New drugs and treatment options for HIV infection

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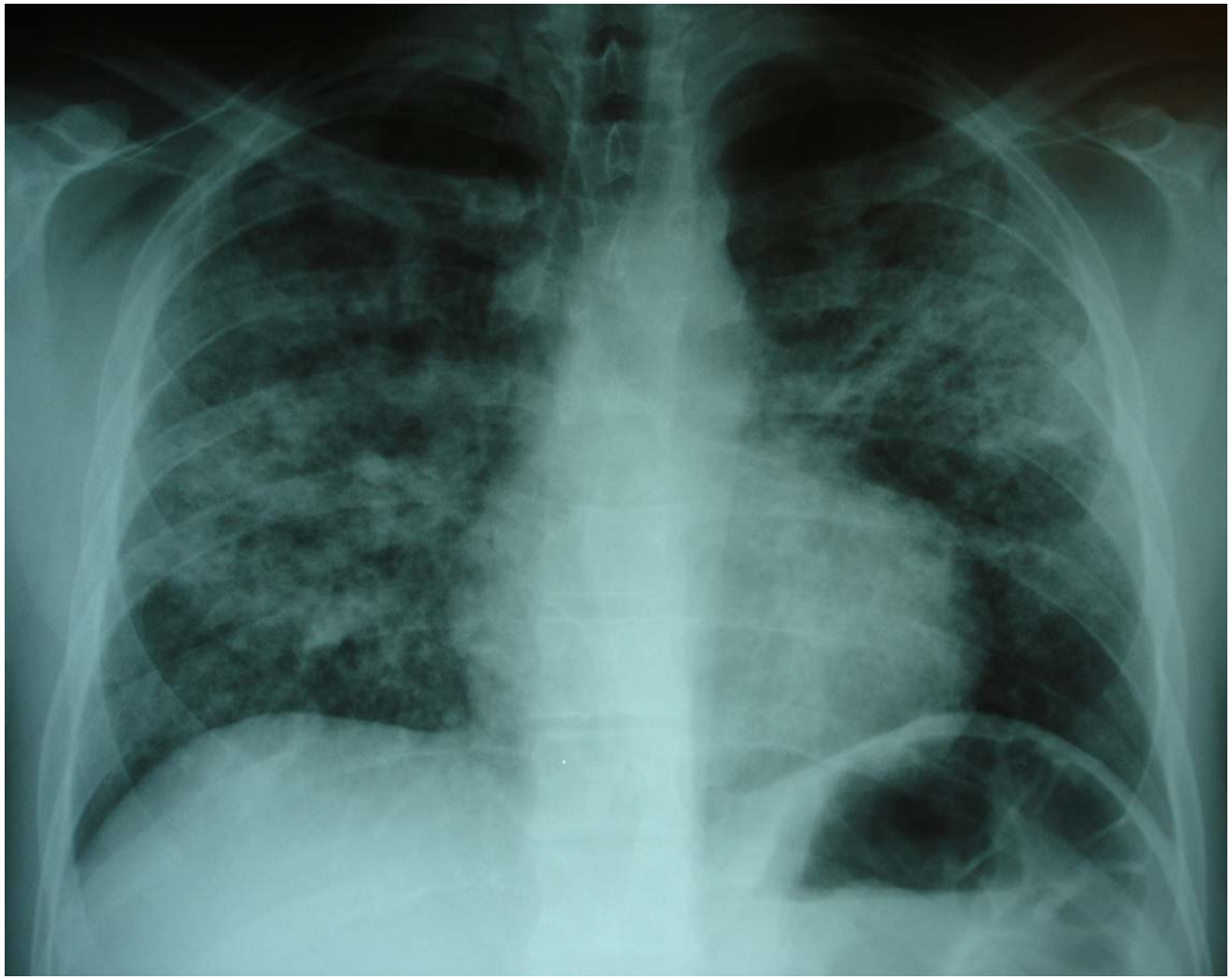
University of Cologne

ESCMID Summerschool
Regensburg, July 23, 2008

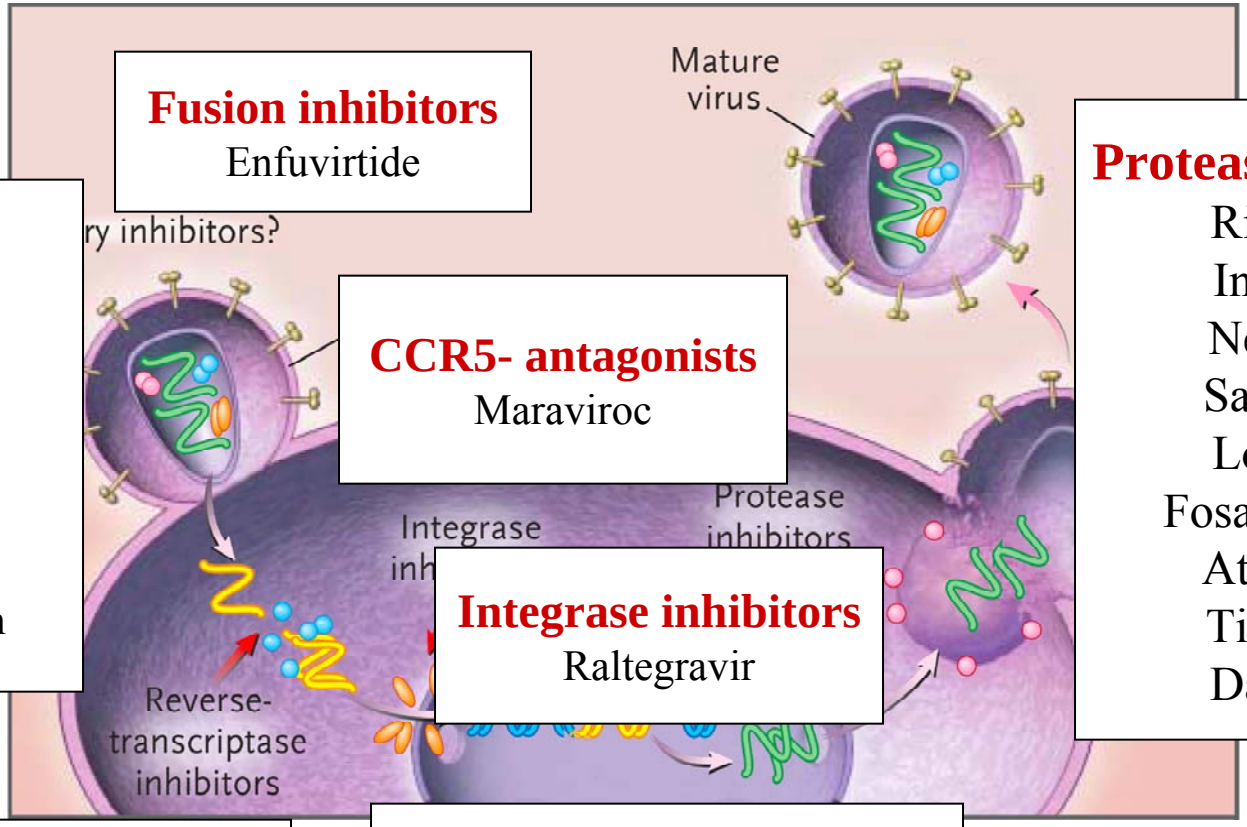
Case 1: 40 year old man with PCP and newly diagnosed HIV infection



How would you treat?

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

Antiretroviral drugs 20008



Fusion inhibitors
Enfuvirtide

CCR5- antagonists
Maraviroc

Integrase inhibitors
Raltegravir

NRTI
Abacavir
Lamivudin
Stavudin
Didanosin
Zidovudin
Tenofovir
Emtricitabin

Protease inhibitors
Ritonavir
Indinavir
Nelfinavir
Saquinavir
Lopinavir
Fosamprenavir
Atazanavir
Tipranavir
Darunavir

Reverse Transcriptase-Inhibitors
nucleoside (NRTI)
non nucleoside (NNRTI)

NNRTI
Nevirapin
Efavirenz
Etrarvirine

Diagnostic tests before initiation of ART

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

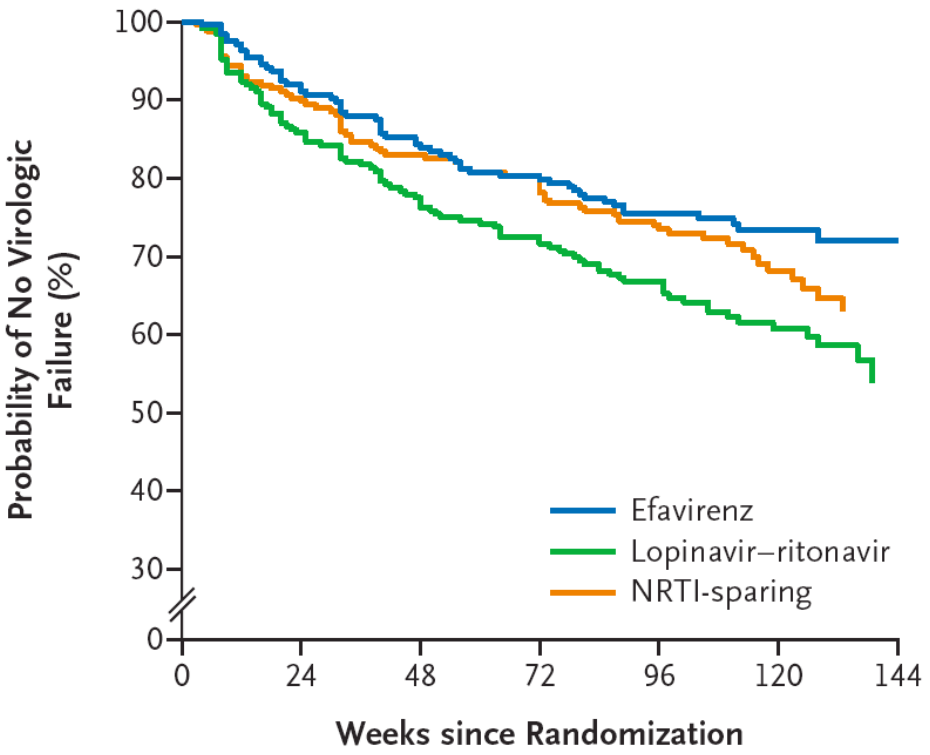
Initial treatment of HIV infection (1. choice)

2 NRTI	+	1 NNRTI	or	1 PI/r*
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

DHHS- Panel, 29. Januar 2008; http://aidsinfo.nih.gov

Which combination for initial ART?



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

Randomisation between 3 treatment arms

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

SA Riddler et al., NEJM 2008; 358:2095

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%

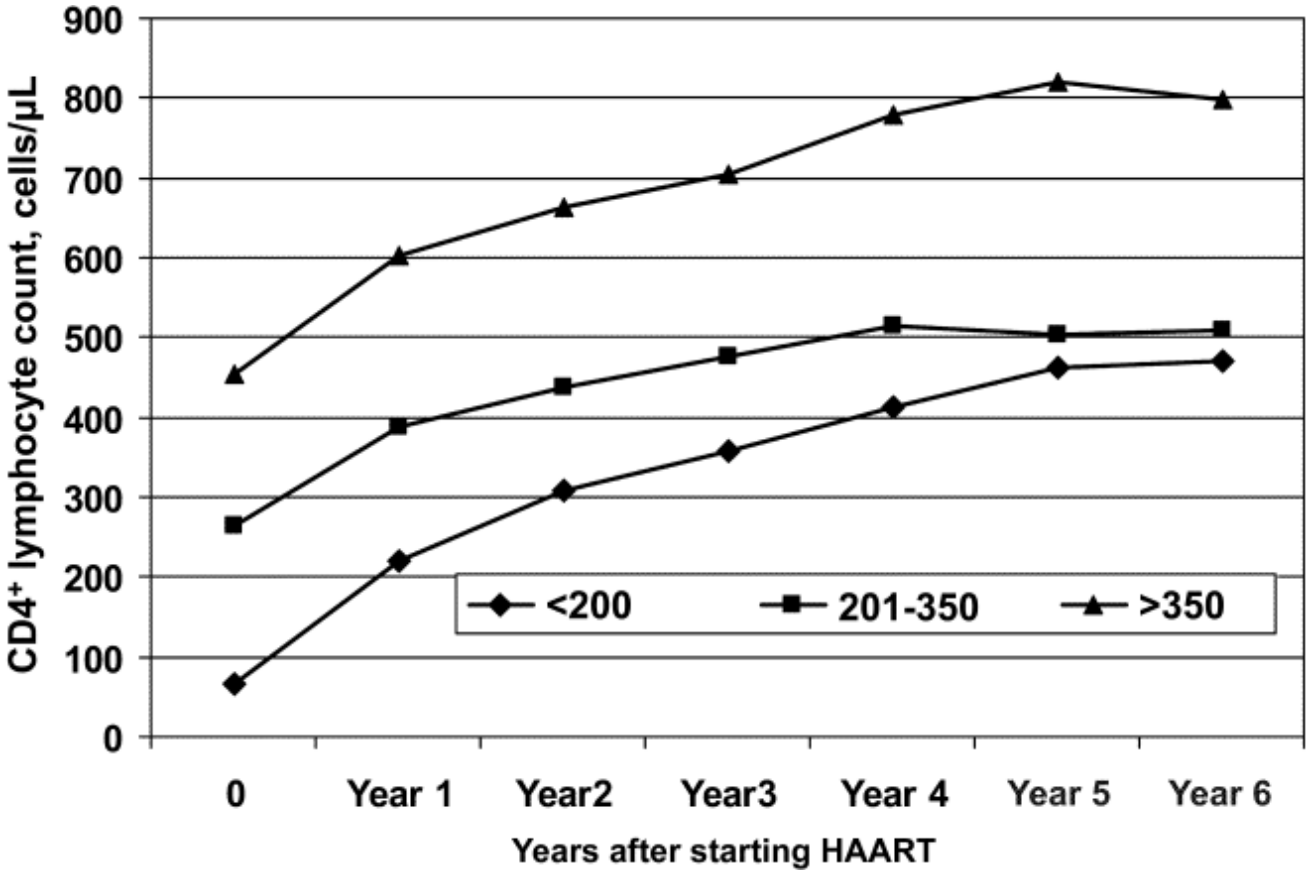
Vo et al., J Infect Dis 2008; 197:1685

- ACTG 5142 study
- HIV-RNA 50/mL at 96 weeks

– 89% (Efavirenz group)
– 77% (Lopinavir group)
– 83% (NRTI- sparing group)

SA Riddler et al., NEJM 2008; 358:2095

Immunologic response to initial ART



RD Moore et al, Clin Infect Dis 2007; 44:441

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/μL

Multi- drug resistance (3- class resistance)

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

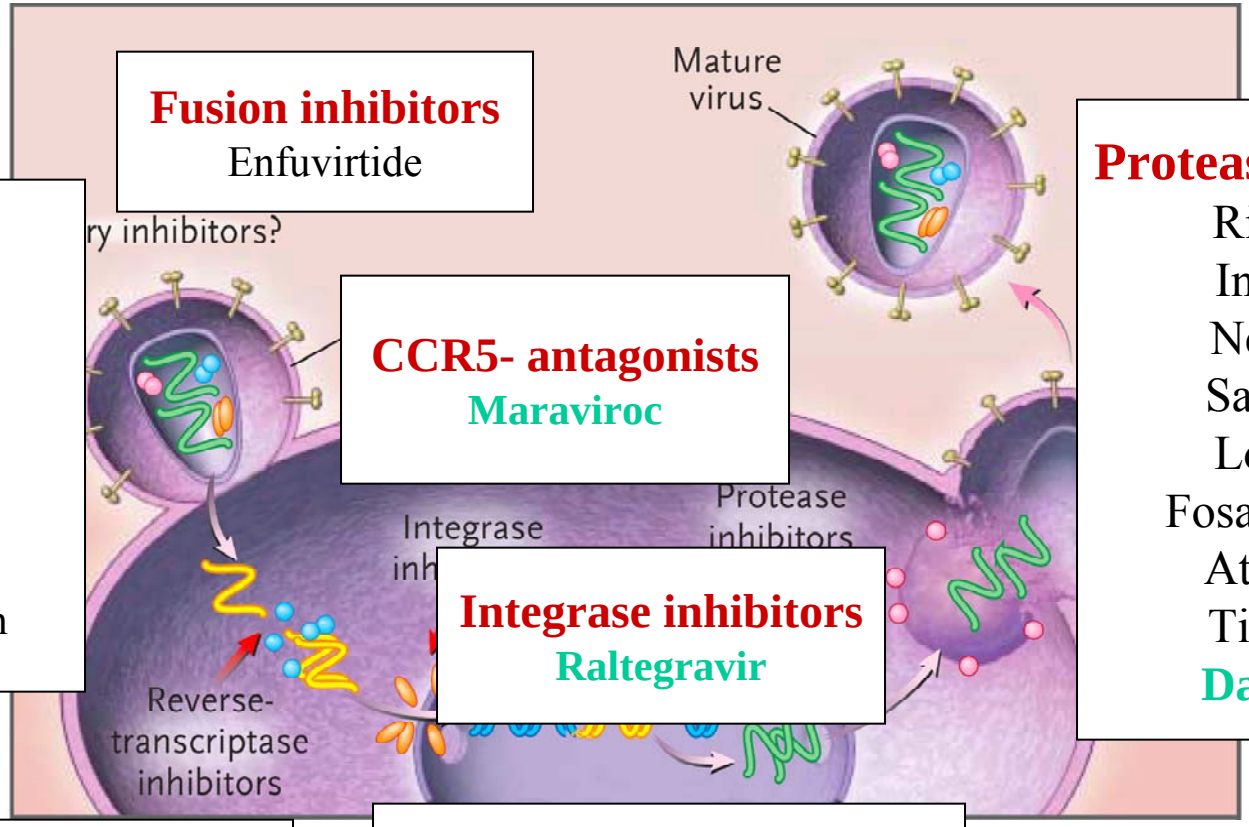
Resistance mutations in

- 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



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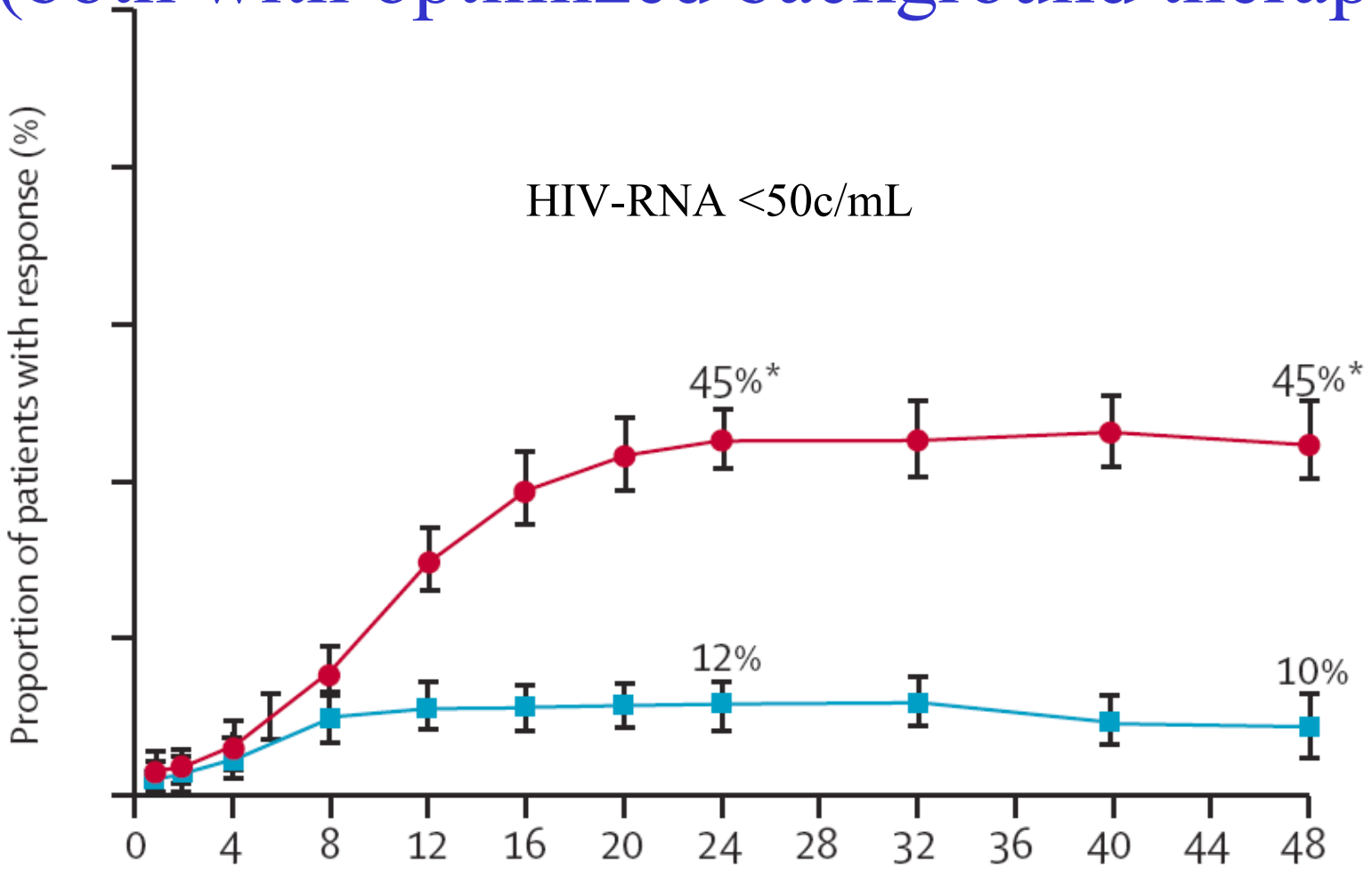
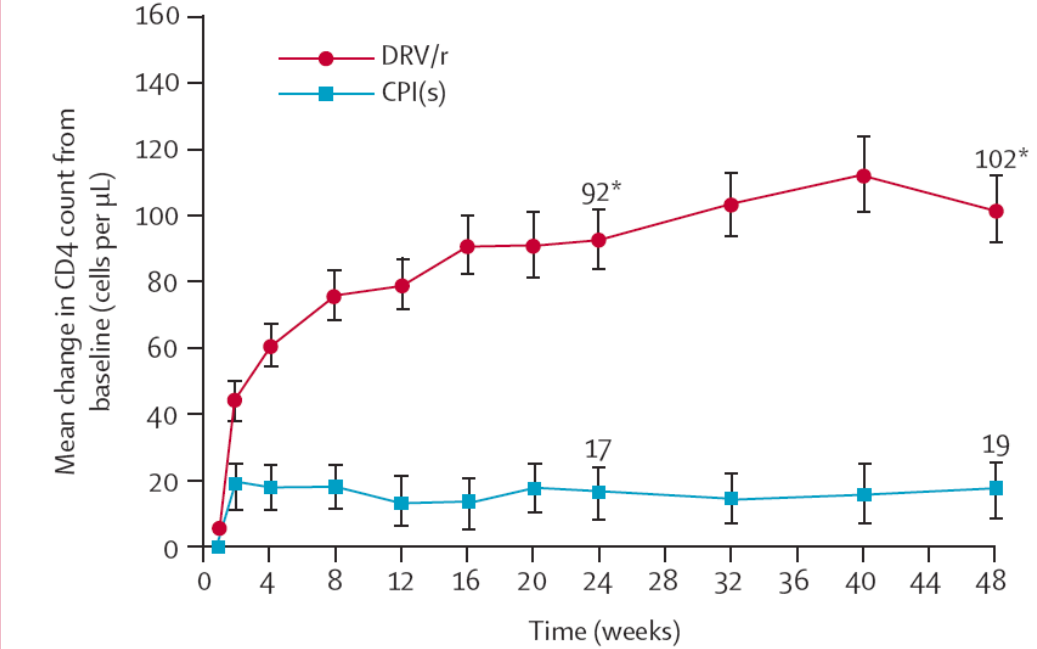
POWER studies: Darunavir/r versus Placebo (both with optimized background therapy)



Clotet *et al*. Lancet 2007;369:1169-78

POWER studies: CD4+ cell response



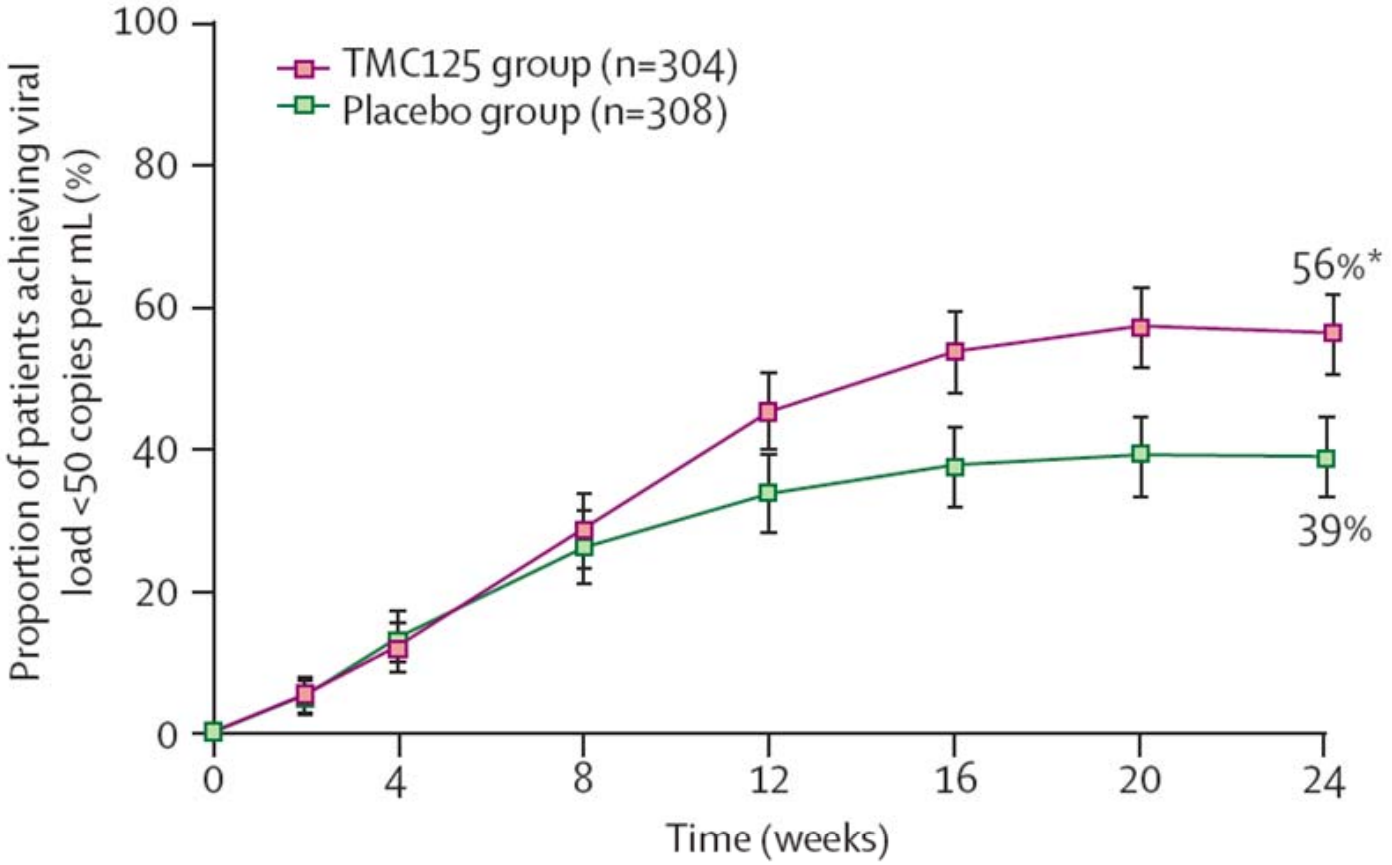
Number of patients

DRV/r	131		131		131		130	120	110
CPI s	124		124		124		124	121	120
DRV/r (observed)	130	117	119	116	113	118	111	102	84
CPI s (observed)	121	114	108	98	67	57	49	32	27

DRV/r: Darunavir (+ low dose ritonavir)
CPI: Control protease inhibitor

Clotet *et al*. Lancet 2007;369:1169-78

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



Madruga *et al*. Lancet 2007;370:29-38

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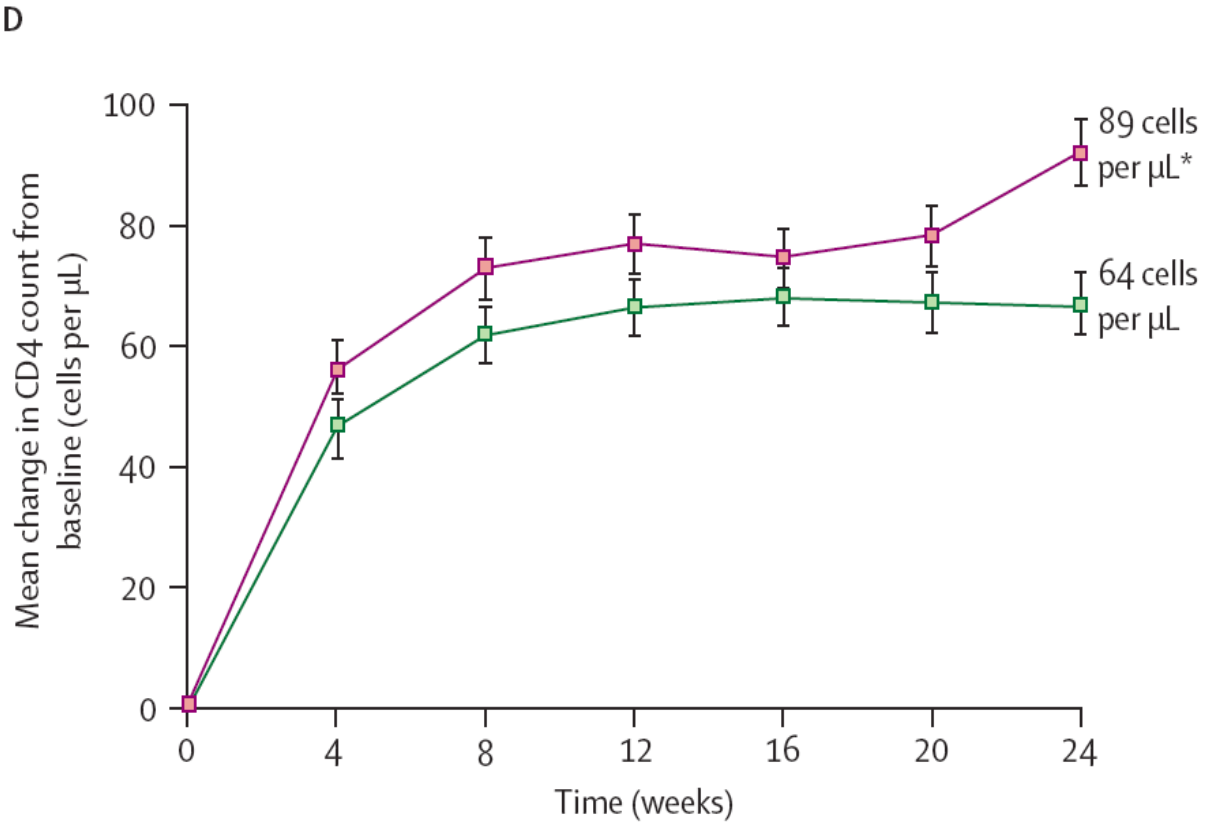

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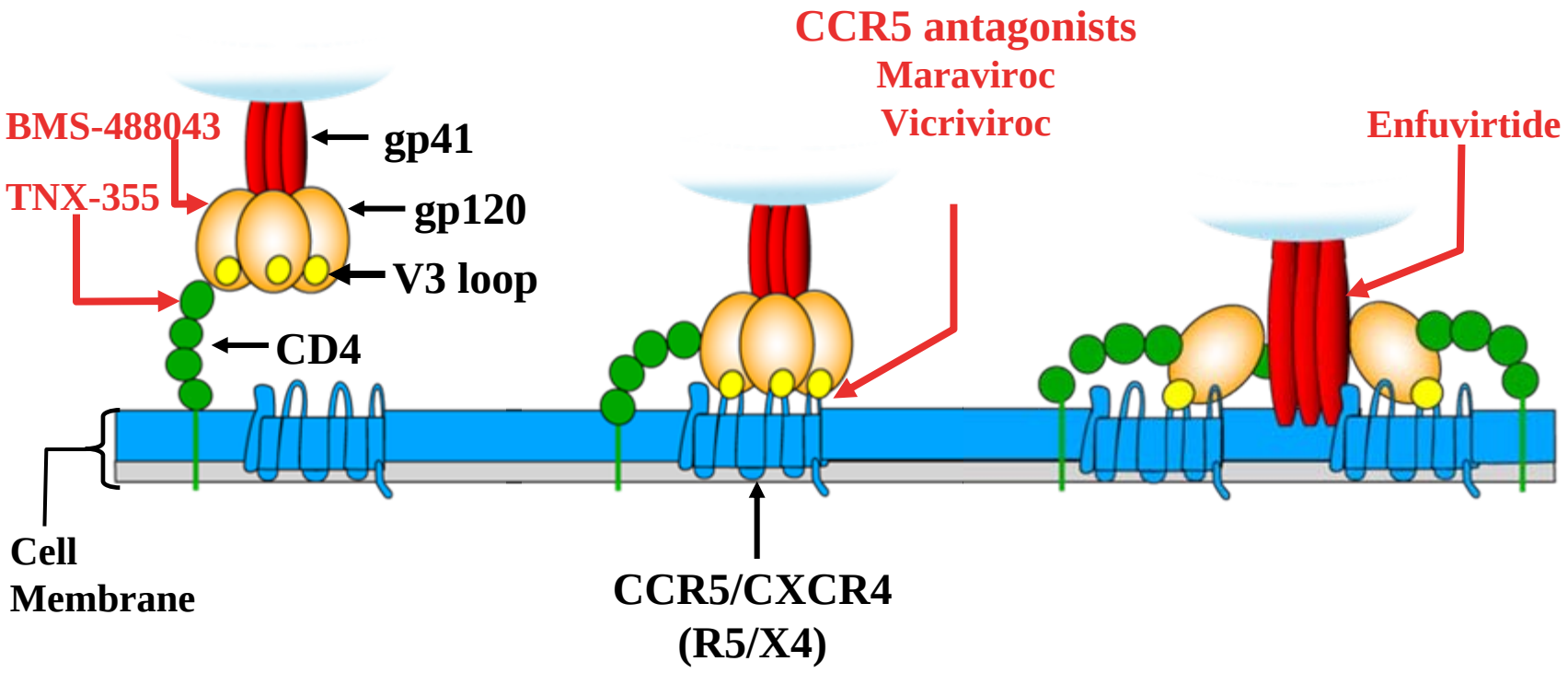
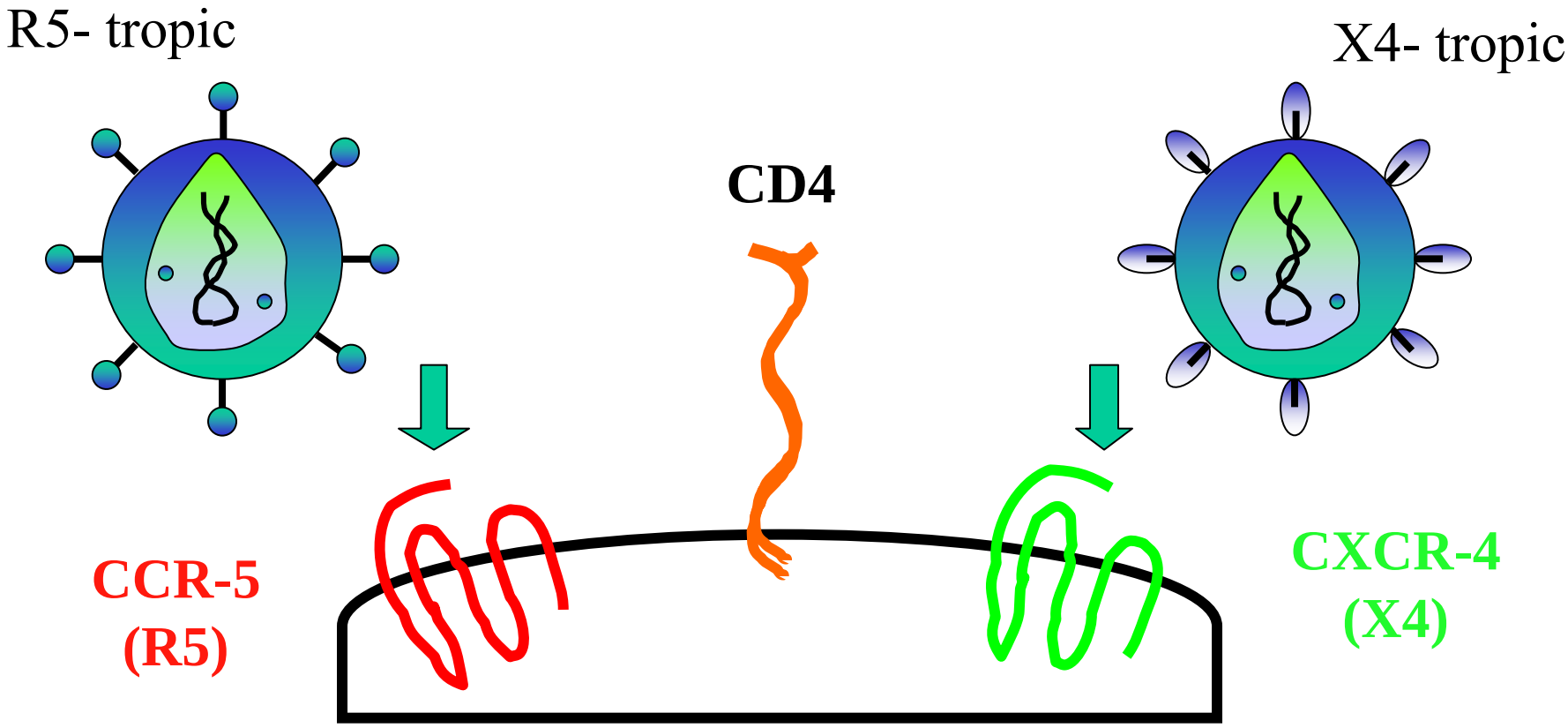
Steps of HIV entry

CD4 Binding → **Co-receptor Binding** → **Virus-Cell Fusion**



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

Coreceptors used for HIV entry

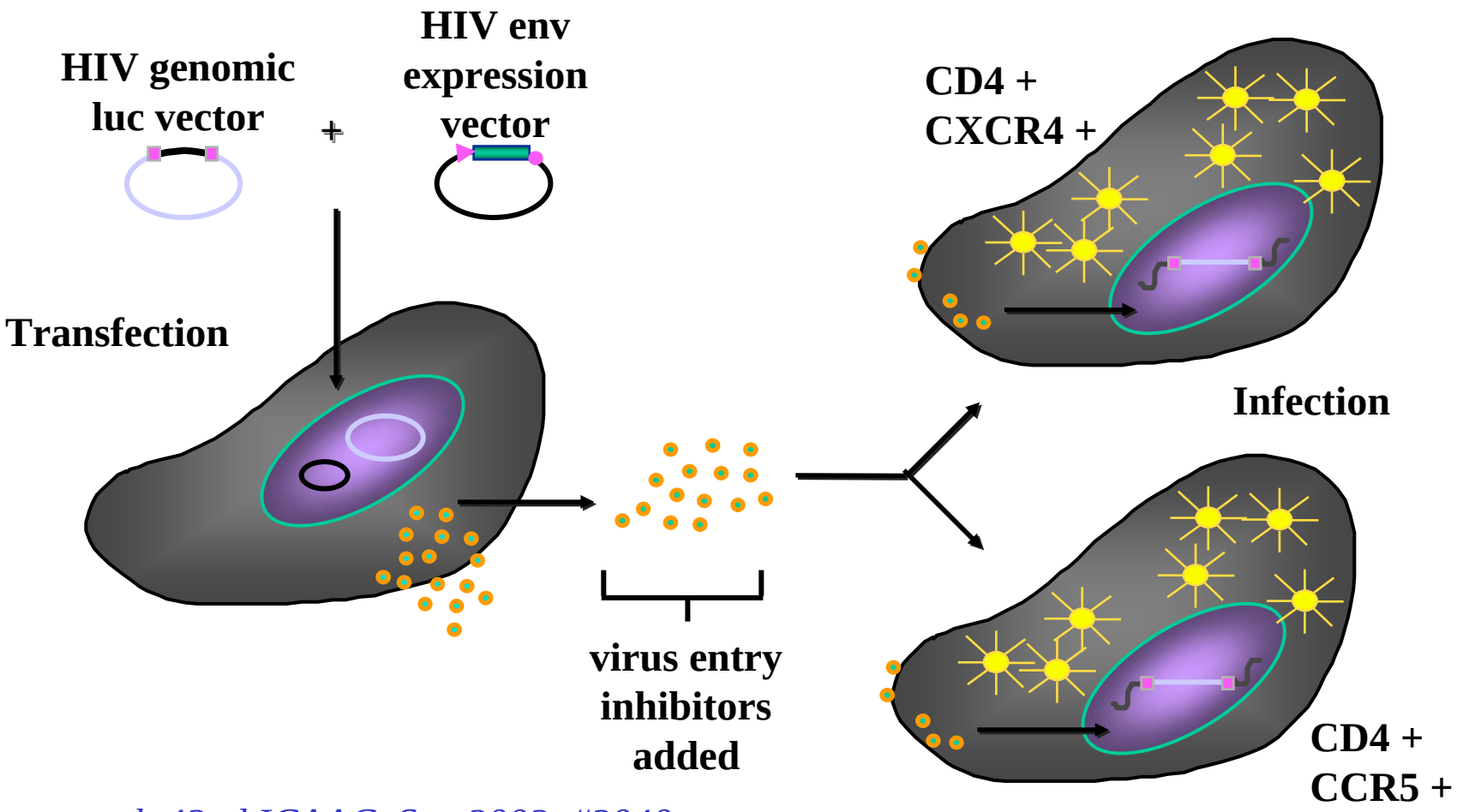


- predominant in early stages
- transmission of HIV

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

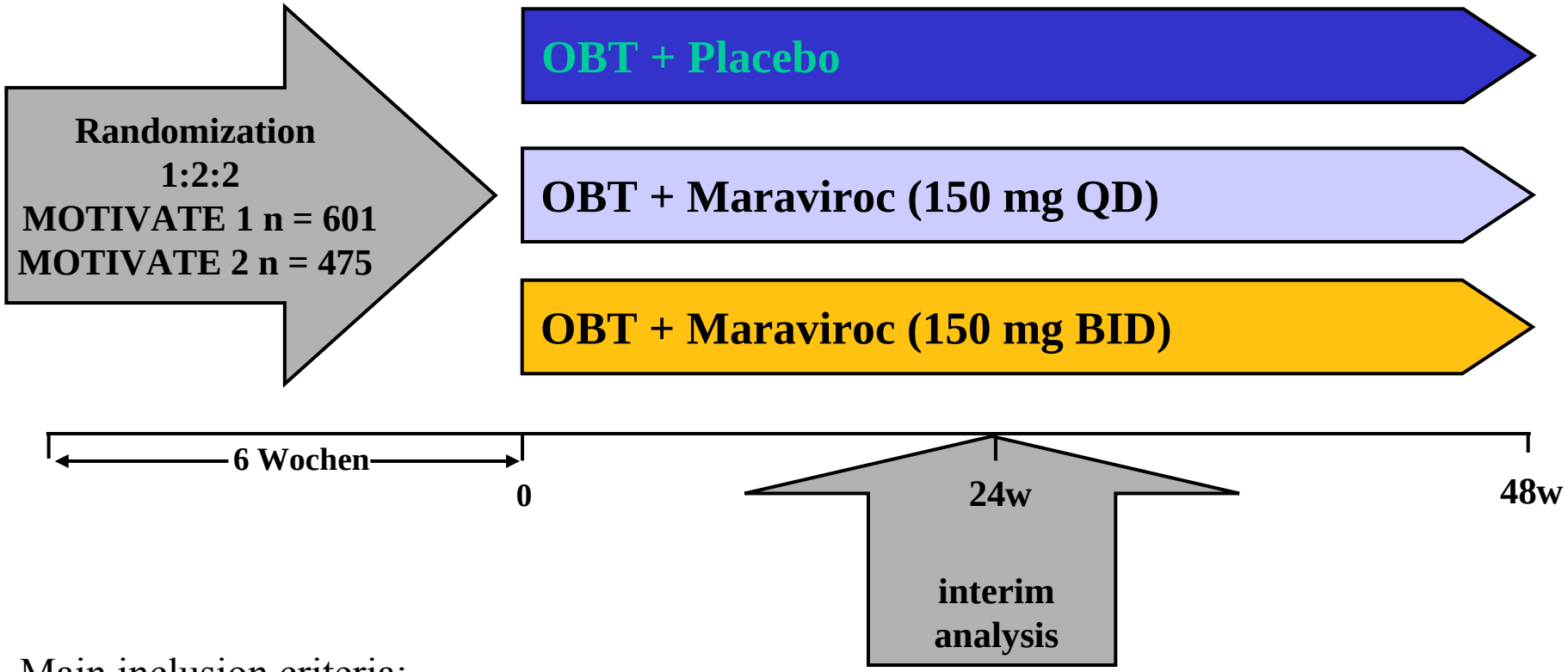
Viral tropism has to be determined for usage of CCR5-antagonists

Phenotypic HIV entry assay



W. Huang et al. 42nd ICAAC, Sep 2002, #2040

Maraviroc: MOTIVATE 1 & 2 Study design

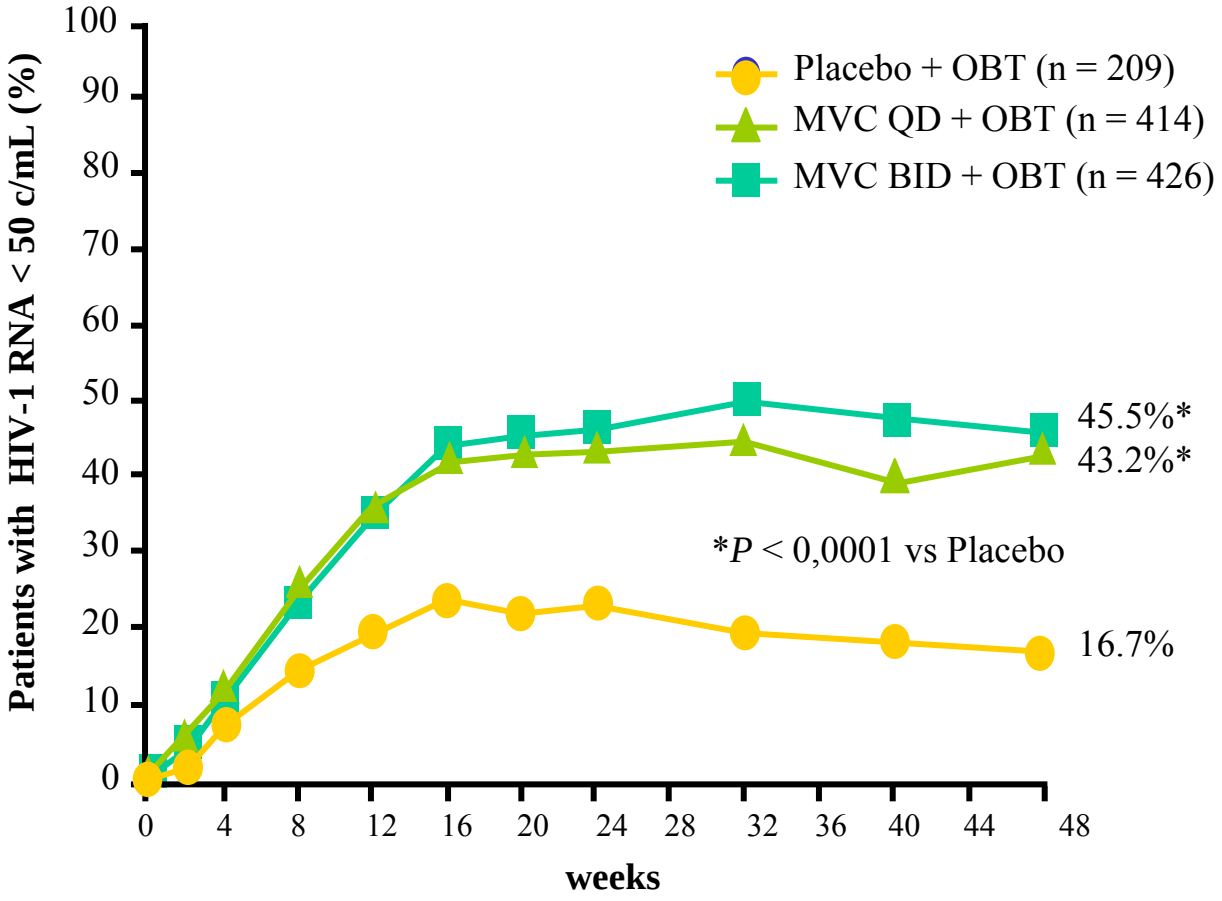


Main inclusion criteria:

- R5 HIV-1 infection
- HIV-1-RNA ≥ 5,000 copies/mL
- 3 class experienced

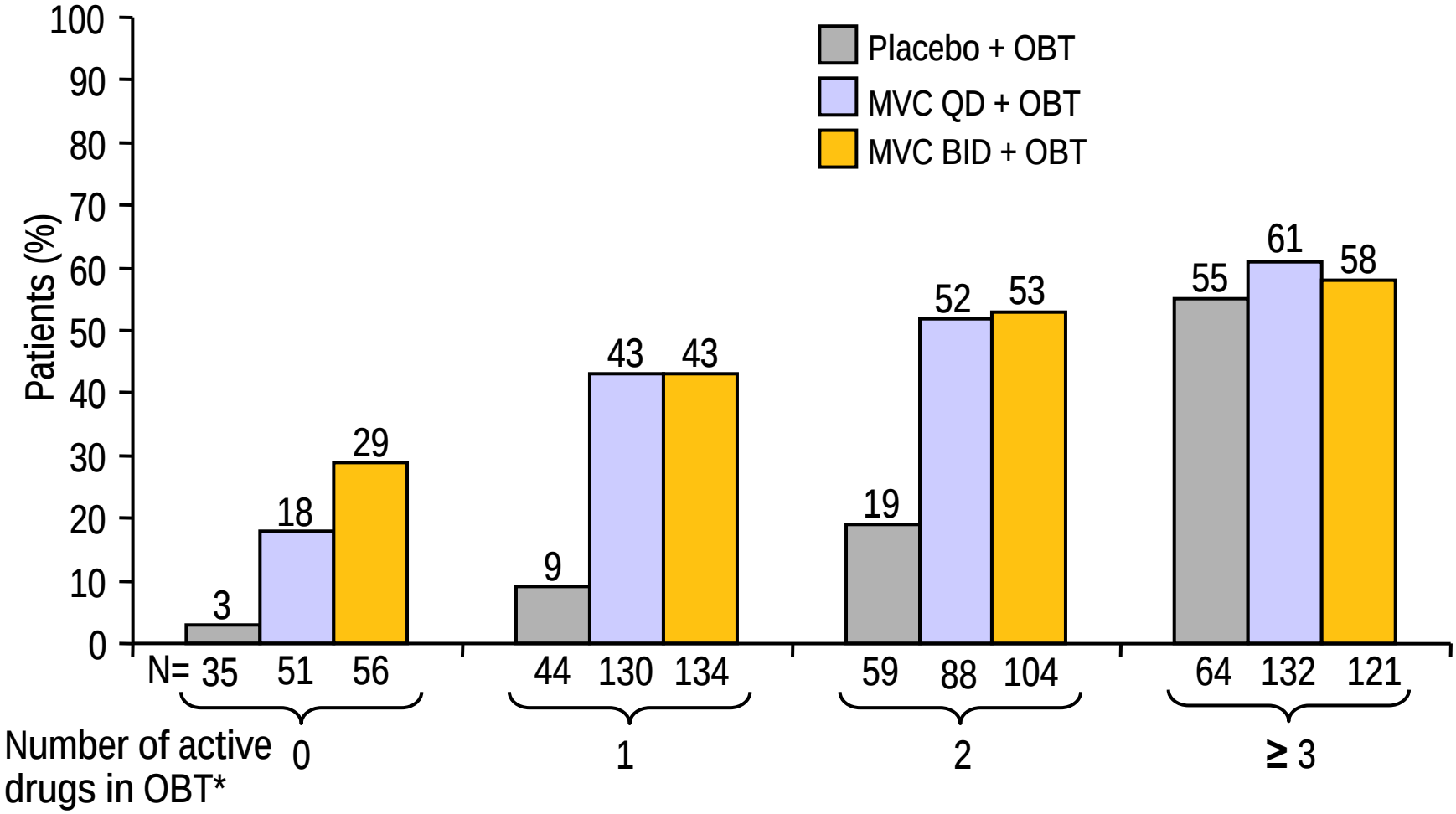
M. Nelson et al, CROI 2007 # 104aLB

MOTIVATE 1 & 2: Virologic efficacy week 48



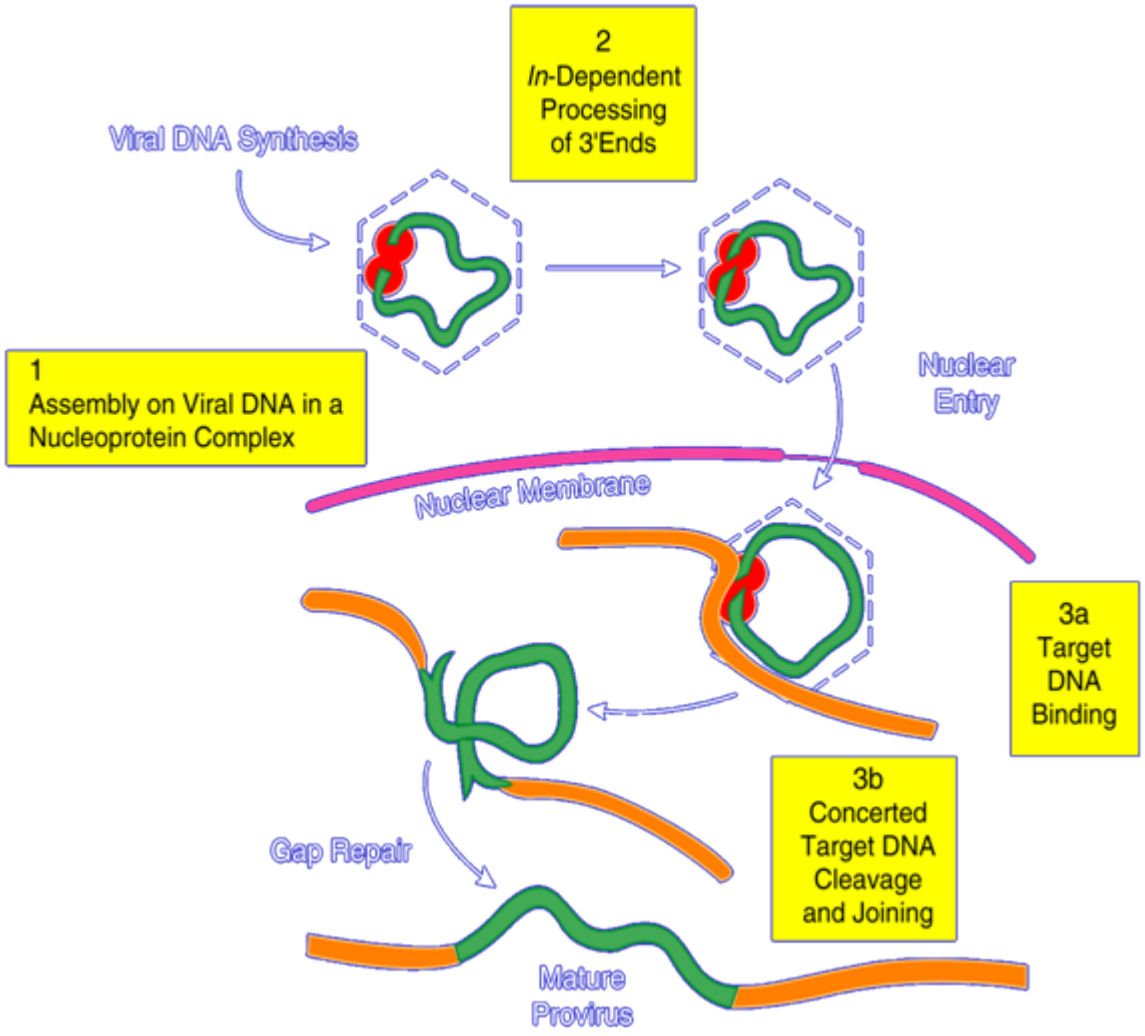
Hardy D, et al. CROI 2008. # 792.

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

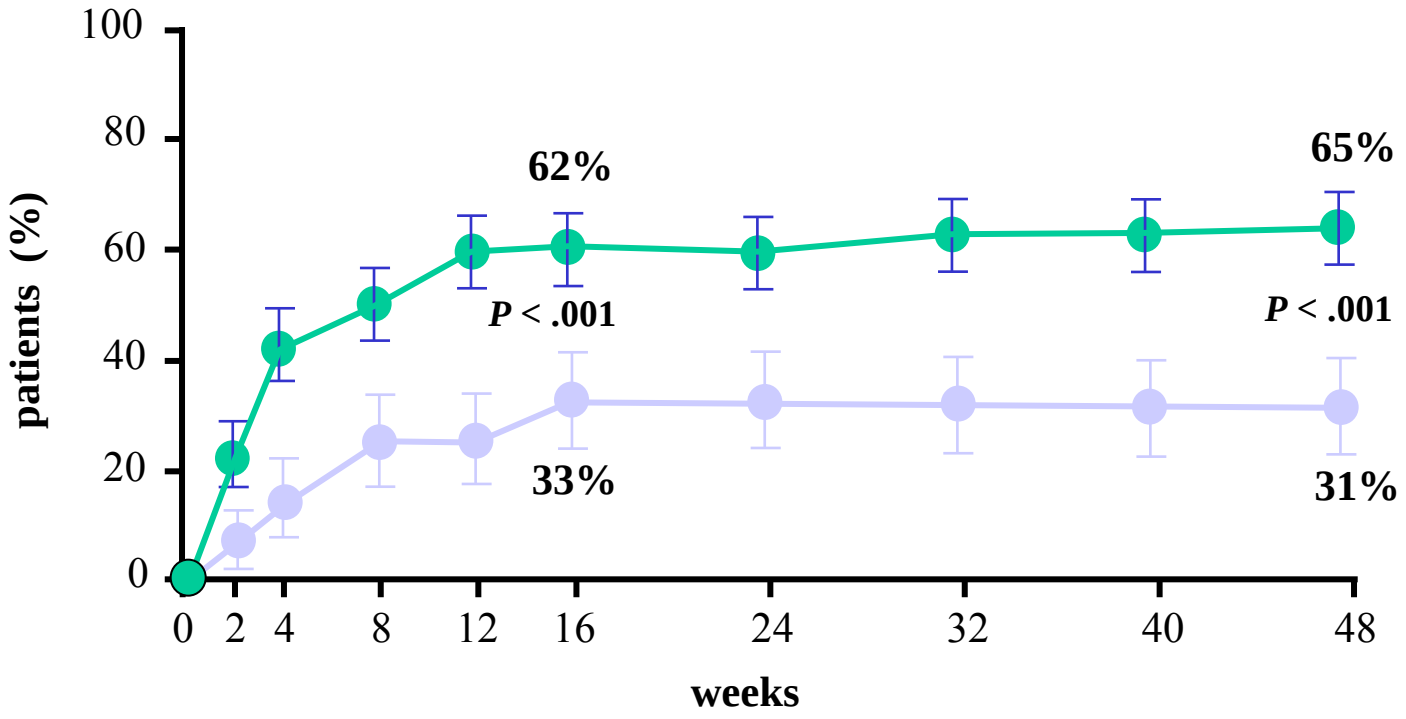


Nelson M, et al; CROI 2007 #104aLB

Integrase inhibition



BENCHMRK 1: virological efficacy week 48

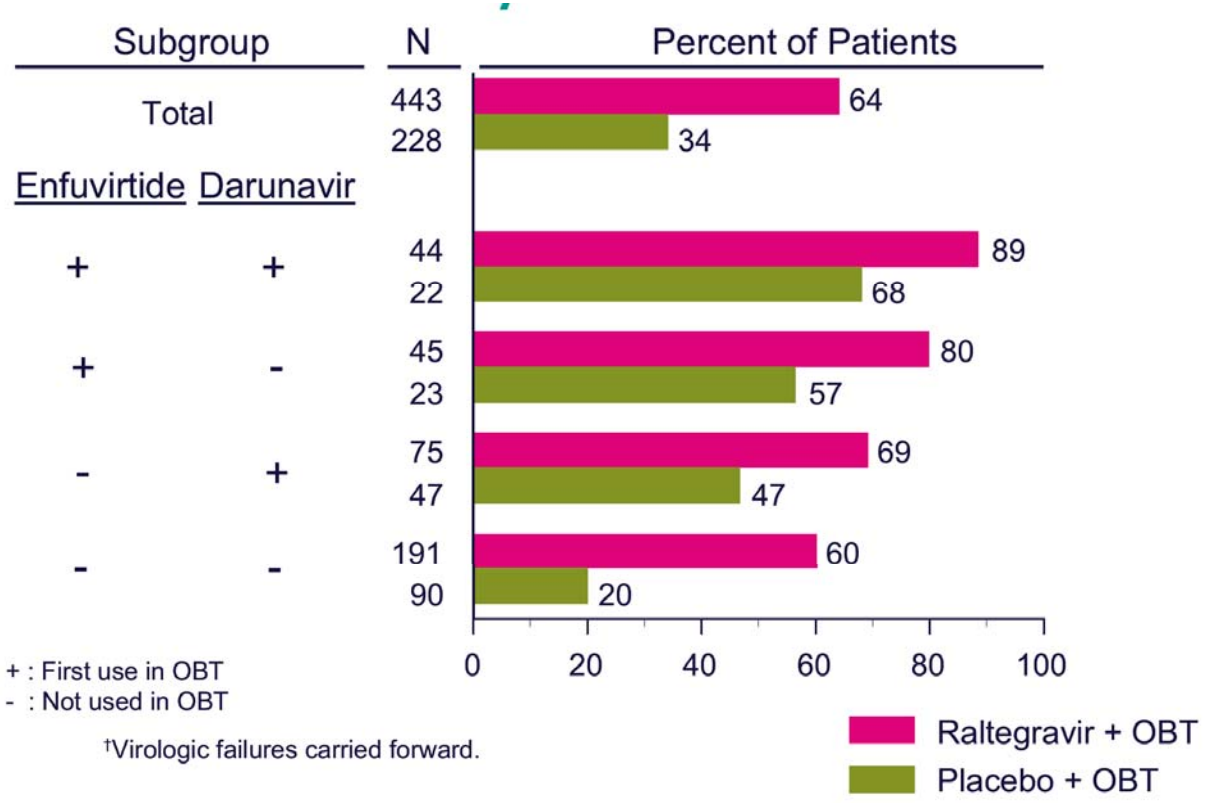


Raltegravir*	n =	232	231	231	230	229	232	229	230	231
Placebo*	n =	118	118	118	118	117	118	118	118	118

Cooper DA, et al. CROI 2008. Abstract 788.

BENCHMRK 1&2: Virological efficacy acoording to drugs in OBT

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 <50c/mL is a therapeutic goal.
- New drugs should be used in combination with other active drugs (≥2), preferably of new class, to achieve long-term efficacy.