Second Generation NNRTIs

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¿Apart from K103N, what number of pre-existing NNRTI mutations (how many) will decrease the activity of etravirine to that comparable to placebo?

a) 1;
b) 2;
c) 3;
d) 4;
e) 5;
f) I do not know, I'm coming to learn.

First-Generation NNRTIs:
Efavirenz
Nevirapine
Delavirdine

NNRTIs Recommended for Initial ART: Efavirenz

- A preferred or recommended option for initial therapy in DHHS and IAS-USA guidelines[1,2]
  - Strengths
    - Highest efficacy combined with 3TC or FTC and a second NRTI
    - Convenient, well tolerated in most
  - Weaknesses
    - Low genetic barrier to resistance
    - High failure rate among patients with transmitted NNRTI resistance
    - CNS adverse effects limit tolerability in some
    - Teratogenicity
    - Associated with increased incidence of lipoatrophy

1. DHHS Guidelines. Available at: http://AIDSinfo.nih.gov. Accessed December 1, 2007.
2. Hammer SM, et al. JAMA. 2006;296:827-843.

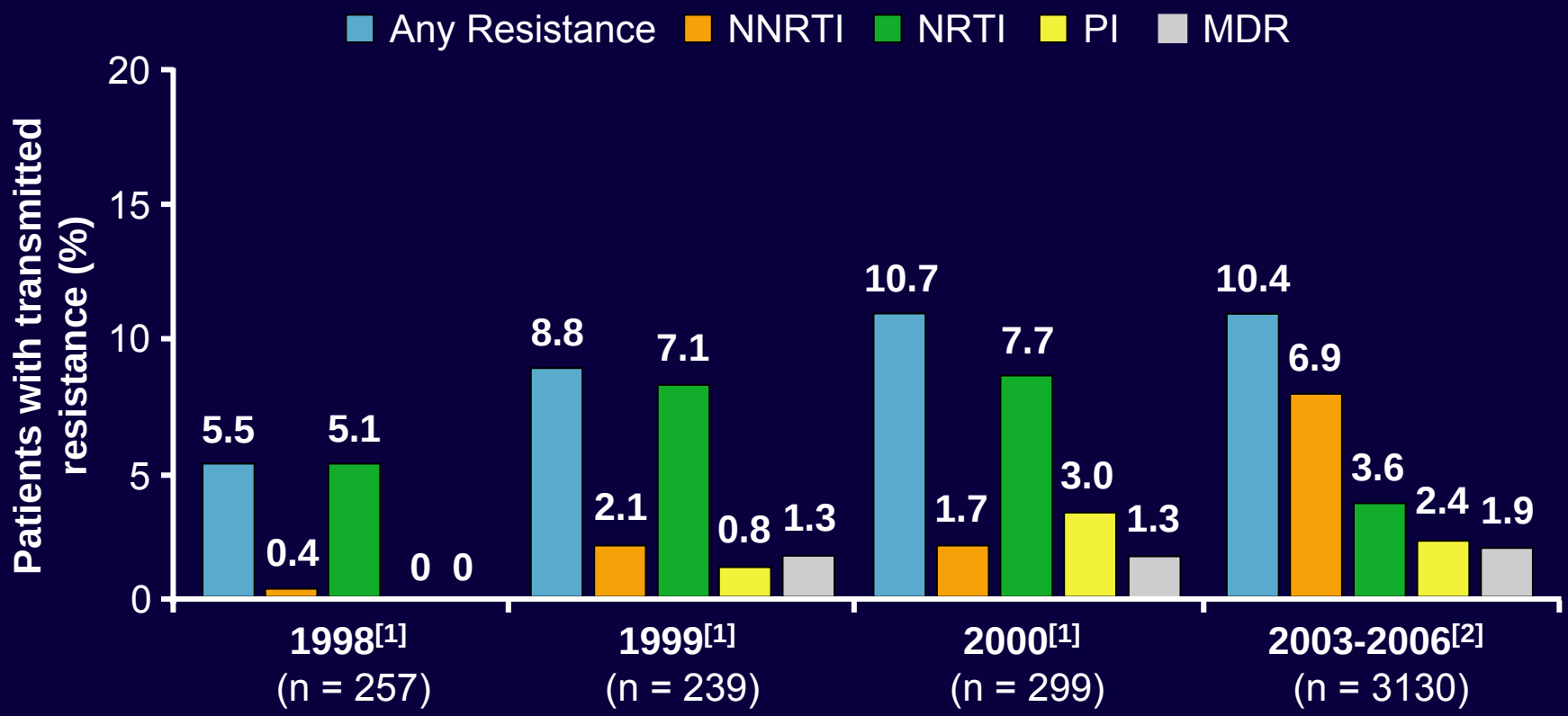
NNRTIs Recommended for Initial ART: Nevirapine

- Recommended option for initial therapy in the IAS-USA guidelines and an alternative option in the DHHS guidelines[1,2]
  - Strengths
    - Similar to EFV in efficacy when combined with NRTIs
    - Well tolerated in most
  - Weaknesses
    - Low genetic barrier to resistance
    - Likely high failure rate among patients with transmitted resistance
    - BID dosing
    - Rash/liver toxicity common; hypersensitivity reactions may be severe
    - Not recommended in men with CD4+ > 400 cells/mm^3 and women with CD4+ > 250 cells/mm^3

1. DHHS Guidelines. Available at: http://AIDSinfo.nih.gov. Accessed December 1, 2007.
2. Hammer SM, et al. JAMA. 2006;296:827-843.

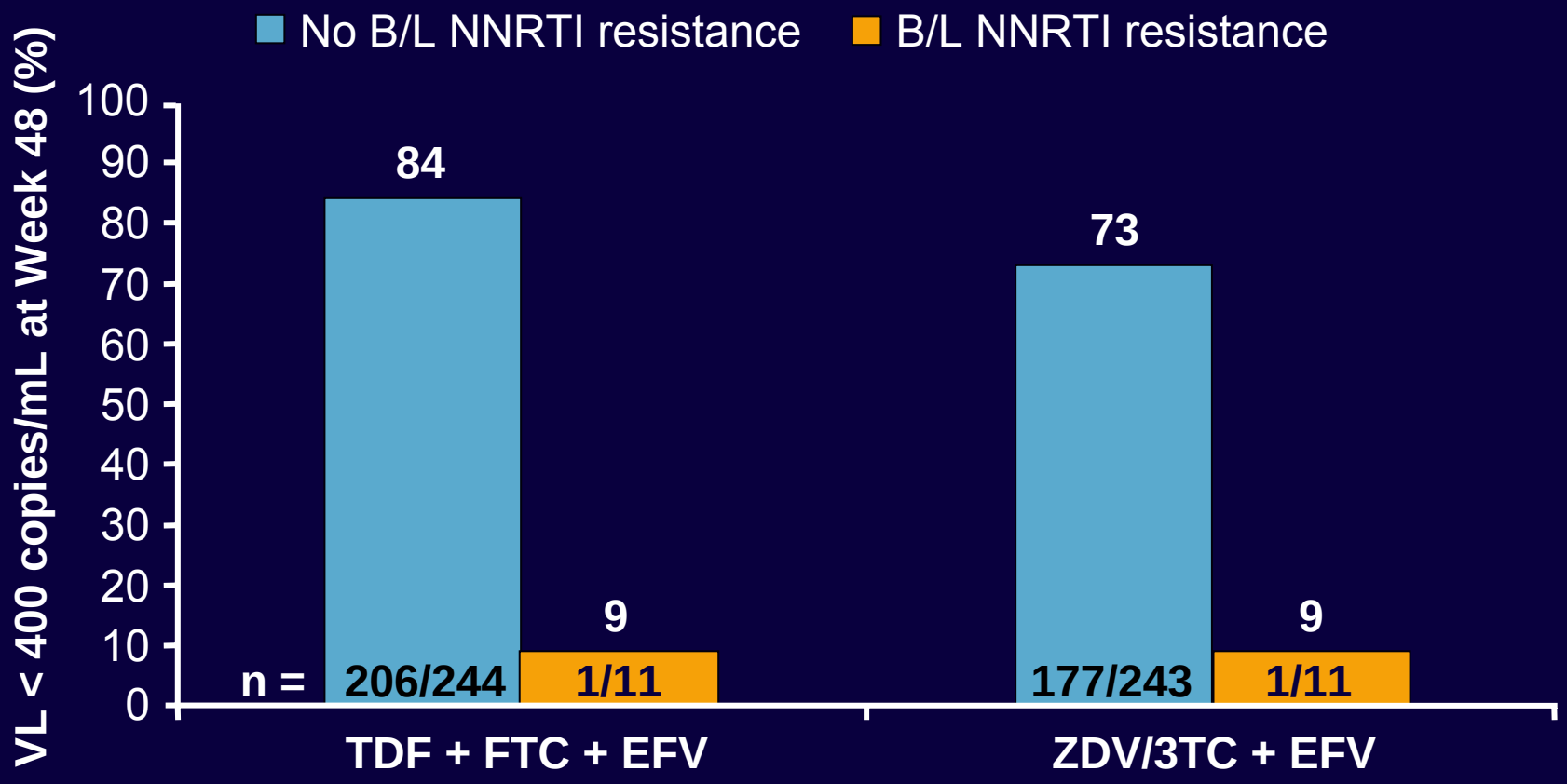
Prevalence and Clinical Consequence of Transmitted NNRTI Resistance and Minority Variants

CDC Survey: Patterns of Transmitted Drug Resistance



1. Bennett D, et al. CROI 2002. Abstract 372.
2. Wheeler W, et al. CROI 2007. Abstract 648.

GS 934: Baseline NNRTI Resistance Reduces Virologic Response



Gallant JE, et al. N Engl J Med. 2006;354:251-260.

Prevalence of Minority Variants and Association With Virologic Failure

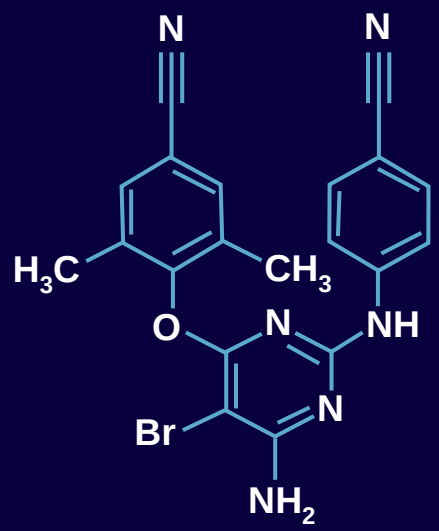
- Prevalence of minority variants assayed in 205 treatment-naive patients determined to have wild type HIV by bulk sequencing
  - Wild type samples screened with RT-PCR assay: ≥ 1 mutations in 34/205 (17%); MDR mutations in 2%
- Clinical relevance of baseline minority variants investigated in 2 studies, CNA 30021/30024: EFV + 3TC + ABC or ZDV
  - Assayed viral failures (n = 95) and control suppressors (n = 220)
  - 9 (3%) patients over all had BL minority variants (K103N, Y181C, or M184V)
  - 7/9 (78%) of patients with detected BL minority variants experienced VF
  - Mutations detected by RT-PCR significantly correlated with VF (*P* = .0038, Fisher exact test)

Johnson J. CROI 2007. Abstract 639.

Next-Generation NNRTIs:
Etravirine (TMC125)
Rilpivirine (TMC278)
UK-453,061

Next-Generation NNRTI: Etravirine (Intelence)

- In vitro characteristics
  - EC_{50} WT HIV-1: 1.4 nM
- Phase I pharmacokinetics
  - Elimination half-life: 30-40 hours
  - Metabolized by/inducer of cytochrome P450 CYP3A
  - Inducer of uridine diphosphate glucuronyl transferase
- Phase IIa: treatment-naive patients
  - 2.0 log_{10} decline in plasma HIV-1 RNA over 7 days
- Phase IIa: treatment-experienced patients failing initial NNRTI regimen
  - 0.86 log_{10} decline in plasma HIV-1 RNA over 7 days

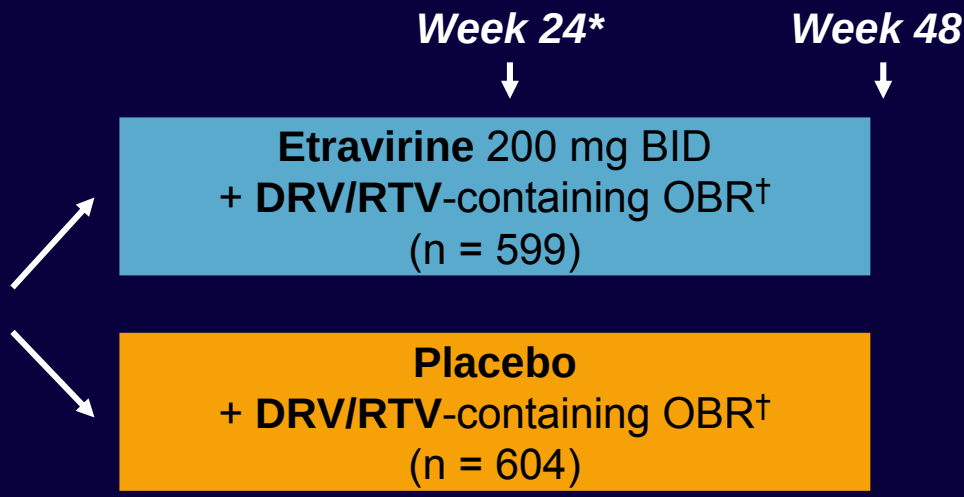


de Bethune MP, et al. ICAAC 2000. Abstract 1841. Piscitelli S, et al. Pharmacology Workshop 2002. Abstract 5.3. Gruzdev B, et al. AIDS. 2003;17:2487-2494. Gazzard BG, et al. AIDS. 2003;17:F49-F54.

DUET-1 and -2: Etravirine + DRV/RTV-Containing OBR Phase III Trials

HIV-infected patients with VF on current HAART regimen, history of ≥ 1 NNRTI resistance mutations, ≥ 3 primary PI mutations, HIV-1 RNA > 5000 copies/mL

DUET-1: N = 612;
DUET-2: N = 591



*Planned Week 24 analysis: primary endpoint HIV-1 RNA < 50 copies/mL (TLOVR).
†Investigator-selected OBR to consist of DRV/RTV (600/100 mg/mL) + ≥ 2 NRTIs ± ENF.

Madruga JV, et al. Lancet. 2007;370:29-38. Lazzarin A, et al. Lancet. 2007;370:39-48. Mills A, et al. IAS 2007. Abstract WESS204.1. Katlama C, et al. IAS 2007. Abstract WESS204.2. Cahn P, et al. ICAAC 2007. Abstract H-717.

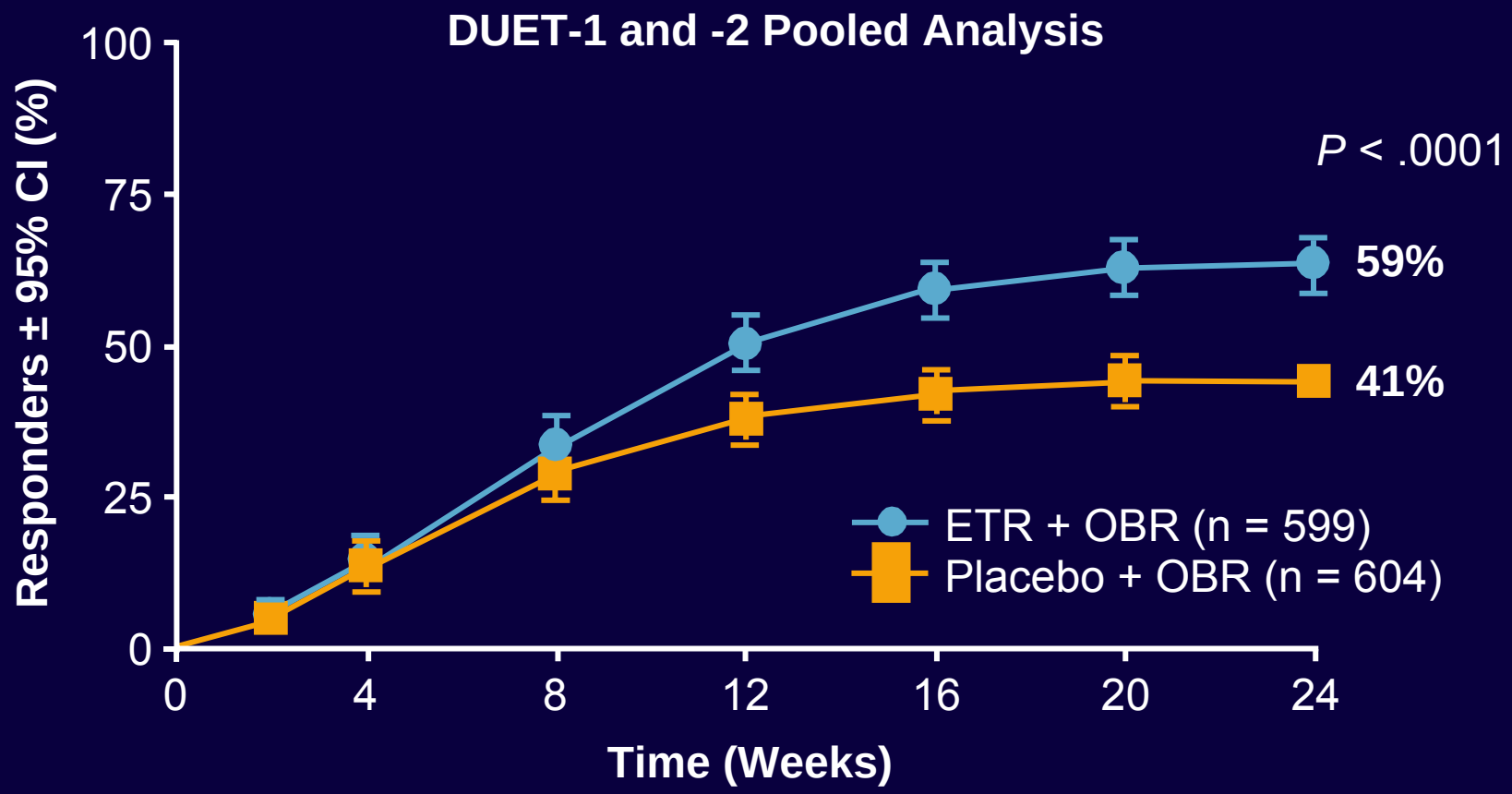
DUET-1 and DUET-2

- DUET-1
  - South and Central America, France, Thailand, Puerto Rico, USA
- DUET-2
  - Australia, Canada, Europe, USA

Baseline data	Placebo (n=604)	Etravirine (n=599)
Median CD4 (cells/mm^3)	109	99
Mean HIV RNA (log_{10} copies/mL)	4.8	4.8
OBT (%)		
Enfuvirtide	47	46
0 active drugs	16	17
1 active drug	39	37

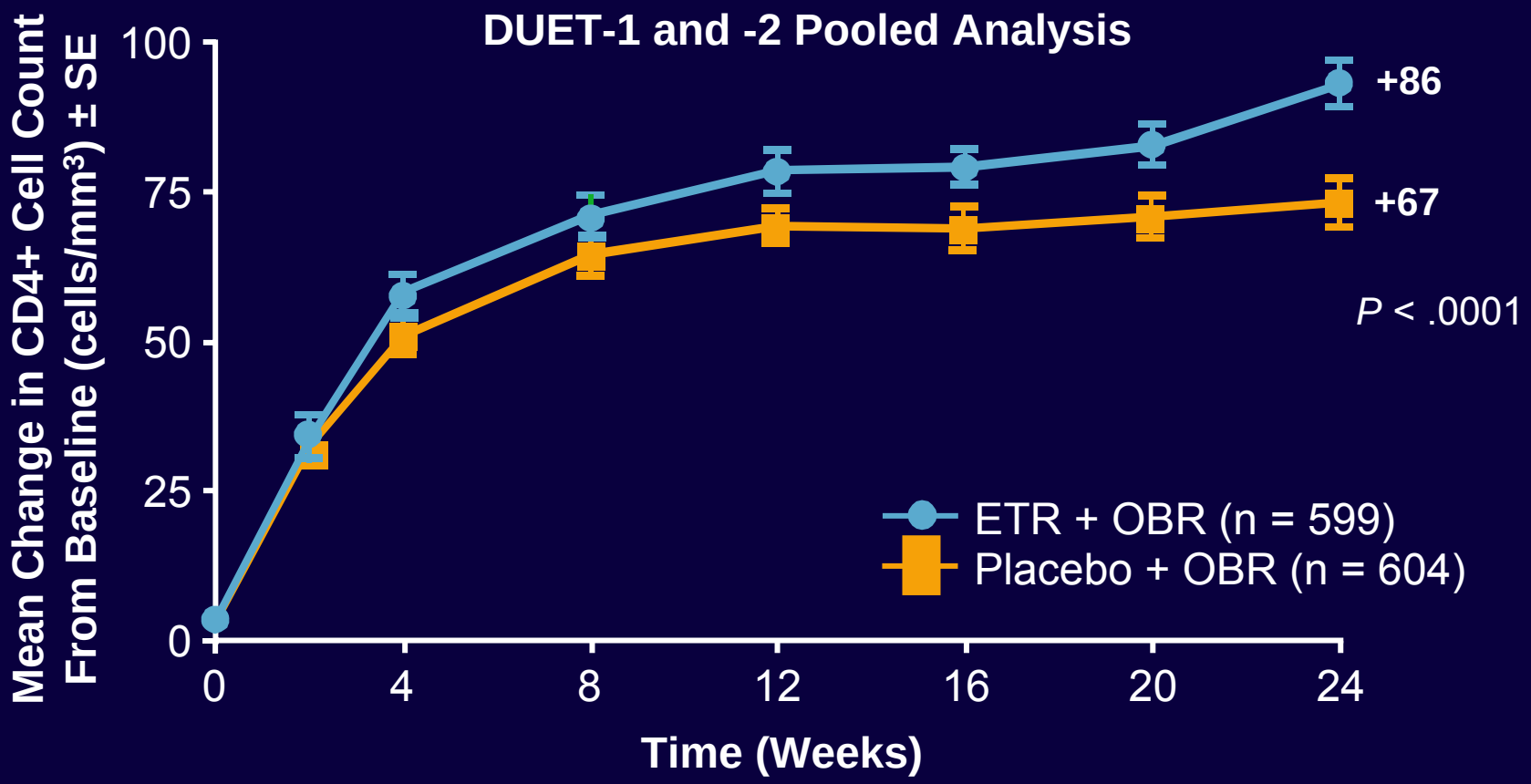
Madruga JV, et al. Lancet. 2007;370:29-38. Lazzarin A, et al. Lancet. 2007;370:39-48. Mills A, et al. IAS 2007. Abstract WESS204. Katlama C, et al. IAS 2007. Abstract WESS204. Cahn P, et al. ICAAC 2007. Abstract H-717.

DUET-1 and -2: Patients With VL < 50 c/mL at Week 24 (ITT TLOVR)



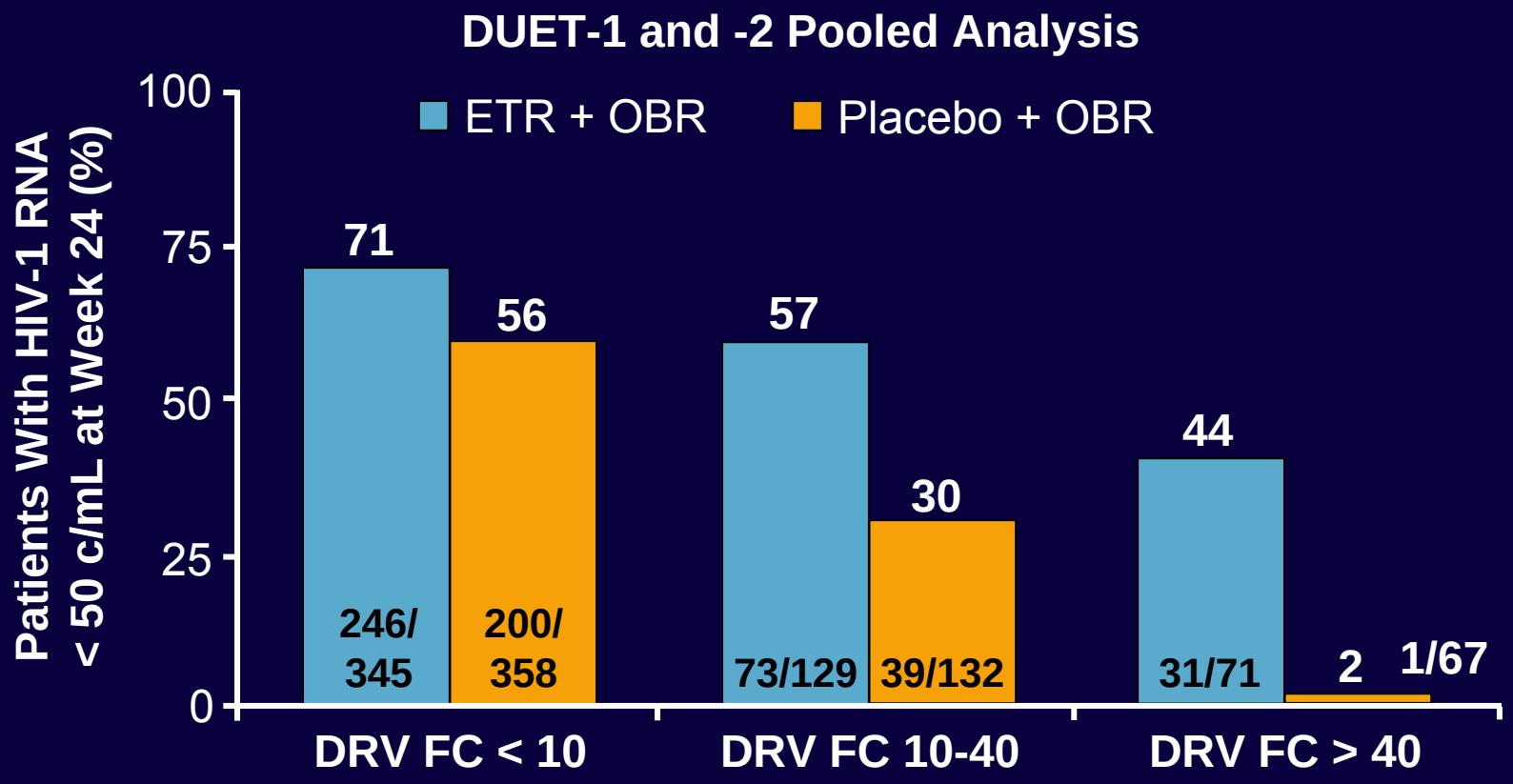
Cahn P, et al. ICAAC 2007. Abstract H-717.

DUET-1 and -2: Change in CD4+ Cell Count From Baseline (ITT NC = F)

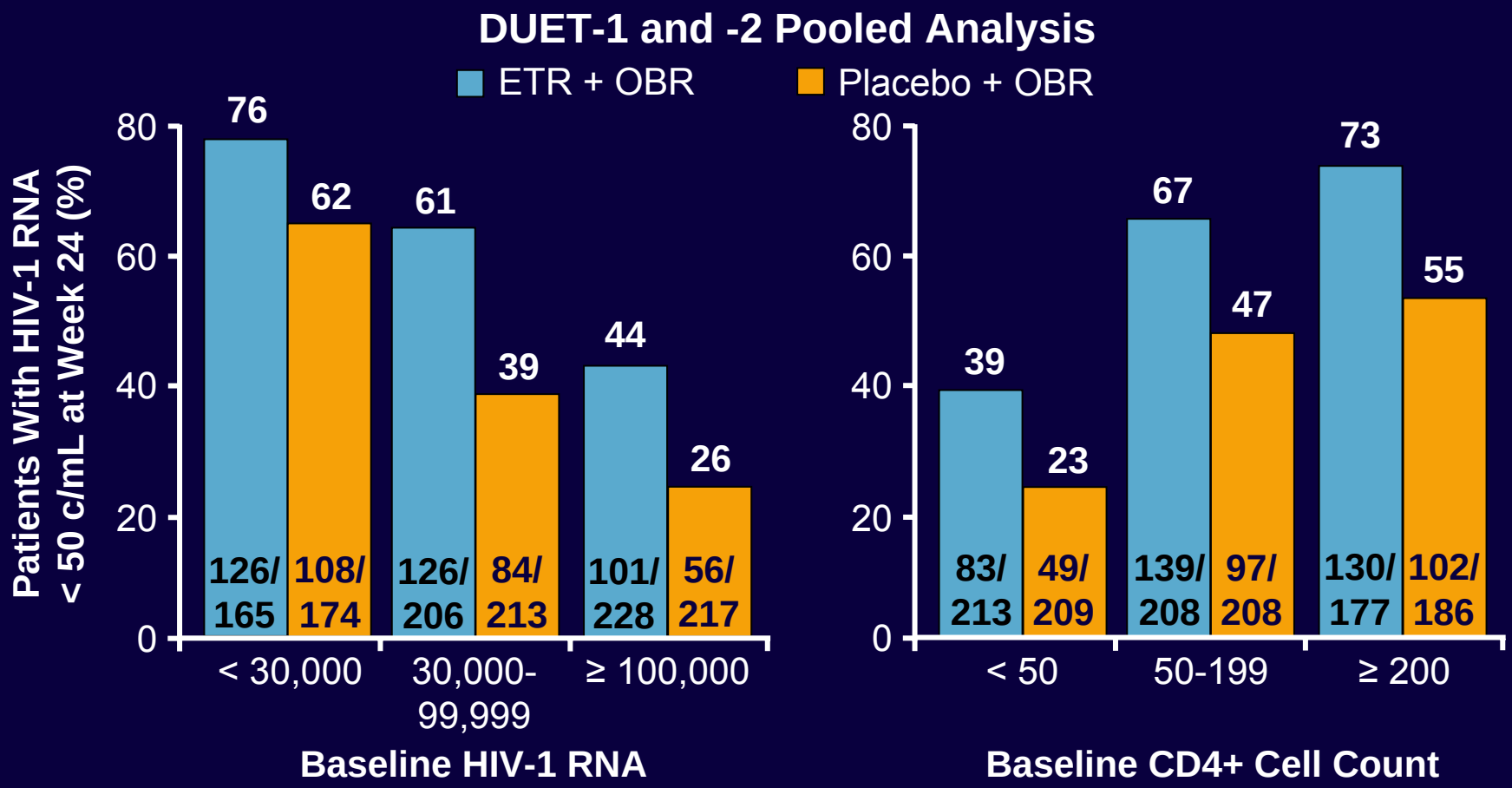


Cahn P, et al. ICAAC 2007. Abstract H-717.

DUET-1 and -2: Response (< 50 c/mL) According to BL DRV Fold Change



DUET-1 and -2: Response (< 50 c/mL) According to BL CD4+ and VL



Cahn P, et al. ICAAC 2007. Abstract H-717.

DUET-1 and -2: Any Grade Adverse Events at Week 24

Adverse Events Through Week 24, %	Etravirine (n = 599)	Placebo (n = 604)
Adverse event of any grade	93	93
▪ Rash (all types)	17*	9
▪ Diarrhea	15	20
▪ Nausea	14	11
▪ Headache	9	12
▪ Neurologic disorders	15	19
▪ Psychiatric disorders	13	15
▪ Hepatic adverse events	5	5

*P = .0001 vs placebo.

Cahn P, et al. ICAAC 2007. Abstract H-717.

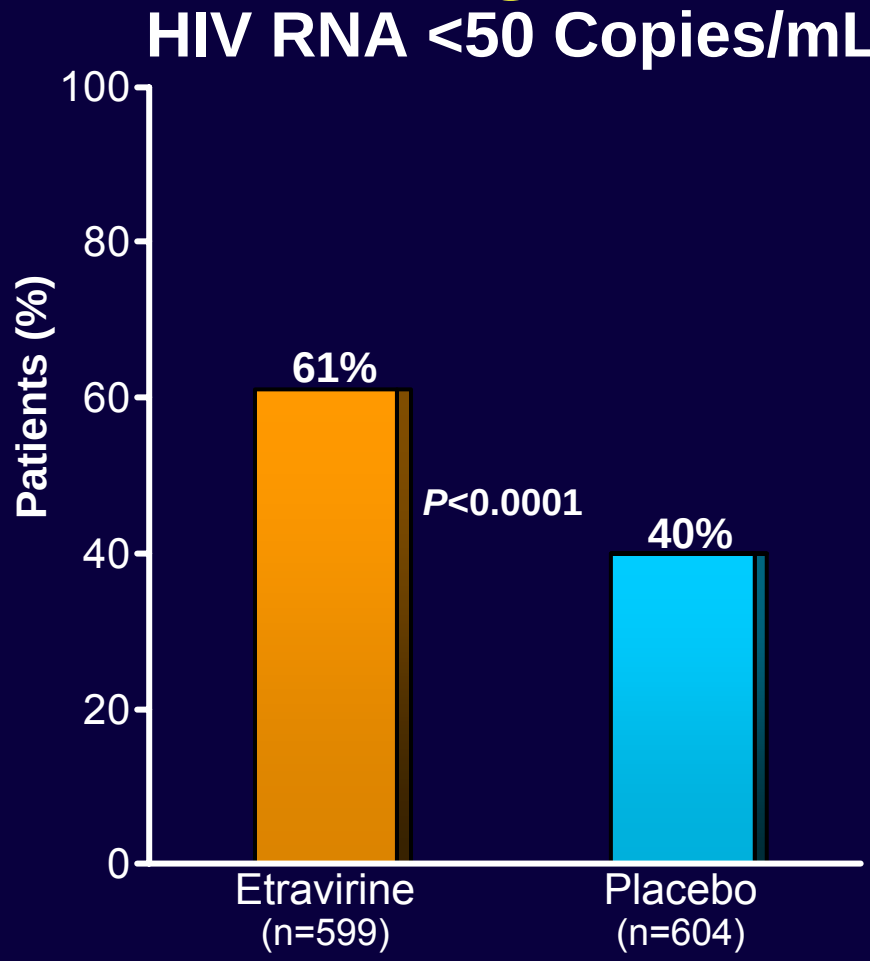
DUET-1 and -2: Any Grade Adverse Events at Week 24

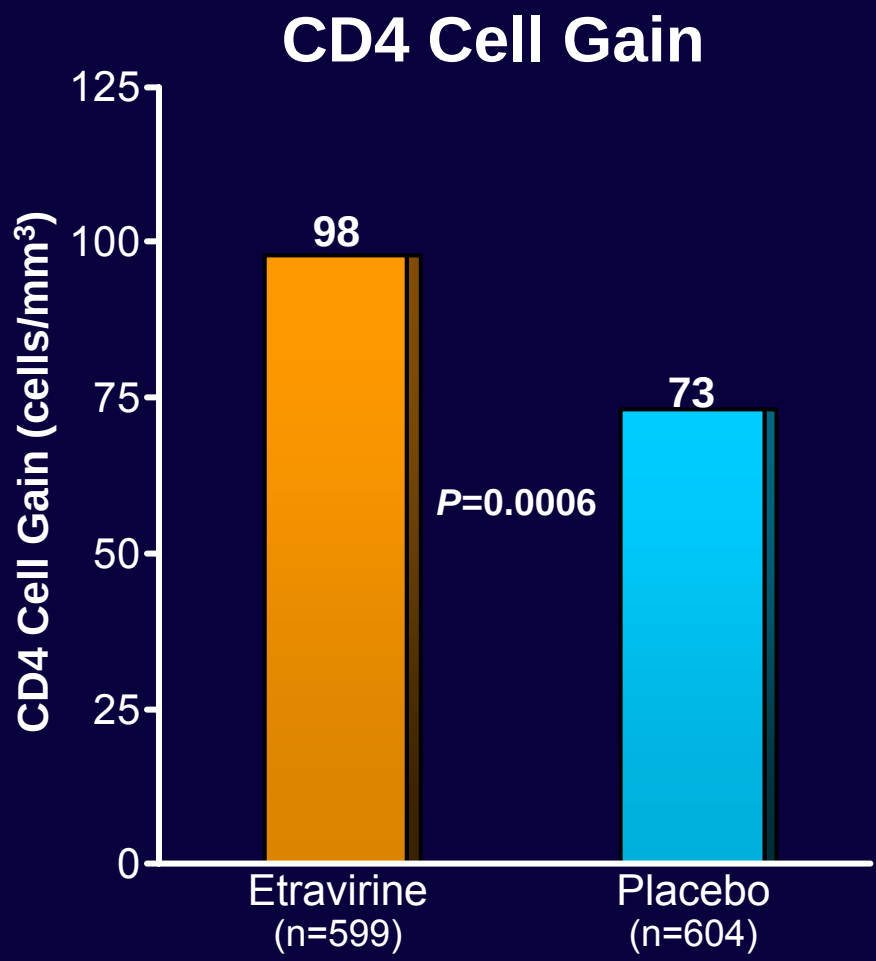
- Elevations in total cholesterol and low density lipoprotein (LDL) cholesterol, and initiation of lipid-lowering therapy were more common in etravirine-treated subjects compared with those in the placebo arm.

- Patients coinfected with hepatitis B or C had a higher incidence of AST (SGOT) and ALT (SGPT) abnormalities.

•**Intelence package insert Jan. 2008.**

DUET 1/2: Combined Virologic and Immunologic Outcomes at Week 48





Haubrich R, et al. 15th CROI. Boston, 2008. Abstract 790.
Johnson M, et al. 15th CROI. Boston, 2008. Abstract 791.

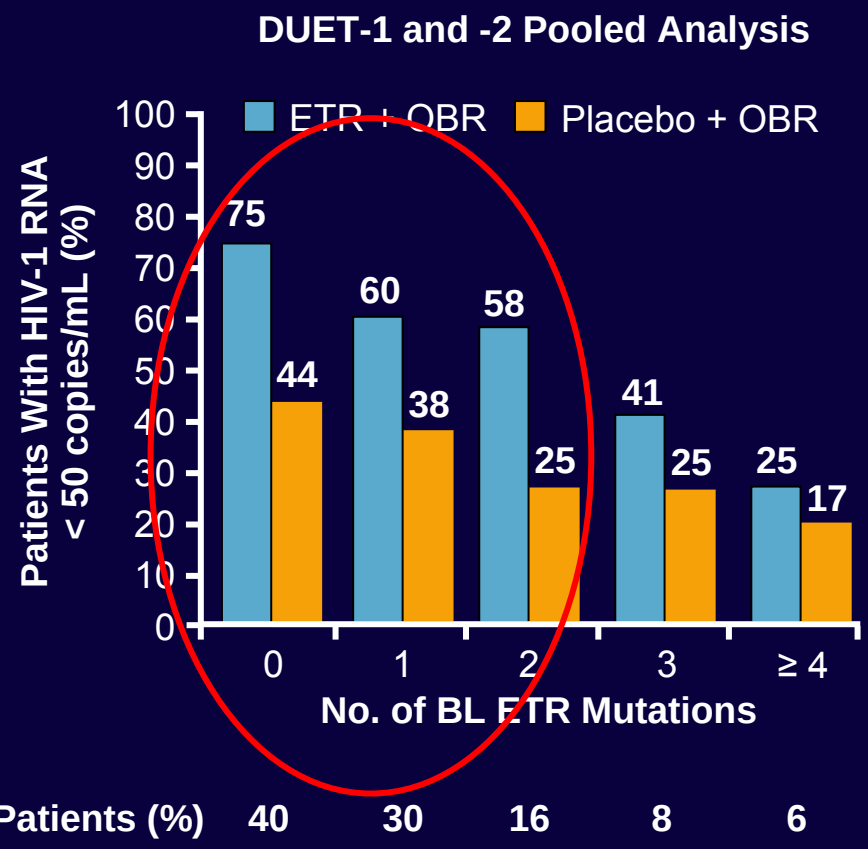
DUET 1/2: Combined 48-Week Safety

- Most common adverse events were diarrhea, rash (any type), and nausea
- Rashes
  - More frequent with etravirine versus placebo
    - DUET-1: 22% versus 11% (*P*=0.0003)
    - DUET-2: 17% versus 11% (*P*=0.0577)
  - Median onset of 12 to 17 days and duration of 14 to 18 days
  - Usually mild-to-moderate in severity
    - Grade 3: 1% to 1.4%
    - Grade 4: 0%
  - Infrequently required discontinuation (2.0% to 2.4%)

Haubrich R, et al. 15th CROI. Boston, 2008. Abstract 790.
Johnson M, et al. 15th CROI. Boston, 2008. Abstract 791.

DUET-1 and -2: BL ETR Mutations and Virologic Response at Week 24

- 13 mutations associated with ETR resistance
  - V90I
  - L100I
  - V106I
  - Y181C/I/V
  - A98G
  - K101E/P
  - V179D/F
  - G190A/S
- Presence of ≥ 3 ETR mutations associated with response similar to overall placebo + OBR response
  - 70% of patients had 0 or 1 ETR resistance mutations at BL
  - 14% of patients had ≥ 3 ETR resistance mutations at BL



Cahn P, et al. ICAAC 2007. Abstract H-717.

TMC125-C227: ETR vs PI in NNRTI-Experienced, PI-Naive Patients

- PI-naive patients failing first-line NNRTI-based regimen with ≥ 1 NNRTI resistance mutations; study discontinued after DSMB review
  - ETR 800 mg BID + 2 NRTIs vs Investigator-selected PI + 2 NRTI
- Unexpectedly large numbers of BL resistance mutations in this first-line VF population
  - 37% of ETR group and 35% of PI group recycled 1 NRTI
  - 9% of ETR group and 12% of PI group recycled > 1 NRTI
- VL declined by 1.3 $\log_{10}$ copies/mL in ETR arm at Week 8 but rebounded
  - By contrast, continual VL decline in PI arm
- Underscores need to use at least 2 active agents in all regimens
  - Etravirine should not be combined with NRTIs only, in patients with first-line NNRTI-based regimen failure.

Woodfall B, et al. Glasgow 2006. Abstract PL5.6.

Etravirine (Intelence) Dosing

- 100 mg tablets 2 po twice daily

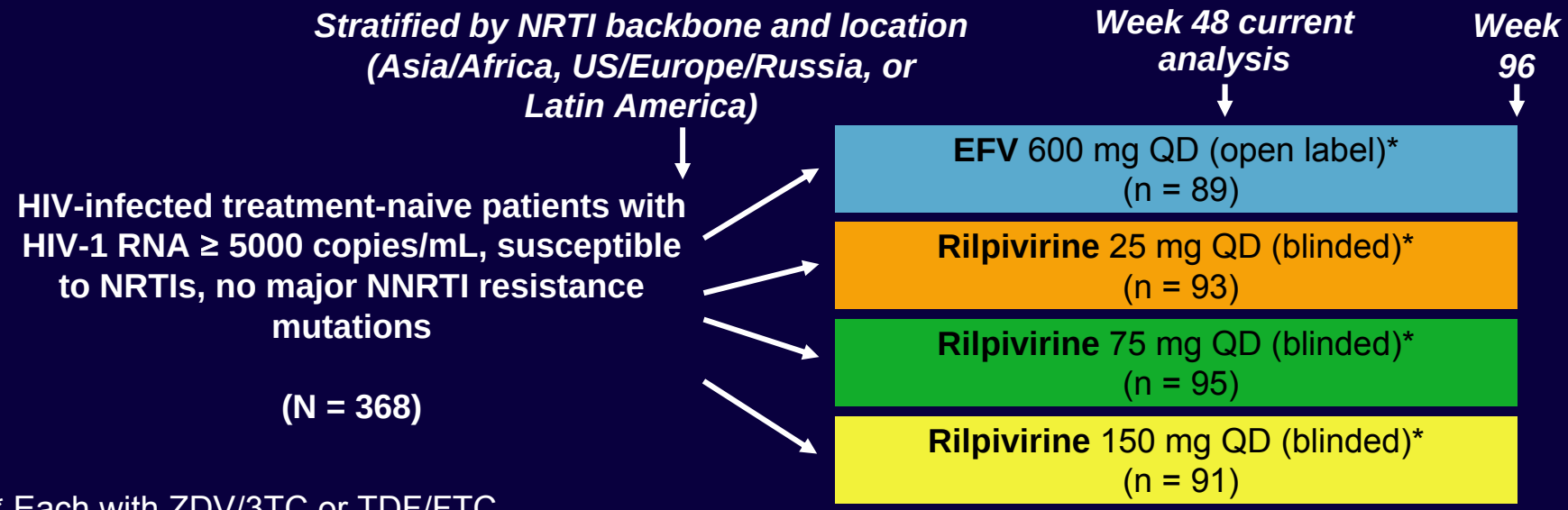
- Pregnancy category B. No clinical trial data in pregnancy.

Next-Generation NNRTI: Rilpivirine (TMC278)

- In vitro characteristics
  - EC_{50} WT HIV: 0.5 nM
- Phase I pharmacokinetics
  - Elimination half-life: 38 hours
  - Once-daily dosing
- Phase IIa
  - Approximately 1.2 log_{10} decline in VL over 7 days with little difference between doses (25, 50, 100, 150 mg)

de Bethune MP, et al. CROI 2005. Abstract 556.

TMC278-C204: Rilpivirine vs EFV in Treatment-Naive Patients



* Each with ZDV/3TC or TDF/FTC

Results at Week 48 (ITT-TLOVR)	Rilpivirine 25 mg (n = 93)	Rilpivirine 75 mg (n = 95)	Rilpivirine 150 mg (n = 91)	EFV 600 mg (n = 89)
VL < 50 copies/mL, %	81	80	77	81
Mean Δ in CD4+ count, cells/mm³	+125	+145	+143	+127

Yeni P, et al. EACS 2007. Abstract P7.2/07.

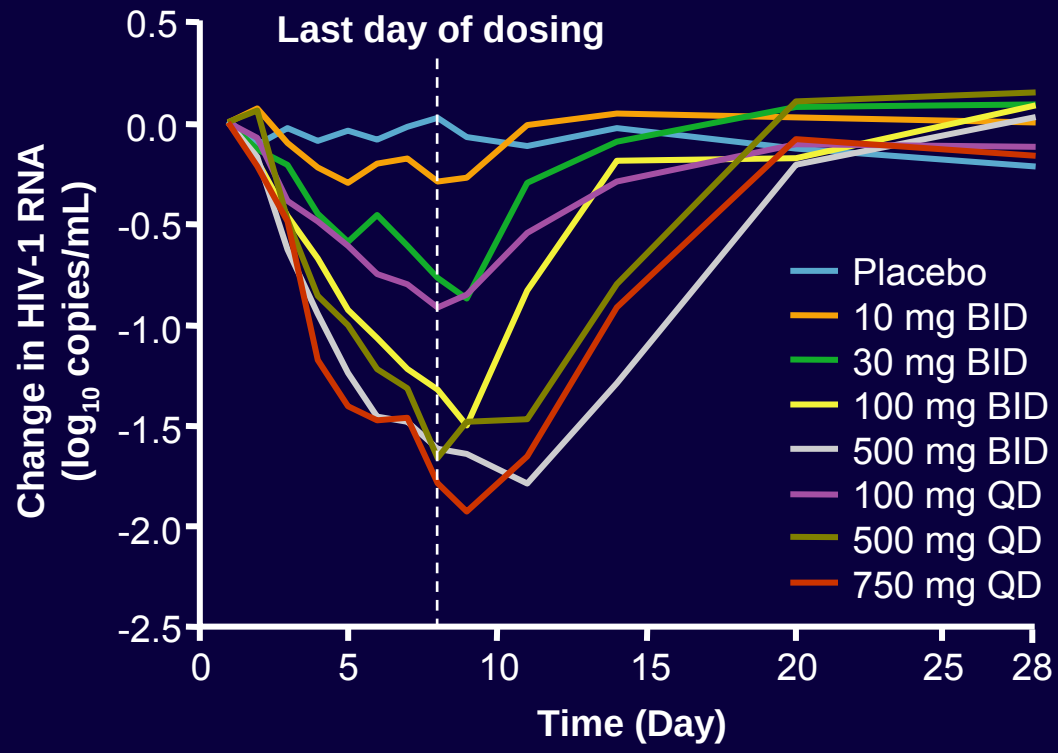
TMC278-C204: Any Cause CNS AEs and Metabolic Parameters

Patient Outcome at Week 48	Rilpivirine			EFV 600 mg (n = 89)
	25 mg (n = 93)	75 mg (n = 95)	150 mg (n = 91)	
AE, regardless of causality, %[1]				
Any CNS disorder	34	35	31	53
Vertigo	1	2	0	11
Dizziness	11	7	8	30
Somnolence	3	3	4	11
Abnormal dreams/nightmares	1	6	0	10
Mean lipid change from baseline[2]				
TC, mg/dL	8	3	5	31
LDL, mg/dL	3	1	-1	15
HDL, mg/dL	5	6	5	12
TC-to-HDL ratio	-0.4	-0.6	-0.4	-0.3
TG, mg/dL	-5	-19	-5	18

Yeni P, et al. EACS 2007. Abstract P7.2/07.

Antiviral Activity With Varying Doses of UK-453,061

- In vitro characteristics
  - IC_{90} of ~12 nM against WT HIV
- Phase I pharmacokinetics
  - Elimination half-life: 7-11 hours
  - Metabolized by CYP3A and glucuronidation



Corbau R, et al. ICAAC 2007. Abstract 2751.
Fätkenheuer G, et al. IAS 2007. Abstract WESS202.

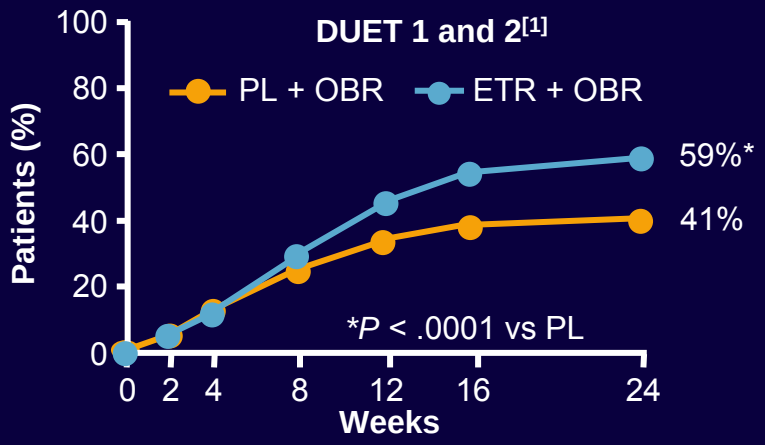
Clinical Strategies for Use of Next-Generation NNRTIs in Treatment-Experienced Patients

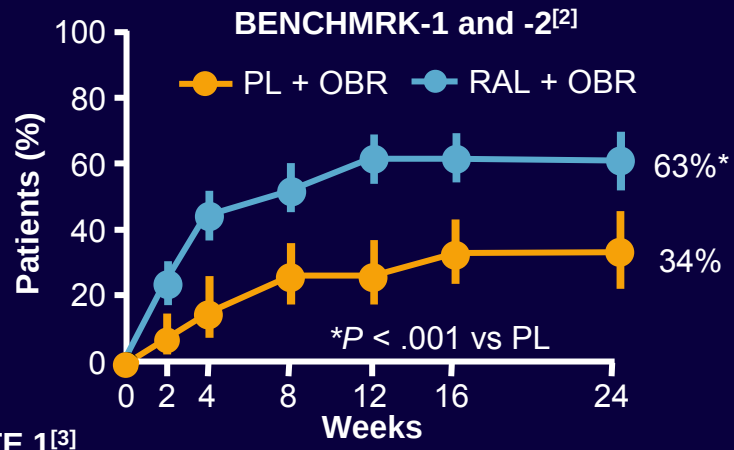
Goals of Therapy for Treatment-Experienced Patients

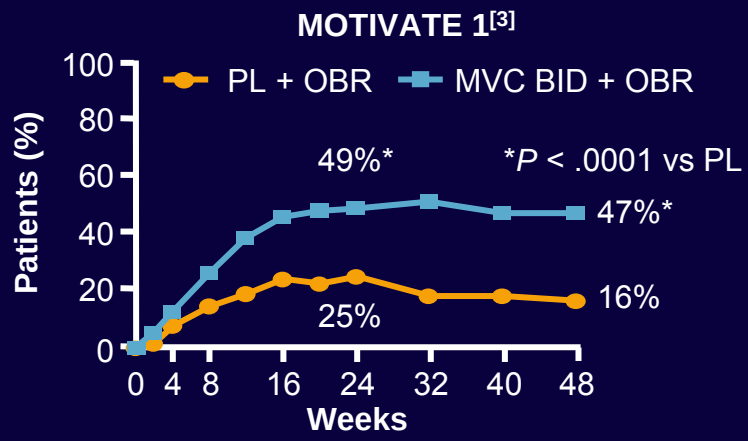
- "In those with prior treatment and drug resistance, the goal is to resuppress HIV-1 RNA levels maximally and prevent further selection of resistance mutations, if possible"—US DHHS Guidelines, December 1, 2007[1]
- "Trials with newer antiretroviral agents have shown that it is possible to achieve plasma HIV-1 RNA levels below 50 copies/mL even in highly treatment–experienced patients"—IAS-USA Guidelines, August 2006[2]

1. DHHS Guidelines. Available at: http://AIDSinfo.nih.gov. Accessed December 1, 2007.
2. Hammer SM, et al. JAMA. 2006;296:827-843.

Is VL < 50 Achievable in Treatment-Experienced Patients With MDR HIV?



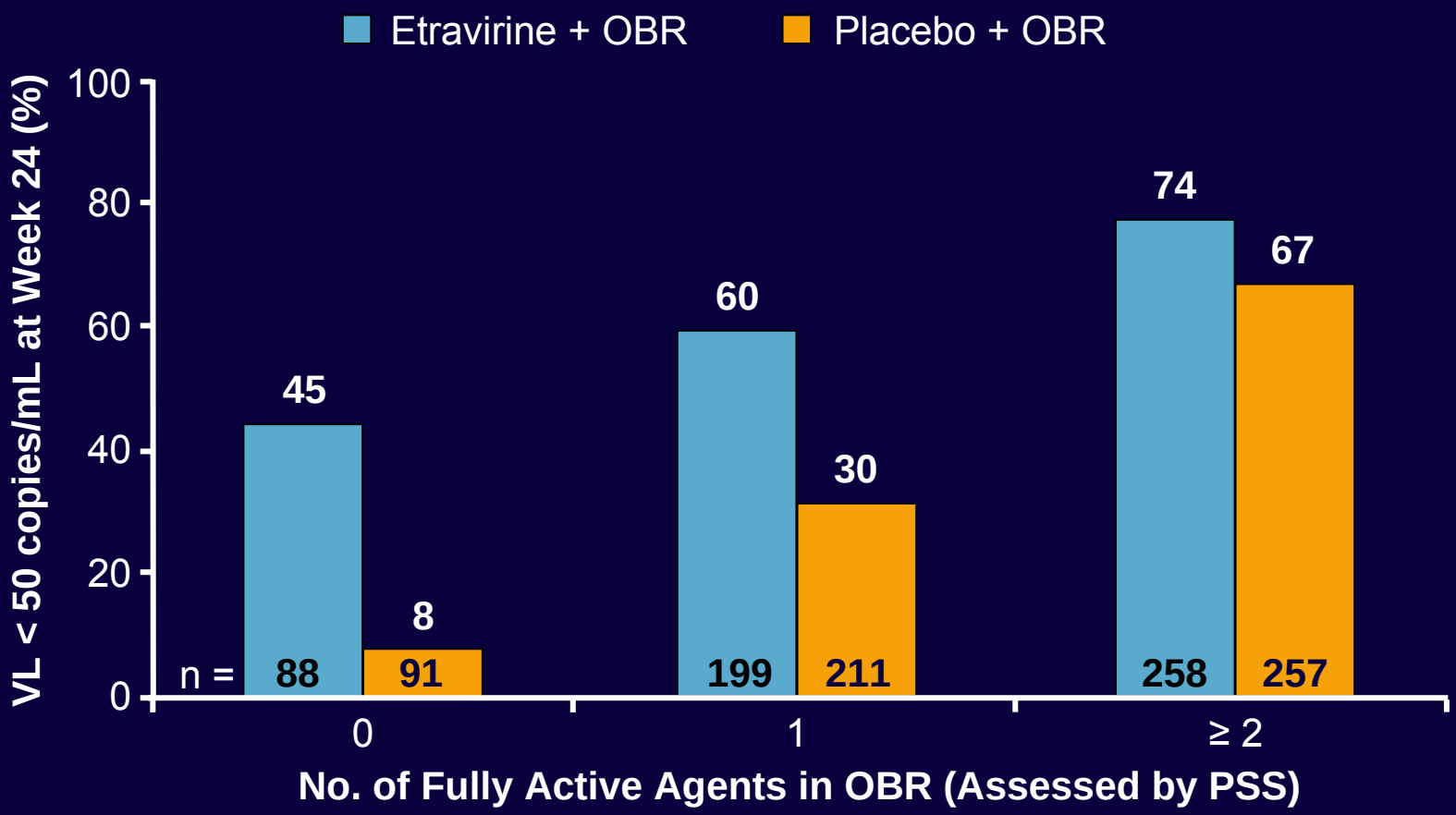




1. Cahn P, et al. ICAAC. 2007. Abstract H-717. 2. Kumar P, et al. EACS 2007. Abstract P7.2/06.
3. Lalezari J, et al. ICAAC 2007. Abstract H-718a.

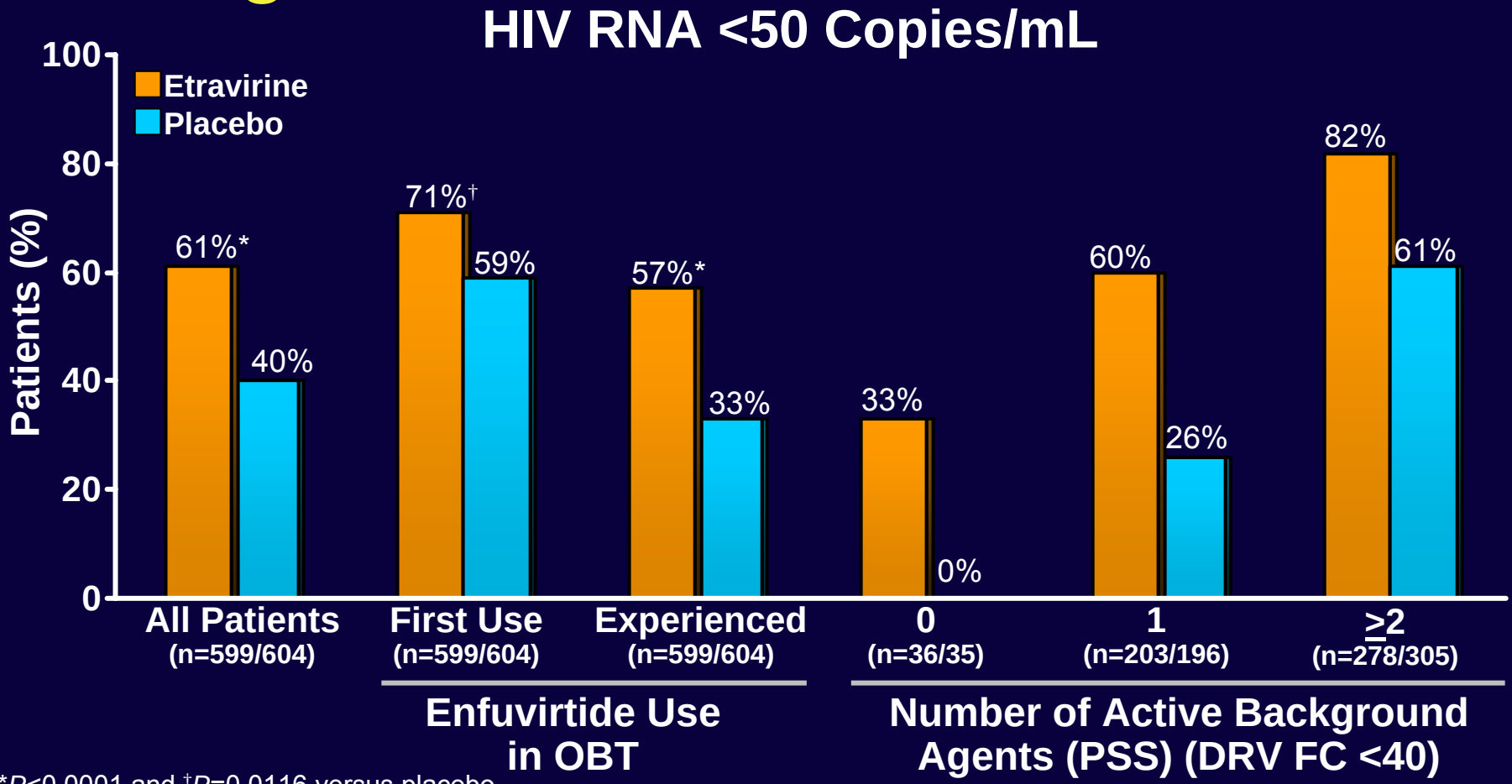
Importance of Multiple Active Agents for Treatment-Experienced Patients

DUET 1 and 2: Response Based on Active Agents in OBR



Cahn P, et al. ICAAC 2007. Abstract H-717.

DUET 1/2: Virologic Outcomes at Week 48



*P<0.0001 and †P=0.0116 versus placebo.
All patients received darunavir + RTV plus optimized NRTIs and optional enfuvirtide.

Haubrich R, et al. 15th CROI. Boston, 2008. Abstract 790.
Johnson M, et al. 15th CROI. Boston, 2008. Abstract 791.

Clinically Relevant Drug Interactions Between Etravirine and Other ARVs

Drug*	Effect on Exposure	Dosing Recommendations
ATV[1,2]	ATV ↓ 14%, ETR ↑ 50%	**Not recommended** due to decrease in ATV C_{min}
ATV/RTV[1]	ATV↓ 17%, ETR ↑ 30%	No change in dosing
DRV/RTV[2]	DRV ↔, ETR ↓ 37%	No change in dosing
FPV/RTV[2]	APV ↑ 30%	May require change in FPV dosing; no data on ETR
LPV/RTV[2]	LPV ↔, ETR ↔	No change in dosing
TPV/RTV[2]	TPV ↔, ETR ↓ 76%	**Not recommended**
MVC	MVC ↓ 53%, ETR ↔	Change MVC dose to 600 mg BID when combined with ETR alone; MVC dosed at 150 mg BID when combined with ETR + DRV/RTV
RAL	RAL ↓, ETR ↔	No change in dosing
TDF	TDF ↔, ETR ↔	No change in dosing

*Drugs administered at standard doses.

1. Schöller-Gyüre M, et al. Glasgow 2006. Abstract P278.
2. Kakuda T, et al. Glasgow 2006. Abstract PL5.2

ETR Drug-Drug Interaction Summary

Allowed
No dose adjustment necessary

NRTIs
- ddI
- TDF

PIs
- ATV/RTV
- DRV/RTV
- LPV/RTV
- SQV/RTV
- LPV/SQV/RTV

Integrase
- RAL
- ELV/RTV

Other drugs
- Atorvastatin
- Clarithromycin*
- Methadone
- OCs
- Omeprazole
- Paroxetine
- Ranitidine
- Rifabutin

Allowed
Dose adjustment may be necessary

PIs
- FPV/RTV

CCR5As
- MVC

Other drugs
- Sildenafil

Not recommended

PIs
- Unboosted
- RTV full-dose
- TPV/RTV

NNRTIs
- EFV
- NVP

* Alternative recommended when treating *Mycobacterium avium* complex

Clinical Strategies for Utilizing ETR in Treatment-Experienced Patients

Which patients are appropriate candidates for ETR?

- ETR likely to have activity in most treatment-experienced pts
  - Detection of ≥ 3 ETR mutations associated with substantially decreased response: 14% of DUET patients had ≥ 3 ETR mutations
- ETR well tolerated in most patients
  - Rash most common AE (17% vs 9% in placebo arm, *P* < .0001)
  - Mild in severity, led to discontinuation in only 2.2% of patients
  - More common in women
  - No increased risk with prior NNRTI-related rash

Clinical Strategies for Utilizing ETR in Treatment-Experienced Patients

How can ETR be effectively utilized with other agents?

- ETR should be combined with at least 1 other active drug

- In phase III DUET studies of treatment-experienced patients with NNRTI-resistant virus, ETR superior to placebo when each combined with DRV/RTV-containing OBR

Clinical Strategies for Utilizing ETR in Treatment-Experienced Patients

- ETR not as effective as PI-based regimen in patients failing initial NNRTI-based regimen in combination with NRTIs with reduced or no activity
  - However, in the DUET trials there was a substantial ETR effect when there was no susceptibility to other drugs in the OBR (PSS or GSS = 0).
- Available data suggest that ETR can be combined with most ARVs without dose adjustments
  - Should not be combined with unboosted PIs, other NNRTIs, or TPV/RTV
  - MVC should be dosed at 600 mg with ETR alone and 150 mg when combined with ETR + DRV/RTV

¿Apart from K103N, what number of pre-existing NNRTI mutations (how many) will decrease the activity of etravirine to that comparable to placebo?

a) 1;
b) 2;
c) 3;
d) 4;
e) 5;
f) I'm sorry, I did not learn.