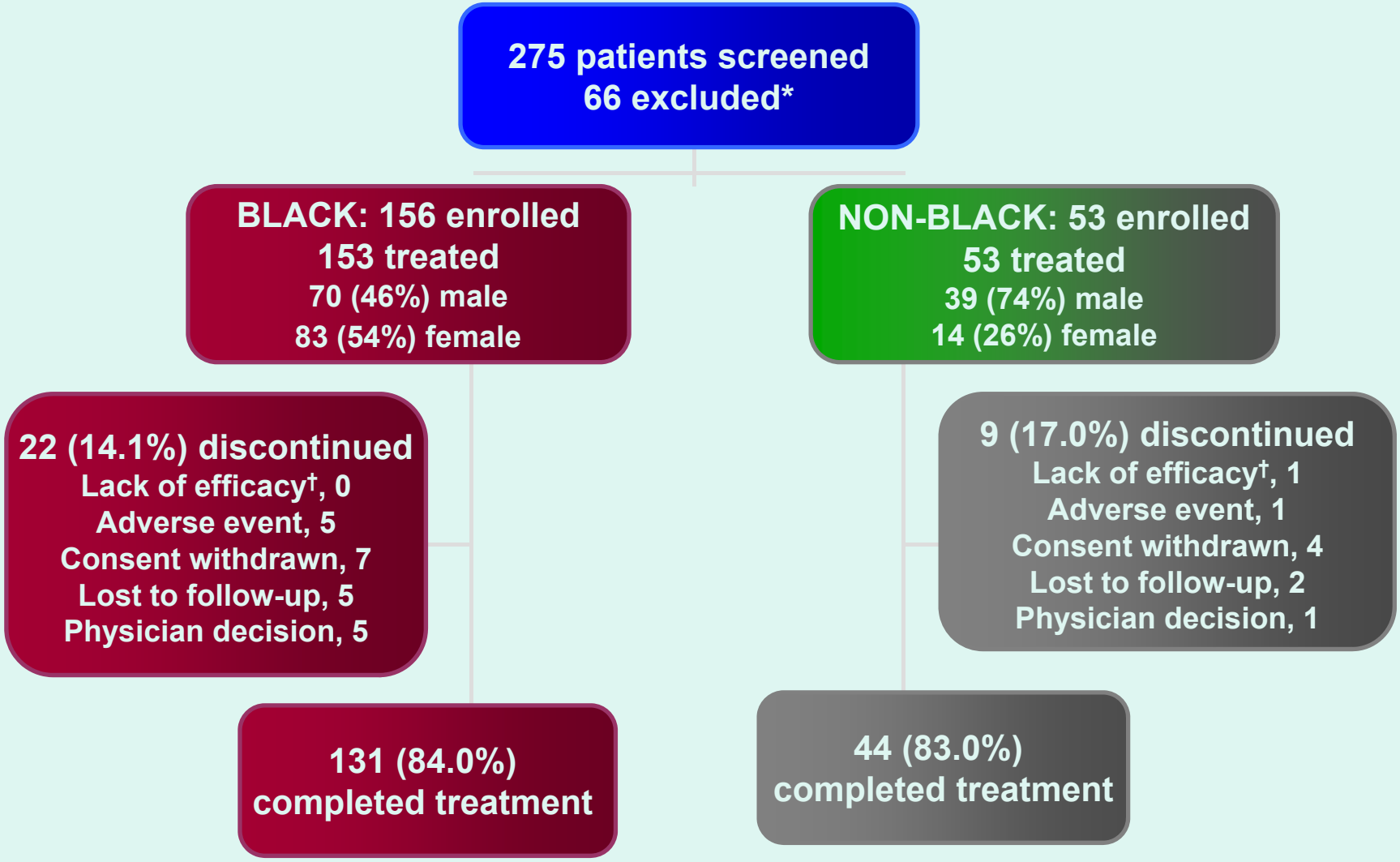
Patient Disposition by Gender



* 59 screen failures (29 unlikely to adhere to study procedures, 21 with confounding conditions, 11 with limited options for OBT, 8 for other reasons), 5 subjects withdrew, 1 adverse event, 1 lost to follow-up.

† as determined by investigator.

Patient Disposition by Race



* 59 screen failures (29 unlikely to adhere to study procedures, 21 with confounding conditions, 11 with limited options for OBT, 8 for other reasons), 5 subjects withdrew, 1 adverse event, 1 lost to follow-up.

† as determined by investigator.

Patient Disposition by Treatment Experience

	Previously Treated			
	Failure	**Intolerant**	**Treatment Naïve**	**Total**
	n (%)	n (%)	n (%)	n (%)
Enrolled	98	89	22	209
Treated	97 (99.0)	88 (98.9)	21 (95.5)	206 (98.6)
Completed study	85 (86.7)	72 (80.9)	18 (81.8)	175 (83.7)
Discontinued	12 (12.2)	16 (18.0)	3 (13.6)	31 (14.8)
lack of efficacy †	1 (1.0)	0	0	1 (0.5)
adverse event	3 (3.1)	2 (2.2)	1 (4.5)	6 (2.9)
consent withdrawn	3 (3.1)	6 (6.7)	2 (9.1)	11 (5.3)
lost to follow-up	3 (3.1)	4 (4.5)	0	7 (3.3)
physician decision	2 (2.0)	4 (4.5)	0	6 (2.9)

† as determined by investigator.

Baseline Patient Characteristics

	Previously Treated		Treatment Naïve	Total
	Failure (N=97)	**Intolerant**† (N=88)	(N=21)	(N=206)
Mean age (SD)	44.0 (9.2)	46.9 (9.0)	38.5 (10.1)	44.7 (9.5)
Gender, % Female	47.4	50.0	33.3	**47.1**
Race, % Black	72.2	78.4	66.7	**74.3**
Region, % North America	78.4	96.6	95.2	87.9
% South America	11.3	1.1	0	5.8
% South Africa	10.3	2.3	4.8	6.3
vRNA copies/mL (median)	15100	49	85700	6440
% with vRNA $>10^5$ copies/mL	20.6	10.2	42.9	18.4
Median CD4 count (cells/µl)	190	375	168	236
% with CD4 ≤200 cells/µl	53.6	23.9	57.1	41.3
% Hepatitis B or C	13.4	13.6	9.5	13.1
% Non-Clade B	13.4	2.3	9.5	8.3

† Among patients intolerant to prior therapy, 62.5% had HIV RNA < 50 copies/mL at baseline.

% of Patients with HIV RNA < 50 copies/mL† at Week 48

	Previously Treated							
	Failure		Intolerant ‡		Treatment Naive		Total	
	n/N	% (95% CI)	n/N	% (95% CI)	n/N	% (95% CI)	n/N	% (95% CI)
Male	33/50	66.0 (51.2, 78.8)	33/41	80.5 (65.1, 91.2)	10/14	71.4 (41.9, 91.6)	76/105	72.4 (62.8, 80.7)
Female	27/44	61.4 (45.5, 75.6)	28/39	71.8 (55.1, 85.0)	6/7	85.7 (42.1, 99.6)	61/90	67.8 (57.1, 77.2)
Black	44/69	63.8 (51.3, 75.0)	43/62	69.4 (56.3, 80.4)	11/14	78.6 (49.2, 95.3)	98/145	67.6 (59.3, 75.1)
Non-black	16/25	64.0 (42.5, 82.0)	18/18	100 (81.5, 100)	5/7	71.4 (29.0, 96.3)	39/50	78.0 (64.0, 88.5)
Total	60/94	63.8 (53.3,73.5)	61/80	76.3 (65.4, 85.1)	16/21	76.2 (52.8, 91.8)	137/195	70.3 (63.3, 76.6)
‡ BL HIV RNA ≤50 copies/mL			44/50	88.0 (75.7, 95.5)				
‡ BL HIV RNA >50 copies/mL			17/30	56.7 (37.4, 74.5)				

† Treatment-Related Discontinuation = Failure (TRD=F) approach

CD4 Cell Count (cells/mm^3)
Change from Baseline to Week 48†

	Previously Treated							
	Failure		**Intolerant**		**Treatment Naive**		**Total**	
	N	Mean change (95% CI)	N	Mean change (95% CI)	N	Mean change (95% CI)	N	Mean change (95% CI)
Male	48	111 (77, 145)	38	55 (15, 94)	13	146 (59,232)	99	94 (69, 119)
Female	41	161 (120, 202)	38	73 (27, 119)	6	294 (140, 448)	85	131 (99, 163)
Black	66	141 (110, 173)	61	62 (27, 98)	12	209 (109, 309)	139	112 (88,136)
Non-black	23	113 (62, 164)	15	69 (17, 122)	7	164 (13, 316)	45	106 (70,143)
Total	89	134 (107, 160)	76	64 (34, 93)	19	193 (117, 268)	184	111 (91,131)

† Observed failure (OF) approach

Summary of PK Parameters

	Female		Male		Ratio (Female / Male)	
	N	LS Mean (% CV) †	N	LS Mean (% CV) †	GMR (90% CI)	P-value
C_{all} (nM)	91	338 (147)	105	381 (134)	0.89 (0.69, 1.13)	0.422
GM C_{12hr} (nM)	60	331 (137)	58	282 (165)	1.17 (0.84, 1.64)	0.423
C_{min} (nM)	91	99 (196)	105	83 (197)	1.20 (0.89, 1.61)	0.322
	Black		**Non-Black**		**Ratio (Black / Non-Black)**	
	N	LS Mean (% CV) †	N	LS Mean (% CV) †	GMR (90% CI)	P-value
C_{all} (nM)	146	353 (121)	50	385 (203)	0.92 (0.69, 1.22)	0.613
GM C_{12hr} (nM)	90	285 (139)	28	385 (186)	0.74 (0.50, 1.09)	0.199
C_{min} (nM)	146	93 (189)	50	80 (221)	1.17 (0.83, 1.64)	0.457

† Back-transformed from log scale. LS Mean = Geometric Least-Squares Mean;

% CV = 100 x sqrt(exp(s2)-1), where s2 is the observed variance on the natural log scale.

Summary of Virologic Failures and Resistance Data

	Previously Treated		
No. of patients with:	Failing (N=97)	Intolerant (N=88)	Treatment-Naïve (N=21)
Virologic Failure †	30	13	5
Resistance data available	24	11	3
RAL 'signature' mutations	9	2	0
AA 148	6	0	0
AA 155	4	2	0
Other RAL resistance mutations*	1	0	1
No RAL resistance mutations	14	9	2

† (1) HIV RNA >50 copies/mL at Week 24 (confirmed at least 1 week apart), OR (2) virologic relapse after initial response: HIV RNA >50 copies/mL (on 2 consecutive measurements at least 1 week apart) after initial response with HIV RNA <50 copies/mL.

* includes L74M, E92E/Q, T97T/A, F121C, V151V/I, G163G/R, I203M.

Adverse Event (AE) Summary

	Male (N=109)		Female (N=97)	
% of patients with:	Black (N=70)	Non-Black (N=39)	Black (N=83)	Non-Black (N=14)
Clinical adverse events	74.3	76.9	66.3	85.7
Drug-related AE†	14.3	15.4	27.7	21.4
Serious AE	12.9	7.7	8.4	14.3
Serious & drug-related AE	1.4	0	3.6	0
Discontinued due to AE	1.4	0	3.6	0
Laboratory adverse events	7.1	15.4	13.3	7.1
Drug-related AE†	2.9	2.6	3.6	0
Serious AE	0	0	1.2	0
Serious & drug-related AE	0	0	0	0
Discontinued due to AE	0	0	1.2	0

† determined by investigator to be possibly, probably, or definitely related to any study therapy.

Most Common* Drug-Related† Clinical Adverse Events

	Male (N=109)		Female (N=97)	
% of patients with:	Black (N=70)	Non-Black (N=39)	Black (N=83)	Non-Black (N=14)
Abdominal discomfort	0	0	2.4	0
Diarrhea	1.4	2.6	2.4	0
Nausea	2.9	5.1	4.8	0
Vomiting	1.4	2.6	2.4	0
Myalgia	0	0	2.4	0
Headache	1.4	0	2.4	0

* Present in ≥2% of any group

† Determined by investigator to be possibly, probably, or definitely related to raltegravir alone or in combination with background ART.

% of Patients with Grade 3 / 4 Laboratory Abnormalities

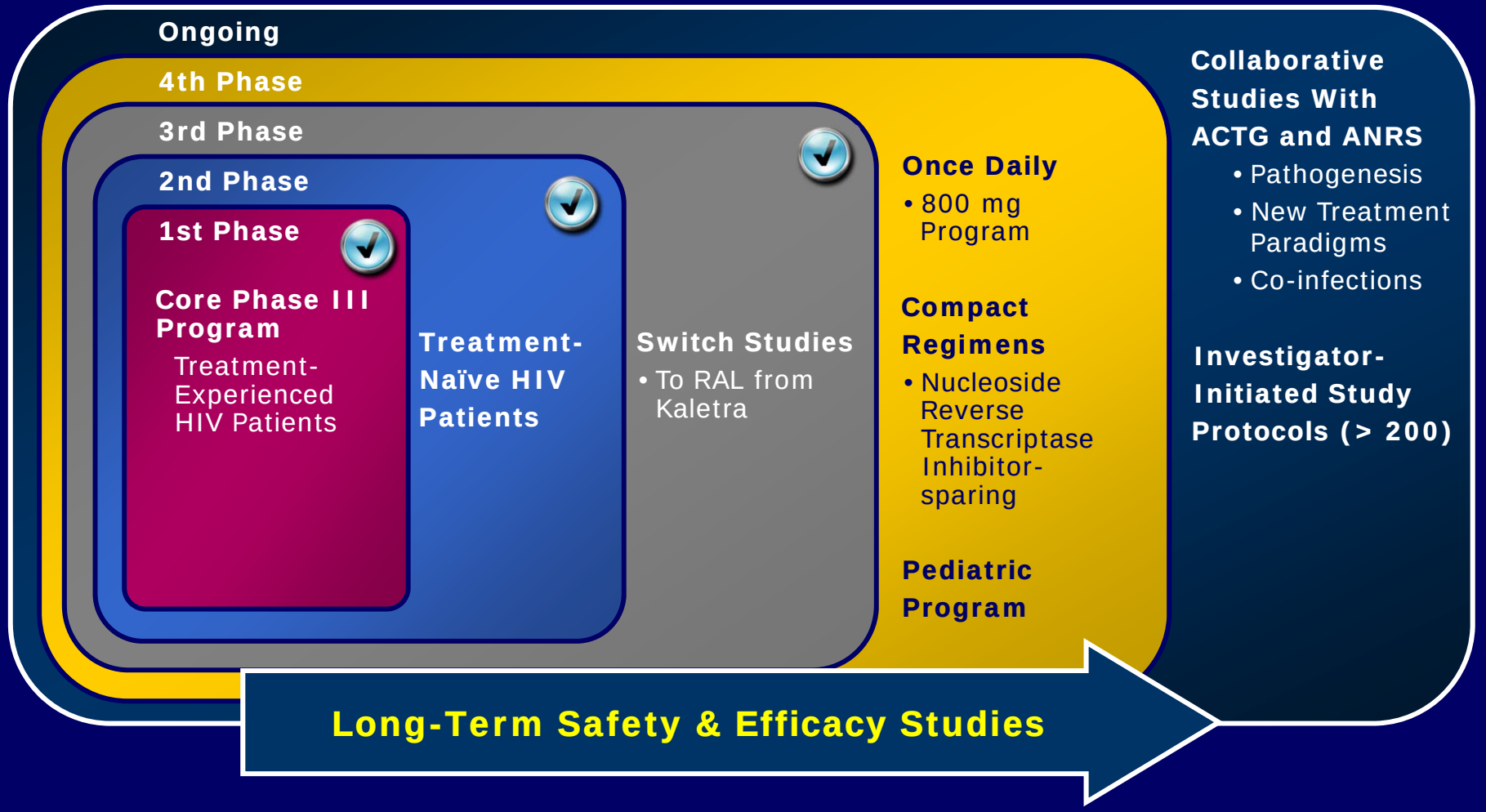
	Toxicity Criteria*	Male (N=109)	Female (N=97)	Black (N=153)	Non-Black (N=53)
Absolute neutrophil count	< 750/μL	3.7	2.2	3.3	1.9
Hemoglobin	< 7.4 g/dL	0	1.1	0.7	0
Platelet count	< 50,000/μL	0.9	0	0	1.9
Fasting LDL cholesterol	≥190 mg/dL	4.8	1.3	4.1	0
Fasting total cholesterol	>300 mg/dL	3.4	3.8	3.1	5.0
Fasting triglycerides	>750 mg/dL	2.2	0	0.8	2.5
Fasting glucose	>250 mg/dL	2.3	1.3	2.4	0
Total bilirubin	>2.5 x ULN	1.8	3.2	2.0	3.8
Serum creatinine	>1.8 x ULN	0.9	0	0.7	0
Aspartate aminotransferase	>5 x ULN	2.8	1.1	1.3	3.8
Alanine aminotransferase	>5 x ULN	2.8	1.1	1.3	3.8
Alkaline phosphatase	>5 x ULN	0	1.1	0.7	0
Creatine kinase	≥10 x ULN	1.8	0	1.3	0

* Division of AIDS Toxicity Criteria; ULN = upper limit of normal.

Conclusions

- After 48 weeks of treatment in a very diverse cohort of HIV-infected patients
  - Raltegravir 400 mg BID had potent efficacy regardless of gender or race.
  - Raltegravir 400 mg BID was generally safe and well tolerated.
  - Overall, 15% of patients discontinued: 17% of women vs 13% of men; 14% of black patients vs 17% of non-black patients.
  - Raltegravir PK parameters calculated from sparse sampling were consistent with expectations based on prior studies of raltegravir 400 mg BID; there was no significant effect of gender or race (black vs non-black) on PK.

Raltegravir Clinical Development



ACTG = Aids Clinical Trials Group; ANRS = Agence Nationale de Recherche sur le SIDA et les Hepatites Virales