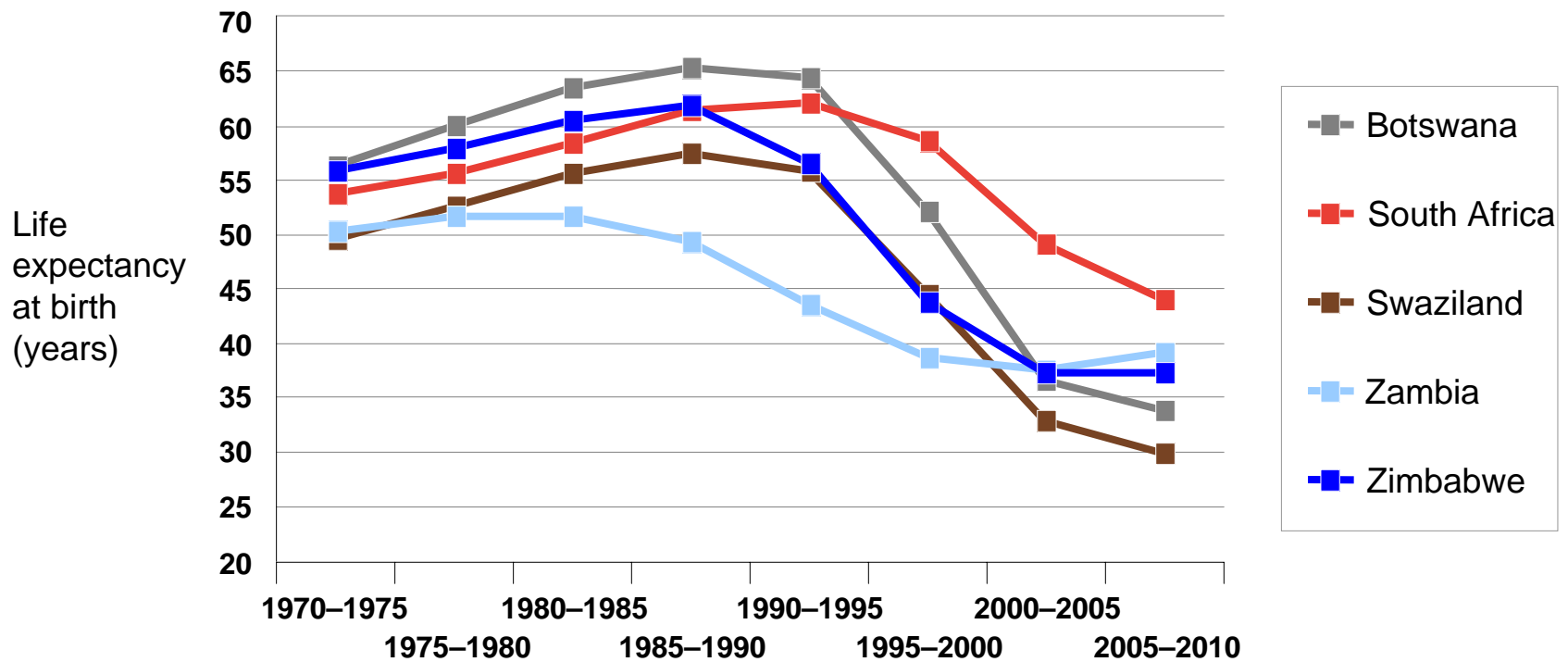
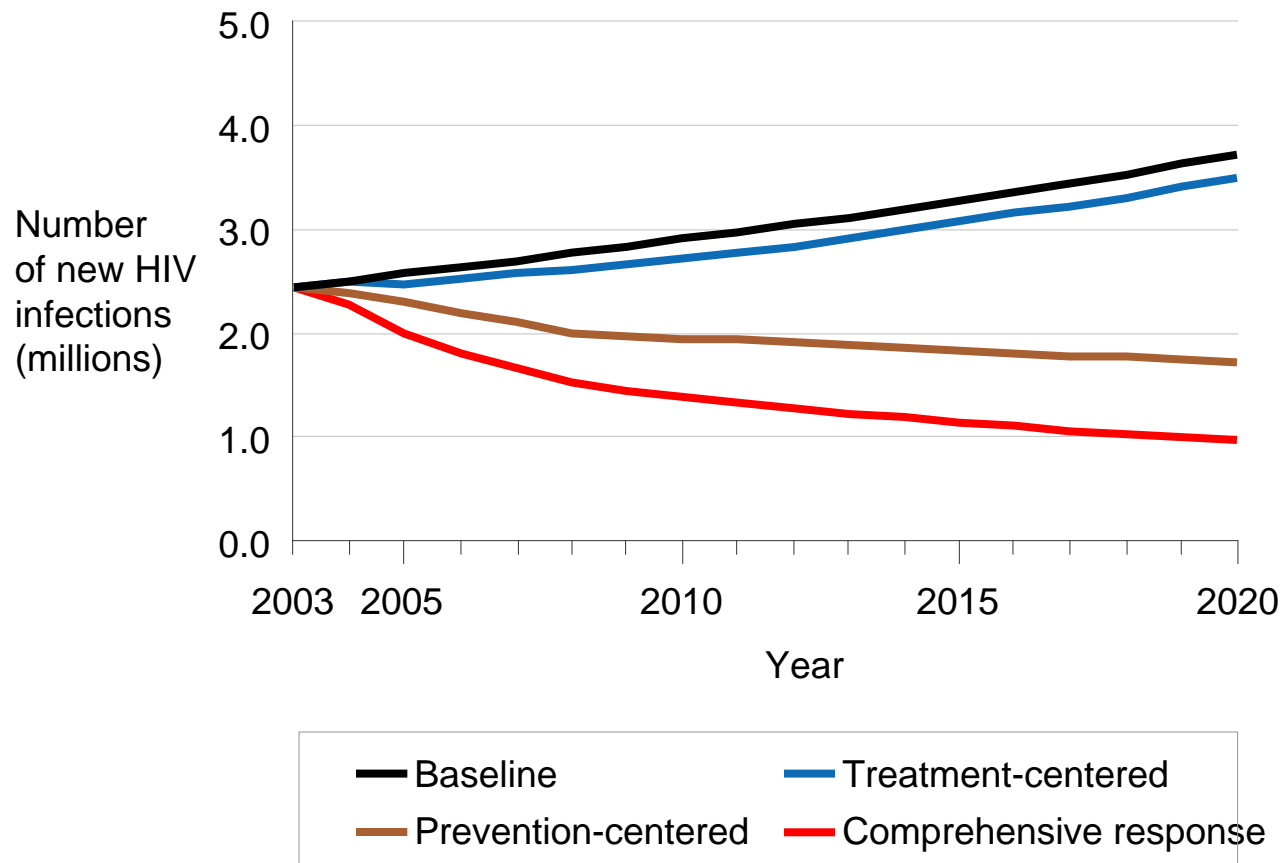


Impact of AIDS on life expectancy in five African countries, 1970–2010



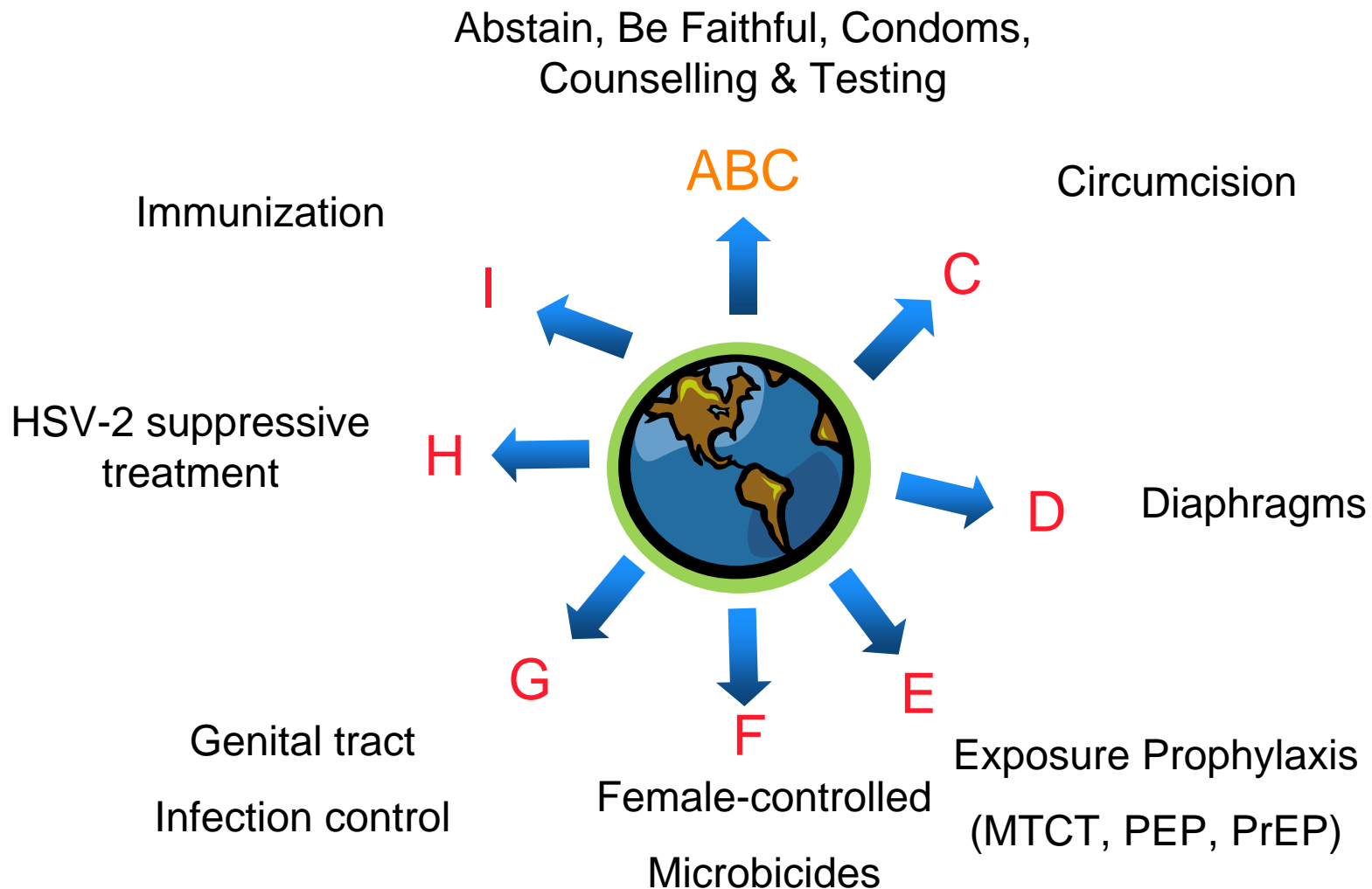
Source: United Nations Population Division (2004). World Population Prospects: The 2004 Revision, database.

Impact of three scenarios on HIV infection in sub-Saharan Africa, 2003–2020



Source: Salomon JA et al. (2005). Integrating HIV prevention and treatment: from slogans to impact

HIV Prevention Efforts

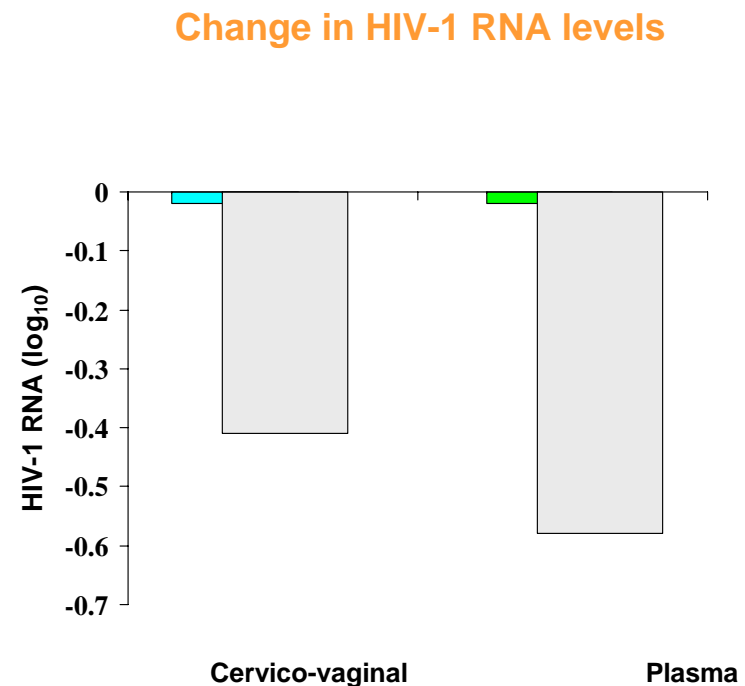


Circumcision

- Kenya HIV incidence, n=1719
 - Circumcised 7.3%
 - Uncircumcised 24.9%
- Male circumcision 61% protection for HIV in one, small randomized trial
 - Cost effective
- 2 large prospective studies ongoing
 - Newly circumcised don't have more unsafe sex

Efficacy of valacyclovir maintenance to reduce shedding of HIV (ANRNS 1285A)

- Randomized, double-blind, placebo-controlled of val-ACY in HIV-1+ women¹
 - Not on HAART, non-pregnant, CD4+ >200 cells/mm³
 - Positive serology for HSV-2
- Cervico-vaginal and plasma HIV-1 RNA levels determined every 2 weeks for 80 days, then randomized
 - 70 placebo, 70 val-ACY 500 mg BID
- val-ACY group had decreased:
 - Frequency of shedding of HIV and HSV
 - Vaginal HIV RNA
 - Plasma HIV RNA
- episodic treatment of genital ulcers with ACY for 5 days did not reduce shedding of HIV²



Women controlled prevention

- Most new infections in women
- Some cultural/family opposition to barrier prevention
- Need female control of prevention
- ABC ineffective and gender unequal

PREP not just for HIV

- Malaria
- Influenza
- Rheumatic fever
- HIV OI prophylaxis

Monkey studies

N = 18	Control	17/18 got SIV
N = 4	PO TDF	3/4 got SIV
N = 6	IV FTC	4/6 got SIV
N = 6	PO TDF	2/6 got SIV
N = 6	PO TVD	0/6 got SIV

PREP

- Not clear how predictable animal model is to humans
- Is rectal challenge applicable to vaginal challenge
- Must be restricted to truly HIV neg to avoid resistance and transmission of resistant strains
- Studies can be done faster than vaccine trials

Open Trials

<u>Location</u>	<u>Group</u>	<u>Sponsor</u>	<u>Drug</u>	<u>Results</u>
Botswana	Young adults	CDC	TVD	2008
Ghana	Women	FHI	TDF	2006
Peru	MSM	NIH	TVD	2009
Thailand	IDUs	CDC	TDF	2008
US	MSM	CDC	TDF	

Closed Trials

<u>Location</u>	<u>Group</u>	<u>Sponsor</u>	<u>Drug</u>	<u>Results</u>
Cambodia	Women	FHI	-	2007
Malawi	Men	FHI	-	2007
Nigeria	Women	FHI	-	2007
Comeroon	Women	FHI	-	2007

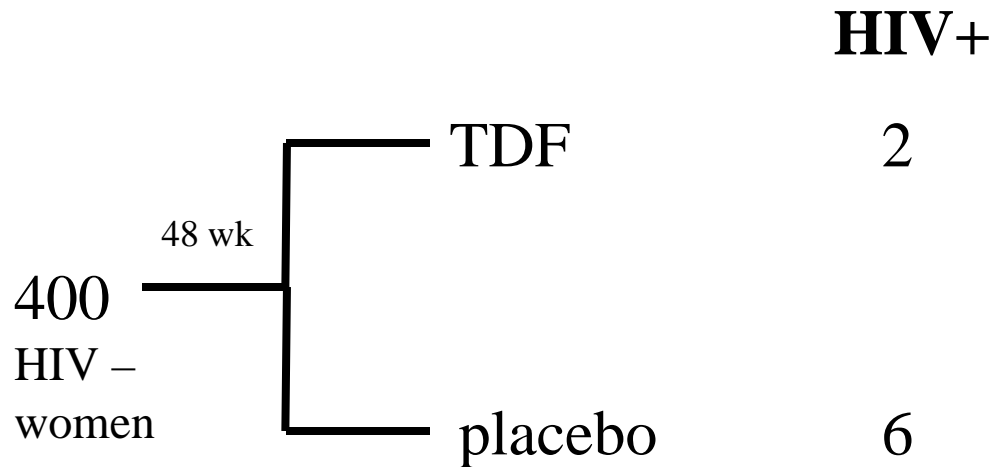
All closed prematurely due to protests, concerns

- follow up care
- access to meds for seroconverters
- is adequate prevention counseling provided

Investment in PREP

- CDC - \$20 million
- Gates - \$16 million
- NIH - \$14.5 million
- Gilead - \$4 million

Ghana PrEP



- No TDF resistance
- Minimal AE
- No increased sex



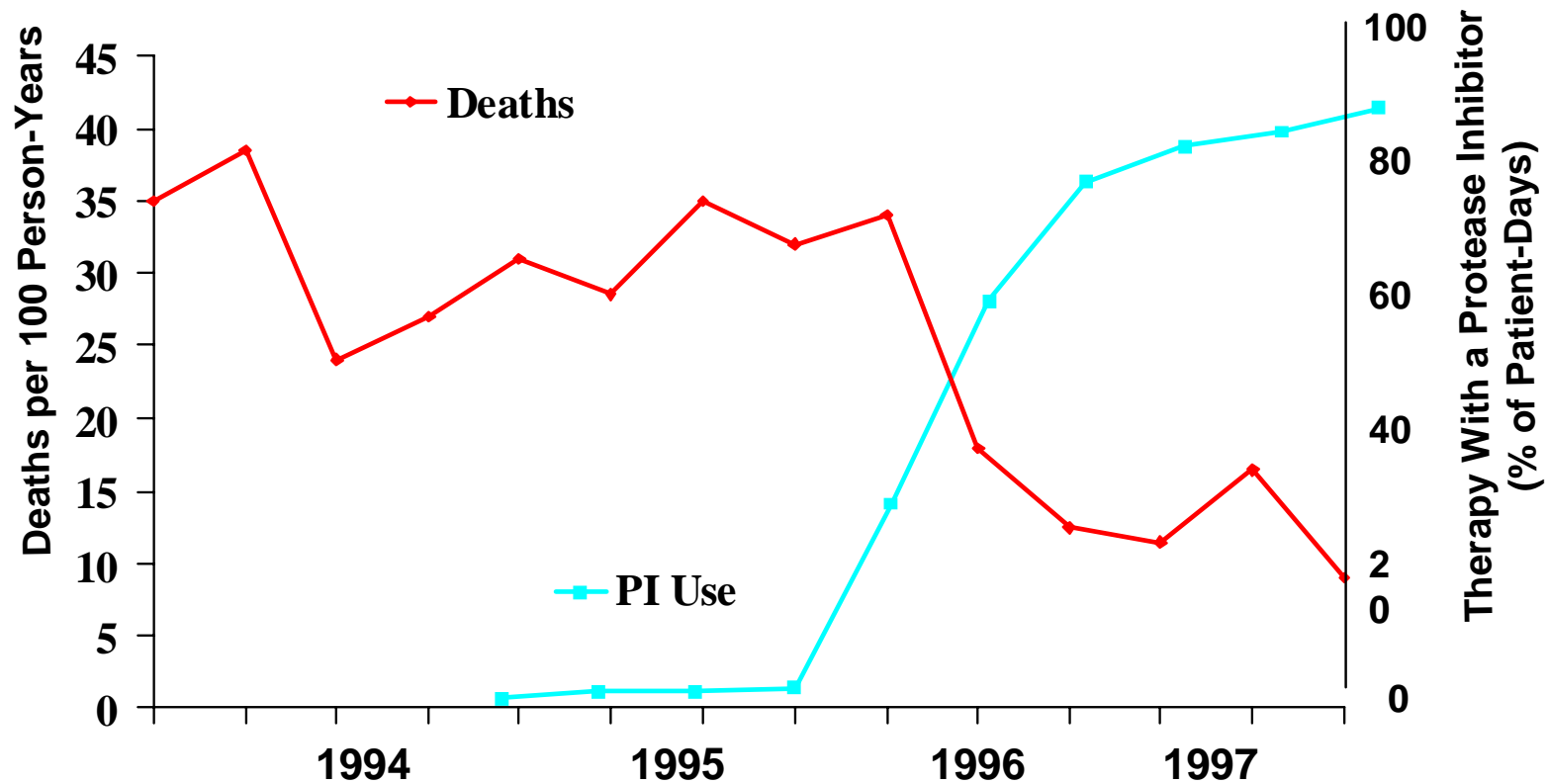
Microbicides

- Chemical products applied to vagina/rectum to prevent HIV by:
 - Prevent STD
 - Maintain normal vaginal flora
 - Epithelial barrier
 - Entry inhibitors (CCR5)
- 5 large studies in Africa, data 2008

Nothing for us without us

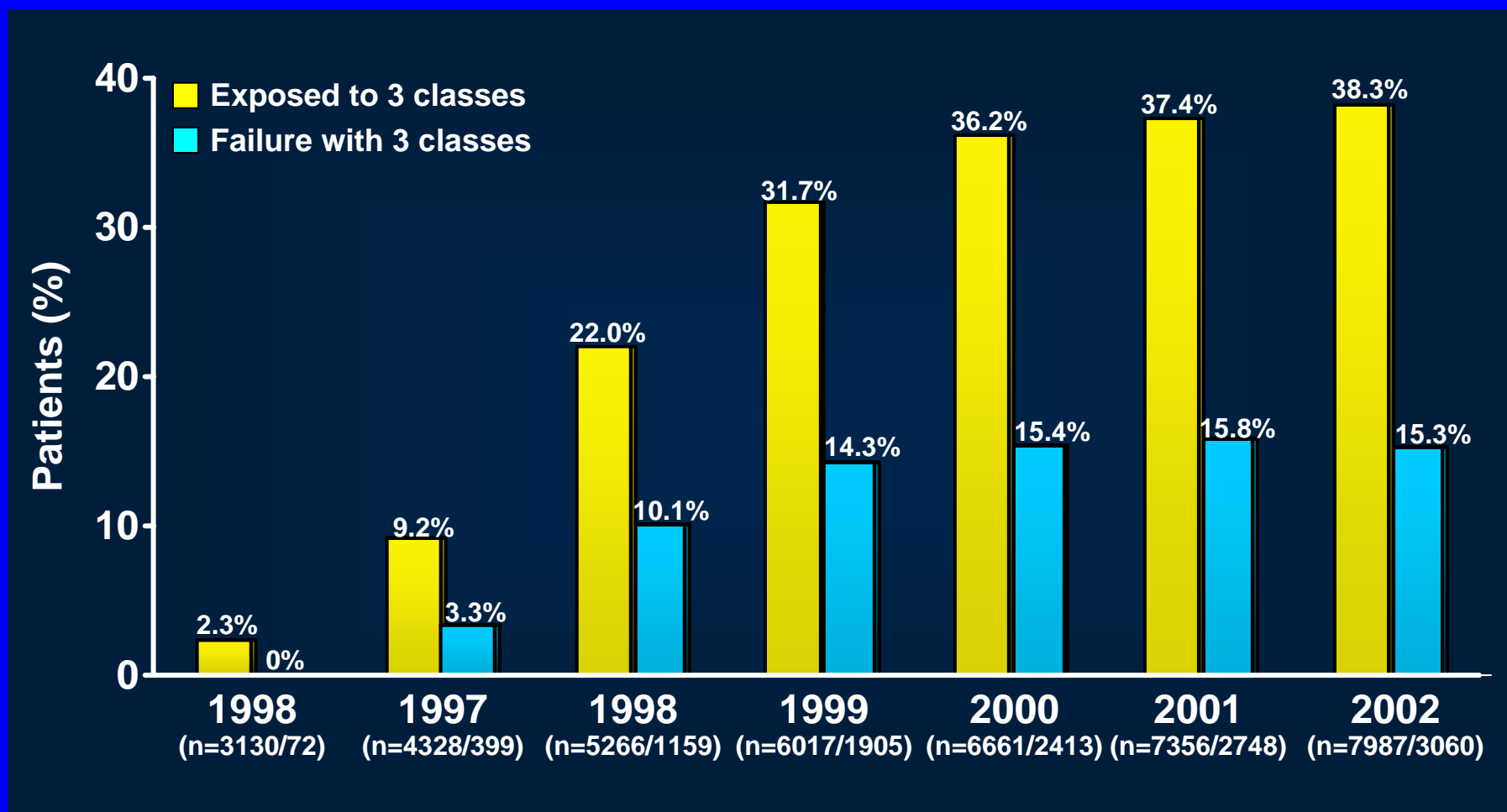
- Vulnerable populations need to have a seat at the table to discuss and participate in solutions
- IDU, MSM, TG, prisoners etc

Mortality and Frequency of Use of PI-Containing Regimens Among HIV+ Patients with CD4+ Counts <100 cells/mm³*



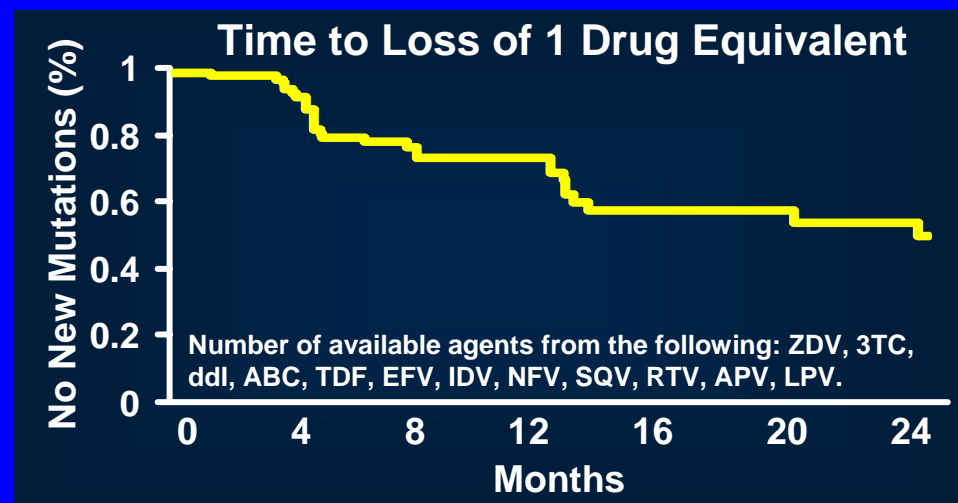
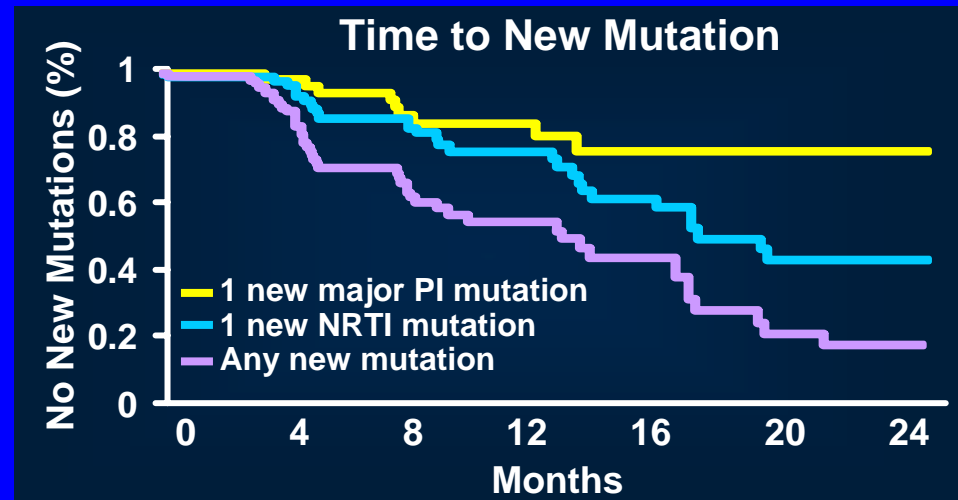
Palella. *N Engl J Med.* 1998;338:853-860.

Triple-Class Exposure and Failure: UK CHIC Study



SCOPE Cohort: Risk of Delayed Switch on Stable Antiretroviral Therapy

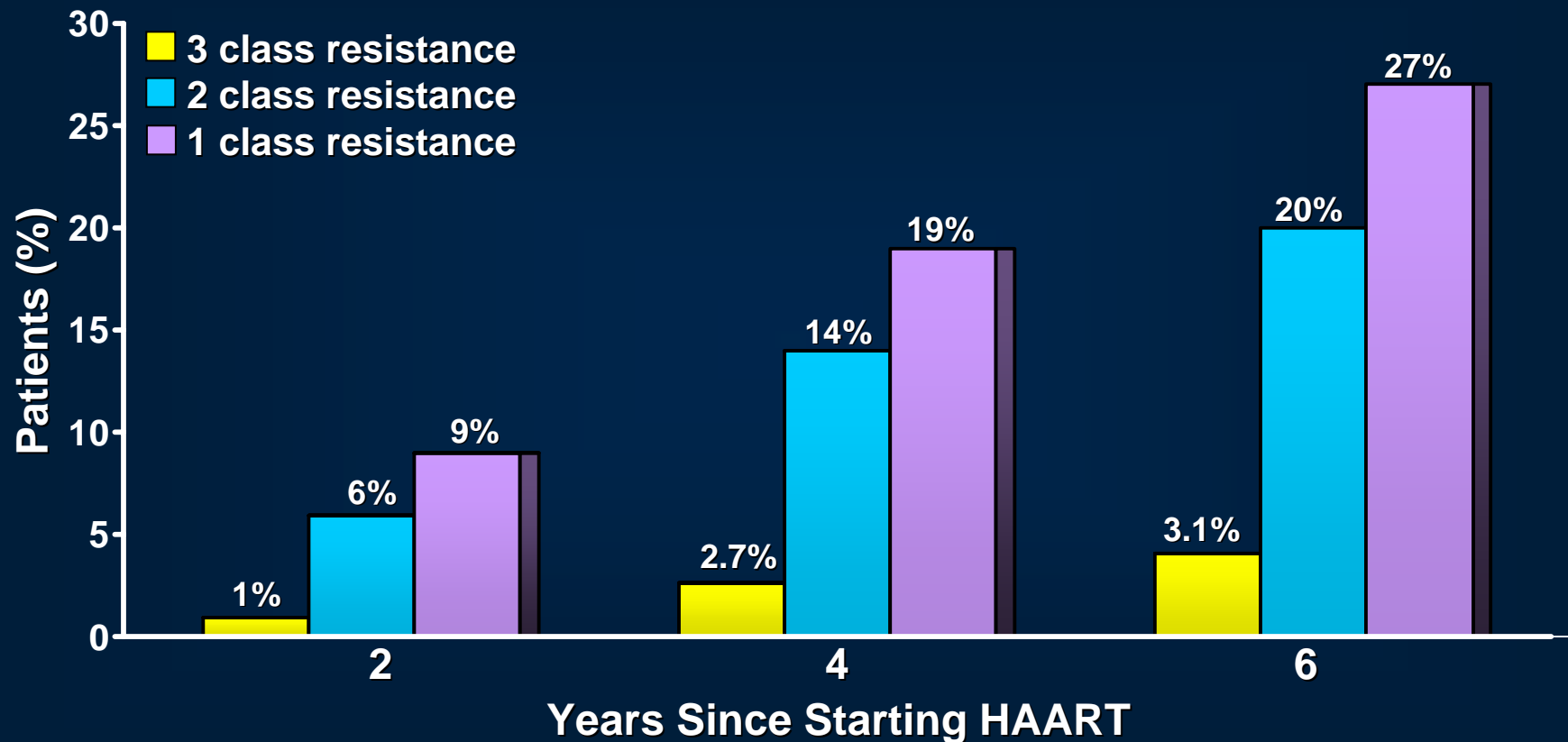
- Treatment-experienced patients (n=106)
 - Stable ART for ≥ 120 days
 - HIV RNA >1000 c/mL
 - ≥ 1 resistance mutation
- Emergence of new mutations at 1 year
 - Any mutation: 44%
 - NAM: 23%
 - PI: 18%



Hatano H, et al. 13th CROI. Denver, 2006. Abstract 615.

Long-Term Risk of Developing Drug Resistance on HAART: UK CHIC Study

Time to Multi-Class Resistance

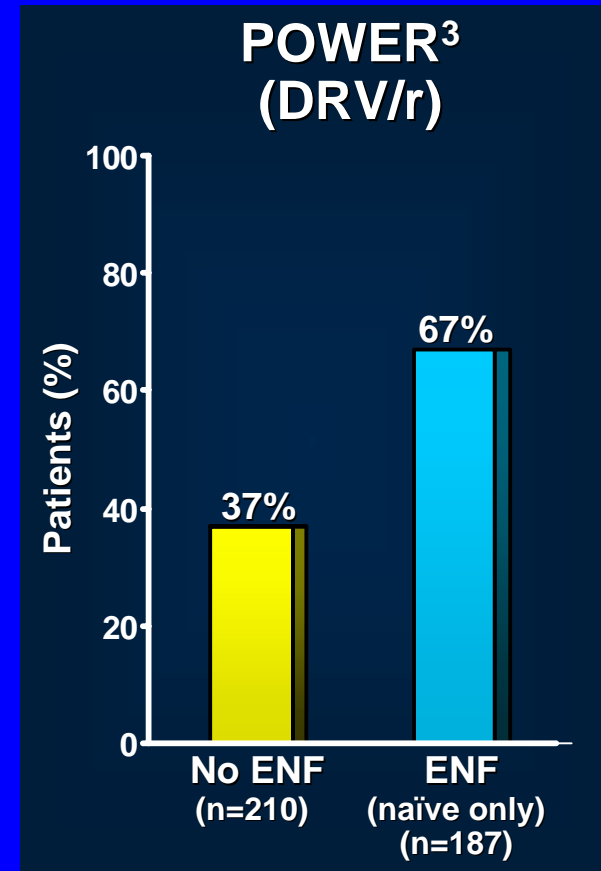
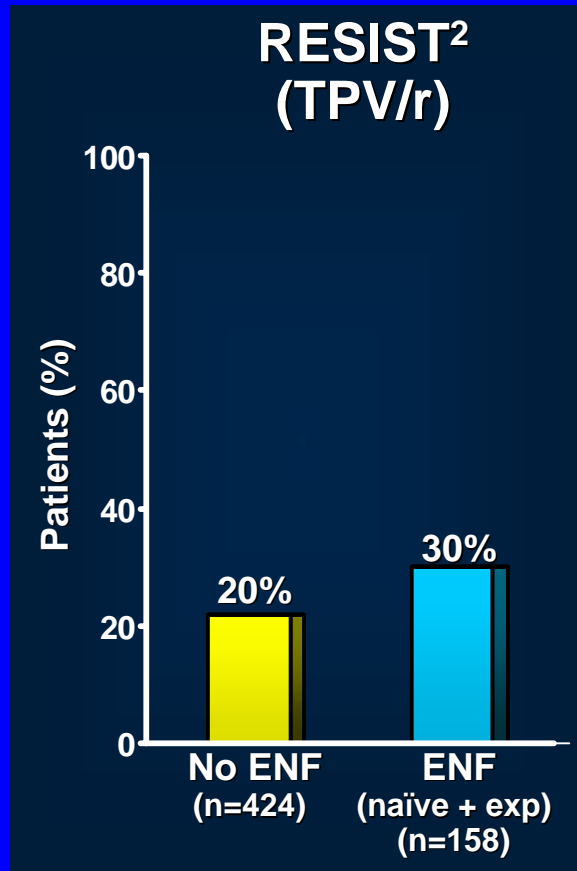
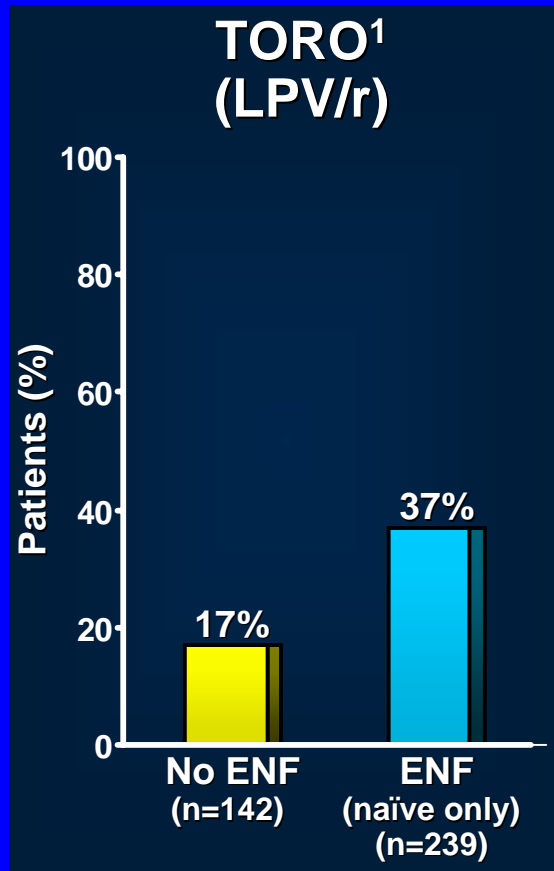


n=4306.

Overall risk of treatment failure: 38% over 6 years.

Phillips AN, et al. *AIDS*. 2005;19:487-494.

Enfuvirtide Increases the Likelihood of Achieving HIV RNA <50 Copies/mL (Week 24)

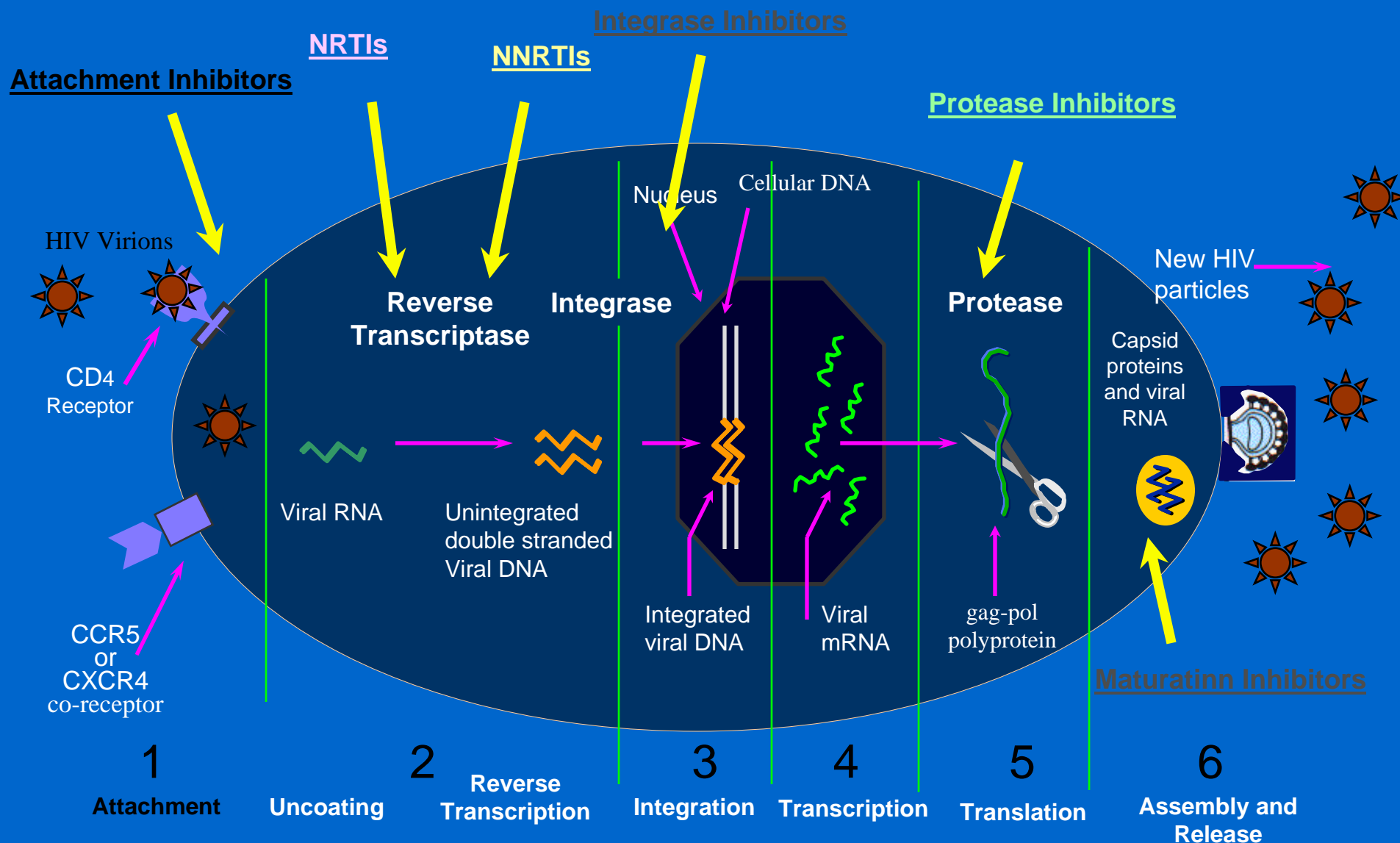


¹Thommes JA, et al. 43rd IDSA. San Francisco, 2005. Abstract 785.

²<http://www.fda.gov/ohrms/dockets/ac/05/briefing/2005-4139b1-02-boehringer.pdf>.

³Katlama C, et al. 12th CROI. Boston, 2005. Abstract 164LB.

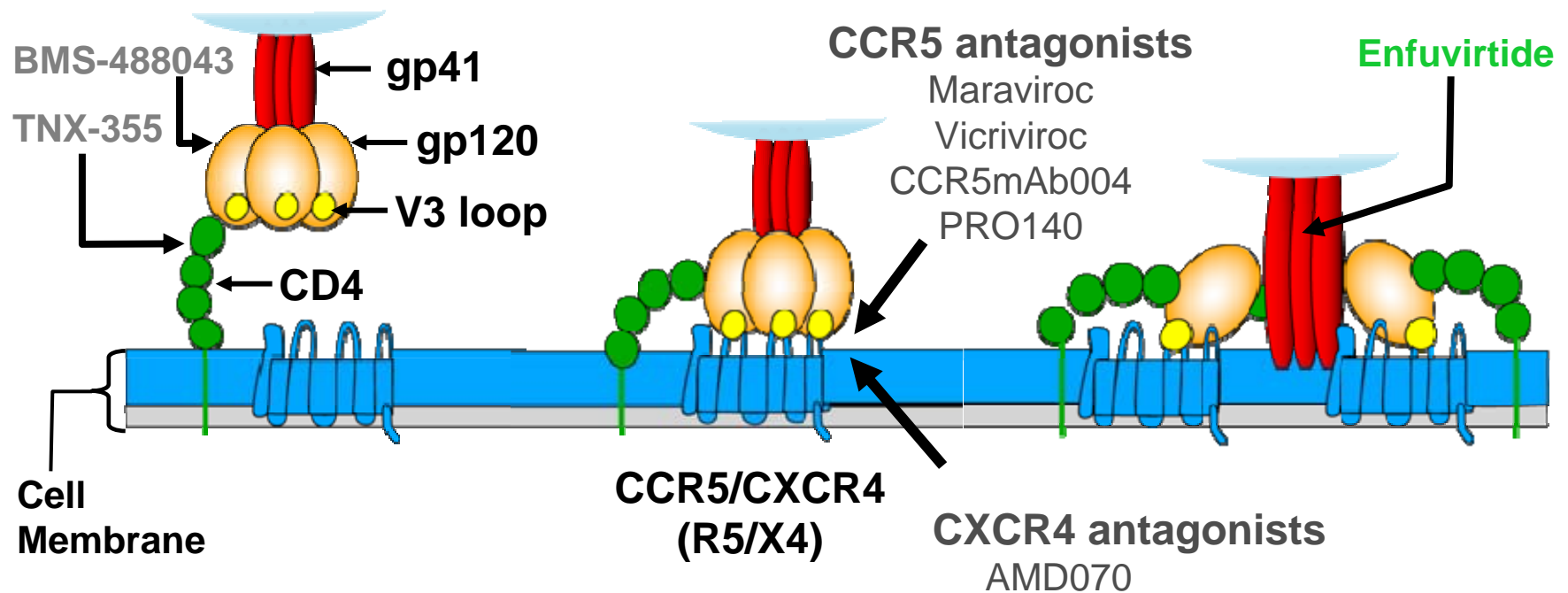
HIV Replication Cycle and Sites of Drug Activity



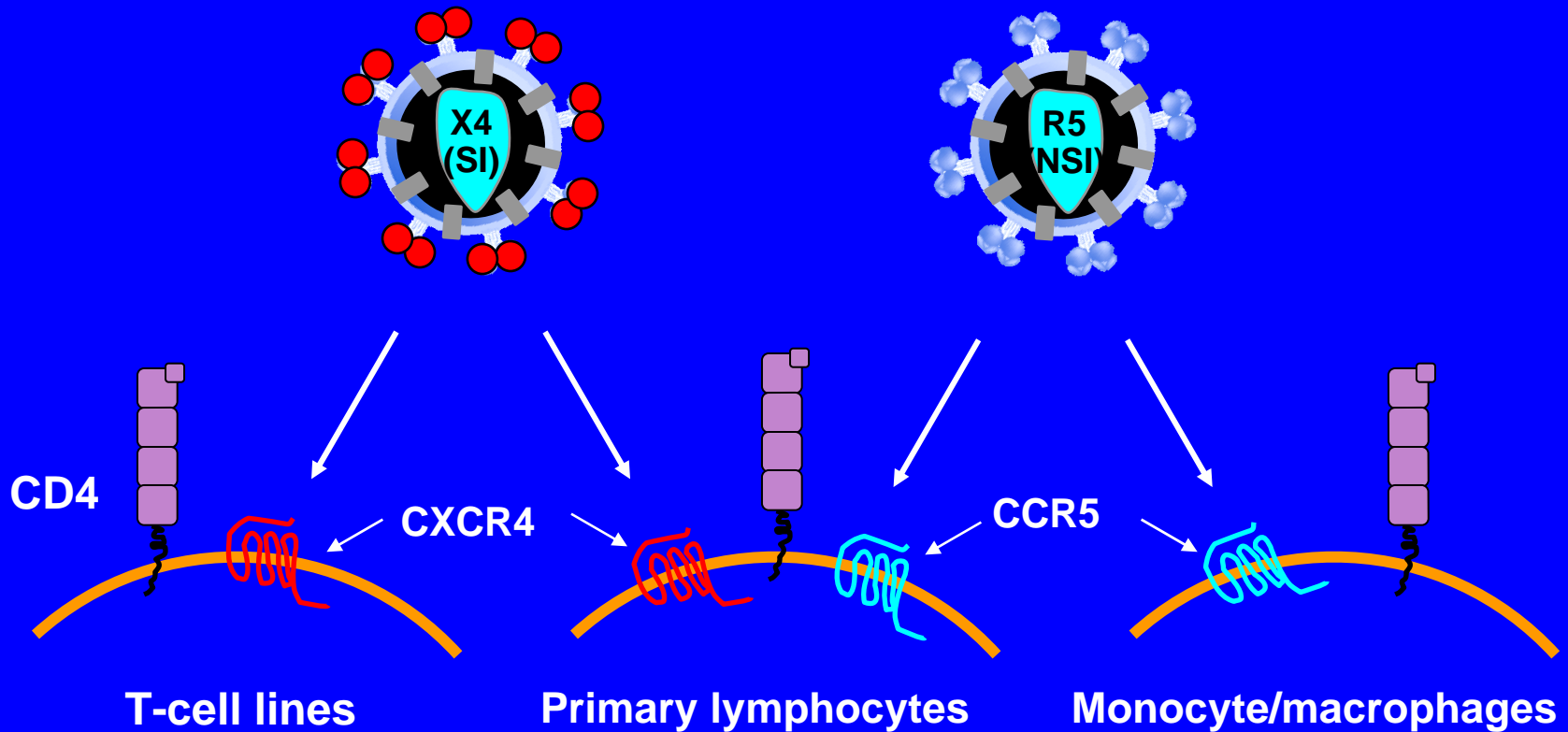
Adapted: Levy JA. HIV and the Pathogenesis of AIDS. 2nd ed. Washington, DC: American Society for Microbiology; 1998:9-11

HIV-1 Entry Inhibitors

CD4 Binding → Coreceptor Binding → Virus-Cell Fusion



Coreceptor Usage of HIV-1 Variants



Prevalence of Coreceptor Tropism

Study	Population	Sample (n)	R5 Only	Dual/Mixed	X4 Only
Demarest et al ^[1]	Naive	325	88%	12%	0%
HOMER ^[2]	Naive	979	82%	18%	0.1%
Moyle et al ^[3]	Naive	402	81%	19%	NA
Demarest et al ^[1]	Experienced	117	67%	28%	5%
Moyle et al ^[3]	Experienced	125	78%	22%	NA
Melby et al ^[4]	Experienced	724	50%	48%	2%
Wilkin et al ^[5]	Experienced	391	49%	47%	4%

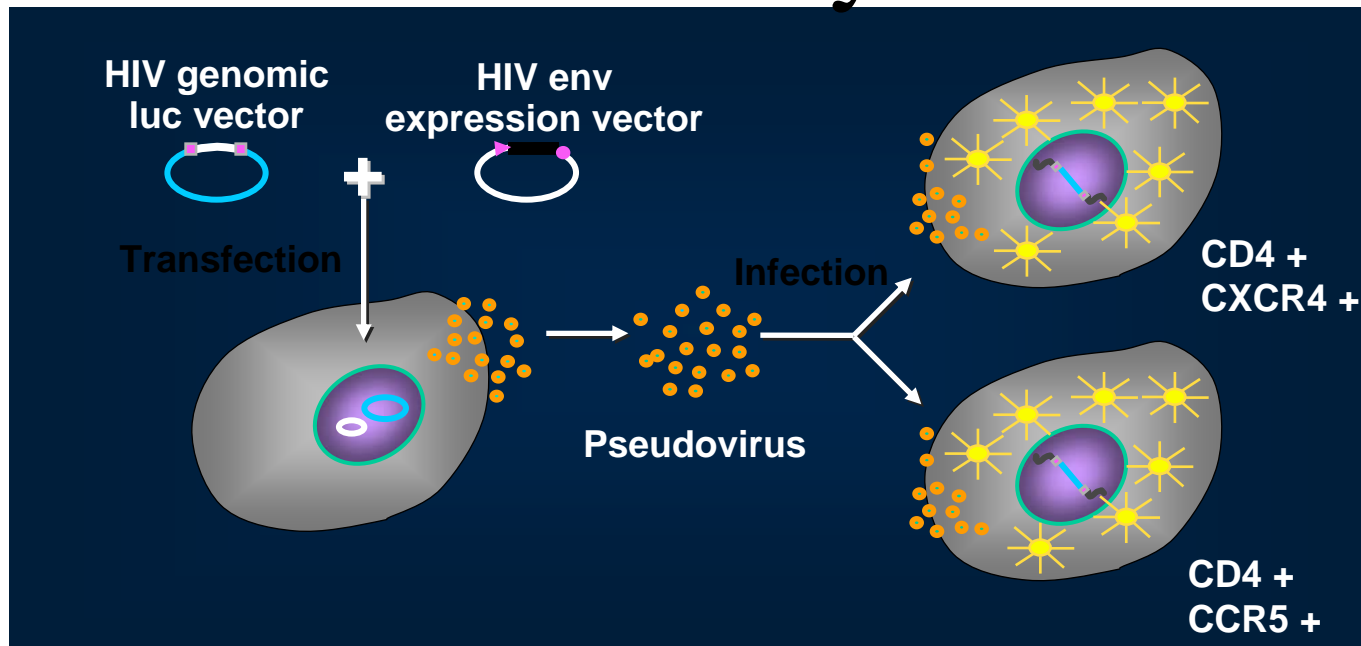
1. Demarest J, et al. ICAAC 2004. Abstract H-1136. 2. Brumme ZL, et al. J Infect Dis. 2005;192:466-474. 3. Moyle GJ, et al. J Infect Dis. 2005;191:866-872. 4. Melby T, et al. CROI 2006. Abstract 233. 5. Wilkin T, et al. CROI 2006. Abstract 655.

Effect of CXCR4 on HIV progression

- Study of frequency and timing of CXCR4-tropism emergence
- 67 pts from Multicenter AIDS Cohort Study selected based on time to AIDS-defining illness following seroconversion or nonprogression
 - Co-receptor tropism determined at 6-12 mo intervals
- 51% developed R5/X4 dual tropism
 - Earliest emergence at 18 mos
 - 24% oscillated b/t R5 and R5/X4
- Emergence R5/X4 was associated with abrupt decline in CD4 cell count w/in 0.75 years (median) and more rapid progression to AIDS ($p < 0.05$)

Progression to AIDS	R5/X4
Rapid	62%
Moderate	64%
Slow	46%
Nonprogressor	31%

HIV Entry Cell Assay



Tropism confirmed by the ability of CCR5 or CXCR4 antagonist to reduce signal

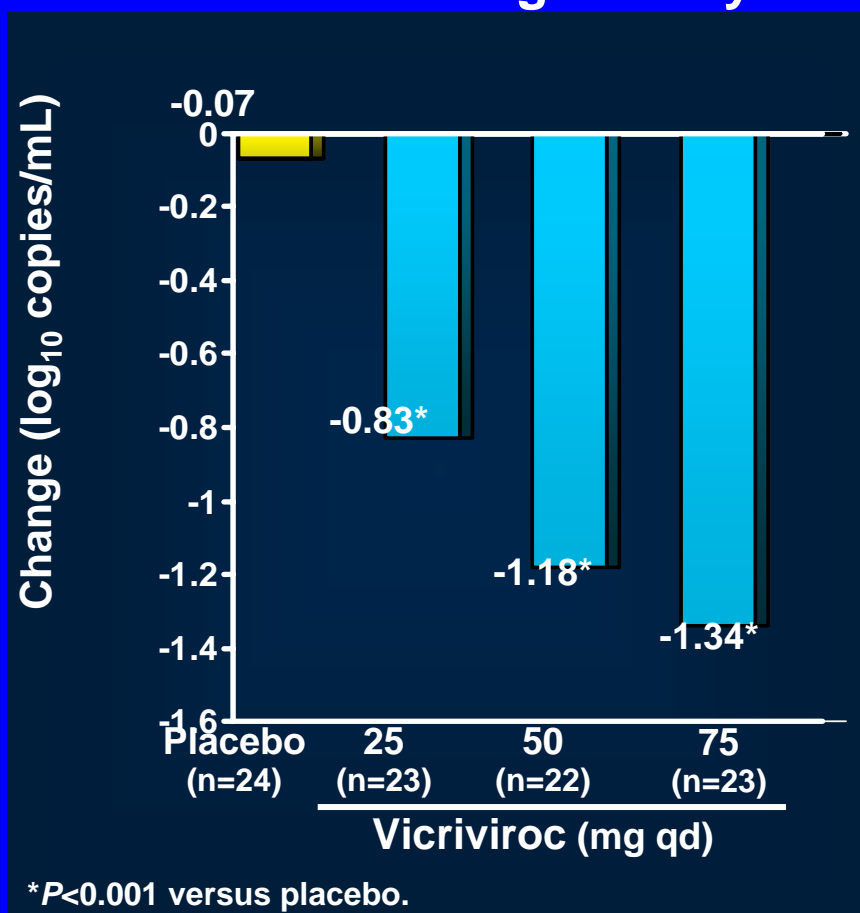
- Limitations
 - >1000 copies/mL
 - May fail to detect X4 when X4 virus is $\leq 10\%$ of the viral population
 - Detects 83% of samples where X4 virus = 5% of the viral population
 - Sequence variation may result in assay failure

Petropoulos CJ, et al. *Antimicrob Agents Chemother.* 2000;44:920-928.
Coakley E, et al. *Curr Opin Infect Dis.* 2005;18:9-15.

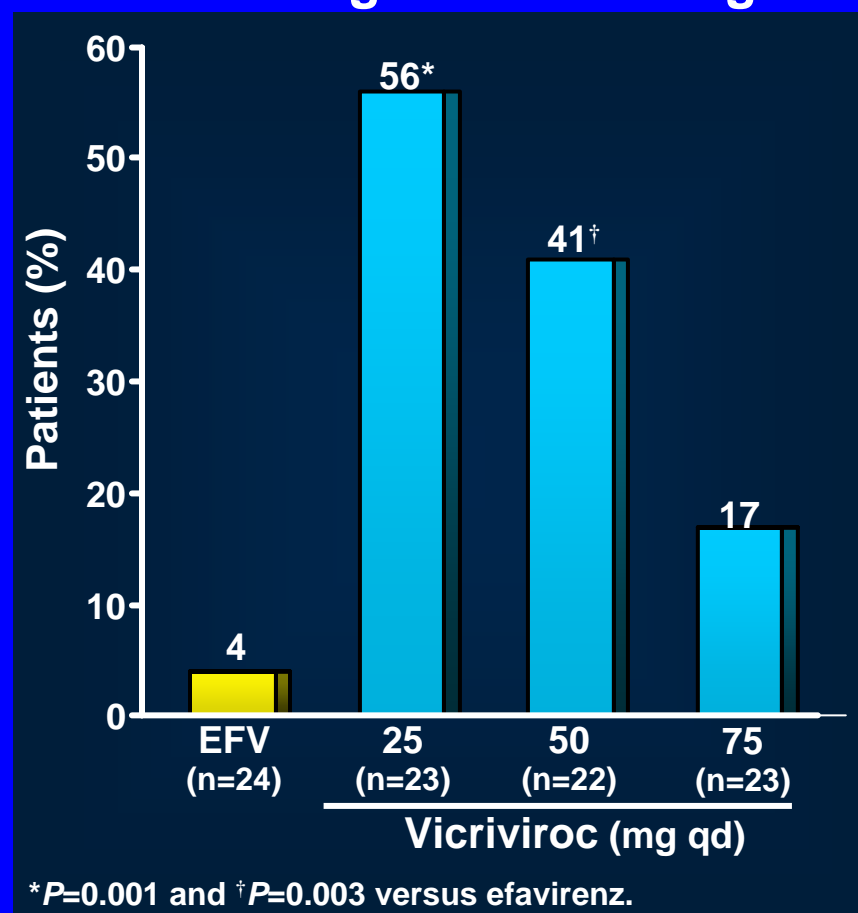
CCR5 in naïve patients

Phase 2b Study: Vicriviroc in Treatment-Naïve Patients

**Monotherapy
HIV RNA Change at Day 14**



**Combination Therapy
Virologic Breakthrough**

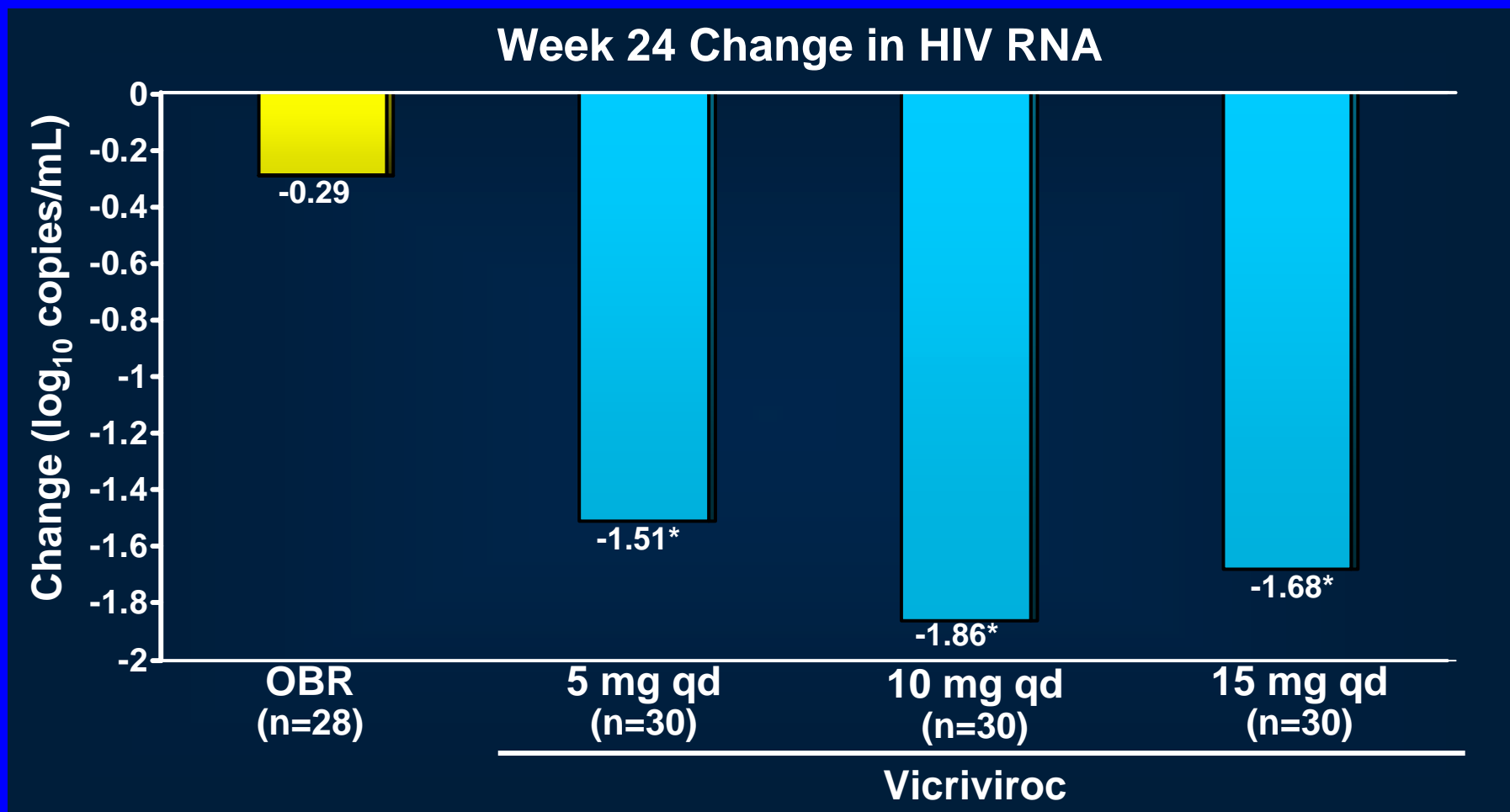


Vicriviroc in Treatment-Naïve Patients: Combination Therapy

- DSMB ended the phase 2b study
 - High rate of virologic breakthrough in the vicriviroc arms
- Resistance profile at breakthrough
 - 22/26 had evaluable genotypes
 - M184V/I: 100%
 - M41L: 4.5%
 - Potential resistance to vicriviroc being investigated
 - Env sequencing: no consistent pattern of mutations detected
- Detection of X4 virus
 - No difference between placebo and vicriviroc arms after 14 days of monotherapy

CCR5 in experienced patients

ACTG 5211: Vicriviroc in Treatment-Experienced Patients



All patients received ritonavir-containing OBR.

* $P < 0.01$ versus OBR.

Gulick R, et al. 16th IAC. Toronto, 2006. Abstract ThLB0217.

Schering CCR5 Vicriviroc

		<u><400, 24wks</u>	<u><50, 24wks</u>
88 R5 only Failing PI/r VL>5k	OB	11%	7%
	5mg qd	STOPPED	STOPPED
	10mg qd	53%	40%
	15mg qd	47%	27%

- 50% screened out for dual tropic
- 5 pts got cancer (4 lymphoma)

Pfizer CCR5

Maraviroc - phase 2B

		<u><400</u>	<u><50</u>
190 3class exp	OB	24%	16%
	R5 qd	24%	21%
	R5 bid	31% } sig	27% } sig

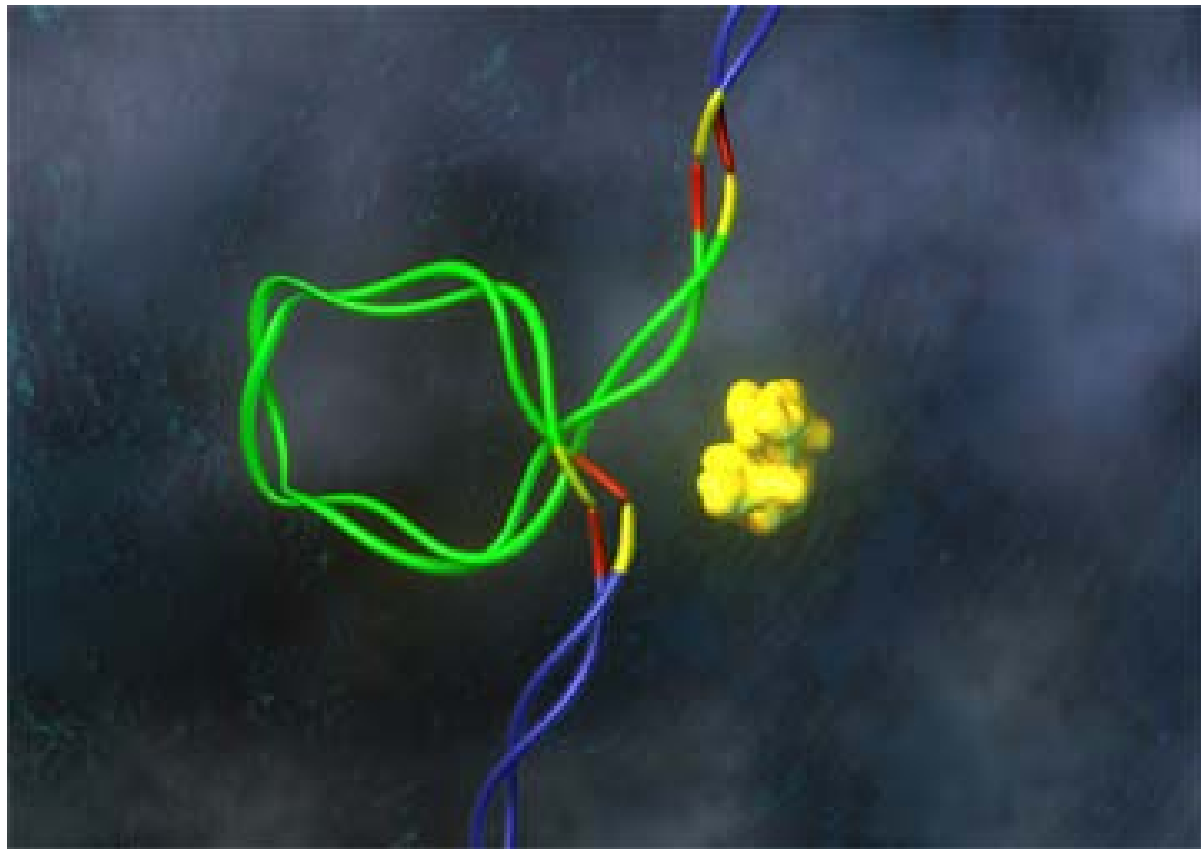
- CCR5 well tolerated
- CCR5 bid sig VL drop c/w OB

CCR5 in dual/mixed patients

Effect of CCR5 Antagonists in Patients With R5/X4 HIV

	OBT	Maraviroc	
		Once-Daily	Twice-Daily
Week 24 change			
HIV RNA (\log_{10} copies/mL)	-0.97	-0.91	-1.20
CD4 (cells/ μ L)	+35	+60	+62

Integrase



Study Design: MK-0518 Protocol 004

- Phase II study multicenter, double –blind, randomized 2 part study
 - Part I monotherapy with MK-0518
 - Part II dose escalation with four doses vs EFV.

197 patients enrolled (85 with wk 16 data)
Mean age 36, 80% M, 69% non white,
34% AIDS, Mean HIV RNA at baseline 4.6-4.8 log₁₀

MK-518 Mono x 2 Week
(100, 200, 300, 400 BID)

MK-518
(100, 200, 300, 400 BID)
(TDF + 3TC)

EFV
(TDF + 3TC)

*Virologic failure defined as early (rebound or lack of suppression by 1 log₁₀) or late (failure to suppress to <200 copies/mL or rebound)

Integrase use in naïve patients

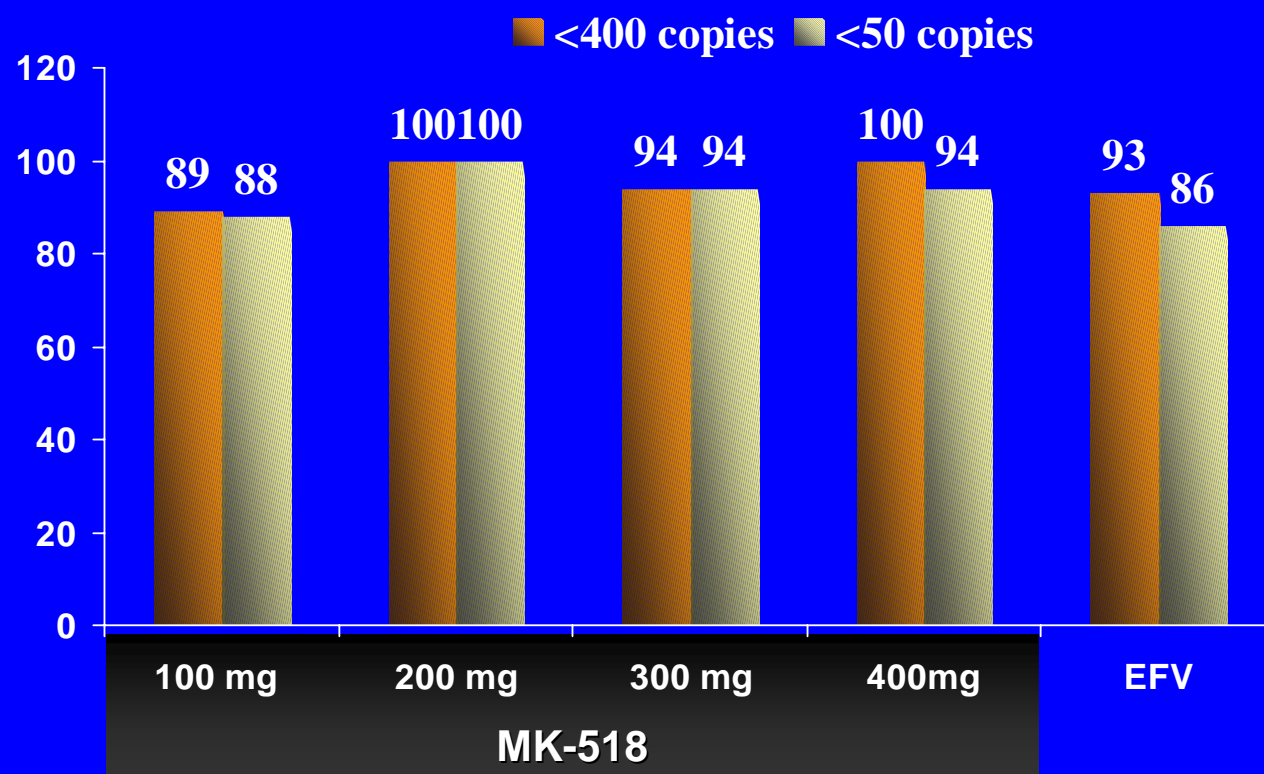
Virologic Efficacy

Efficacy

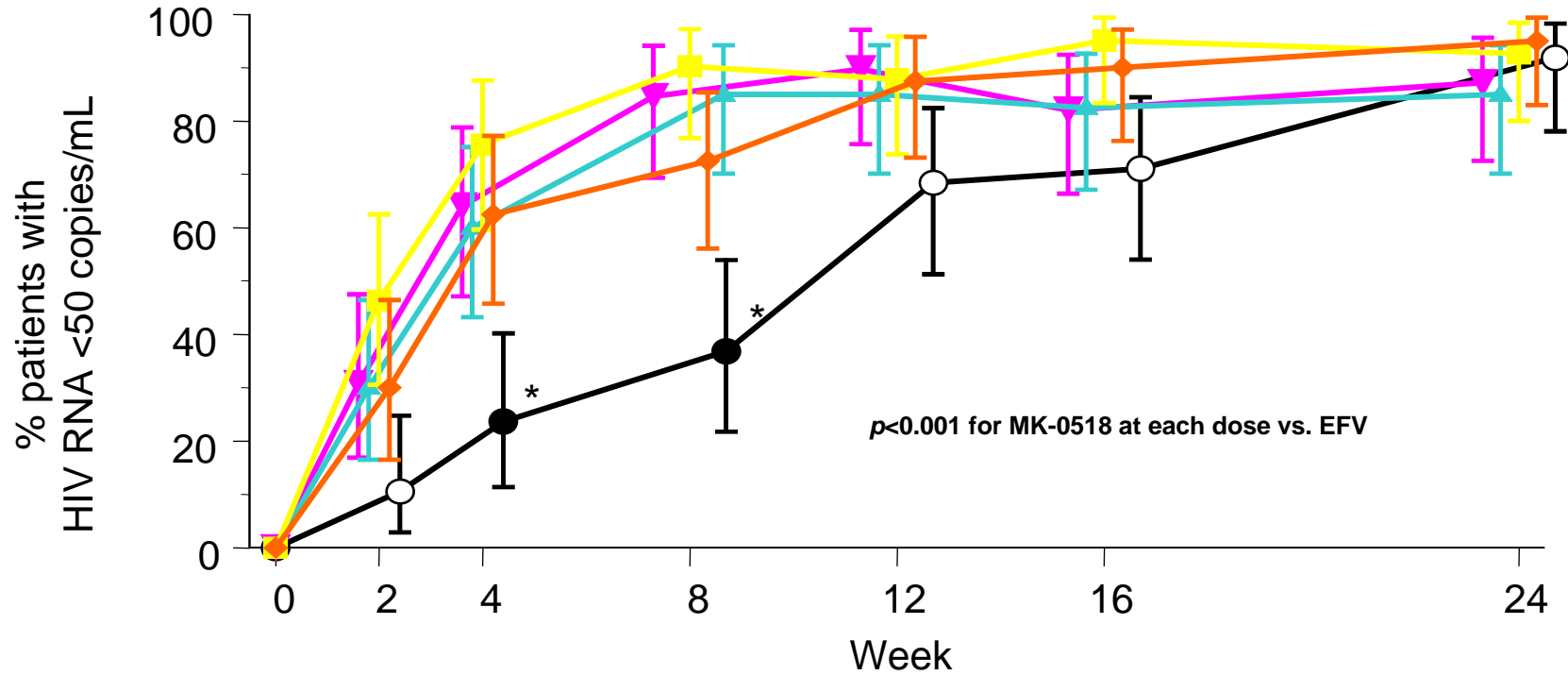
All doses showed > 2.2 log₁₀ decline in HIV RNA with CD4 increases of 75-135 cells/mL

Tolerability

Similar AEs in all groups, nausea, headache and dizziness most common. Infrequent Lab AEs with one d/c in 600 mg group



Protocol 004: Percent (95% CI) of patients with HIV RNA <50 copies/ml (NC=F)



▼	MK-0518 100mg	39	39	39	39	39	39
▲	MK-0518 200mg	40	40	40	40	40	40
■	MK-0518 400mg	41	41	41	41	41	41
◆	MK-0518 600mg	40	40	40	40	40	40
●	Efavirenz	38	38	38	38	38	37