

# New drugs and treatment options for HIV infection

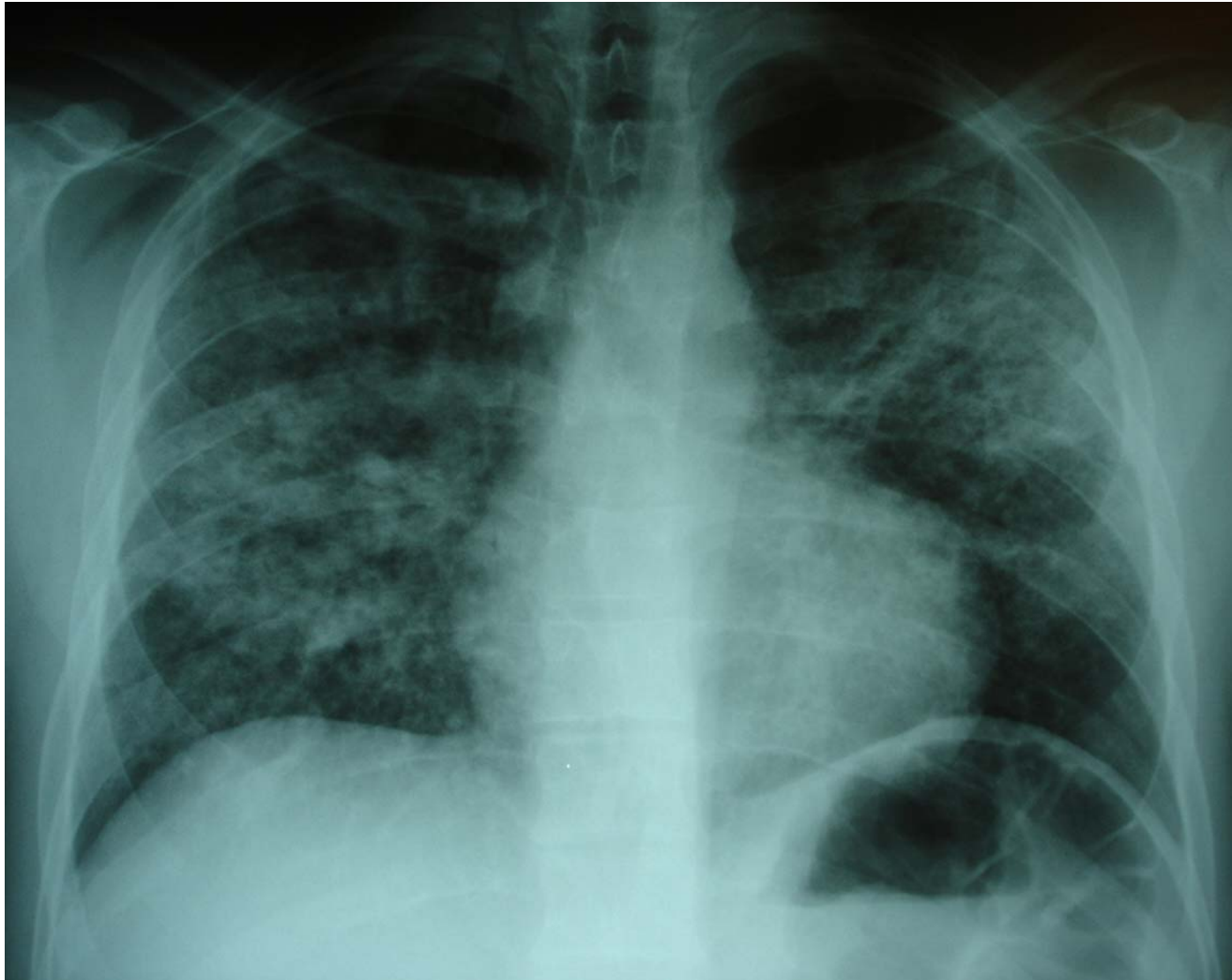
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University of Cologne

ESCMID Summerschool

Regensburg, July 23, 2008

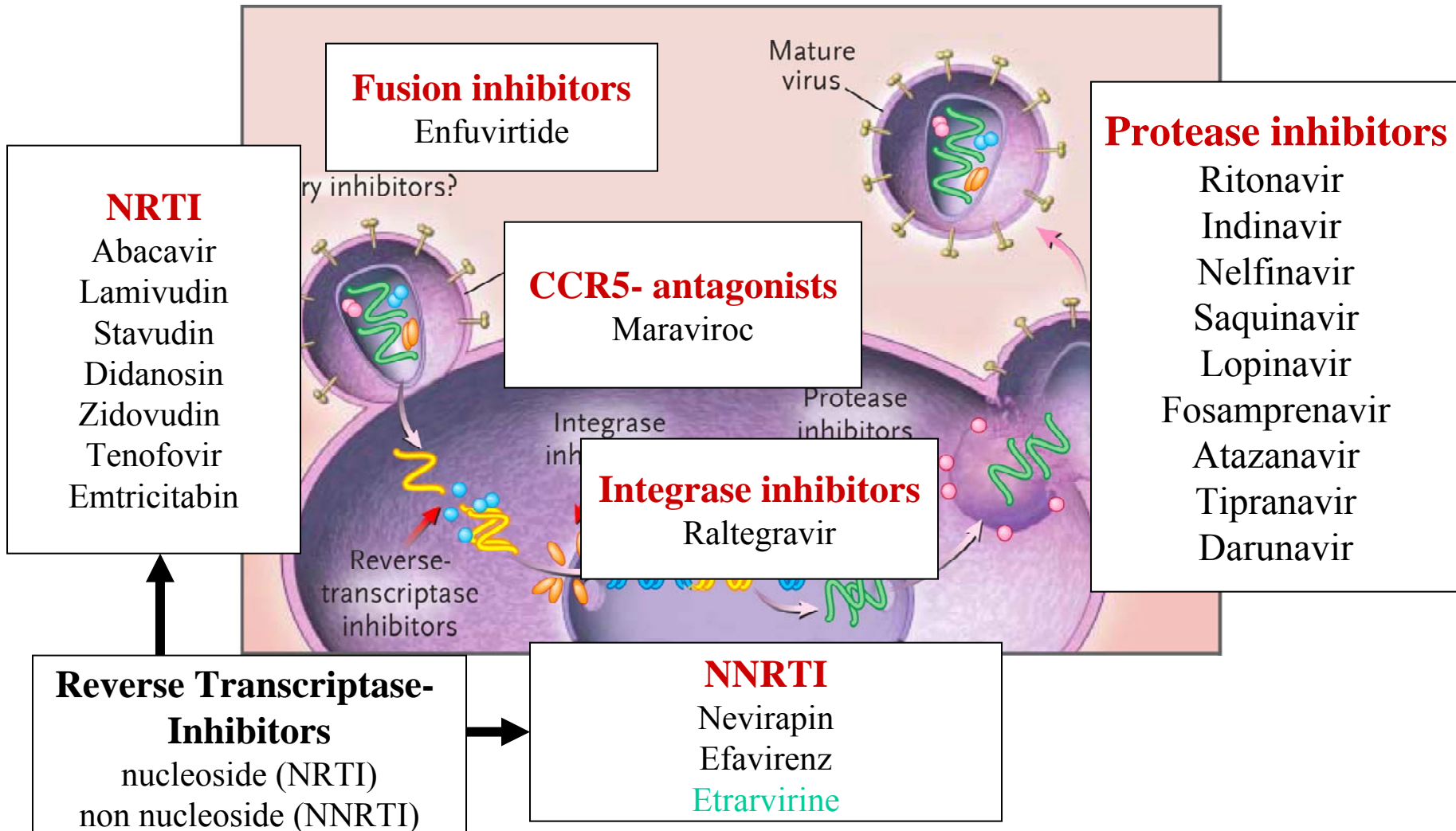
# Case 1: 40 year old man with PCP and newly diagnosed HIV infection



# How would you treat?

- Which drugs?
- Which diagnostic tests do you order?

# Antiretroviral drugs 2008



# Diagnostic tests before initiation of ART

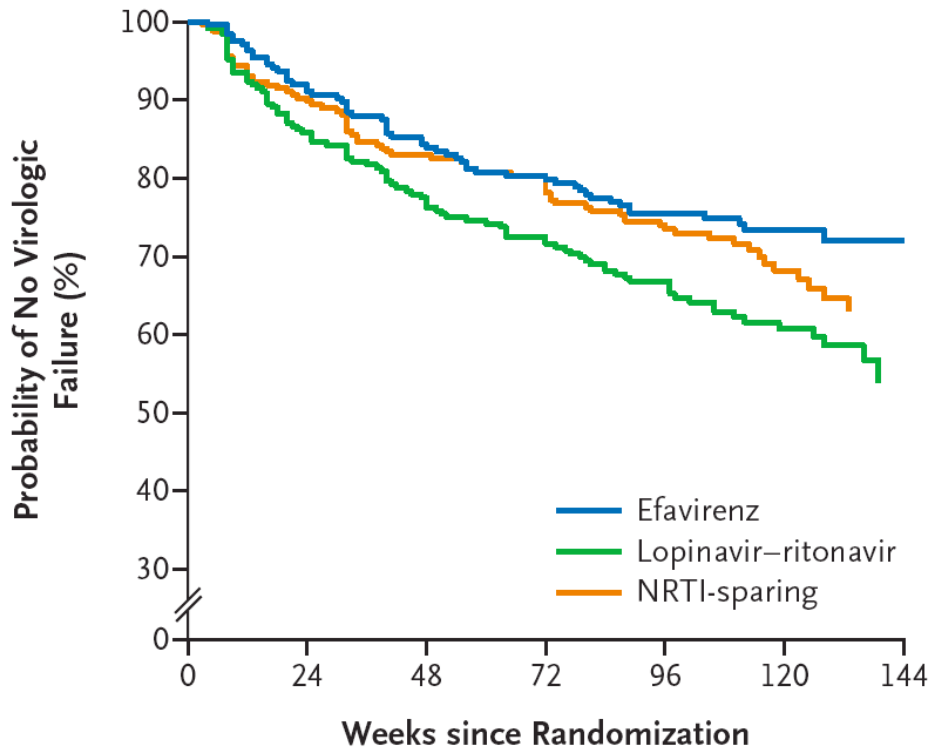
- Blood panel
  - blood count
  - transaminases
  - creatinine
  - lipids
- CD4+ cell count
- HIV-RNA
- HIV resistance testing
- HLA B5701
- Hepatitis B and C
- Syphilis

# Initial treatment of HIV infection (1. choice)

<b>2 NRTI</b>	<b>+</b>	<b>1 NNRTI</b>	<b>or</b>	<b>1 PI/r*</b>
Tenofovir/ Emtricitabine	+	Efavirenz	or	Lopinavir
Abacavir/ Lamivudine	+		or	Fosamprenavir
			or	Atazanavir

NRTI: nucleoside reverse transcriptase inhibitor  
 NNRTI: non nucleoside reverse transcriptase inhibitor  
 PI: protease inhibitor  
 \* with ritonavir booster

# Which combination for initial ART?



Randomisation  
between 3 treatment  
arms

- Efavirenz + 2NRTI
- Lopinavir/r + 2NRTI
- Efavirenz +  
Lopinavir/r (NRTI-  
sparing)

## No. at Risk

Efavirenz	250	210	186	173	142	73	19
Lopinavir- ritonavir	253	210	185	168	140	74	14
NRTI-sparing	250	215	189	181	149	73	17

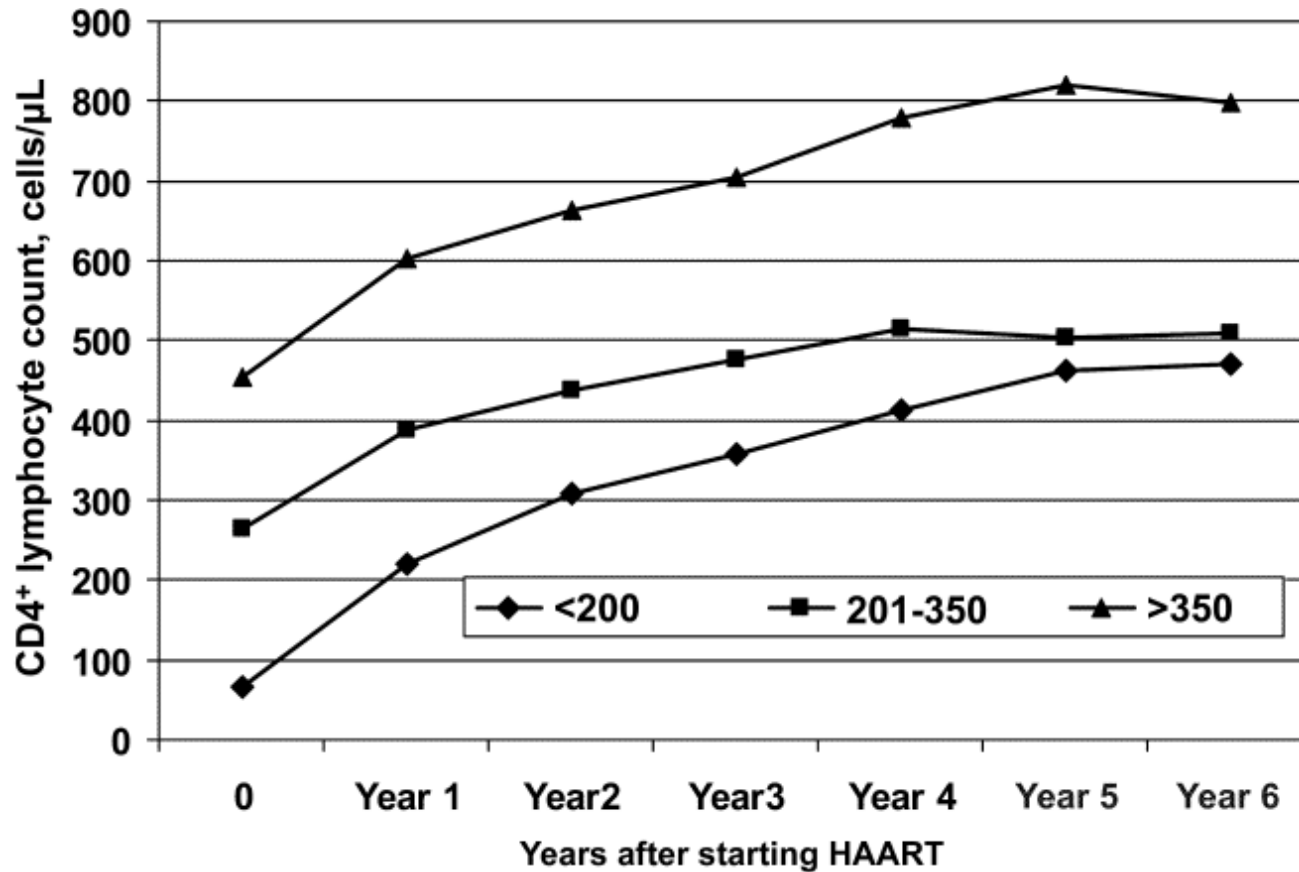
# Virologic efficacy of initial ART (HIV-RNA <50 copies/mL at month 12)

- Swiss HIV cohort
- HIV-RNA <50 c/mL at 48 weeks

– 2000-2001	84.5%
– 2002-2003	90.6%
– 2004-2005	92.6%

- ACTG 5142 study
  - HIV-RNA 50/mL at 96 weeks
- |                             |
|-----------------------------|
| – 89% (Efavirenz group)     |
| – 77% (Lopinavir group)     |
| – 83% (NRTI- sparing group) |

# Immunologic response to initial ART



# Case 2: 48- year old man with a 15 years history of ART (former sexual partner of case 1)

- HIV diagnosis 1990
- start of ART 1993
- multiple changes of therapy due to drug toxicity and treatment failure
- current regimen
  - lopinavir/r
  - tenofovir
  - 3TC
  - abacavir
  - HIV-RNA 25,000 c/mL
- CD4+ cells 80/ $\mu$ L

# Multi- drug resistance (3- class resistance)

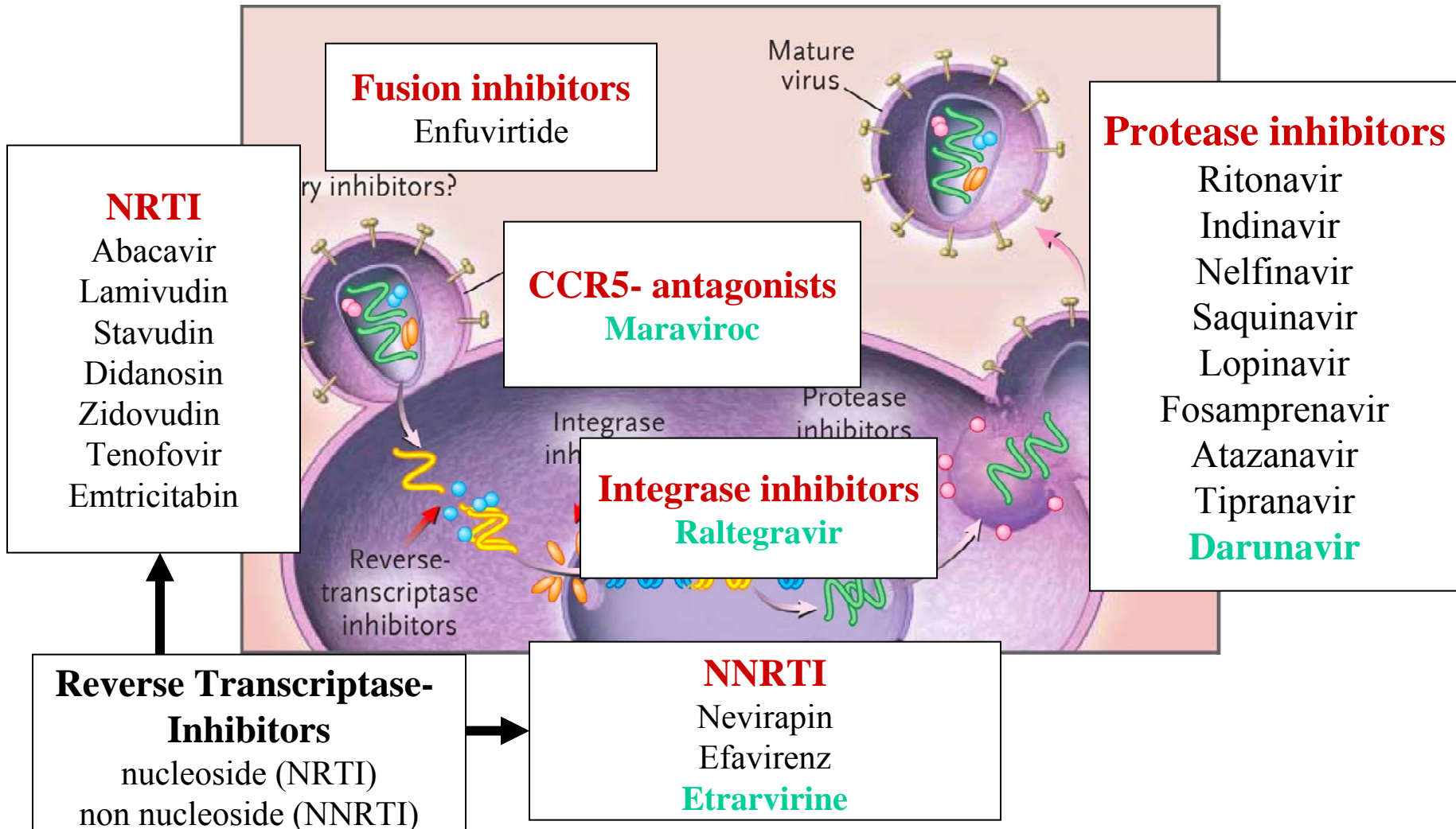
Drug		Matches in database	Proportion of matched samples:			Fold change in IC <sub>50</sub> (Cut-off for normal susceptible range)	Ref.
Trade name	Generic name		within normal susceptible range <sup>2</sup>	above normal susceptible range <sup>2</sup>	above normal susceptible range but below clinical cut-off <sup>2,3</sup>		
			25	50	75 (%)		
<b>NRTI</b>							
Retrovir®	Zidovudine	335				<b>13.0</b> (4.0)	
Epivir®	Lamivudine	367				<b>49.3</b> (4.5)	
Videx®	Didanosine	78				<b>2.2</b> (2.0)	
Hivid®	Zalcitabine	78				<b>2.2</b> (2.0)	
Zerit®	Stavudine	241				<b>1.6</b> (1.8)	
Ziagen®	Abacavir	73				<b>5.0</b> (3.0)	
<b>NNRTI</b>							
Viramune®	Nevirapine	621				<b>58.6</b> (8.0)	
Rescriptor®	Delavirdine	714				<b>146.3</b> (10.0)	
Sustiva®, Stocrin®	Efavirenz	615				<b>306.8</b> (6.0)	
<b>PI</b>							
Crixivan®	Indinavir	163				<b>30.8</b> (3.0)	
Norvir®	Ritonavir	163				<b>42.7</b> (3.5)	
Viracept®	Nelfinavir	164				<b>36.7</b> (4.0)	
Invirase®, Fortovase®	Saquinavir	162				<b>38.9</b> (2.5)	
Agenerase®	Amprenavir	111				<b>2.2</b> (2.0)	
A component of Kaletra®	Lopinavir	15				<b>16.8</b> (2.5)	3

- Resistance mutations in
- NRTI class
  - NNRTI class
  - PI class

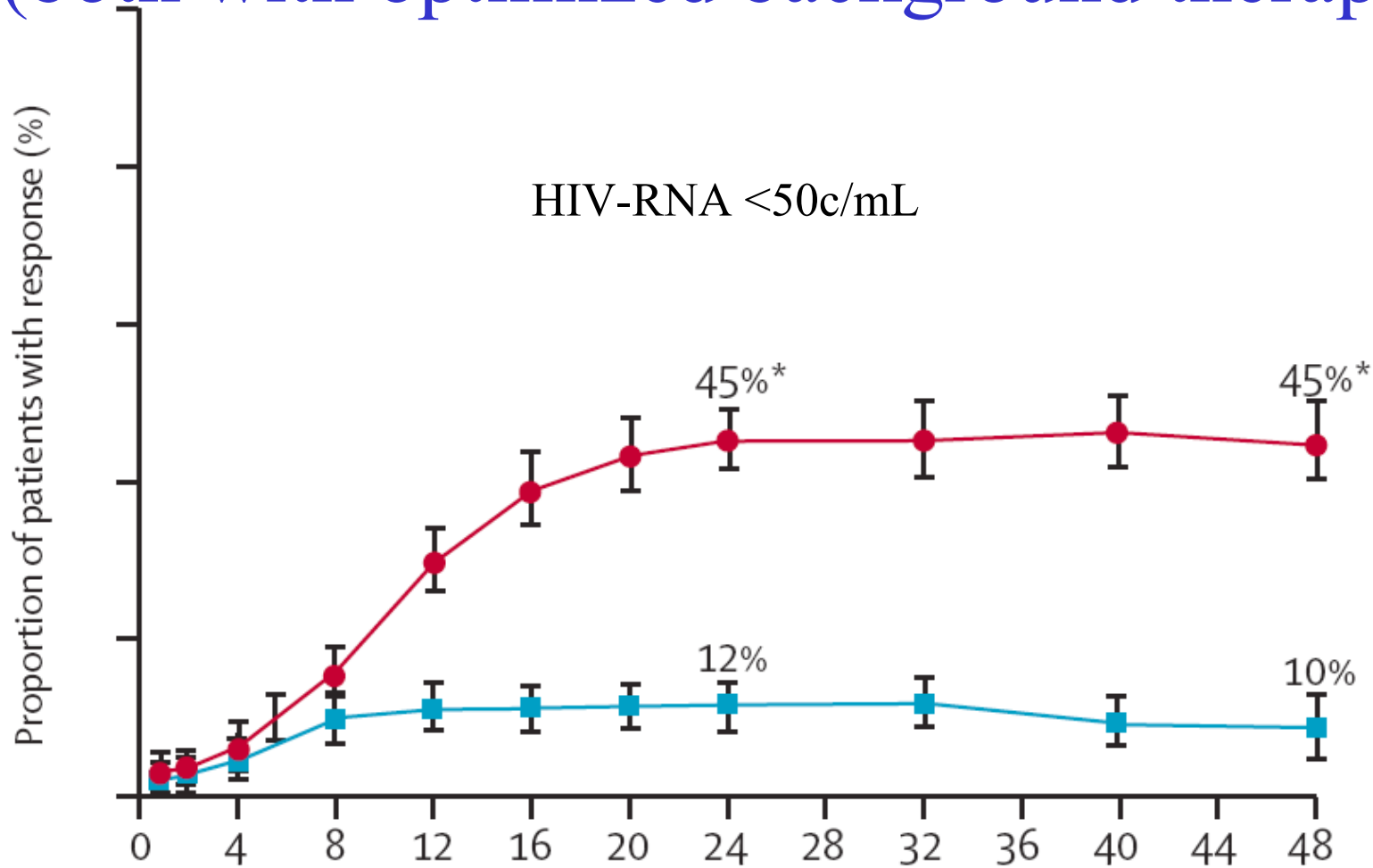
# Treatment options in patients with multi-resistant HIV

- New protease inhibitors with enhanced efficacy in patients with drug resistant HIV
  - darunavir
  - tipranavir
- New NNRTI
  - etravirine
- New classes
  - fusion inhibitor (enfuvirtide)
  - CCR5 inhibitor (maraviroc)
  - integrase inhibitor (raltegravir)

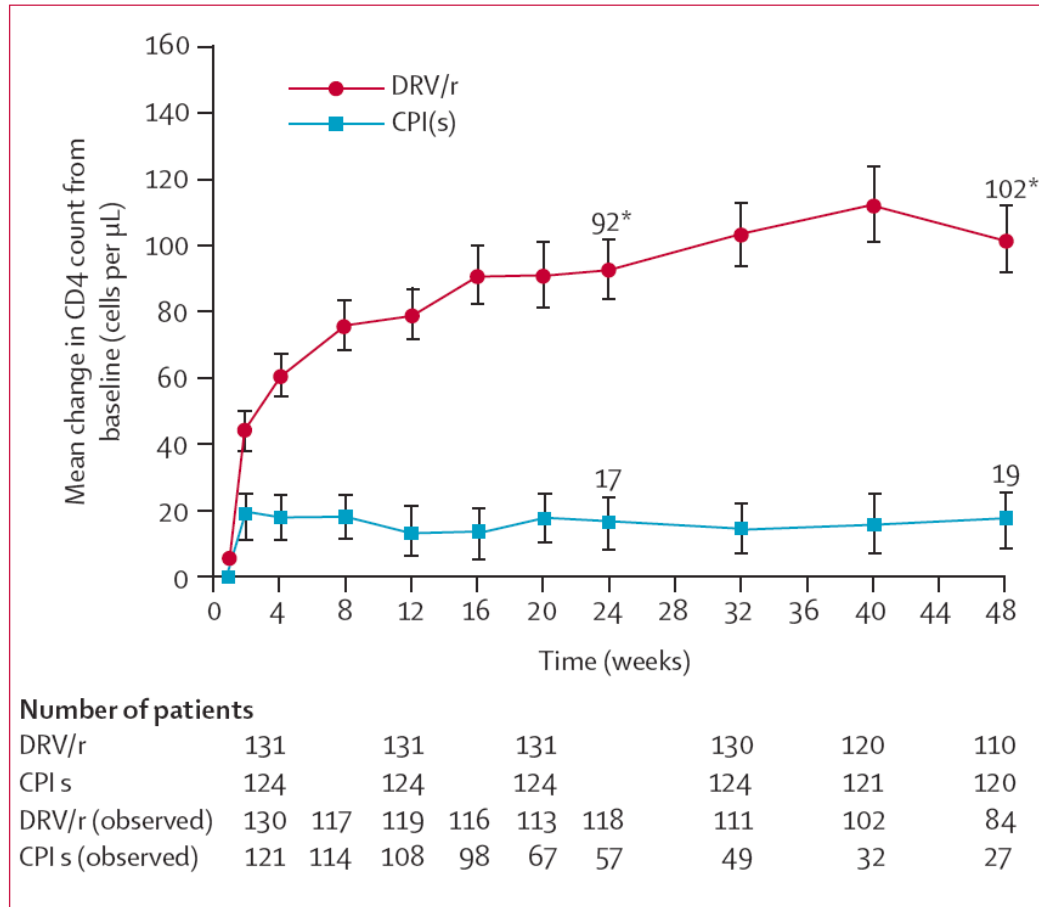
# New drugs



# POWER studies: Darunavir/r versus Placebo (both with optimized background therapy)



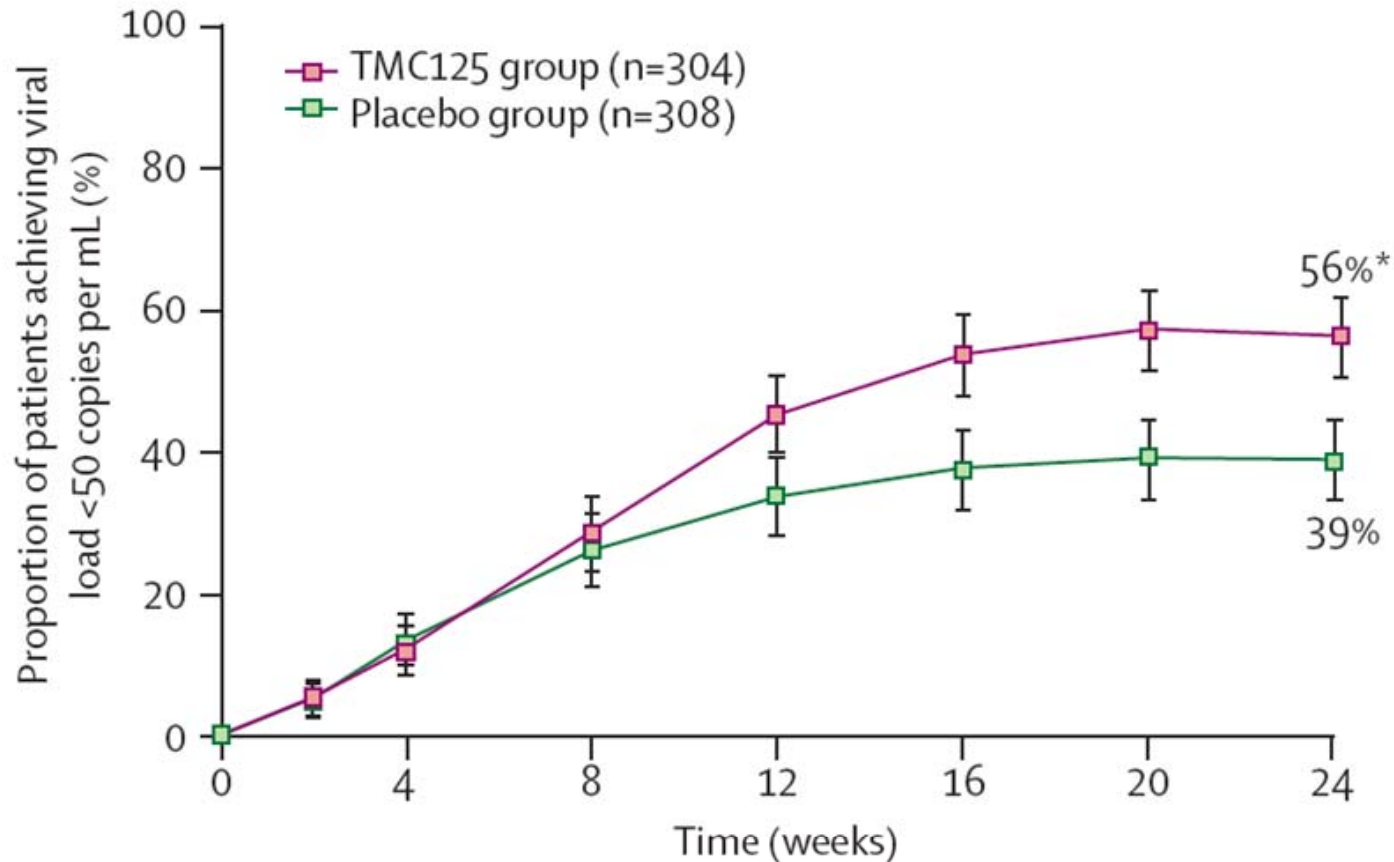
# POWER studies: CD4+ cell response



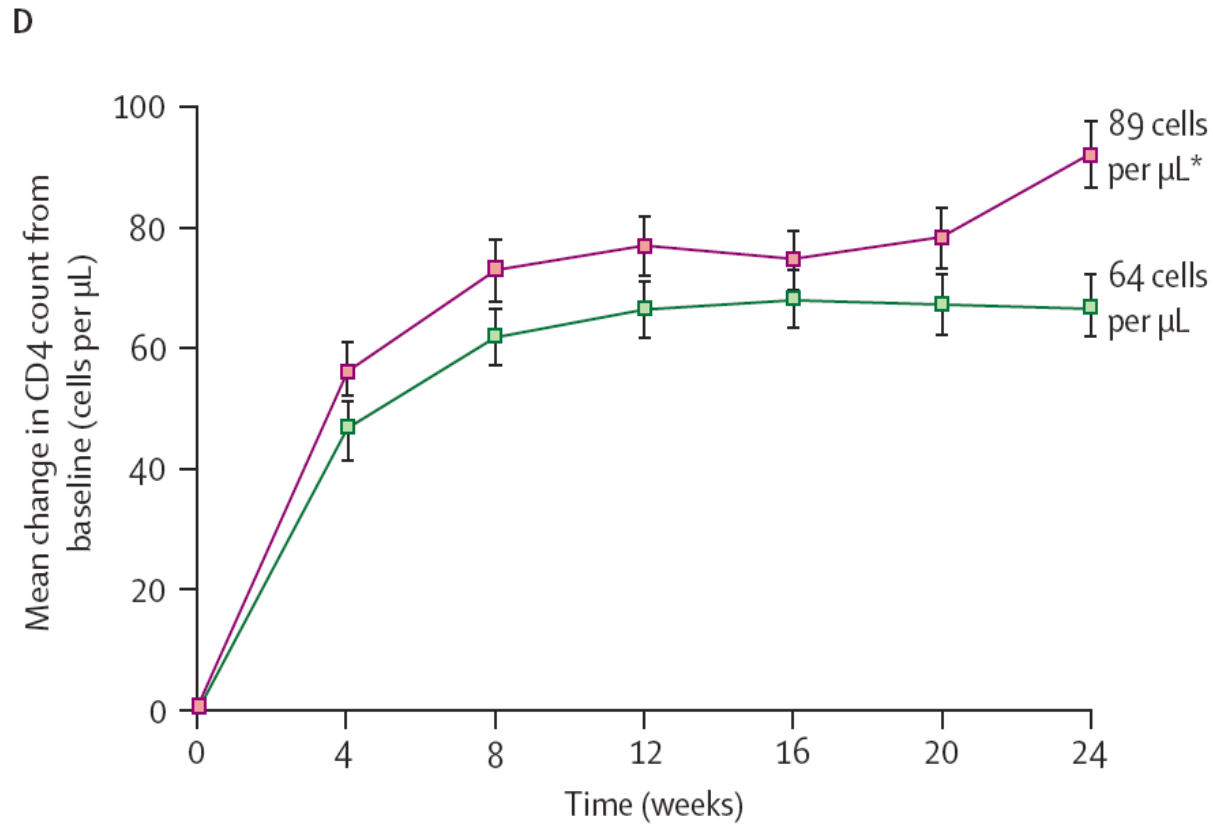
DRV/r: Darunavir (+ low dose ritonavir)

CPI: Control protease inhibitor

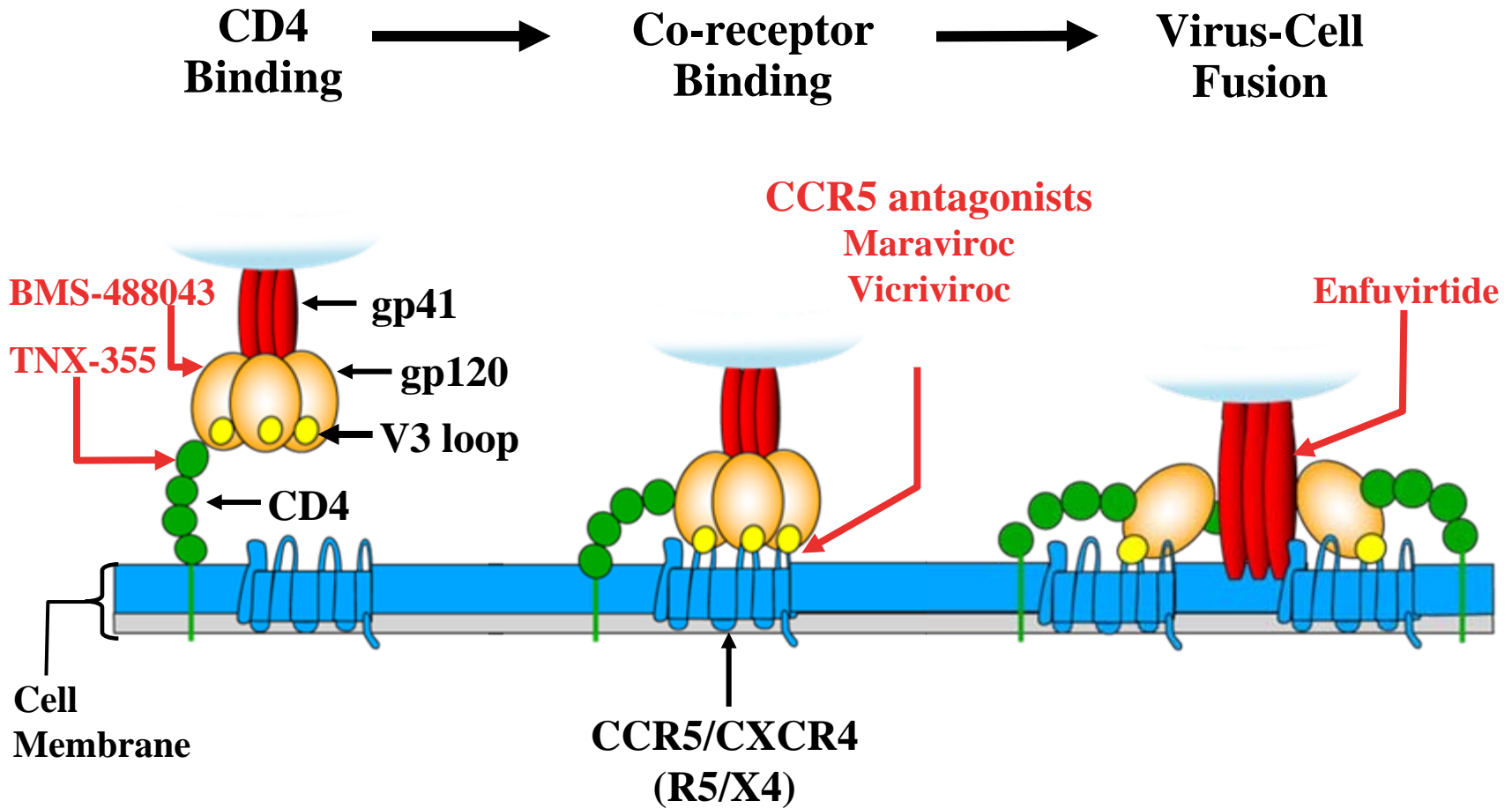
# DUET-1 study: Etravirine (TMC 125) versus placebo (both with optimized background therapy)



# DUET-1 study: CD4<sup>+</sup> cell response



# Steps of HIV entry

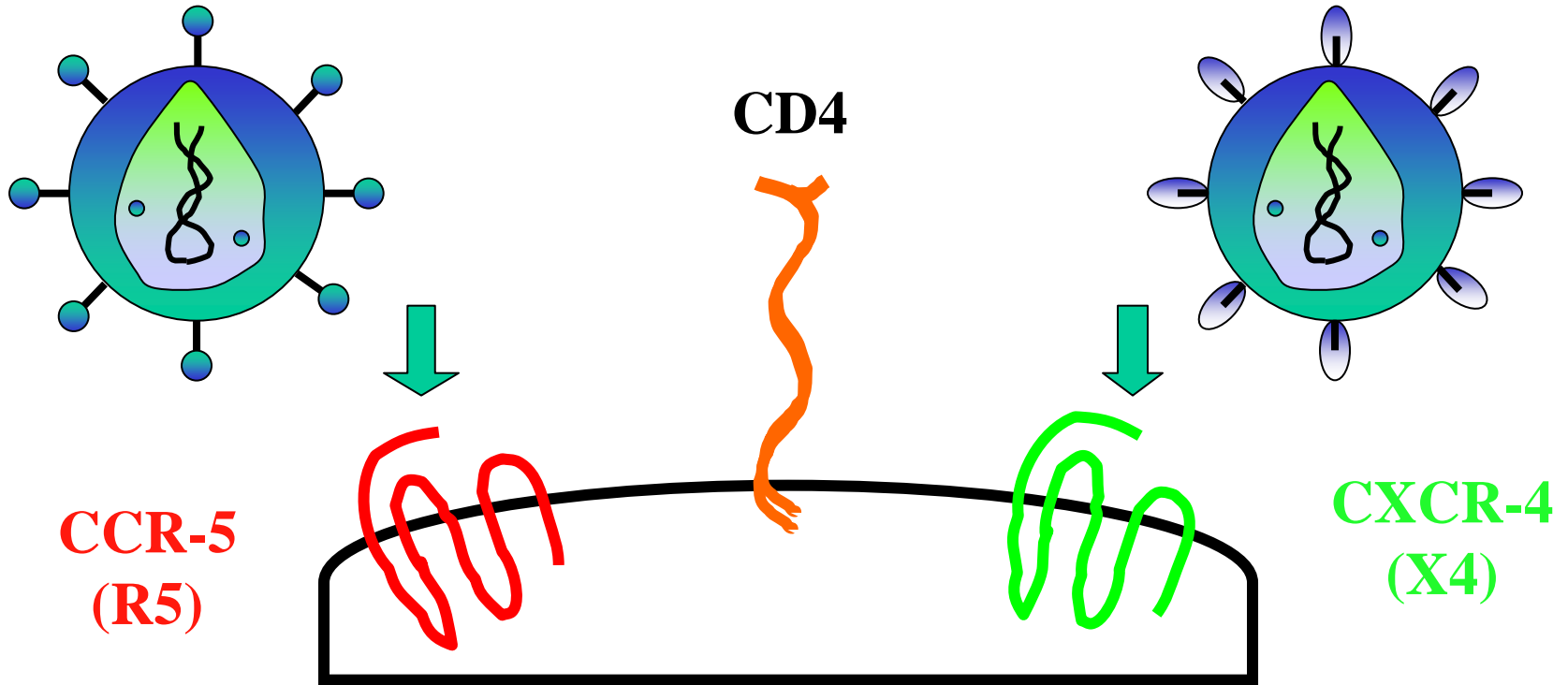


Adapted from Moore JP *et al.* PNAS 2003;100:10598-10602.

# Coreceptors used for HIV entry

R5- tropic

X4- tropic

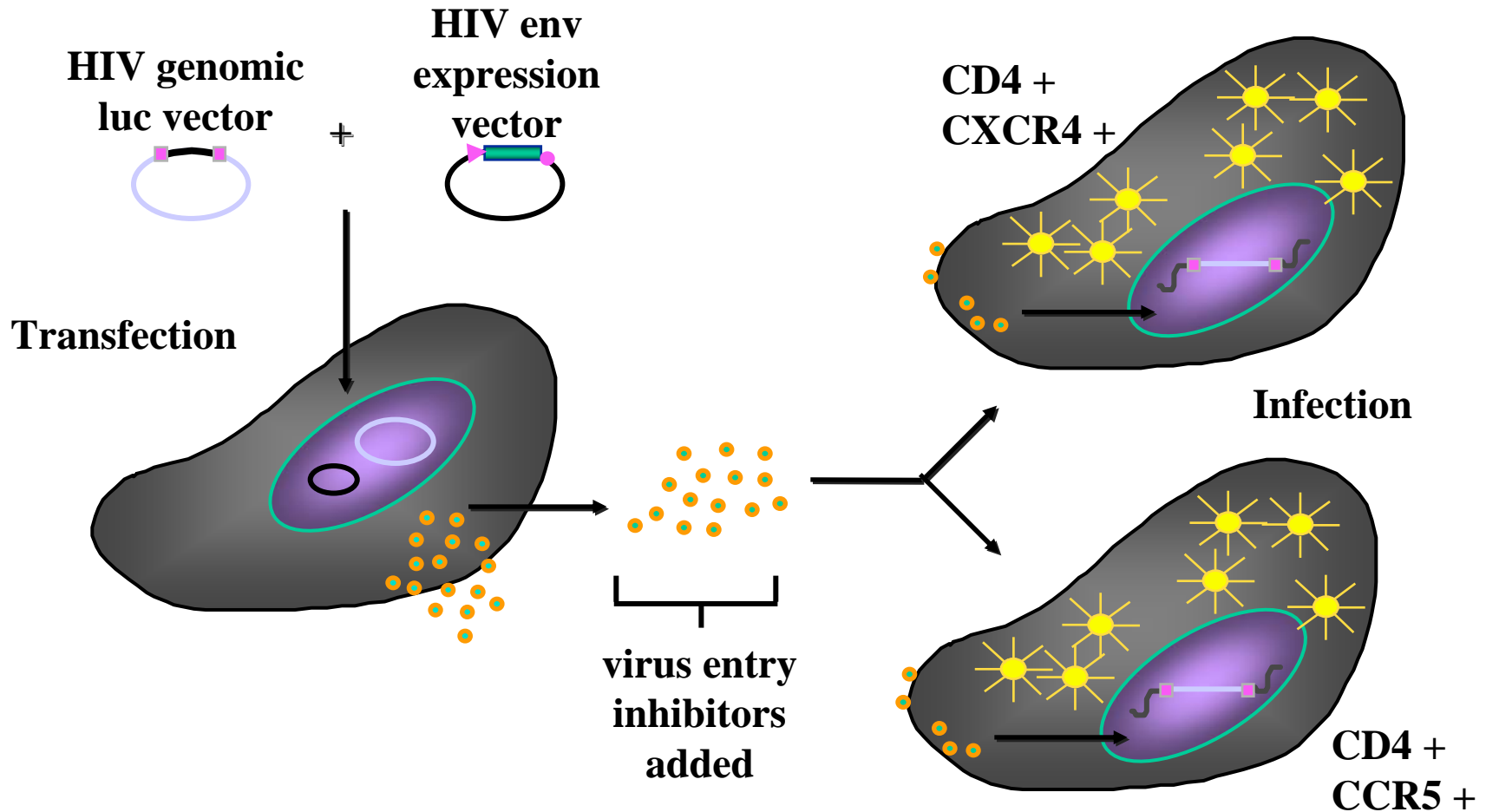


- predominant in early stages
- transmission of HIV

- up to 50% in late stages
- associated with disease progression

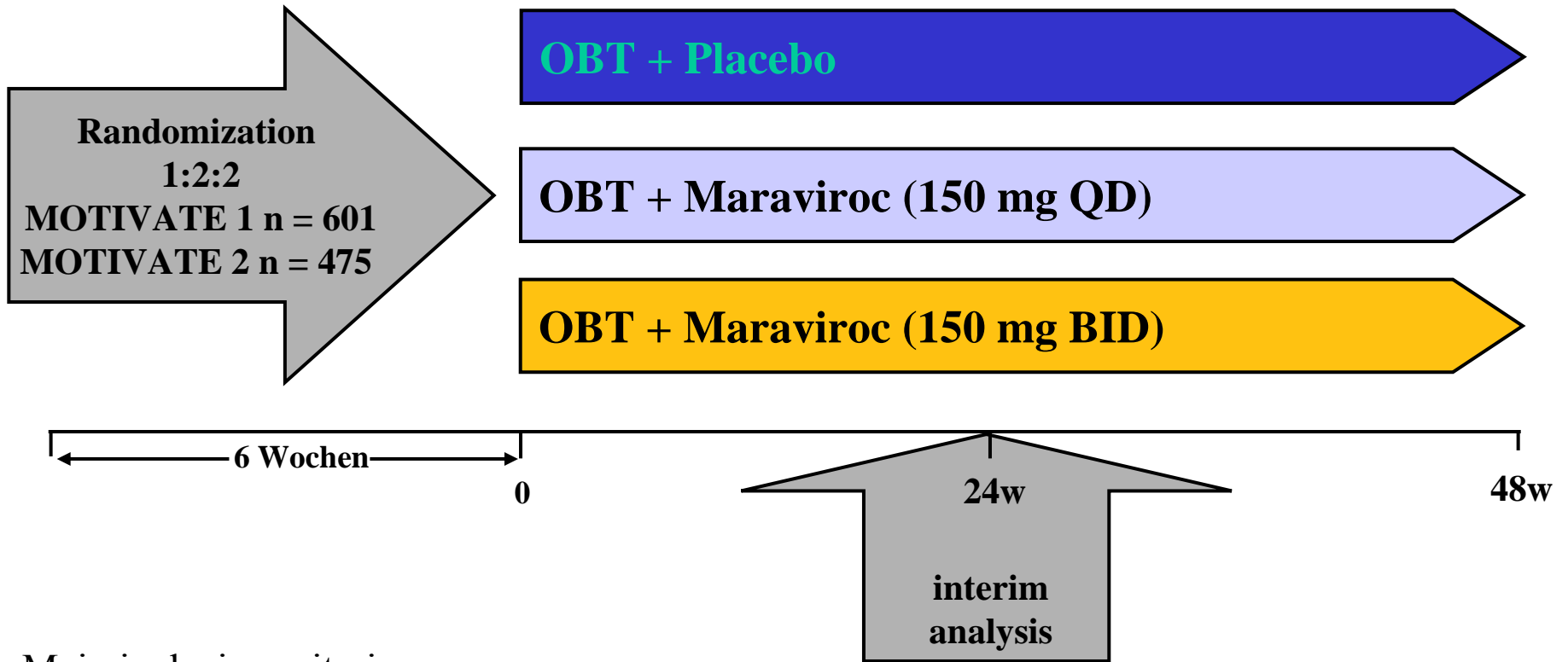
# Viral tropism has to be determined for usage of CCR5-antagonists

## Phenotypic HIV entry assay



# Maraviroc: MOTIVATE 1 & 2

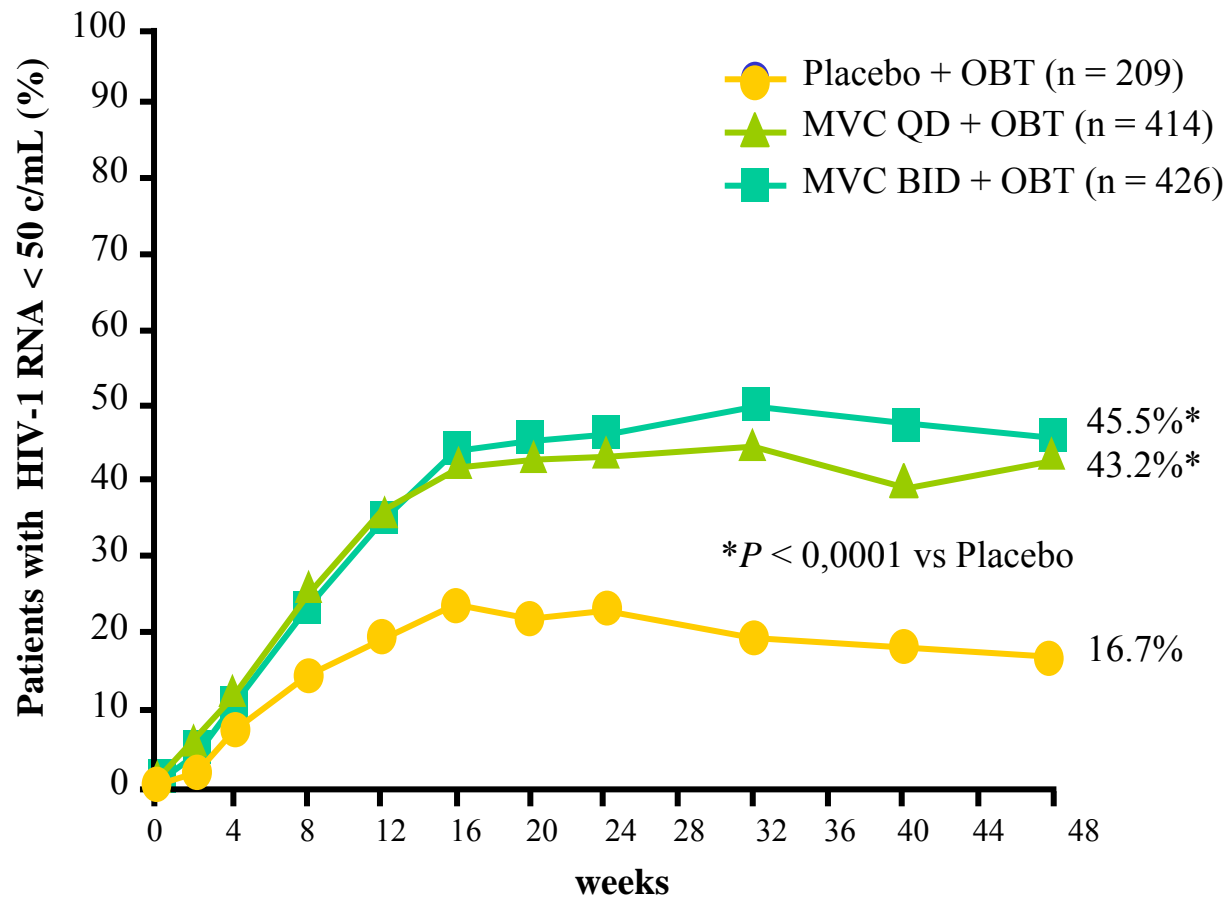
## Study design



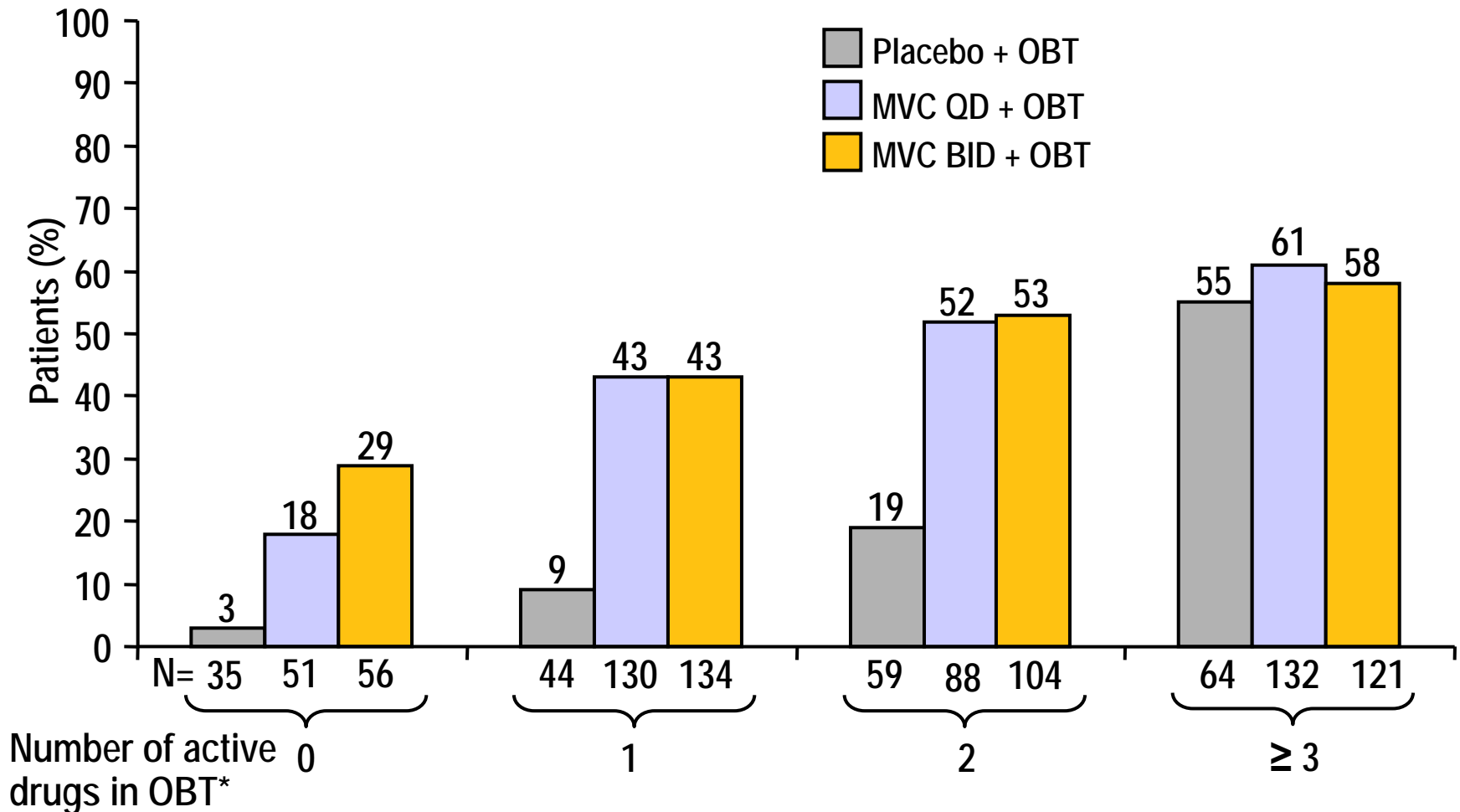
Main inclusion criteria:

- R5 HIV-1 infection
- HIV-1-RNA  $\geq$  5,000 copies/mL
- 3 class experienced

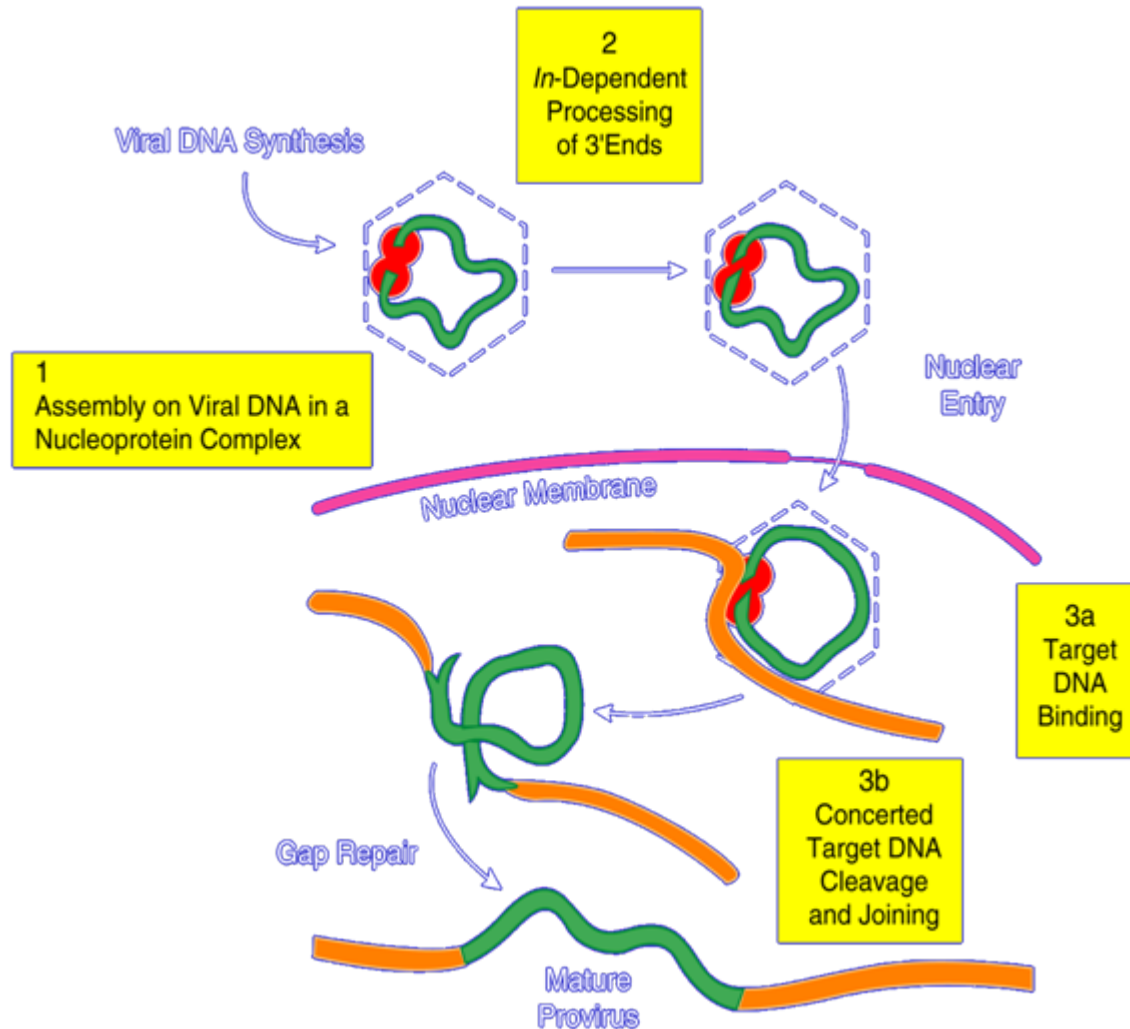
# MOTIVATE 1 & 2: Virologic efficacy week 48



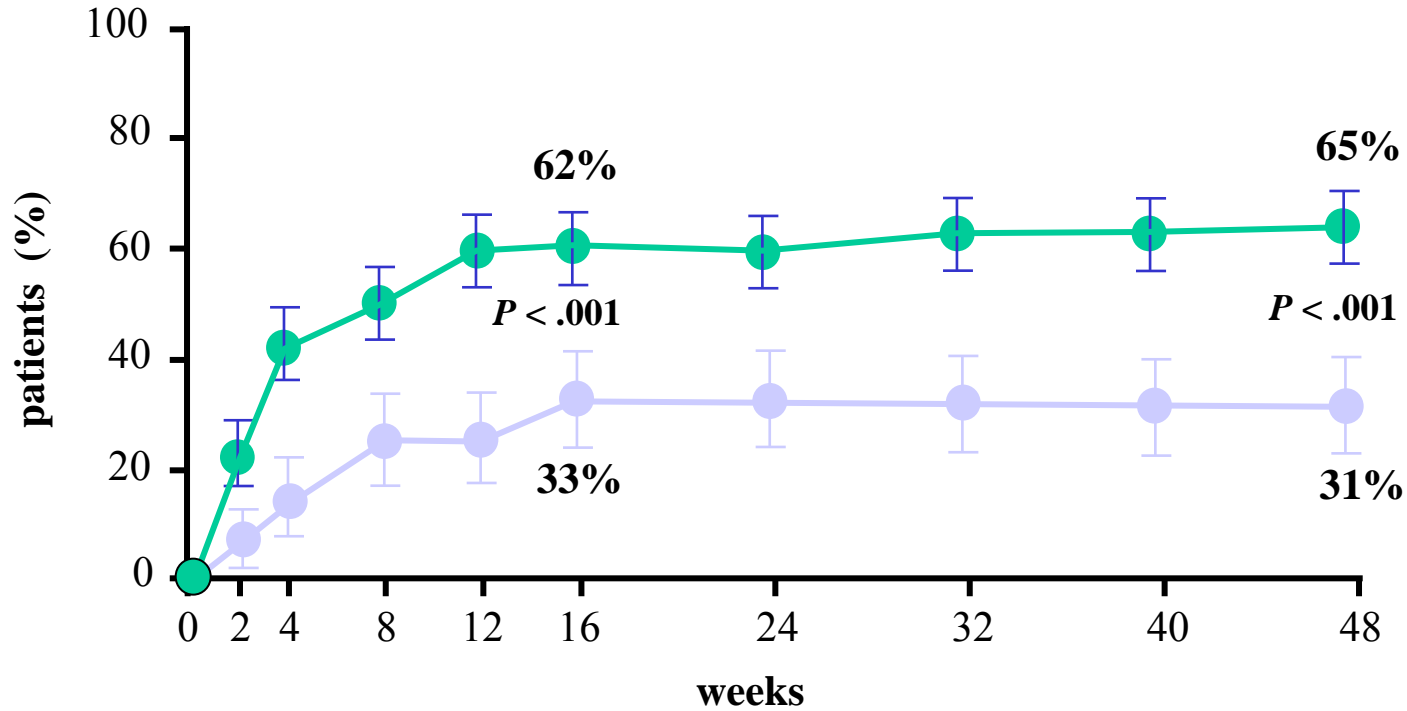
# MOTIVATE: HIV-1 RNA < 50 copies/mL by Number of Active Drugs in OBT



# Integrase inhibition



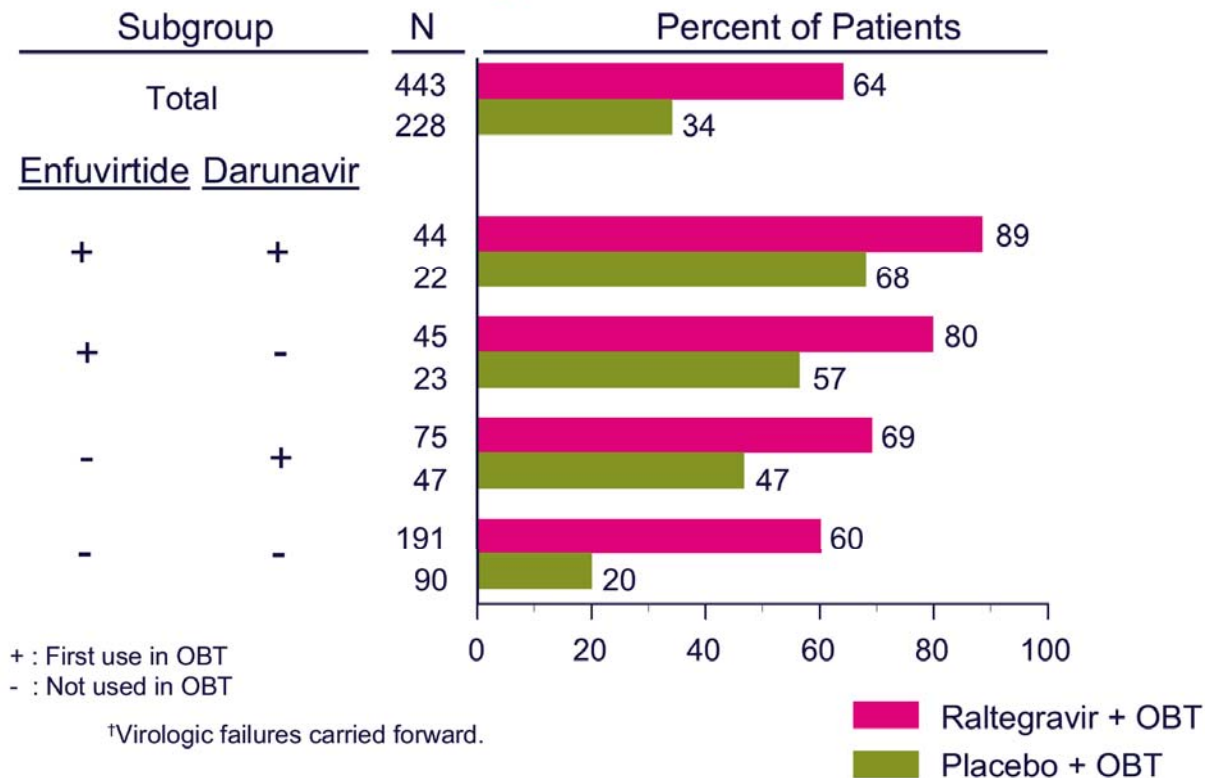
# BENCHMARK 1: virological efficacy week 48



● Raltegravir*	n =	232	231	231	230	229	232	229	230	231
● Placebo*	n =	118	118	118	118	117	118	118	118	118

# BENCHMARK 1&2: Virological efficacy according to drugs in OBТ

HIV-RNA <50c/mL, week 48



Cooper D, et al. CROI 2007. Abstract 105aLB.  
 Steigbigel R, et al. CROI 2007. Abstract 105bLB.

# Conclusion

- Very potent drugs and excellent treatment options for treatment naïve patients are available in 2008.
  - Nearly all patients can be treated successfully.
- Outcome in treatment experienced patients is substantially improved.
  - HIV-RNA  $<50\text{c/mL}$  is a therapeutic goal.
- New drugs should be used in combination with other active drugs ( $\geq 2$ ), preferably of new class, to achieve long-term efficacy.