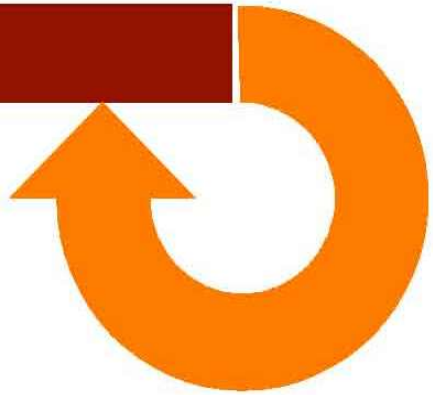
ACRN Review Course

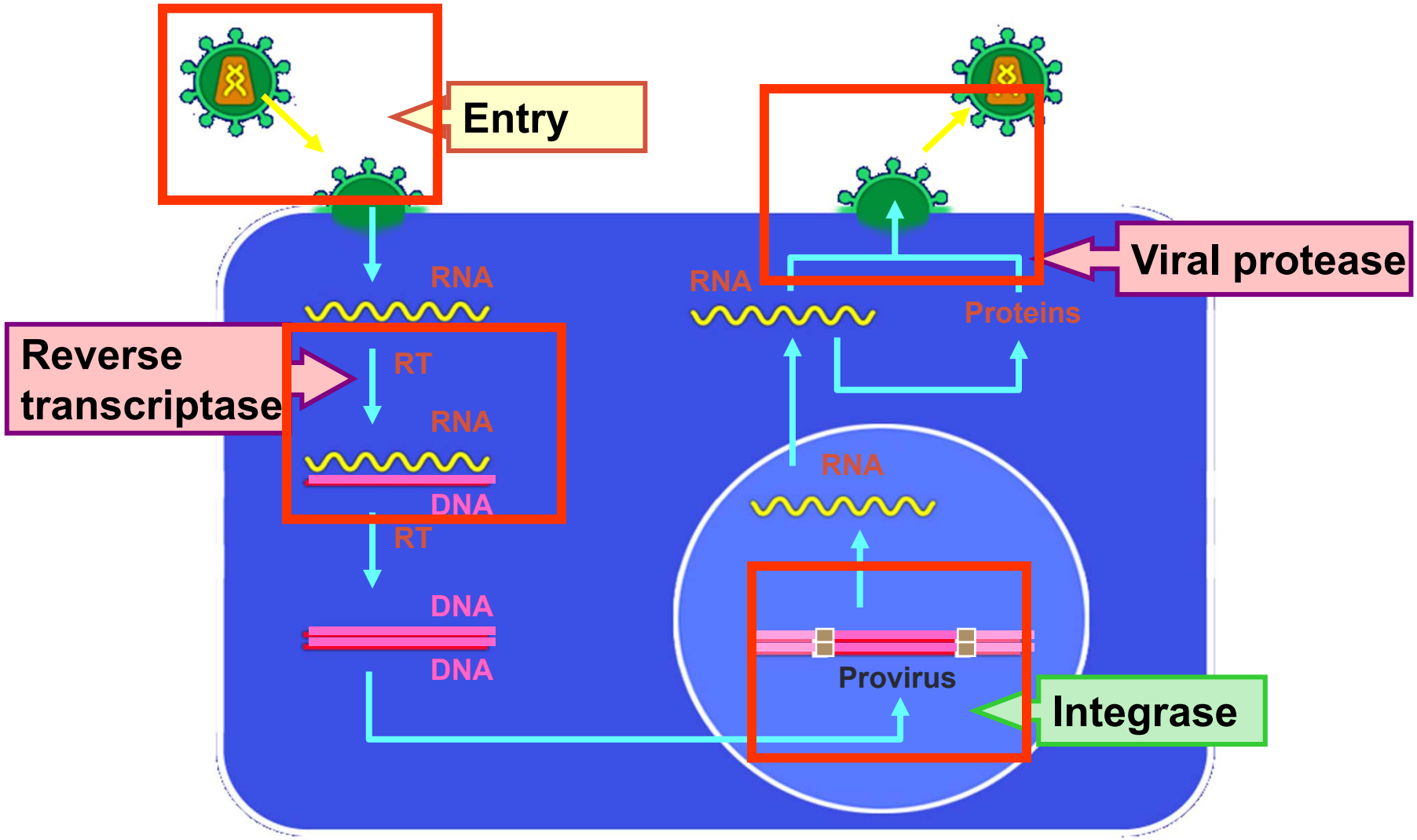


ANTIRETROVIRAL AGENTS AND THEIR TOXICITIES

Objectives

- Identify the 5 classes of antiretroviral medications
- Describe how each class of antiretroviral medications works against the HIV Virus at the level of the CD4 cell
- Review key studies related to HAART (highly active antiretroviral medications)
- List key toxicities and drug interactions of the antiretroviral classes and individual antiretroviral medications
- Review the current guidelines on the administration of antiretroviral medications

HIV-1 Lifecycle



U.S. FDA Approved Antiretroviral Drugs 2014

NRTI/NtRTIs

- Zidovudine
- Didanosine
- Stavudine
- Lamivudine
- Abacavir
- Emtricitabine
- Tenofovir
- ZDV/3TC
- ZDV/ABC/3TC
- ABC/3TC
- TDF/FTC
- TDF/FTC/EFV*
- TDF/FTC/RPV*

*Multiple class coformulation

NNRTIs

- Nevirapine
- Delavirdine
- Efavirenz
- Etravirine
- Rilpivirine

Integrase Inhibitors

- Dolutegravir
- Raltegravir
- TDF/FTC/Elvitegravir/Cobicistat*
- ABC/3TC/Dolutegravir*

PIs

- Saquinavir
- Ritonavir
- Indinavir
- Nelfinavir
- Lopinavir/r
- Atazanavir
- Fosamprenavir
- Tipranavir
- Darunavir

Entry Inhibitors

- Enfuvirtide
- Maraviroc

U.S. FDA Approved Antiretroviral Drugs 2014

DHHS Recommended or Alternative Therapies for Initial Treatment

NRTI/NtRTIs

- Tenofovir(TDF)
- Emtricitabine(FTC)
- Abacavir(ABC)
- Lamivudine(3TC)

NNRTIs

- Efavirenz
- Rilpivirine

PIs

- Atazanavir/r
- Darunavir/r
- Lopinavir/r

Integrase Inhibitors

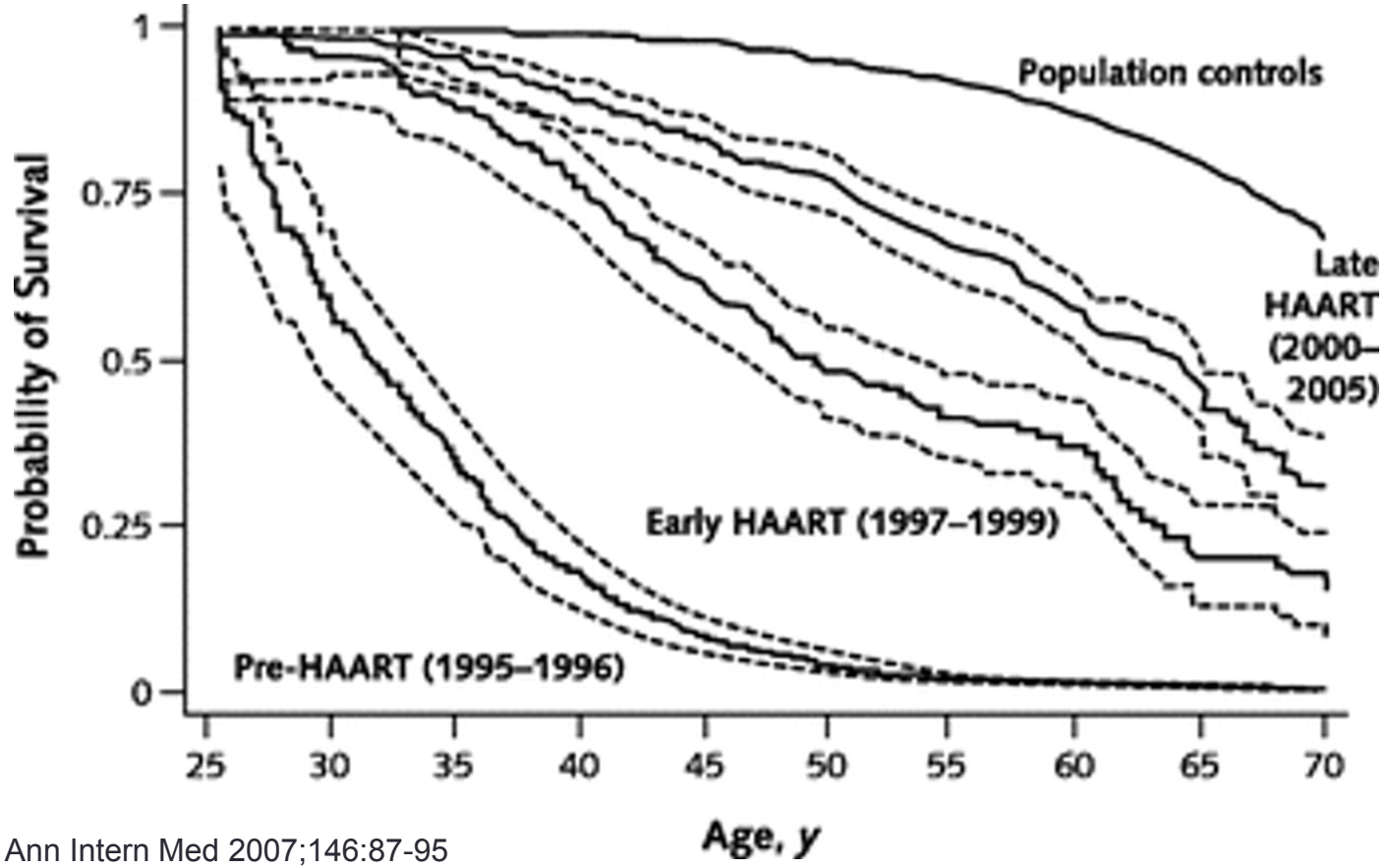
- Dolutegravir
- Raltegravir

Co-Formulated Combinations

- TDF/FTC
- ABC/3TC
- TDF/FTC/Efavirenz
- TDF/FTC/Rilpivirine
- TDF/FTC/Elvitegravir/Cobicistat
- ABC/3TC/Dolutegravir??

Median Survival from Age 25 Increases for HIV Infected Individuals in Denmark

General Population	51.1 yrs
Pre-HAART (1995-1996)	7.6 yrs
Early HAART (1997-1999)	22.5 yrs
Late HAART (2000-2005)	32.5 yrs
No Hep C	38.9 yrs



Lohse, N. et. al. Ann Intern Med 2007;146:87-95

Rate of Virologic Failure of First Regimens Is Declining

Hopkins HIV Cohort (1996-2002)

- All patients starting triple therapy (n=1255)
- Virologic failure (HIV RNA >400 copies/mL) at 6 months (*P*<0.01 for trend)
  - 1996: 56.2%
  - 1997-8: 45.8%
  - 1999-00: 29.7%
  - 2001-02: 27.6%

5 Observational Cohorts (1996-2002)

- All patients starting triple therapy (n=4143)
- Virologic failure (HIV RNA >500 copies/mL) at 6 to 12 months (*P*<0.001 for trend)
  - 1996: 40%
  - 1997: 42%
  - 1998: 39%
  - 1999: 34%
  - 2000: 31%
  - 2001: 30%
  - 2002: 25%

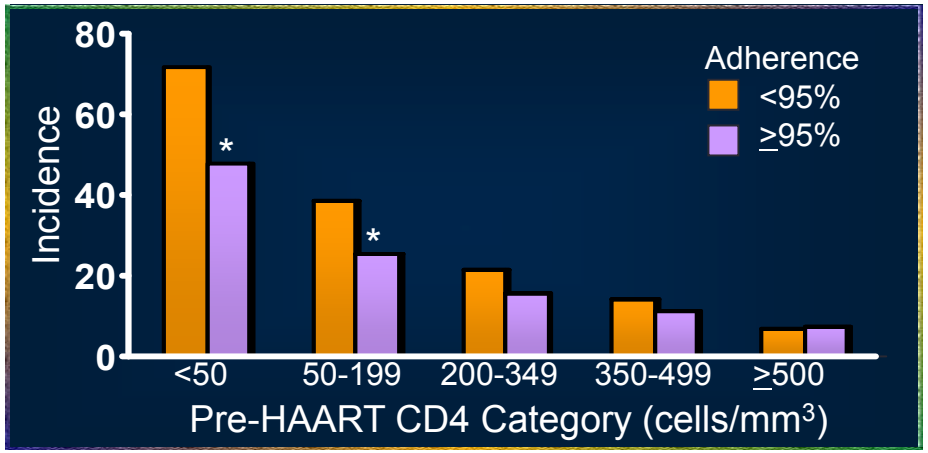
Moore RD, et al. *JAIDS*. 2005;39:195-198
Lampe F, et al. *Arch Intern Med*. 2006;166:521-528.

HOPS Cohort: Improved Outcomes With Early Initiation of HAART

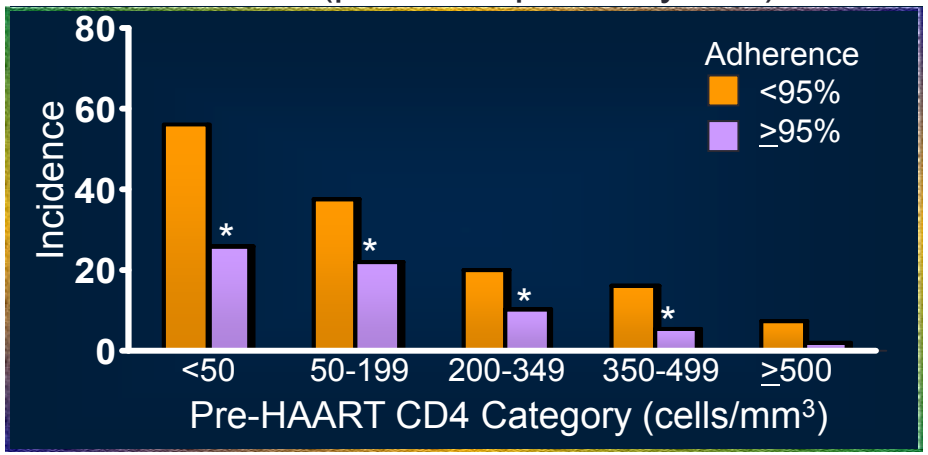
- Prospective cohort (n=4421)
  - 8-year follow-up
- Higher pre-HAART CD4 cell count and ≥95% adherence
  - Lower incidence of:
    - Mortality
    - OIs
  - Higher percentage achieving HIV RNA <50 copies/mL (*P*<0.01)
- These data suggest there are immunologic benefits and less toxicity when HAART is initiated earlier and is continuous

**P*<0.05.

Mortality (per 1000 person-years)

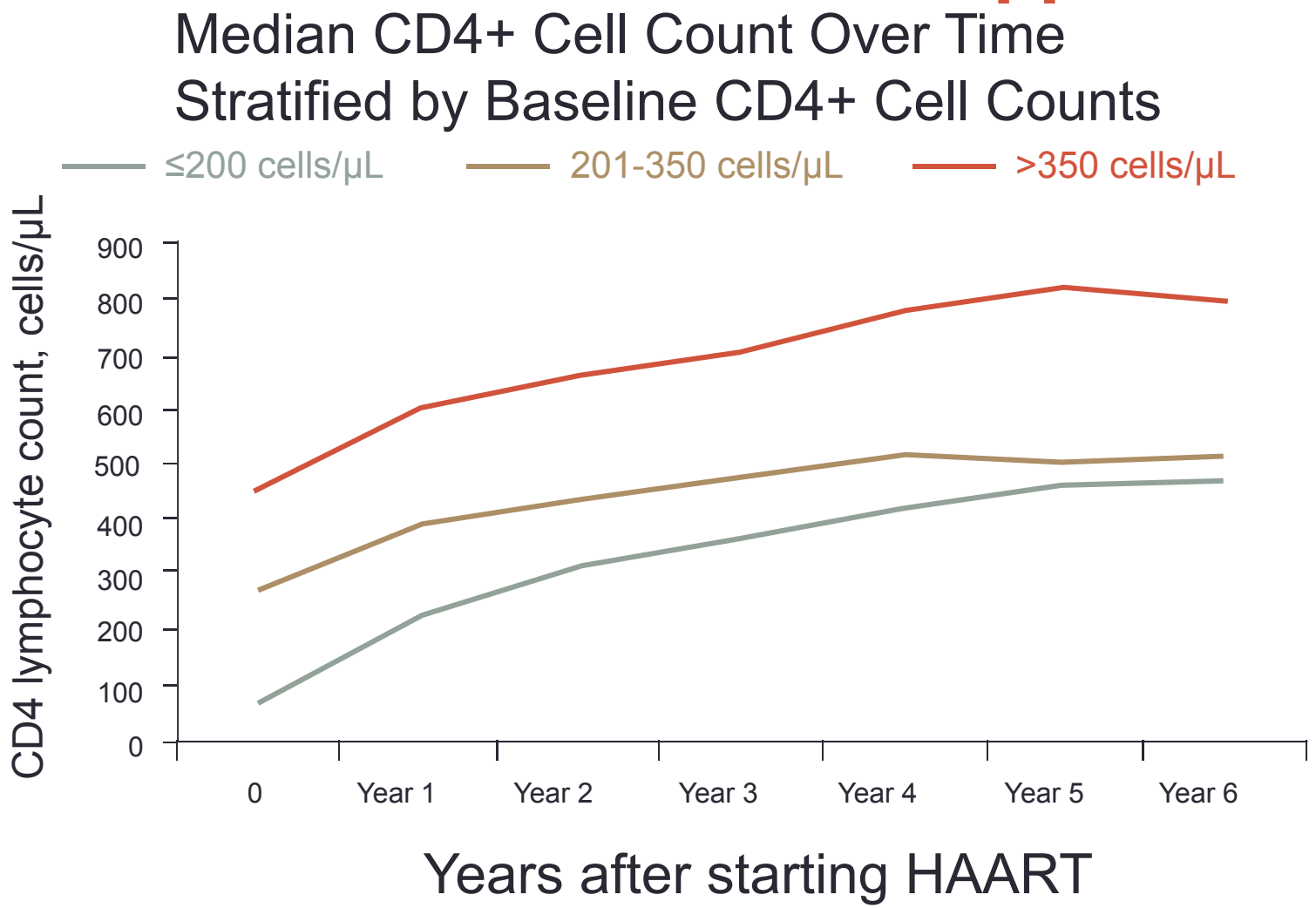


OIs (per 1000 person-years)



Lichtenstein KA, et al. 13th CROI. Denver, 2006. Abstract 769.

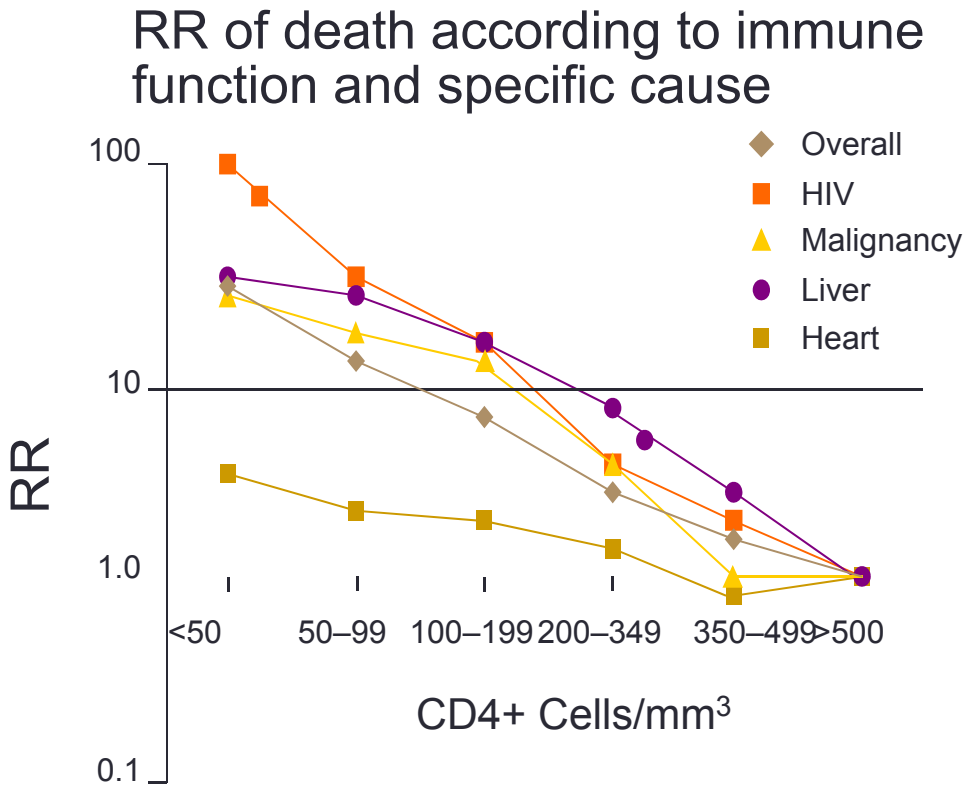
Immune Recovery by Baseline CD4+ T-cells in Patients with Sustained Viral Suppression



Moore RD, Keruly JC. Clin Infect Dis. 2007;44:441–446.

CD4+ T-cell Count Associated with Risk of Non–HIV Related Death (D:A:D Study)

- Cohort study of >23,000 patients in Europe, Australia, USA
- 1248 (5.3%) deaths 2000–2004 (1.6/100 person-years)
  - Of these, 82% on ART
- Both HIV- and non–HIV-related mortality associated with CD4+ cell count depletion, suggesting role for immunosuppression in causes of death typically considered not HIV-related*



Weber R et al. 12th CROI; 2005; Boston. Abstract 595 and AIDS. 2008 Oct 18;22(16):2143-53.

*Liver-related: Chronic viral hepatitis, liver failure (other); malignancy-related: malignancy, non-AIDS non-hepatitis; heart-related: MI, other CVD, other heart disease

HOPS Cohort: Delay in Initiating HAART Increases Risk of Toxicities

- Prospective cohort (n=4421)
- 8-year follow-up
- Higher pre-HAART CD4 cell count associated with decreased risk of toxicity
- These data suggest that a delay in initiating HAART increases the risk of toxicities

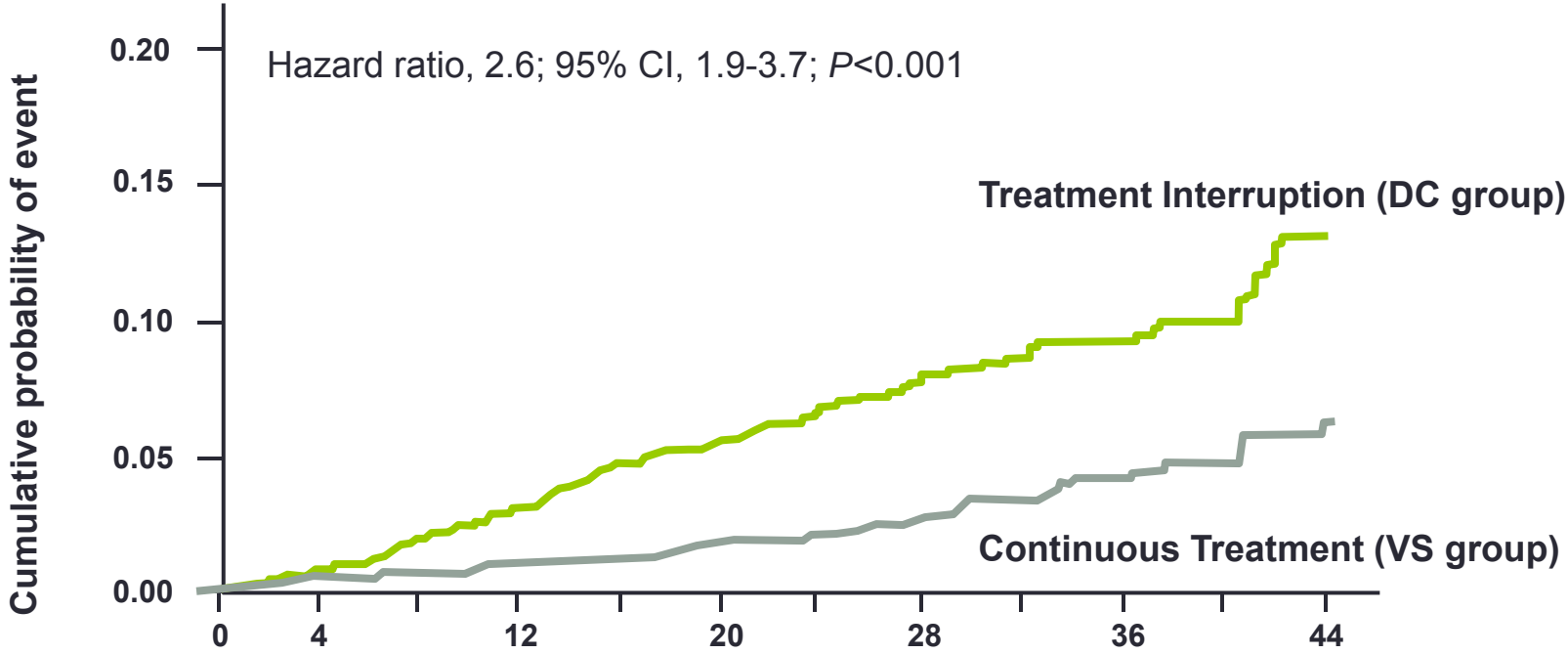
Adjusted Odds Ratios (95% CI)

Pre-HAART CD 4 cell count (cells/mm^3)	Renal Insufficiency (113/2156)	Peripheral Neuropathy (301/2222)	Lipoatrophy (176/361)
200-349	0.5* (0.3-0.8)	0.6* (0.5-0.9)	0.4* (0.2-0.8)
350-499	0.7 (0.4-1.2)	0.6* (0.4-0.9)	0.3* (0.2-0.6)
≥500	0.3* (0.2-0.6)	0.7* (0.5-0.9)	0.5* (0.3-0.9)
Taking <95% of prescribed HAART	**1.7* (1.2-2.6)**	**1.4* (1.1-1.8)**	0.6* (0.3-0.9)

*P<0.05. Numbers in yellow represent significant increase.

Lichtenstein KA, et al. 13th CROI. Denver, 2006. Abstract 769

SMART: Treatment Interruption Associated With Higher Rates of AIDS-Related OI or Death (Any Cause)



No. at Risk						
Drug conservation	2074	1301	870	540	372	162
Viral suppression	2081	1310	906	572	388	173

The Strategies for Management of Antiretroviral Therapy (SMART) Study Group. *N Engl J Med*. 2006;355:2283-2296. Adapted with permission from *New England Journal of Medicine*. © 2006.

Mean Annual Expenditures per Patient by Cost Component and CD4 category

CD4 strata (cells/mL)	Total	ARV	Non-ARV	Hospital	Other Outpt.	Physician/clinic
< 50	$36,532	$10,885	$14,882	$8,353	$1,909	$533
50-199	$23,864	$11,862	$6,685	$3,369	$1,416	$532
200-349	$18,274	$11,935	$3,452	$1,186	$1,365	$336
≥ 350	$13,885	$9,407	$1,855	$1,408	$930	$285
All	$18,640	$10,500	$4,240	$2,342	$1,199	$359

Patients with CD4 counts < 50 expend 2.6 times more health care dollars than those with CD4 counts ≥ 350 (P<0.001)

Chen, et al. Clin Infect Dis. 2006;42(7):1003-10.

NA-ACCORD: Effect of Early versus Deferred Antiretroviral Therapy for HIV on Survival

Table 3. Risk of Death Associated with Deferral of Antiretroviral Therapy, According to CD4+ Count at Baseline, with Adjustment for HIV RNA Level, Age, and Sex.*

Variable	351-to-500 CD4+ Count		More-Than-500 CD4+ Count	
	Relative Risk (95% CI)	P Value	Relative Risk (95% CI)	P Value
Without inclusion of HIV RNA data				
Deferral of antiretroviral therapy	1.69 (1.26–2.26)	<0.001	1.94 (1.37–2.79)	<0.001
Female sex	1.21 (0.89–1.64)	0.24	1.85 (1.33–2.59)	<0.001
Older age (per 10-yr increment)	1.68 (1.48–1.91)	<0.001	1.83 (1.62–2.06)	<0.001
Baseline CD4+ count (per 100 cells/mm^3)	1.13 (0.72–1.78)	0.59	0.93 (0.87–0.99)	0.03
With inclusion of HIV RNA data				
Deferral of antiretroviral therapy	1.63 (1.21–2.19)	0.002	1.85 (1.20–2.86)	0.006
Female sex	1.47 (1.02–2.12)	0.04	1.35 (0.85–2.15)	0.20
Older age (per 10-year increment)	1.89 (1.69–2.11)	<0.001	1.81 (1.58–2.07)	<0.001
Baseline CD4+ count (per 100 cells/mm^3)	0.74 (0.55–1.00)	0.06	0.97 (0.89–1.05)	0.45
Baseline HIV RNA level (per $\log_{10}$ copies/ml)	1.11 (0.96–1.28)	0.15	1.13 (0.96–1.33)	0.14

* The CD4+ count was measured in cells per cubic millimeter. Results were calculated with the use of Cox regression analyses with inverse probability-of-censoring weights. HIV denotes human immunodeficiency virus.

Kitahata M et al. N Engl J Med 2009;10.1056/NEJMoa0807252

Guidelines Recommendations for When to Start ART

Guideline	Clinical	CD4	Recommendations
DHHS*	•AIDS/Symptomatic Disease •Pregnant women •HIVAN •Hep B (if treat)	Any	Treat
	•Asymptomatic	< 350	Treat (AI – Strong – RCT)
		350-500	Treat (AII - Strong – data from nonRCT/obs)
		>500	Treat (BIII - Moderate – expert opinion)
IAS-USA**	•AIDS/Symptomatic Disease	Any	Treat
	•Asymptomatic	< 500	Treat (Aia)
		≥ 500	Treat (BIII) •Acute phase of primary HIV infection (BIII) •Pregnancy –(Aia) •Coinfected with TB (AIa) •Active HBV (AIIa) •HIVAN (AIIa)

* Panel on Antiretroviral Guidelines for Adult and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services.September18, 2014; p E11. Available at http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf. Accessed 9/18/2014

** Gunthard HF, et al. Antiretroviral Treatment of Adult HIV Infection: 2014 Recommendations of the International Antiviral Society–USA Panel. *JAMA.* 2014: 312(4):410-425..

Guidelines Recommendations for When to Start ART

Guideline	Clinical	CD4	Recommendations
EACS*	AIDS/Symptomatic Disease	Any	Treat
	Asymptomatic	<350	Treat
		350-500	Consider treatment. Treat if: HIVAN, Neurocognitive impariment, Hodgkins lymphoma, HPV-assoc CA, Pregnancy, HBV or HCV
		>500	Consider, treatment. Treat if HIVAN, Neurocognitive impariment, Hodgkins lymphoma, HPV-assoc CA, Pregnancy, HBV on treatment
BHIVA**	AIDS/Symptomatic Disease	Any	Treat
	Asymptomatic	< 350	Treat
		350-500	Treat if: •HBV and HCV •HIVAN, ITP, neurocognitive disorders •Non-AIDS malignancies •To reduce transmission
		>500	HBV Coinfection and HBV treatment indicated HIVAN, ITP, neurocognitive disorders

* EACS. June 2014. Available at: http://www.eacsociety.org/iPortals/0/140601_EACS%20EN7.02.pdf Version 7.02
** British HIV Association. Available at: http://www.bhiva.org/documents/Guidelines/Treatment/2012/hiv1029_2.pdf

Simplified Recommendations: When to Start ART

When the Patient is Ready

Considerations in Starting ART:

- Age
- CD4/Viral Load
- Social
  - Unstable housing
  - Major life crises
  - Perceived stress
  - Stigma/Denial
- OIs/Co-morbidities
  - Mental health
  - Substance Abuse
  - Hepatitis B and C
  - Renal - HIVAN
  - Cardiovascular
  - Malignancies
  - Neurologic

“It’s much more important to know what sort of patient has a disease than what sort of disease a patient has.”

William Osler

“Drugs don’t work if people don’t take them.”

C. Everett Koop

Need to Individualize

- One regimen does not fit all
- Multiple treatment options
- Factors Which Impact Regimen Durability
  - Non-adherence
    - Side effects/toxicities
    - Pill burden
    - Life schedule
    - Social situation
  - Resistance
  - Pharmacokinetics

When is Antiretroviral Therapy Started?

Median CD4 count at start of ART, 2003–5

42 countries, 176 sites, 33,008 patients

- Review of data from 42 countries, 176 sites; n=33,008
- Since 2000, CD4+ cell count at initiation in developed countries remained stable at ~150–200 cells/mm^3, increasing in Sub-Saharan Africa from 50 to 100 cells/mm^3

Egger M et al. 14th CROI; 2007; Los Angeles. Abstract 62.

2014 Guidelines – What to Start

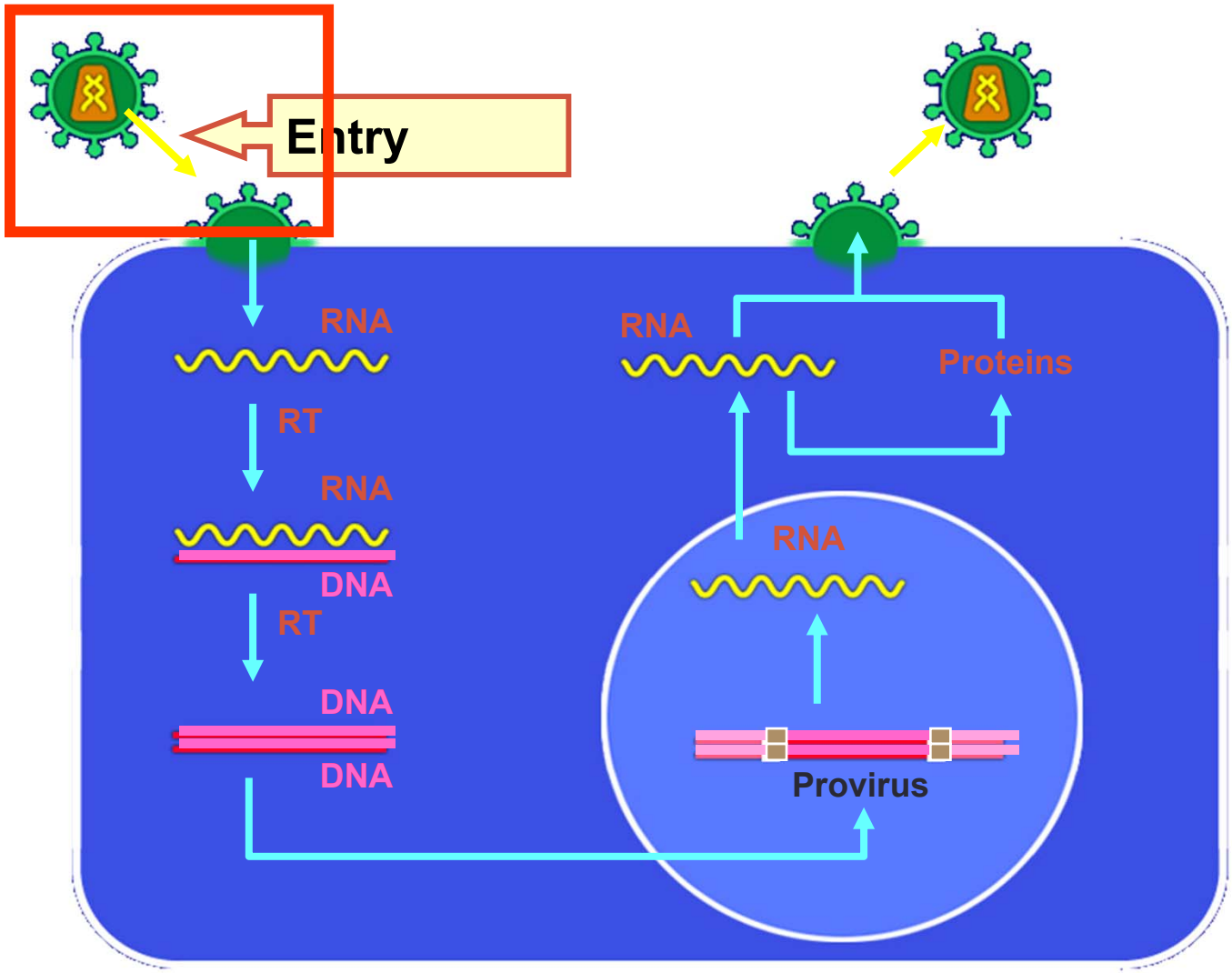
Guideline	NRTI		NNRTI		PI/Integrase	
	Preferred	Alternative	Preferred	Alternative	Preferred	Alternative
DHHS	TDF/FTC	ABC/3TC* *(ZDV/3TC)*	EFV#	RPV	ATV/r QD DRV/r QD RAL BID EVG/Cobicistat DTG	LPV/r QD/ BID
IAS-USA	TDF/FTC	ABC/3TC*	EFV# RPV	NVP	ATV/r DRV/r RAL BID EVG/Cobicistat DTG	LPV/r
EACS	ABC/3TC* TDF/FTC	ddI/3TC or FTC TDF/3TC ZDV/3TC	EFV# RPV	NVP‡	ATV/r QD DRV/r QD RAL BID EVG/Cobicistat	FPV/r BID or QD SQV/r QD LPV/r BID or QD MVC BID
BHIVA	TDF/FTC	ABC/3TC*	EFV#	NVP RPV	ATV/r DRV/r RAL EVG/Cobicistat	FPV/r LPV/r

*Use only if HLA-B*5701 negative. Use with caution in patients with cardiovascular risk or HIV-1 RNA > 100,000 copies/mL.

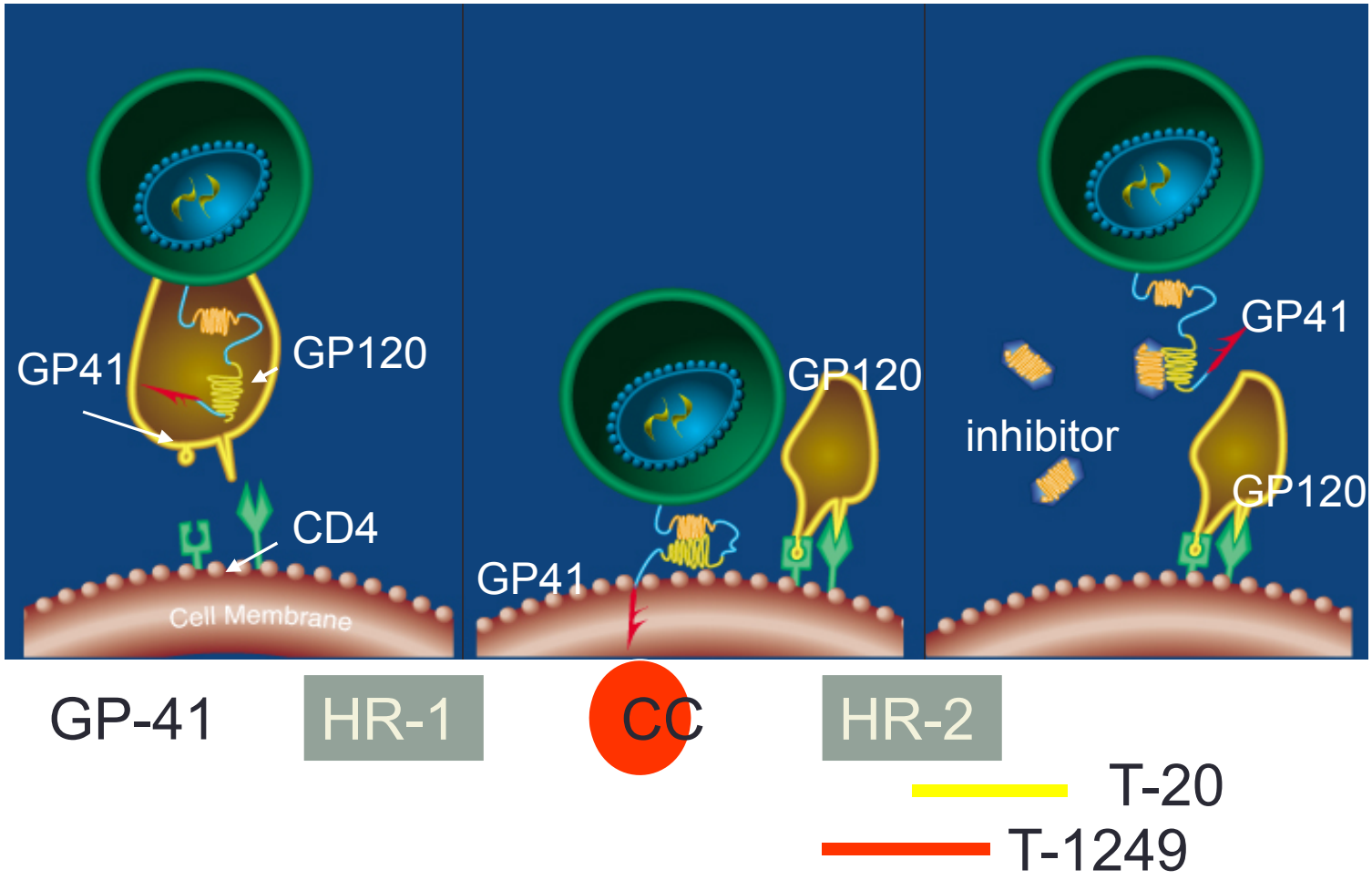
#Except during first trimester of pregnancy or in women with high pregnancy potential. Use caution in patients with unstable psychiatric disease.
‡Only in women with CD4+ cell count < 250 cells/mm3 or in men with CD4+ cell count < 400 cells/mm3
+May be acceptable but use with caution

DHHS Guidelines. Available at http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf. Accessed 9/18/2014. Gunthard HF et al. JAMA. 2014;312:410-425.
EACS guidelines. Available at http://www.eacs.edu/guide. Accessed 9/18/2014. British HIV Association. Available at:
http://www.bhiva.org/documents/Guidelines/Treatment/2012/hiv1029_2.pdf

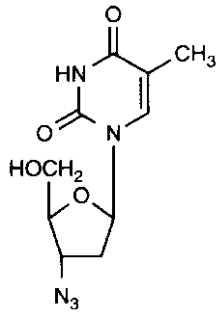
HIV-1 Lifecycle



Fusion Inhibitors

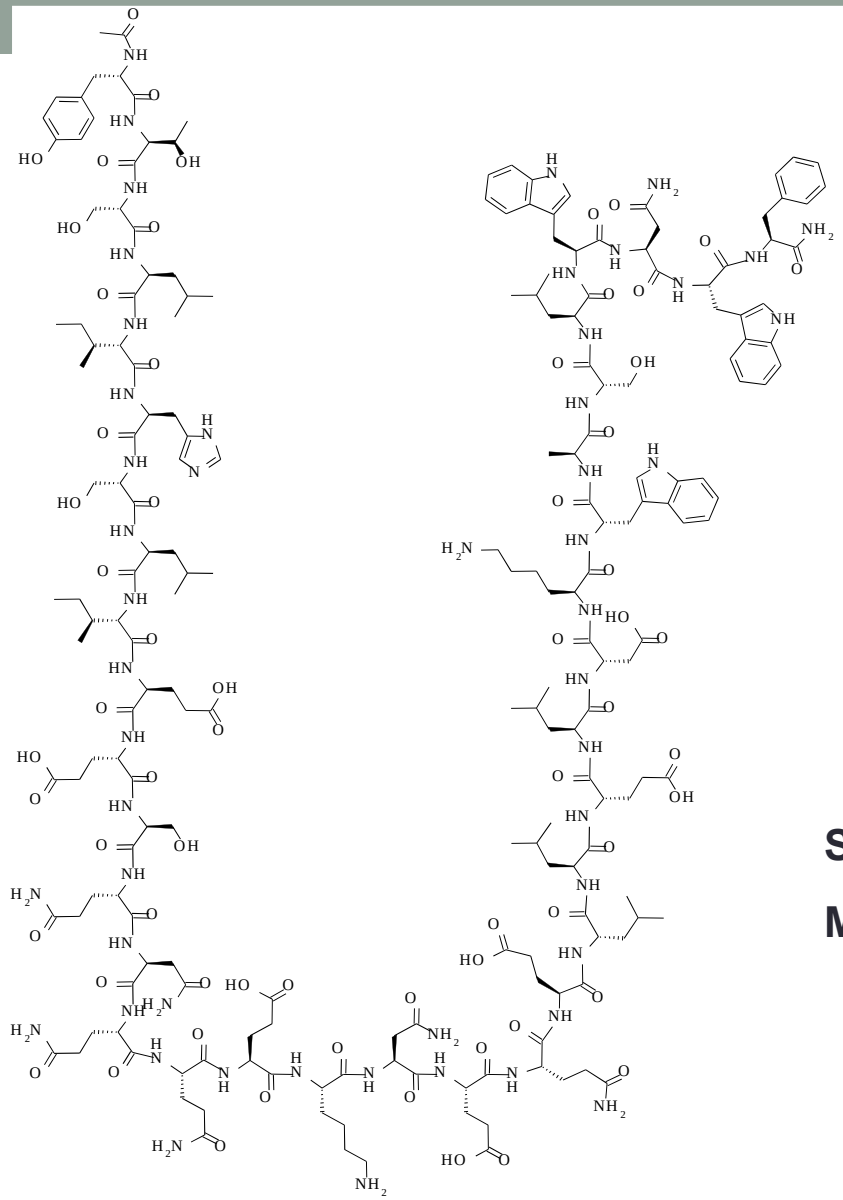


Doms R. State of the Art Lecture. 8th CROI, Chicago, 2001. #14



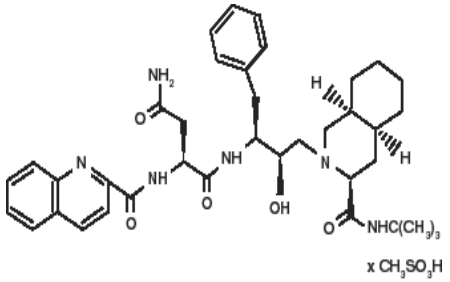
ZIDOVUDINE

M.W. 267



T-20

M.W. 4,492



SAQUINAVIR MESYLATE

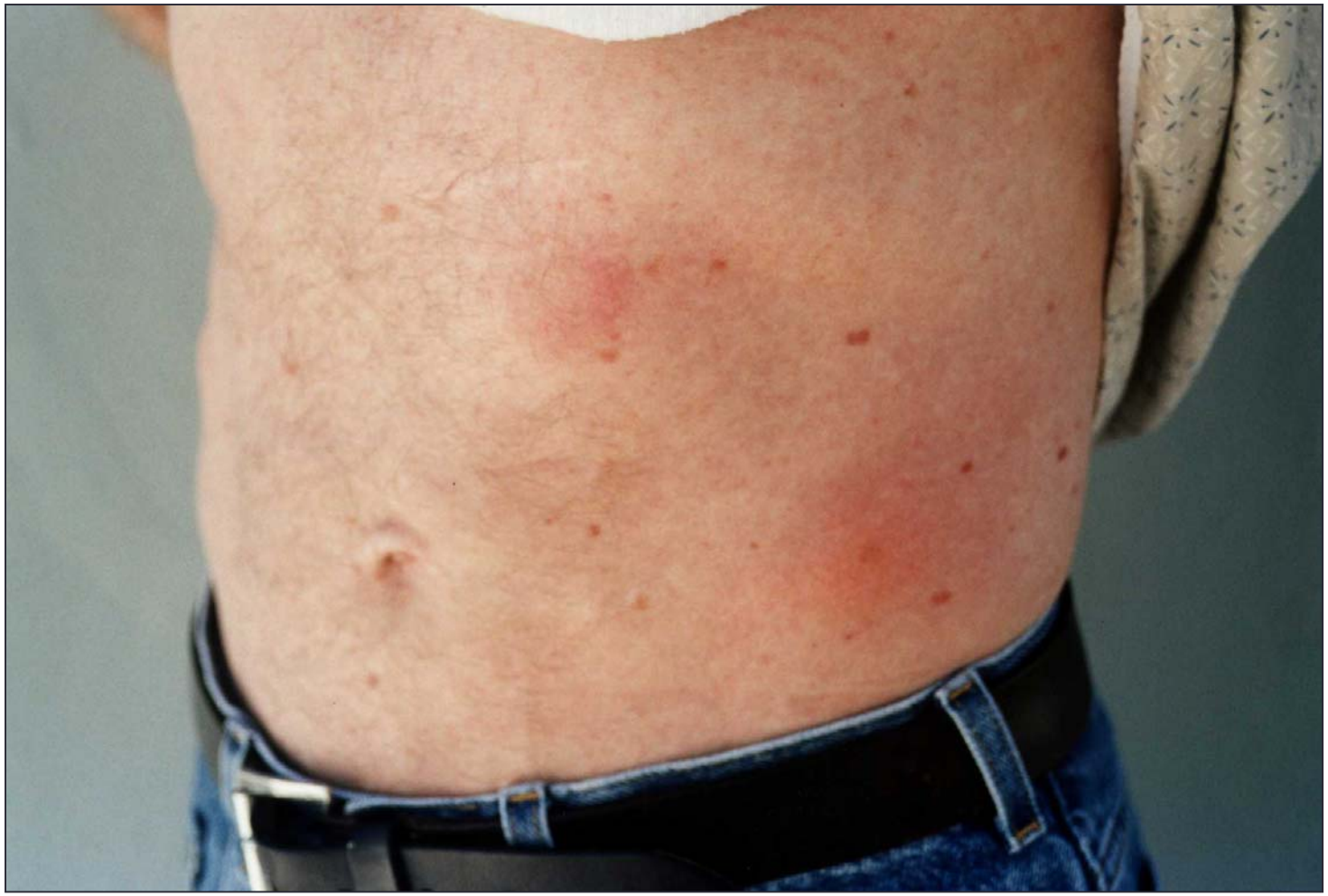
M.W. 767

TORO 1 + 2: Injection site reactions

- ISRs are the most common AE associated with T-20
  - Occur in 98% of patients
- Only 3% discontinued T-20 due to ISRs
- Most common signs/symptoms
  - pain/discomfort, most mild to moderate
  - induration, most < 50 mm
  - erythema, most < 50 mm
  - nodules or cysts, most < 3 cm
- 1% of patients had infections at site of injection
- Mean duration of individual ISR $\leq$ 7 days

Clotet *et al.*, Barcelona, '02
Henry *et al.*, Barcelona, '02

T-20 Related ISR

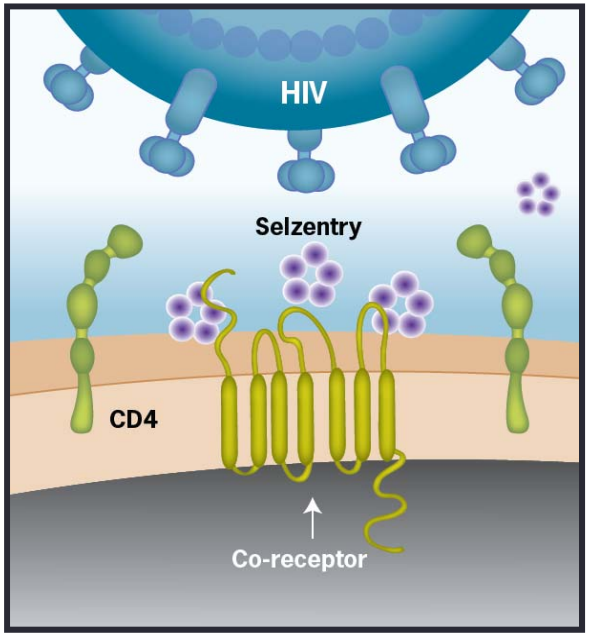


T-20: Other Adverse Events

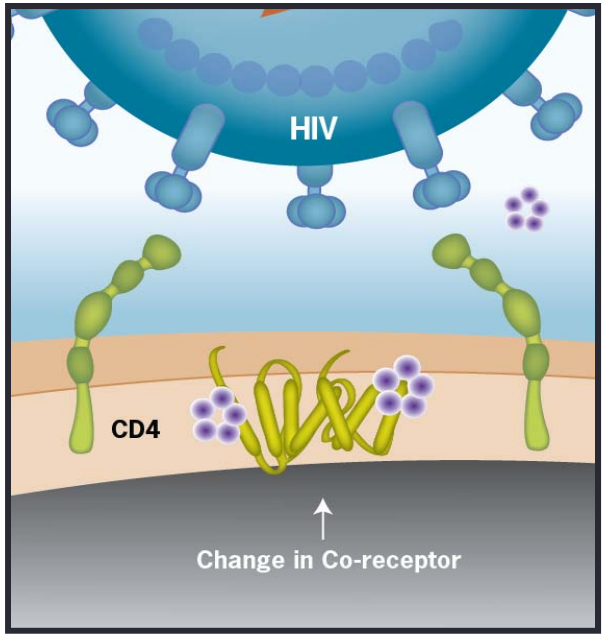
- Limited evidence for differences in most clinical and laboratory endpoints
- Eosinophilia > 700/mm^3 in 10%, > 1400 1.8%
- Hypersensitivity
  - 3 cases confirmed with rechallenge
  - Other possibly related cases GBS, glomerulonephritis
- Pneumonia approx 6 times higher with T-20 in Toro studies
  - One case in OB prior to switch
  - T-20 rate similar to cohort and natural history studies

Maraviroc is a CCR5 Antagonist

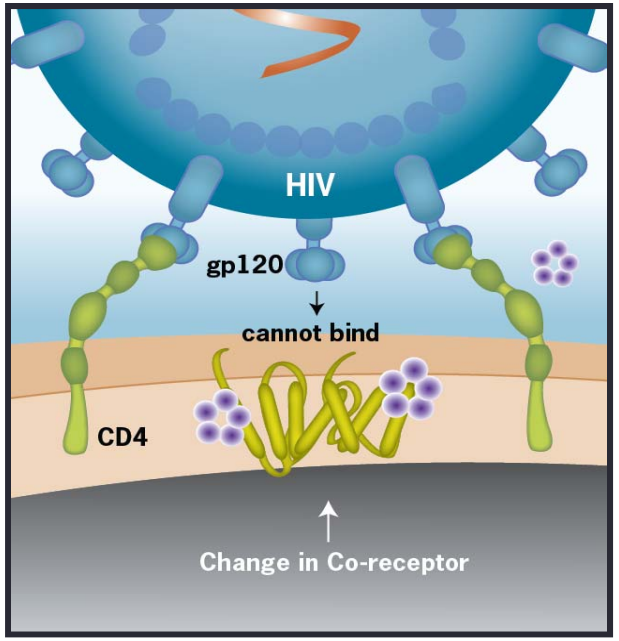
- Selective small-molecule antagonist of the interaction between the human chemokine CCR5 co-receptor and HIV-1 gp120
- Not active against CXCR4-tropic HIV-1



Maraviroc binds to the CCR5 transmembrane domain



CCR5 3-dimensional structure is altered

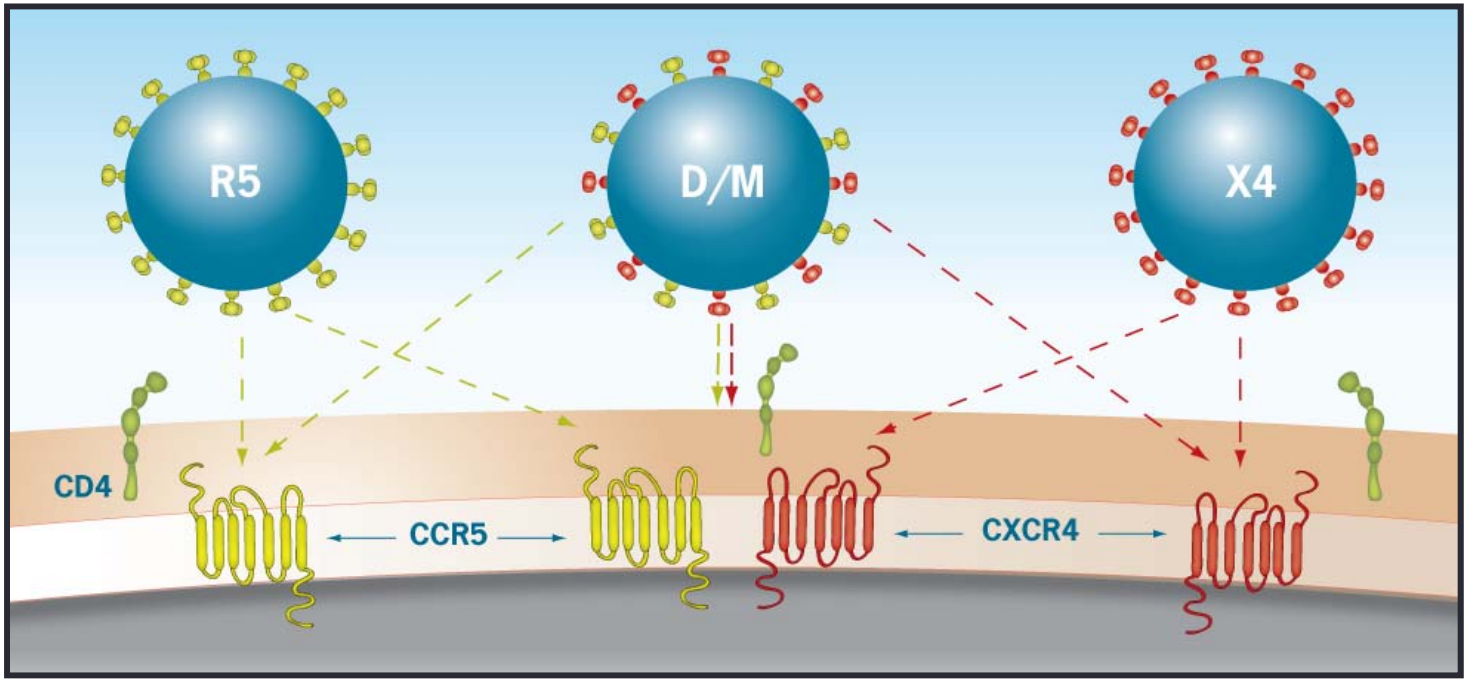


gp120-CD4 complex cannot bind to modified CCR5

Moore J, et al. *Proc Natl Acad Sci U S A.* 2003;100:10598-10602. Yost R, et al. *Am J Health-Sys Pharm*. 2009;66:715-726

Defining Co-Receptor Tropism

- CCR5 and CXCR4 are the primary chemokine co-receptors used by HIV to enter $CD4^+$ T cells



CCR5-tropic (R5) virus enters CD4+ T cells via CCR5

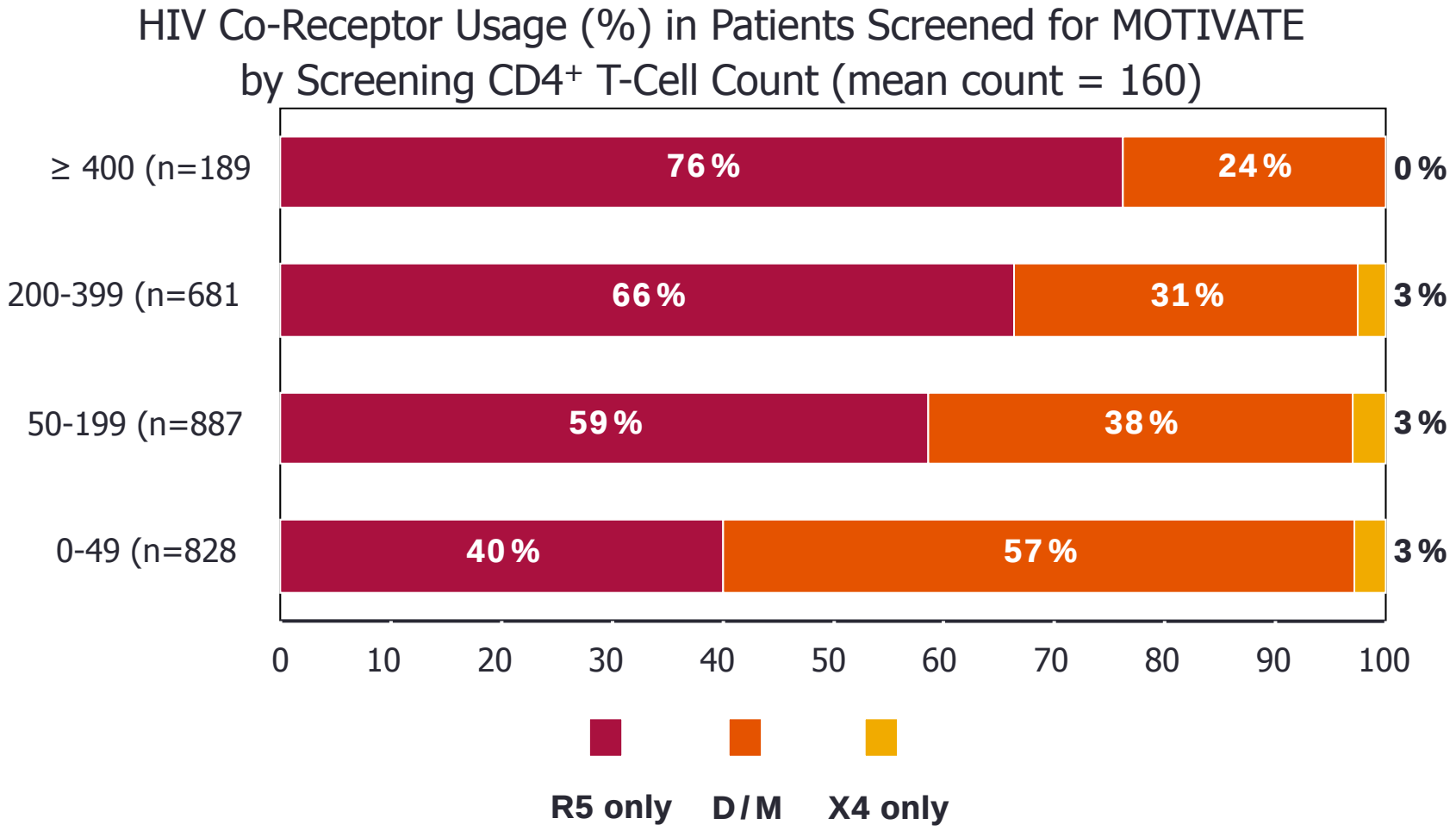
HIV that can use either CCR5 or CXCR4 is called dual

CXCR4-tropic (X4) virus enters CD4

Virus populations containing a mixture of R5-tropic, X4-tropic, and/or dual-tropic HIV are called mixed tropic

Westby E, et al. *Antivir Chem Chemother*. 2005;16:339-354

Viral Tropism Is Associated With CD4+ T-Cell Count



This data is based on the less-sensitive original Trofile assay. Therefore, the data may overestimate the prevalence of CCR5-tropic virus and underestimate the prevalence of D/M and

Clax P, et al. 3rd Intl Workshop HIV Entry. 2007.

Maraviroc Adverse Effects

- Hepatotoxicity
  - Associated with allergic reaction or hepatitis
- Dizziness
- Cough
- Abd pain
- Fever
- Musculoskeletal symptoms
- Rash

- Caution
  - Postural Hypotension
  - Cardiovascular Events in 1.3%

- Potential Risks
  - Increase risk of infection
    - Higher rate of Upper respiratory tract infections vs. placebo (20 vs. 11.5 %)
    - Lower rate of pneumonia (2.1 vs. 4.8%)
  - Increase risk of malignancy

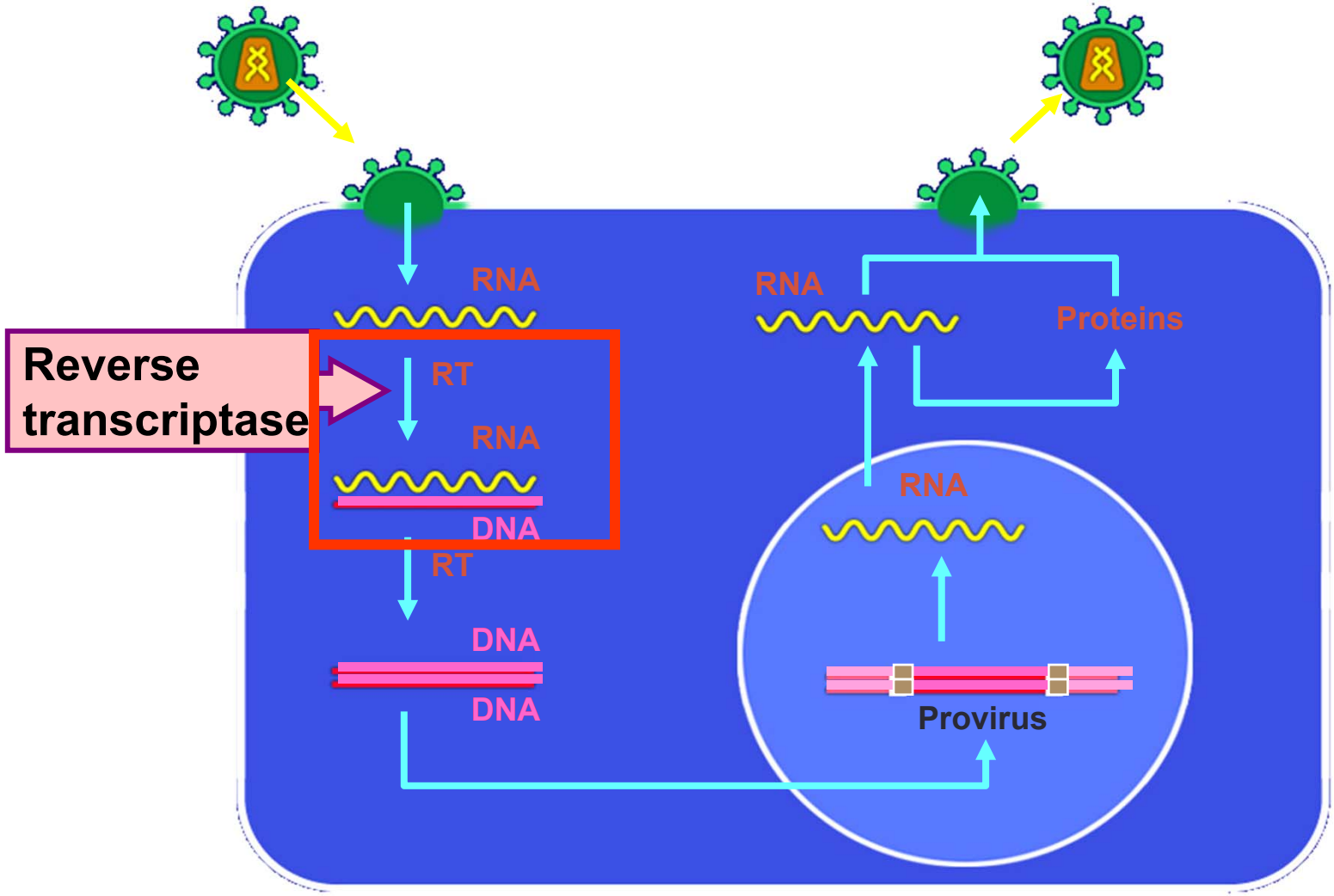
Co-administration of Maraviroc With Potent CYP3A Inhibitors and Inducers Affects Dose Selection

- Co-administration of potent CYP3A inhibitors and/or inducers with maraviroc must be considered when constructing multidrug regimens:
  - Potent CYP3A inhibitors $\rightarrow$ $\uparrow$ maraviroc plasma level
    - Including: efavirenz, rifampin, etravirine, carbamazepine, phenobarbital, phenytoin
    - Dose MVC 150 mg PO BID
  - Potent CYP3A inducers $\rightarrow$ $\downarrow$ maraviroc plasma levels
    - The effect of CYP3A inhibition on maraviroc levels is dominant when potent CYP3A inhibitor is co-administered with an inducer
    - Including: efavirenz, rifampin, etravirine, carbamazepine, phenobarbital, phenytoin
    - Dose MVC 600 mg PO BID

Entry Inhibitor Resistance Mutations

- Enfuvirtide
  - Mutations in First Heptad Repeat (HR-1) of envelope gene
  - 36, 37, 38, 39, 40, 42, 43
  - Polymorphisms and mutations in HR-2 or other regions and coreceptor usage/density may also affect susceptibility
- Maraviroc
  - Outgrowth of DM/X4 virus
  - Mutations in gp120

HIV-1 Lifecycle and Mechanisms of Action of Antiretroviral Agents

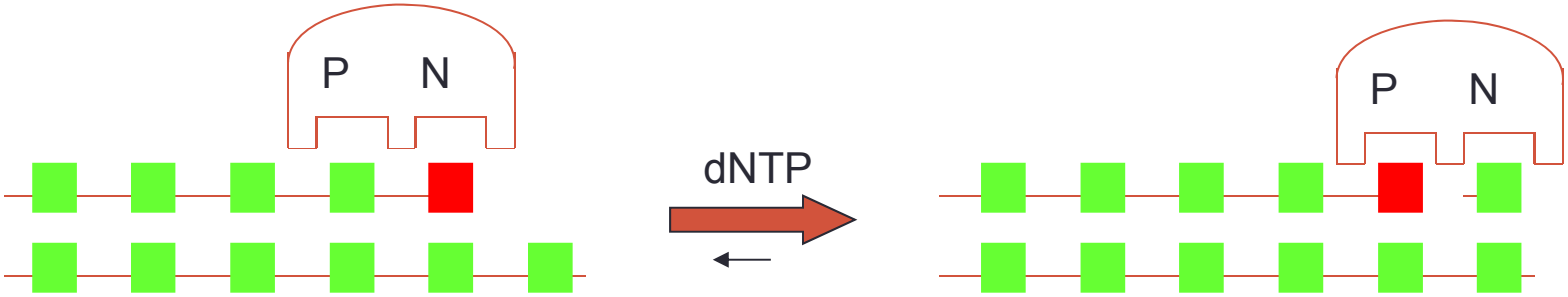


Currently Approved Nucleoside/tide Reverse Transcriptase Inhibitors (NRTI/NtRTIs) in the U.S.

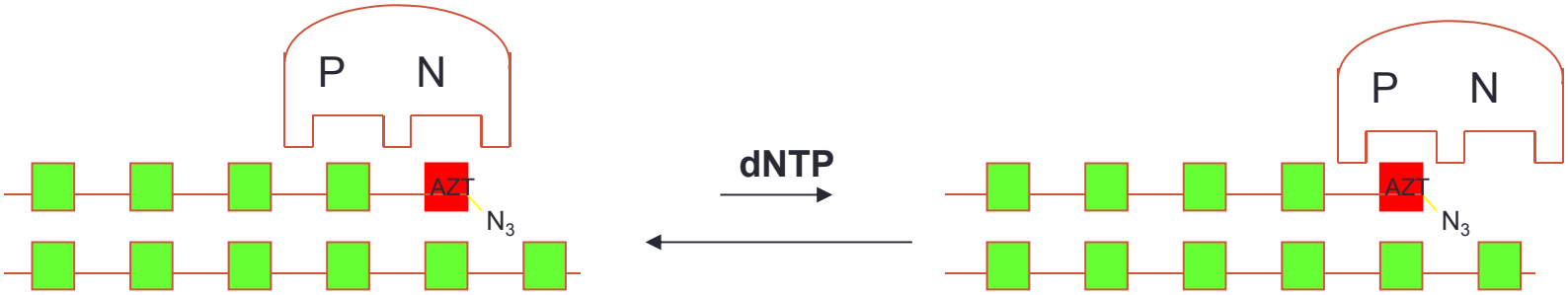
Drug	Other Names	Year Approved
Zidovudine	(AZT, Retrovir)	1987
Didanosine	(ddI, Videx)	1991
Zalcitabine	(ddC, Hivid)	1992
Stavudine	(d4T, Zerit)	1994
Lamivudine	(3TC, Epivir)	1995
Abacavir	(1592, Ziagen)	1998
Tenofovir	(PMPA, Viread)	2001
Emtricitabine	(FTC, Emtriva)	2003

Mechanism of NRTI Function

Nucleotide Incorporation



AZTMP Incorporation



Case 1

- 58 y.o. African American man referred to IHV in November 2001
- PMH: HTN, hand surgery
- FH: DM, HTN
- SH: no IVDU
- CD4 401, RNA not detectable
- Meds: ddI, d4T, Lopinavir/ritonavir

Case 1

- January 2002
  - Seen in ER 3 times in 2 week period for recurrent nausea, vomiting, abd pain
  - Told he had an “inflamed pancreas”
- February 2002 – Routine clinic appt
  - Still with abd pain, Lipase >700
  - Antiretrovirals discontinued
  - Symptoms resolved within several weeks

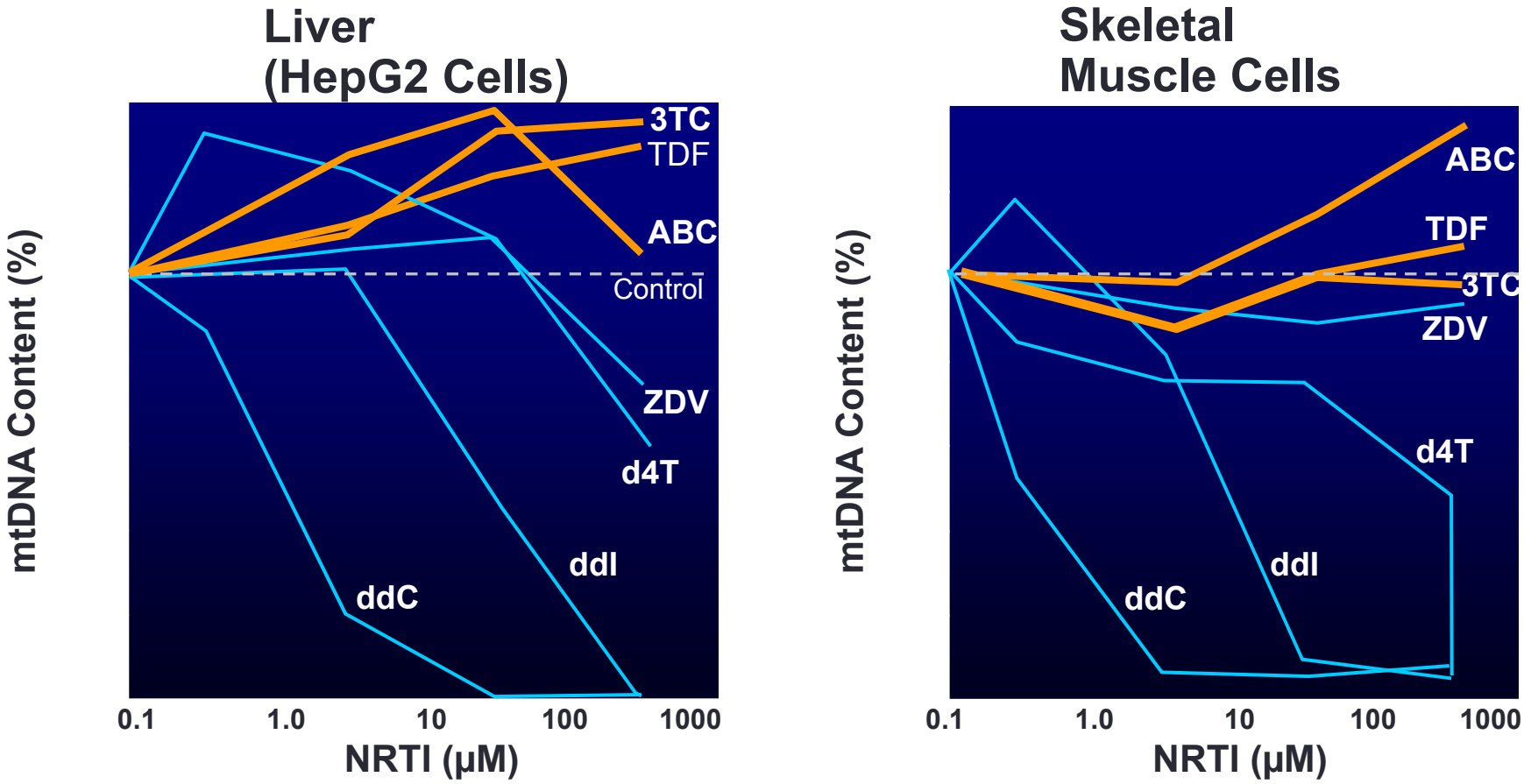
Case 1

- July 2002 - CD4 241
  - Restarted antiretrovirals (TDF, ABC, LPV/r)
- October 2002 – Asymptomatic
  - Glucose 500, Avandia started for diabetes
  - Medications discontinued
- March 2003 - CD4 193, glucose controlled
  - Restarted TDF, ABC, LPV/r
- July 2003 – CD4 330, RNA 63
  - Glucose 110-140

Mitochondrial Toxicities Related to NRTIs

- Neuropathy
- Myopathy
- Myocarditis
- Pancreatitis
- Hepatic steatosis
- Lipodystrophy
- Lactic Acidosis
- Renal tubular defects
- Pancytopenia

Inhibition of Mitochondrial DNA Content After 9 Days of NRTI Exposure



Birkus G, et al. *Antimicrob Agents Chemother.* 2002;46:716-723.

Lactic Acidosis

Symptoms and Laboratory Findings

Symptoms

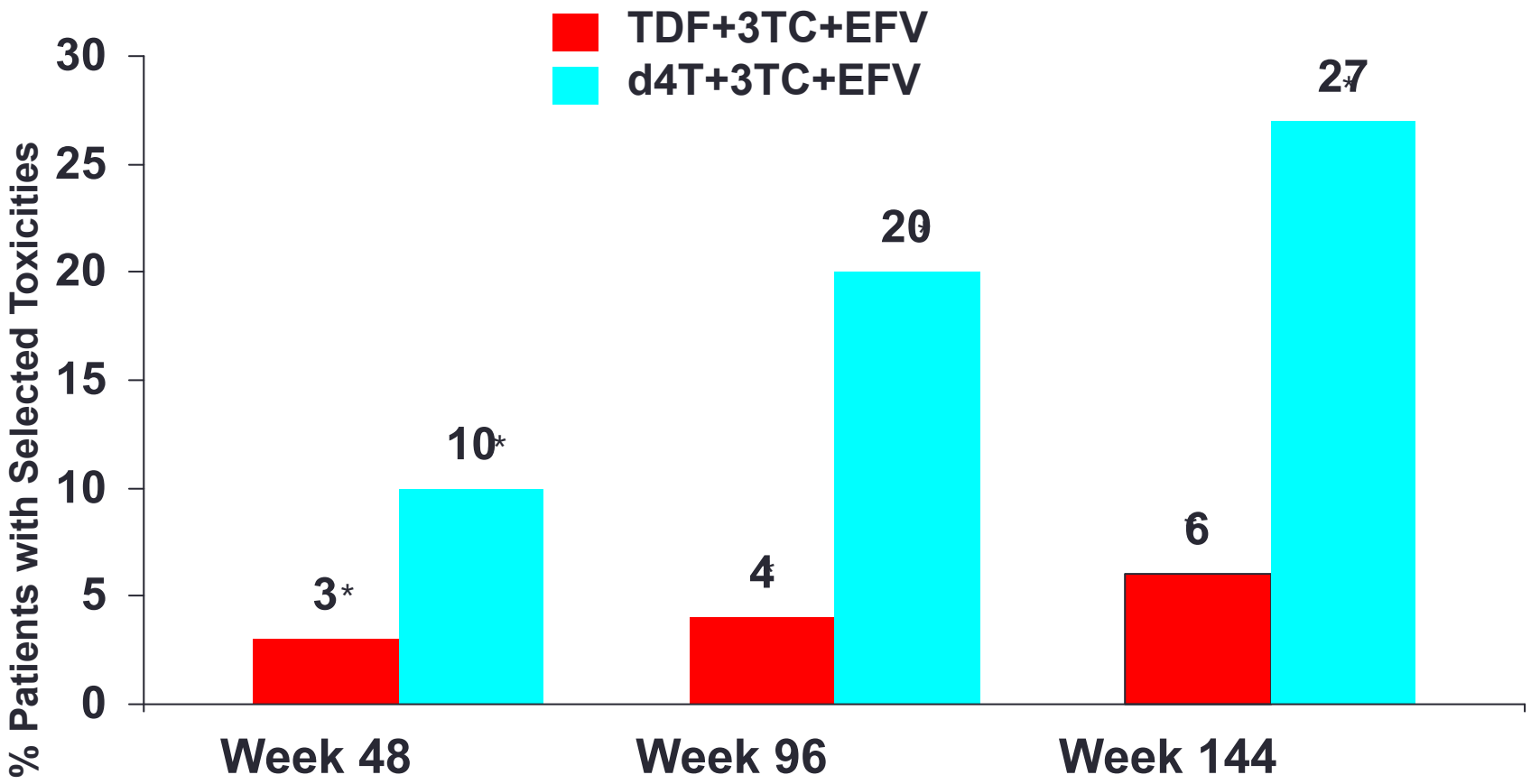
- Nausea and vomiting
- Abdominal pain
- Weight loss
- Malaise
- Dyspnea/tachypnea

Laboratory Findings

- Increased anion gap
- Increased lactic acid levels
- Increased lactate/pyruvate

Study 903: EFZ + 3TC + TDF or d4T

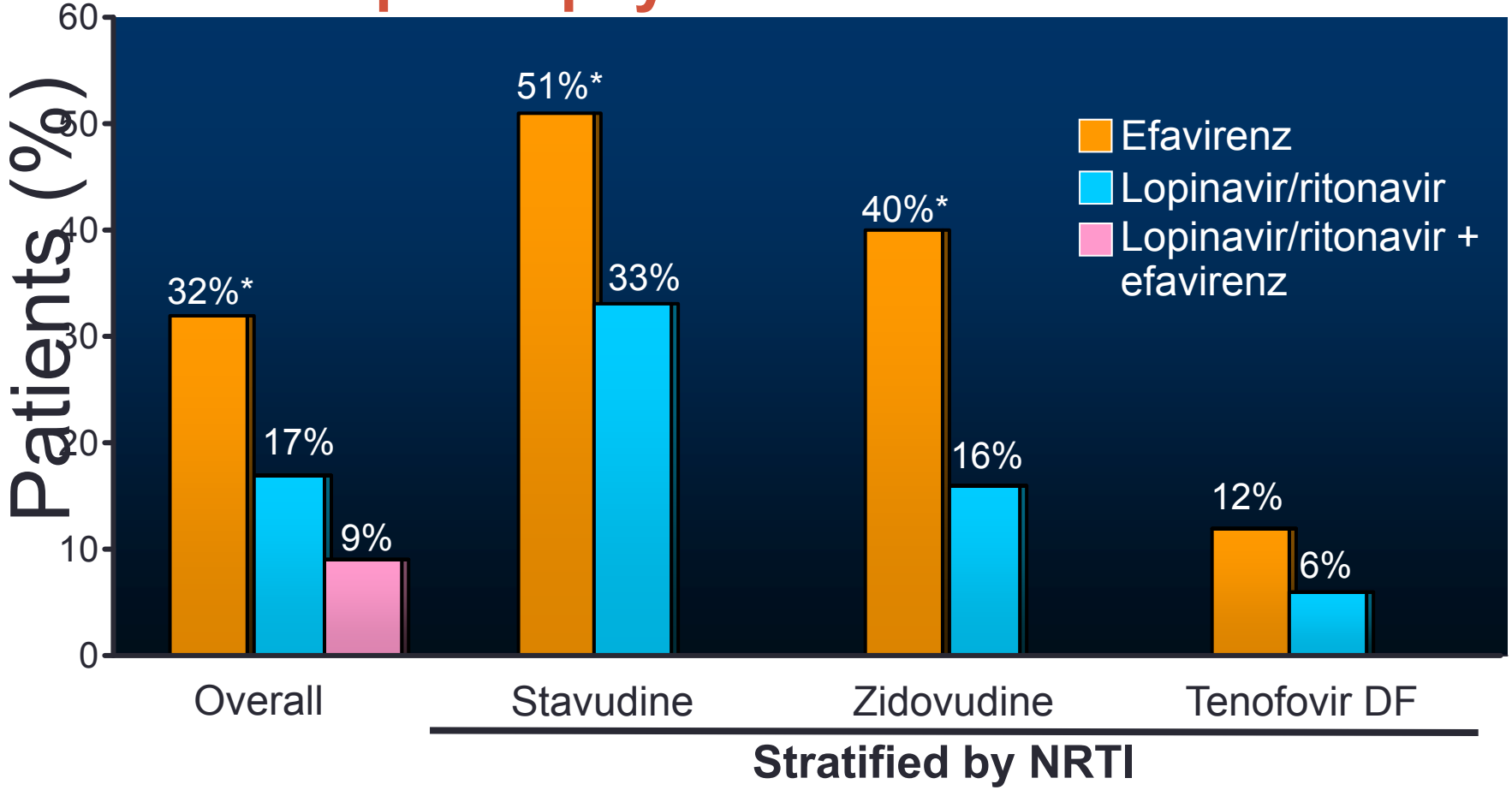
Patients (%) with Selected Toxicities Associated with Mitochondrial Dysfunction+



+ Peripheral neuritis/neuropathy, lipodystrophy (investigator defined), lactic acidosis

* p value < 0.001

ACTG 5142:
Incidence of Lipoatrophy at Week 96



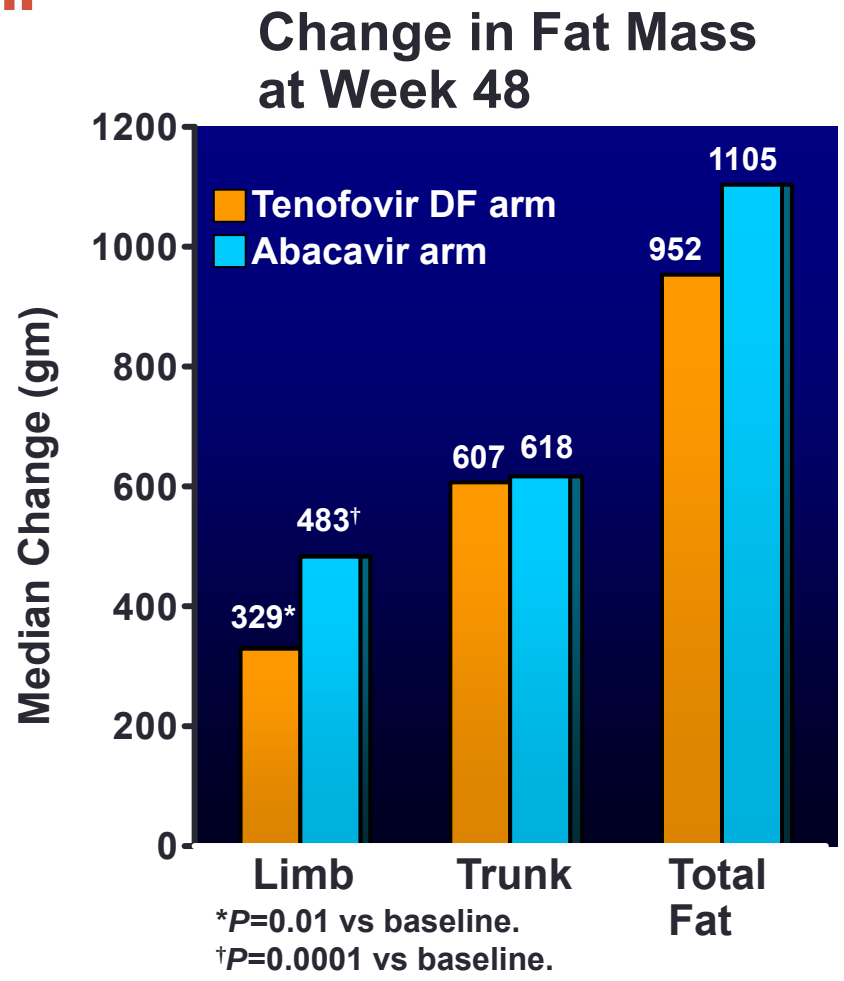
Regardless of NRTI used, incidence of lipoatrophy was higher in the efavirenz arm

Lipoatrophy: ≥20% loss of limb fat from baseline.
*$P \leq 0.01$ versus lopinavir/ritonavir.

Haubrich R, et al. 14th CROI. Los Angeles, 2007. Abstract 38

RAVE Study: 48-Week Results Following Switch to Either Tenofovir DF or Abacavir

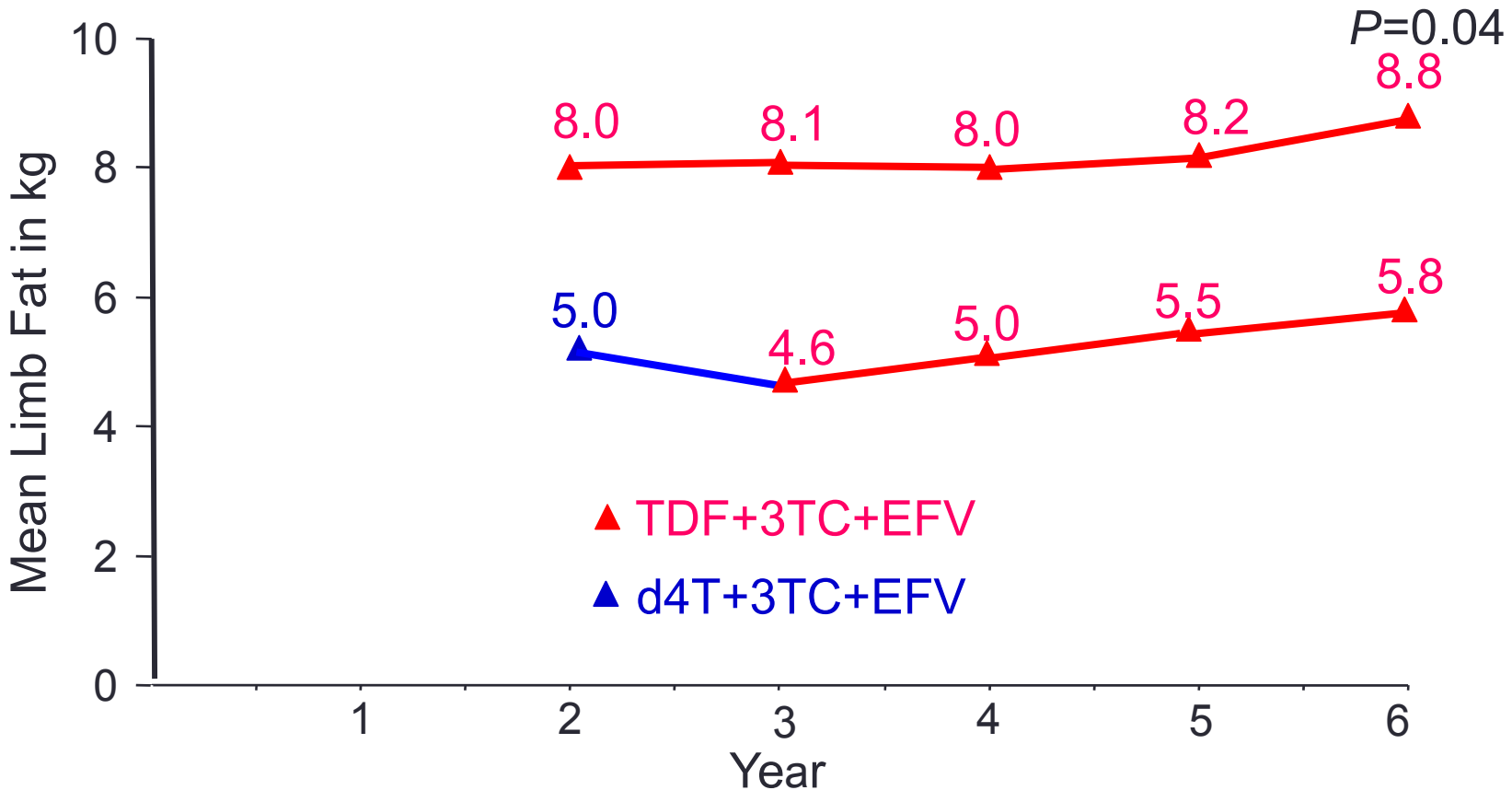
- Open-label switch study
  - 105 patients with self-defined lipoatrophy on thymidine analogue
    - HIV RNA <50 copies/mL
    - Switch to tenofovir DF or abacavir
  - Median weight/limb fat prior to switch
    - Tenofovir arm: 74/3.0 kg
    - Abacavir arm: 72/2.9 kg
- Results at 48 weeks
  - Total limb fat increased to similar extent in both arms over 48 weeks (by DEXA)



Moyle GJ, et al. *AIDS*. 2006;20:2043-2050.

Study 903E: Patients Switching From d4T to TDF

Mean (95% CI) Total Limb Fat – Years 2-6

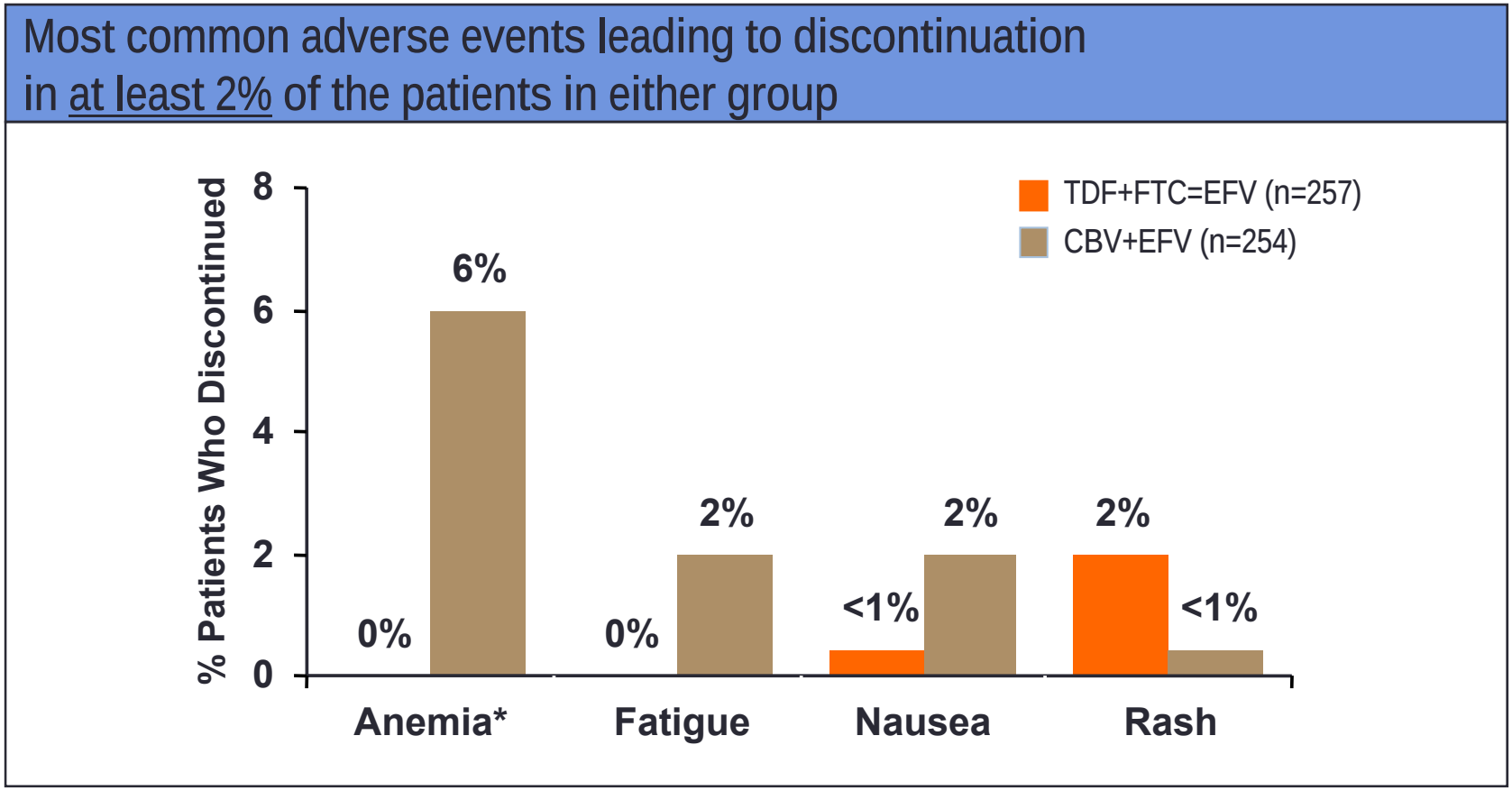


n =	69	69	65	61	58
n =	74	74	74	71	68

Madruga JVR. HIV8, 2006 Glasgow, UK. Poster P120.
Cassetti I. HIV8; 2006; Glasgow, UK. Poster P152.
Data on file, Gilead Sciences.

Study 934: EFV + TDF/FTC vs. ZDV/3TC

Most common adverse events leading to discontinuation 96 weeks



Pozniak A.L., et al. JAIDS 2006; 43(5):535-540

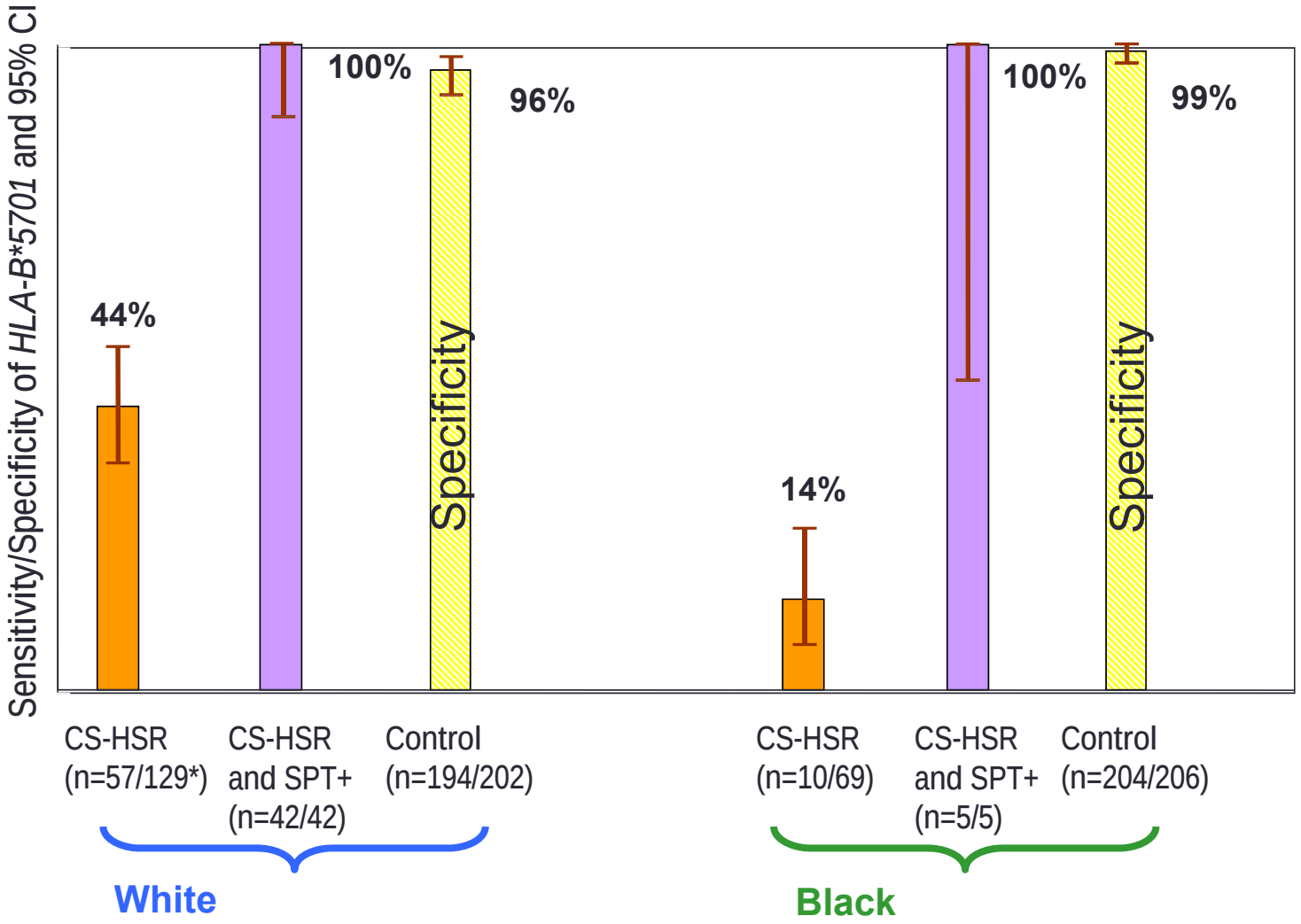
Adverse Effects of NRTIs

- Bone Marrow Suppression
  - Zidovudine (anemia)
- Flatulence
  - tenofovir
- Fatigue
  - Zidovudine (all)
- GI effects
  - All
- Headache
  - All
- Hypersensitivity
  - abacavir
- Lactic Acidosis
  - All
- Myopathy
  - Zidovudine
- Palmar Hyperpigmentation
  - emtricitabine
- Pancreatitis
  - ddI, d4T, ddC
- Peripheral Neuropathy
  - ddI, d4T, ddC
- Renal
  - tenofovir
- Stomatitis
  - ddC

Description of Hypersensitivity Reactions to Abacavir

- Symptoms of multiorgan system involvement
- Four most common symptoms: Major
  - Fever, rash, GI, malaise/fatigue/headache
- Less common (<10%): Minor
  - Edema, musculoskeletal, respiratory symptoms, mucous membrane, constitutional
- Resolves on stopping abacavir
- More severe symptoms, including life-threatening hypotension and death, have occurred on rechallenge
- Rechallenge must not be attempted

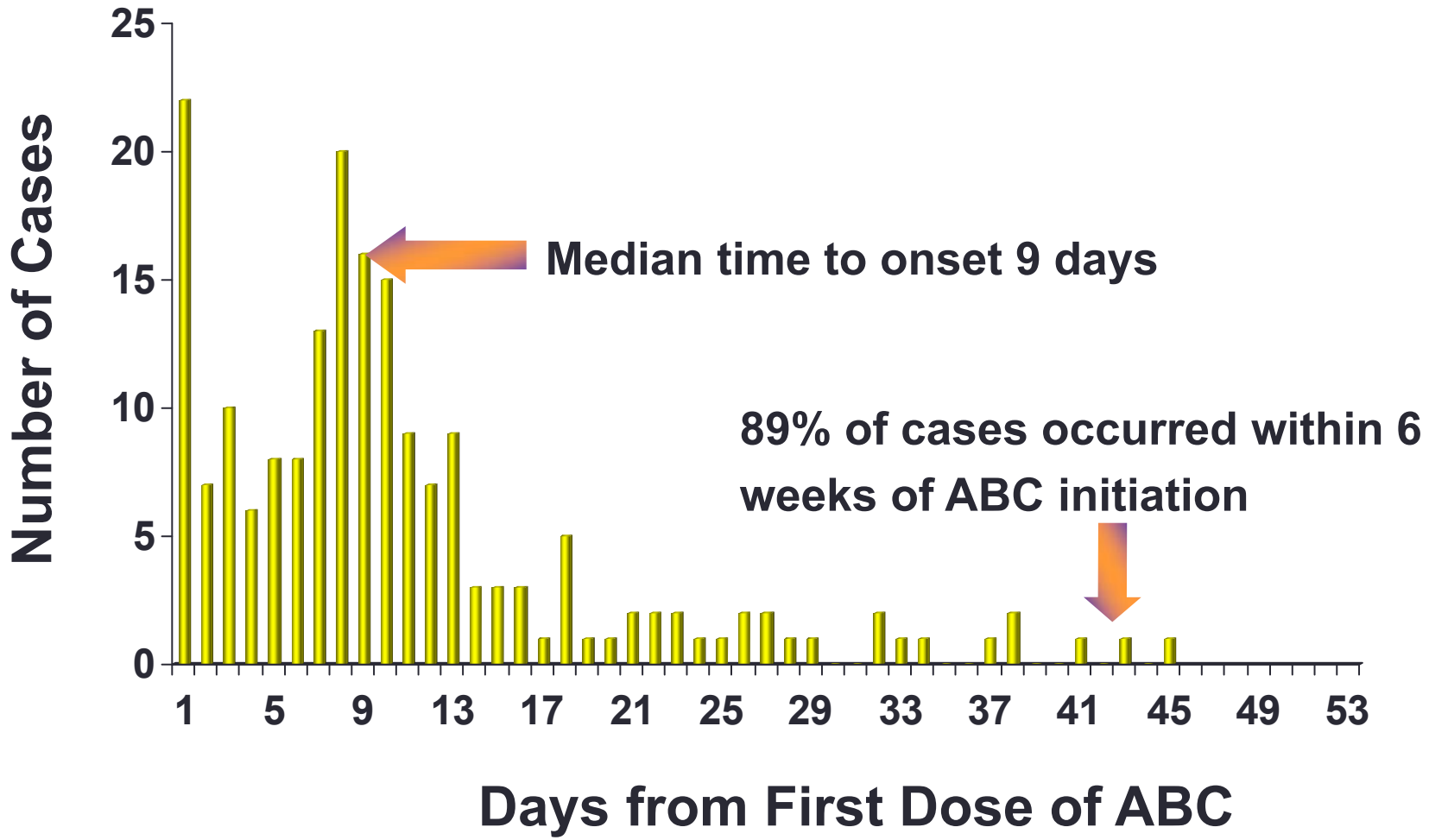
Sensitivity and Specificity of *HLA-B*5701*



**HLA-B*5701* results were not available for one subject.*
When considering the impact of these results in clinical practice, the limited representation of Blacks in this study should be taken into account.

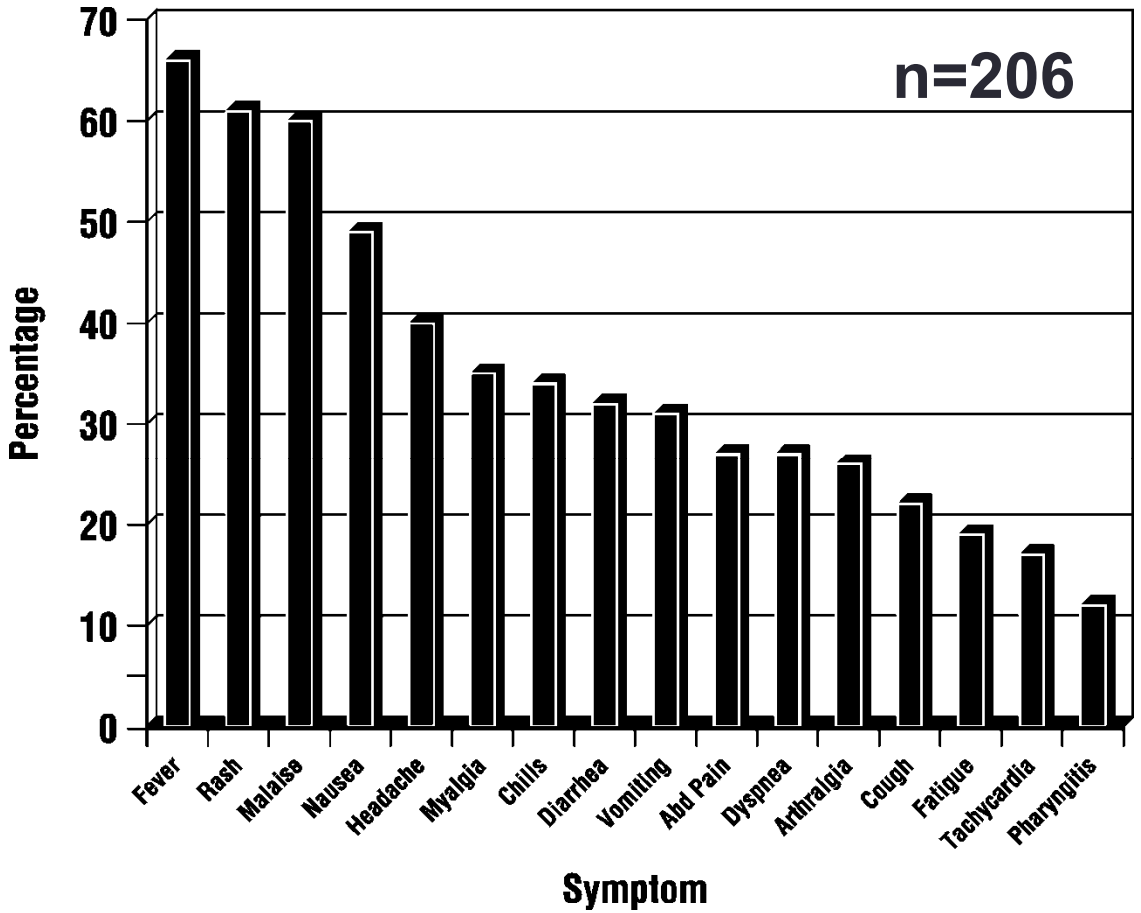
Data on file, GlaxoSmithKline.

Time to Onset of ABC HSR in Clinical Trials (n=206)



Data on file, GlaxoSmithKline.

Most Common (>10%) Symptoms with ABC HSR in 9 Clinical Trials



Overlapping Drug Toxicities

- Peripheral neuropathy
  - didanosine, isoniazid, linezolid, stavudine, zalcitabine
- Bone marrow suppression
  - cidofovir, cotrimoxazole, dapsone, zidovudine, gancyclovir, hydroxyurea, PEG-interferon, ribavirin
- Hepatotoxicity
  - efavirenz, isoniazid, NRTIs, nevirapine, protease inhibitors, isoniazid, rifampin, fluconazole
- Pancreatitis
  - didanosine, stavudine, zalcitabine, pentamidine, ritonavir, cotrimoxazole

D:A:D Study: NRTI Use and Risk of MI

- D:A:D study
  - 33,347 HIV patients on HAART
- 517 patients developed MI over 157,912 person-years of follow-up
  - Recent didanosine use (n=124)
  - Recent abacavir use (n=192)
  - Recent other NRTI use (n=237)
- Recent use of abacavir and didanosine (but not cumulative or past use) associated with increased risk of MI
  - Risk persists regardless of length of use
  - Risk was reversible with discontinuation of drugs
  - Most MIs occurred in patients with existing cardiovascular risk factors

Recent use	Relative Risk (95% CI)	*P* Value
Zidovudine	0.97 (0.76- 1.25)	0.82
Stavudine	1.00 (0.76-1.32)	0.93
Lamivudine	1.25 (0.96-1.62)	0.10
Abacavir	1.90 (1.47-2.45)	0.001
Didanosine	1.49 (1.14-1.95)	0.003

Implications:Use caution in the interpretation of these preliminary findings and await further studies

Sabin C, et al. 15th CROI. Boston, 2008. Abstract 957C.

VA Case Registry: Study Population, Treatment Exposure, Events and Risk Factors

- 19,424 patients enrolled in VA case registry study
  - Follow-up: 76,376 patient-years; mean: 3.93 years/patient
  - ARV exposure: 80% of patients exposed for ≥ 30 days.
    Mean Rx duration: 1.93 years
- Events during period of observation:
  - 278 AMI; Rate: 3.69 (95% CI: 3.28 – 4.15) per 1000 patient-years
  - 868 CVA; Rate: 11.68 (95% CI: 10.93 – 12.48) per 1000 patient-years

	Total (n = 19,424)	AMI (n = 278)	No AMI (n = 19,146)	P value
Age (yrs); median	46	51	46	<0.0001
Male sex; %	98	99	97	0.255
Smoking; %	29	33	28	0.116
Diabetes; %	13	22	13	<0.0001
Hypertension; %	38	68	38	<0.0001
Hypercholesterolemia; %	26	41	26	<0.0001
CKD (% eGFR < 60)*	8	18	7	<0.0001
HCV; %	32	38	31	0.013

Bedimo R, et al. 5th IAS; Cape Town, South Africa; July 19-22, 2009; Abst. MOAB202.

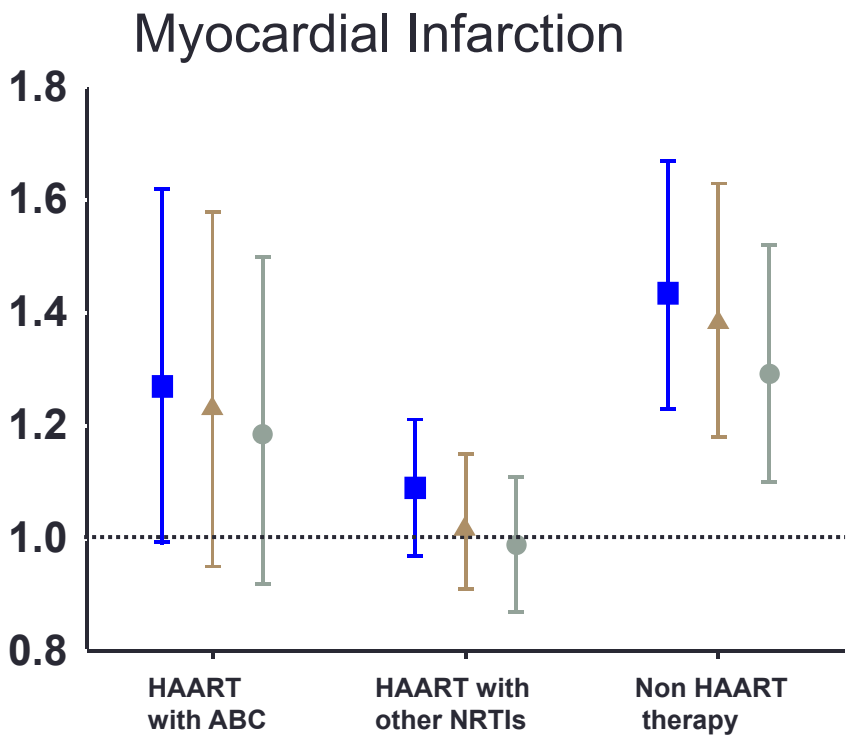
Chronic Kidney Disease Associated With Increased Risk of MI

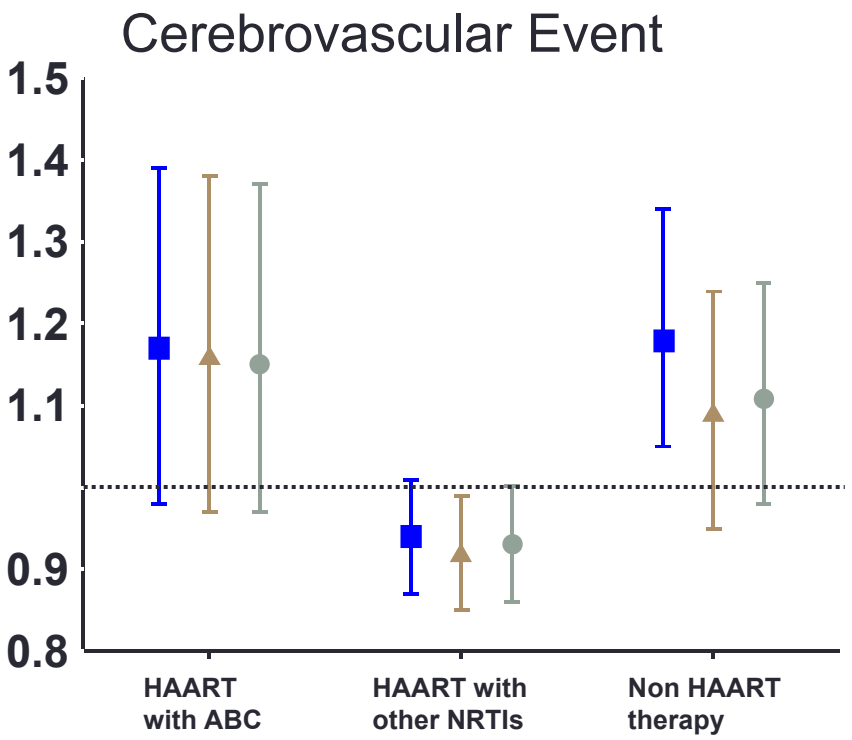
Estimated GFR, mL/min/1.73 m²	MI			CVA		
	Rate per 1000 Pt-Yrs	Unadjusted HR	*P* Value	Rate per 1000 Pt-Yrs	Unadjusted HR	*P* Value
• < 60	11.33	3.85	< .0001	30.58	2.95	.002
• 60-89	3.89	1.33	.048	12.57	1.28	< .0001
• ≥ 90	2.92	Ref	--	9.74	Ref	--

- Pts with CKD significantly more likely to receive ABC vs TDF
  - 12.3% vs 7.2%; $P < .0001$
- CKD (eGFR < 60 mL/min/1.73 m²) associated with higher risk of MI and CVA after adjustment for last ART regimen
  - HR for MI: 3.16 (95% CI: 2.35-4.26)
  - HR for CVA: 2.27 (95% CI: 1.88-2.74)
- HCV not associated with MI or CVA

Bedimo R, et al. IAS 2009. Abstract MOAB202

VA Case Registry: Cumulative Abacavir Use and Risk of Myocardial Infarction and Stroke





- Unadjusted HR of AMI for each PY of exposure to each one of the categories
- Adjusted for most recent estimated GFR (by MDRD method; carried forward).
- Adjusted for traditional risk factors: age, hyperlipidemia, HTN, type 2 DM, and tobacco use.

Bedimo R, et al. 5th IAS; Cape Town, South Africa; July 19-22, 2009; Abst. MOAB202.

ABC Not Associated With MI in FHDH After Controlling for CV Risk Factors

- **In earlier analysis of French Hospital Database on HIV, recent exposure to ABC associated with increased risk of MI[1]**
  - **OR: 1.97 (95% CI: 1.09-3.56; *P* = .025)**
- **After controlling for additional CV risk factors and factors associated with HIV and ART, association no longer observed[2]**
  - **OR: 0.97 (95% CI: 0.86-1.10)**
  - **Risk factors included HTN, smoking, family history of premature CAD, use of cocaine and/or IV drug use, plasma HIV-1 RNA level, CD4/CD8+ cell ratio, and exposure to FTC, ATV, RTV, and TPV**

1. Lang M, et al. CROI 2009. Abstract 43 LB.
2. Costagliola D, et al. IAS 2009. Abstract MOAB201.

- Factors associated with MI in the HIV population include CV risk factors including cocaine and IV drug use, having a detectable HIV-1 RNA, abnormal CD4+/CD8+ cell ratio

Factor	OR (95% CI)
CV risk factors*	
0	1 (Ref)
1-2	16.8 (5.9-48.4)
≥ 3	49.4 (16.4-149.0)
HIV-1 RNA	
≤ 50 c/mL	1 (Ref)
> 50 c/mL	1.6 (1.1-2.1)
CD4+/CD8+ ratio	
≥ 1	1 (Ref)
< 1	1.8 (1.0-3.0)

*Man > 50 yrs or woman > 60 yrs, current smoker or smoking cessation < 3 yrs, family history of premature CAD, hypertension, hypercholesterolemia, diabetes and cocaine and/or IV drug use

Nucleoside/tide Resistance Mutations

- Zidovudine 41, 67, 70, 210, 215, 219
- Didanosine 65, 74 or 3 or more TAMs
- Zalcitabine 65, 69, 74, 184
- Stavudine 41, 65, 67, 70, 210, 215, 219
- Lamivudine 65,184
- Emtricitabine 65,184
- Abacavir 65, 74, 115, 184(+ 2-3 TAMs ↓, 4+ TAMs 0)
- Tenofovir 65, ≥ 3 TAMS with 41 or 210

Multinucleoside Resistance

- Multiple TAMs/NAMs 41, 67, 70, 210, 215, 219
- 69 insertion complex 41, 62, 69, 70, 210, 215, 219
- 151 complex[1] 62, 75, 77, 116, 151

1. Tenofovir retains activity

Predicted NRTI activity based on median phenotypes by genotype*

# Mutations	RT genotype	ZDV	d4T	ddI	3TC/ FTC	ABC	TDF
1	184V/I						
	65R						
2	**65R + 184V/I**						
	74V/I + 184V/I						
	41L + 184V/I						
3	67N + 70R + 184V/I						
	215Y/F* +184V/I						
4	67N + 70R +219E/Q + 184V/I						
	41L + 215Y/F* + 184V/I						
5	41L + 210W + 215Y/F* + 184V/I						

***215Y and 215F both require 2 mutations from wild type**

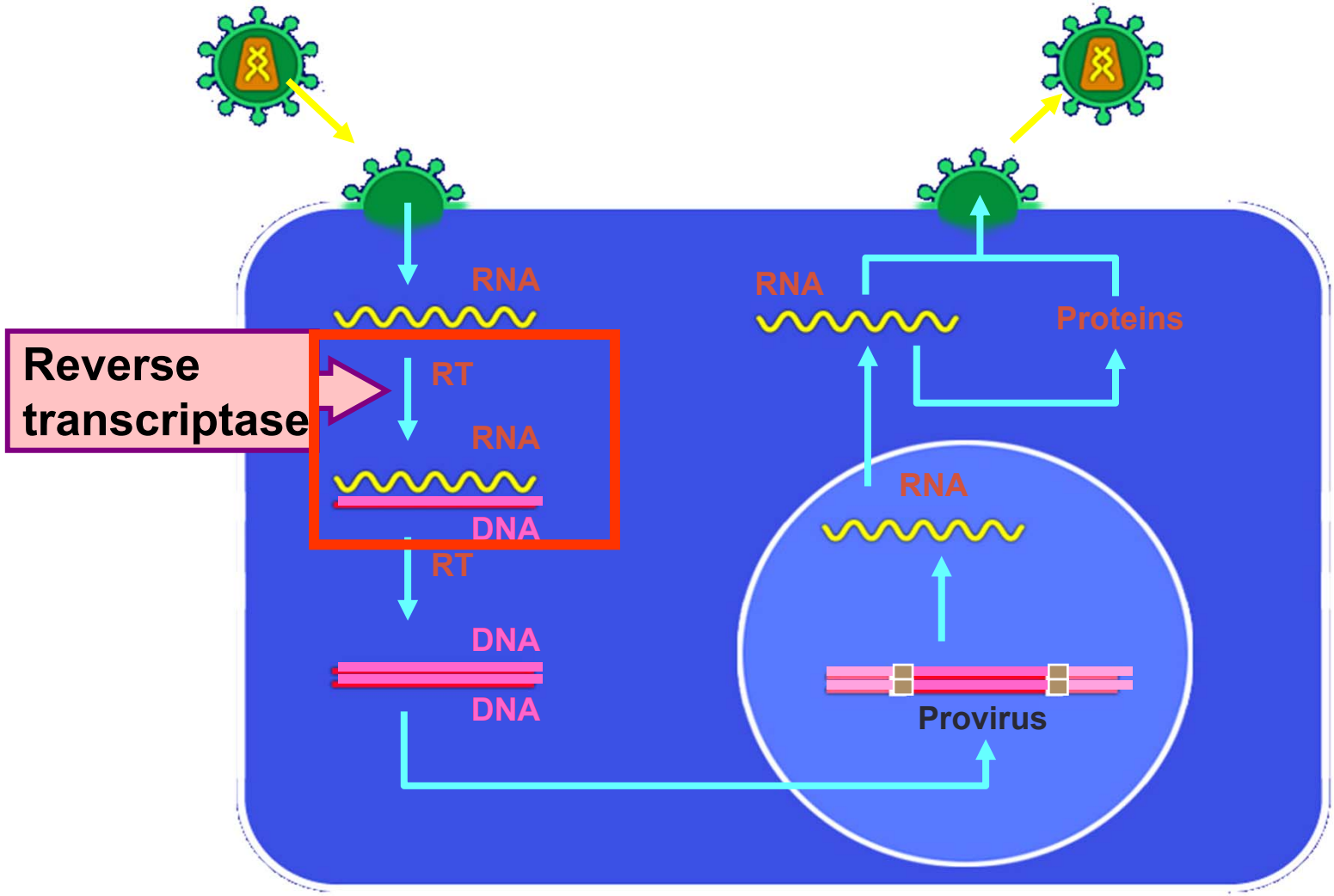
Resistant

Susceptible

Partial

Lanier R, *et al*. *10th CROI,* Boston 2003, #586

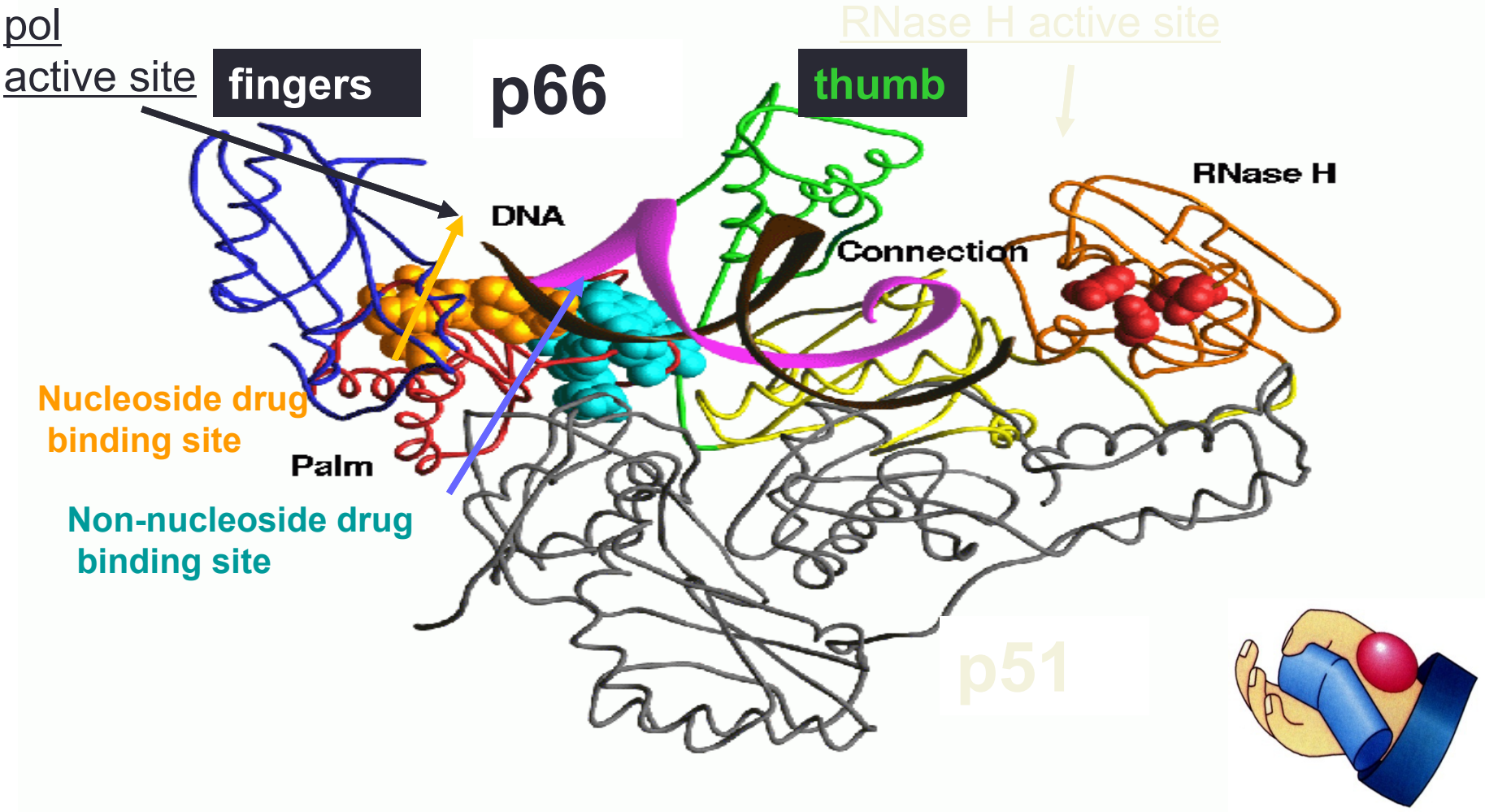
HIV-1 Lifecycle and Mechanisms of Action of Antiretroviral Agents



Currently Approved Non-nucleoside Reverse Transcriptase Inhibitors (NNRTIs) in the U.S.

Drug	Other Names	Year Approved
Nevirapine	(Viramune)	1996
Delavridine	(Rescriptor)	1996
Efavirenz	(Sustiva)	1998
Etravirine	(Intelence)	2008
Rilpivirine	(Edurant)	2011

Crystal Structure of HIV Reverse Transcriptase



Adverse Effects of NNRTIs

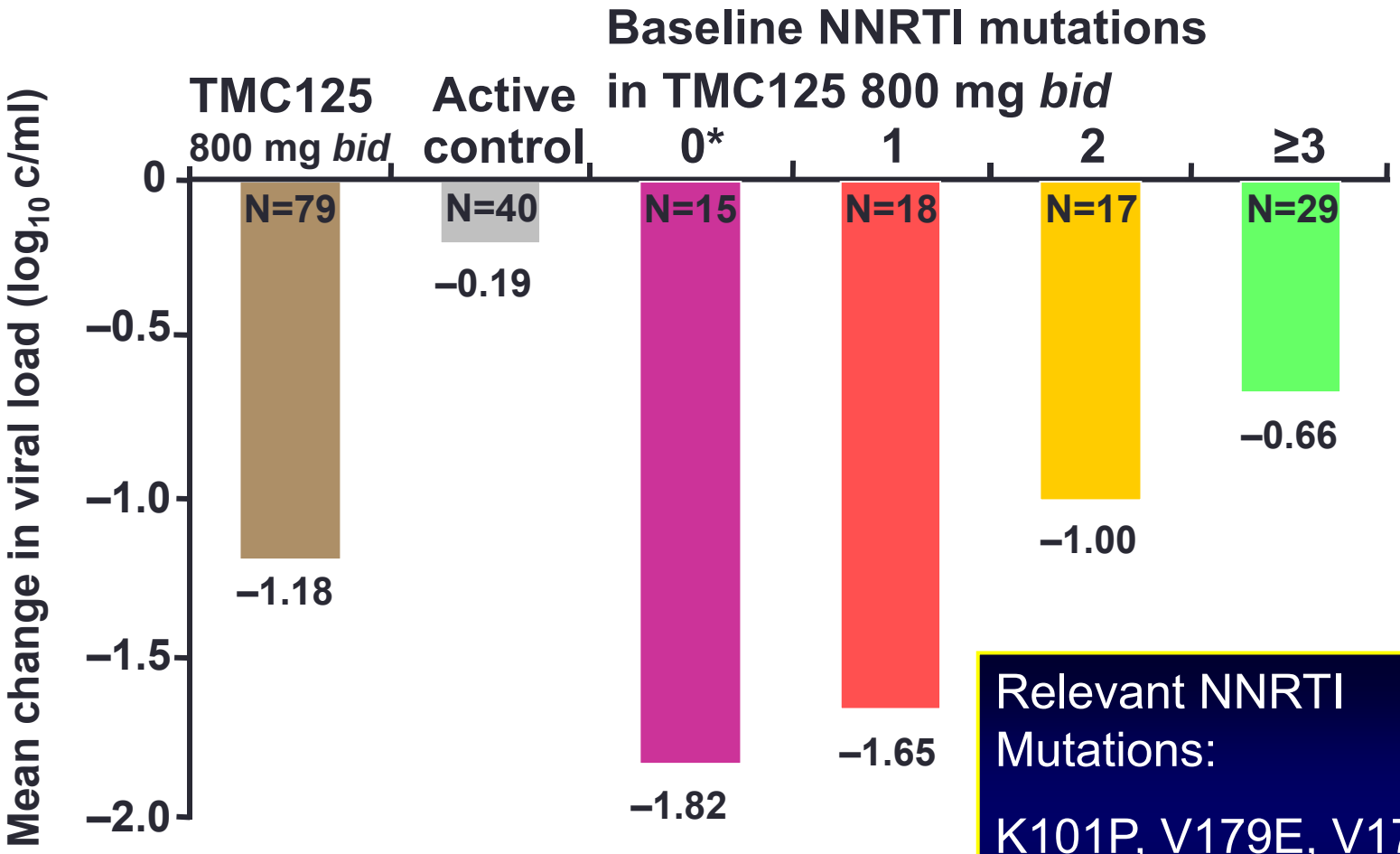
- Rash
  - Occurs in 15-30% of patients
  - Discontinuation of therapy due to rash
    - Nevirapine - 7%
    - Delavirdine - 4%
    - Efavirenz - 1.7%
    - Etravirine – 2%
    - Rilpivirine – 0.1%
- Hepatotoxicity
  - With NVP, seen in higher incidence and contraindicated in
    - Men CD4 > 400
    - Women CD4 > 250
  - Can see in Efavirenz and Etravirine
    - Especially in Hep B/C co-infection
- CNS side effects with Efavirenz

NNRTI Resistance Mutations

Low Mutation Theshold

- Nevirapine 100, 101, 103, 106, 108, 181, 188, 190
- Delavirdine 103, 106, 181, 188, 236
- Efavirenz 100, 101,103, 106, 108, 181, 188, 190, 225
- Etravirine 90, 98, 100, 101, 106, 138,179, 181, 190, 230
- Rilpivirine 90, 100, 101, 138, 179, 181, 189, 190, 221, 227, 230

Etravirine - Number of NNRTI Mutations and Virologic Response at Week 24



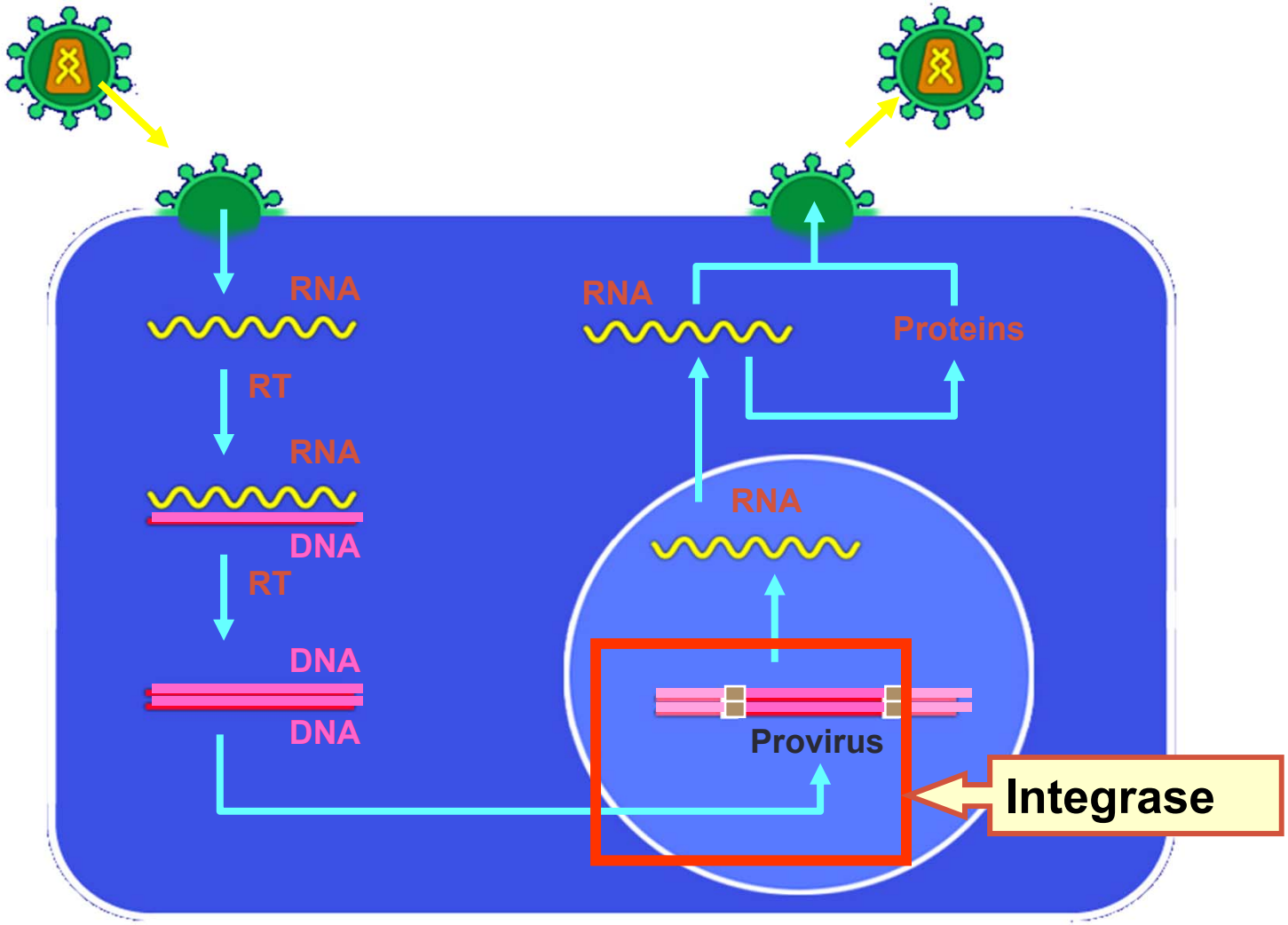
*All subjects had NNRTI mutations from prior genotyping

Vingerhoets J, et al. 13th CROI, Denver, CO, February 5-8, 2006. Abst. 154

Relevant NNRTI Mutations:

K101P, V179E, V179F, Y181I, Y181V, G190S, M230L

HIV-1 Lifecycle and Mechanisms of Action of Antiretroviral Agents



Currently Approved Integrase Inhibitors (INSTIs) in the U.S.

Drug	Other Names	Year Approved
Raltegravir	(Isentress)	2007
Elvitegravir (Coformulated with TDF/FTC and cobicistat only)	(Stribild)	2012
Dolutegravir (Coformulated with ABC/3TC as well as individual agent)	(Tivicay)	2013

Raltegravir Adverse Effects

- Diarrhea
- Nausea
- Headache
- Fever
- Fatigue Abd pain
- Dizziness
- Higher rate of worsening AST, ALT or bilirubin vs. placebo
- Rash

- Toxicities Seen in Trials with Unknown Relationship
  - Malignancies
  - Myopathy
  - Rhabdomyolysis
  - Hypersensitivity
    - Able to rechallenge

Elvitegravir + TDF/FTC/Cobicistat Adverse Effects

- Diarrhea
- Nausea
- Abnormal dreams
- Headache
- Fatigue
- Dizziness
- Rash
- Upper respiratory tract infection

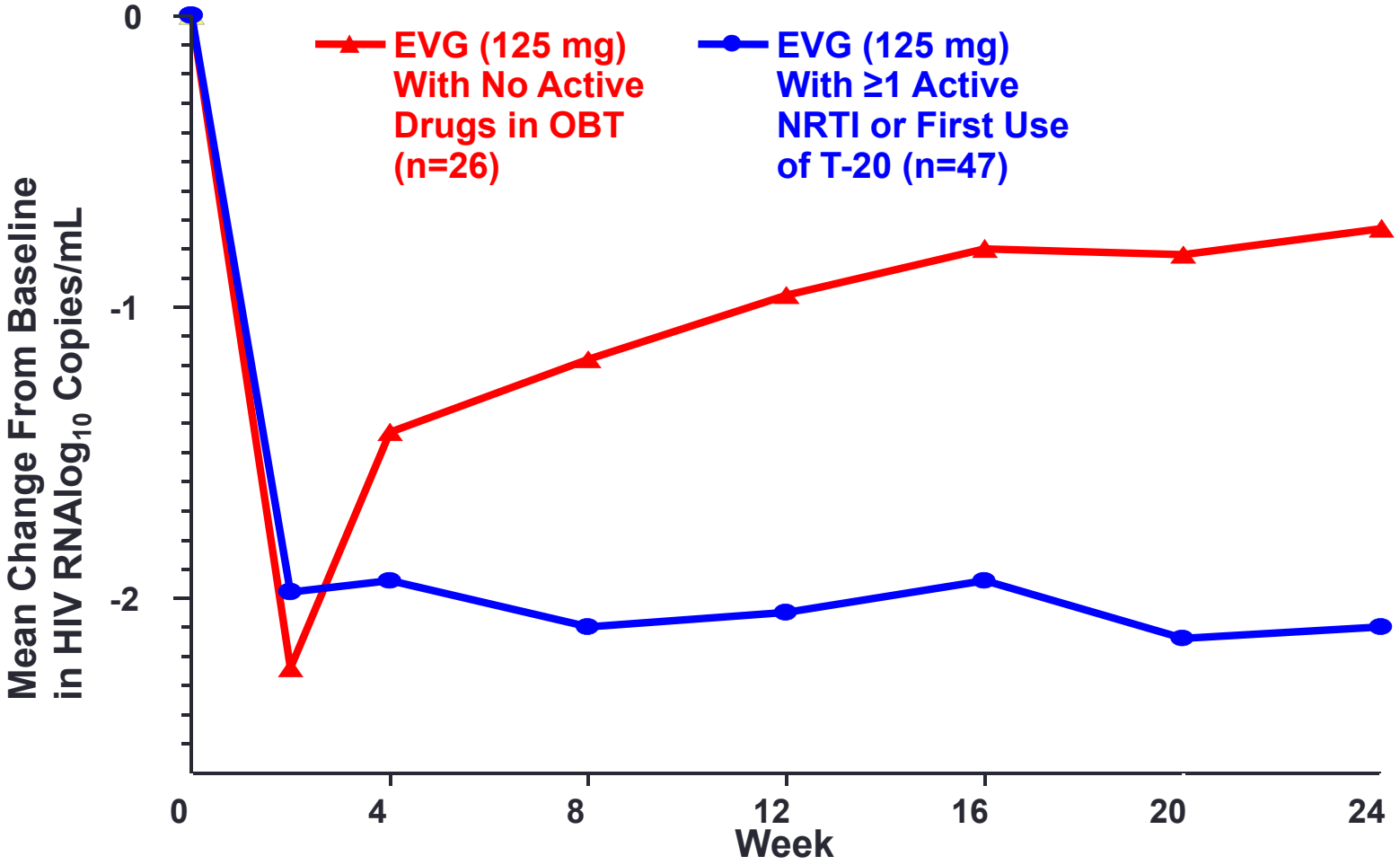
- Renal abnormalities
  - Cobicistat
    - Increases serum creatinine and decrease estimated creatinine clearance (through inhibition of tubular secretion of creatinine)
    - No effect on actual GFR

Dolutegravir Adverse Effects

- Diarrhea
- Nausea
- Headache
- Fever
- Fatigue
- Abd pain
- Dizziness
- Increased AST, ALT or bilirubin

- Renal abnormalities
  - 9-13% decrease in Creatinine clearance
  - No change in actual GFR by Iohexol

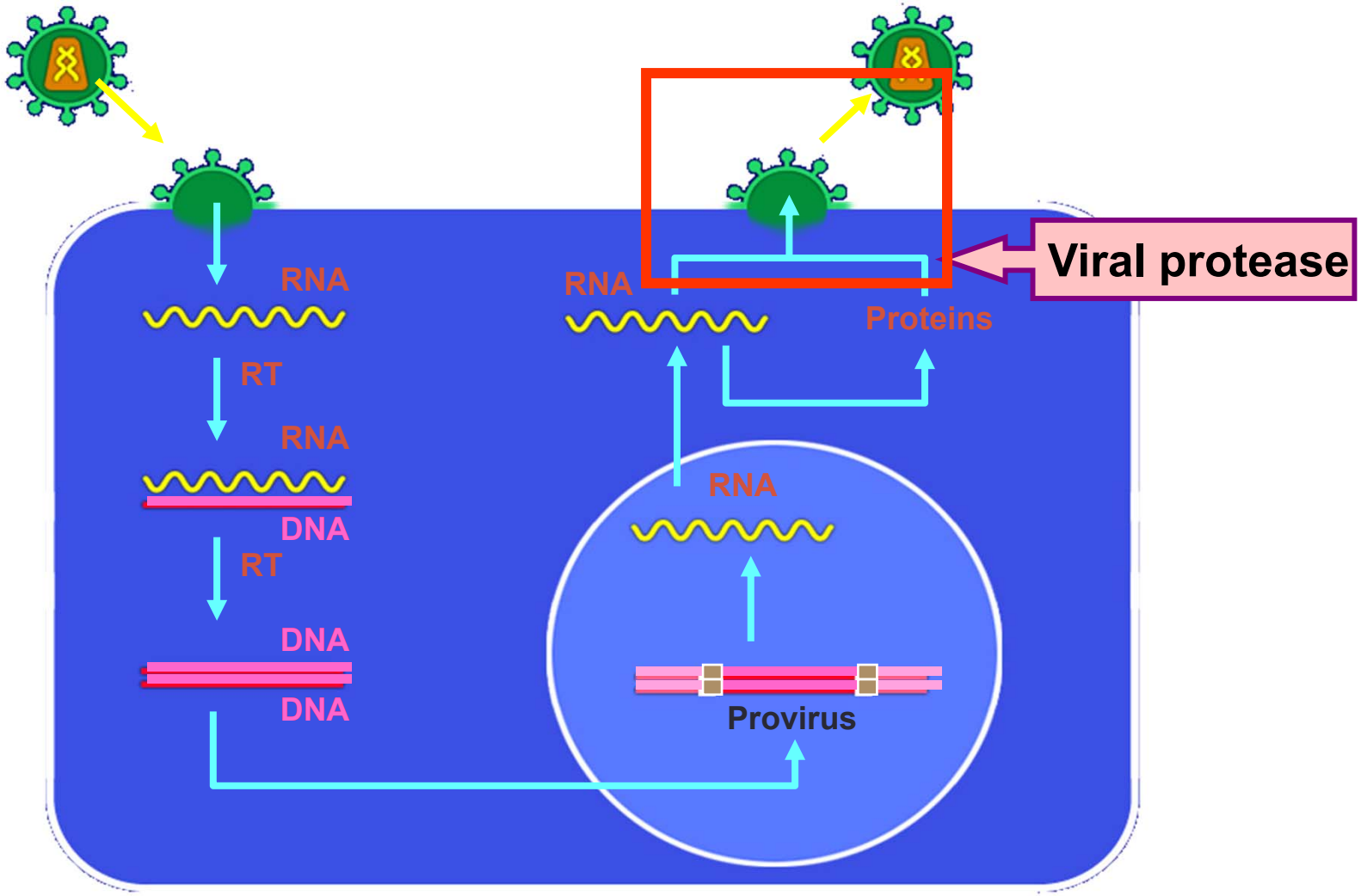
Change in HIV RNA With Elvitegravir (125 mg) Influence of Activity of OBT*



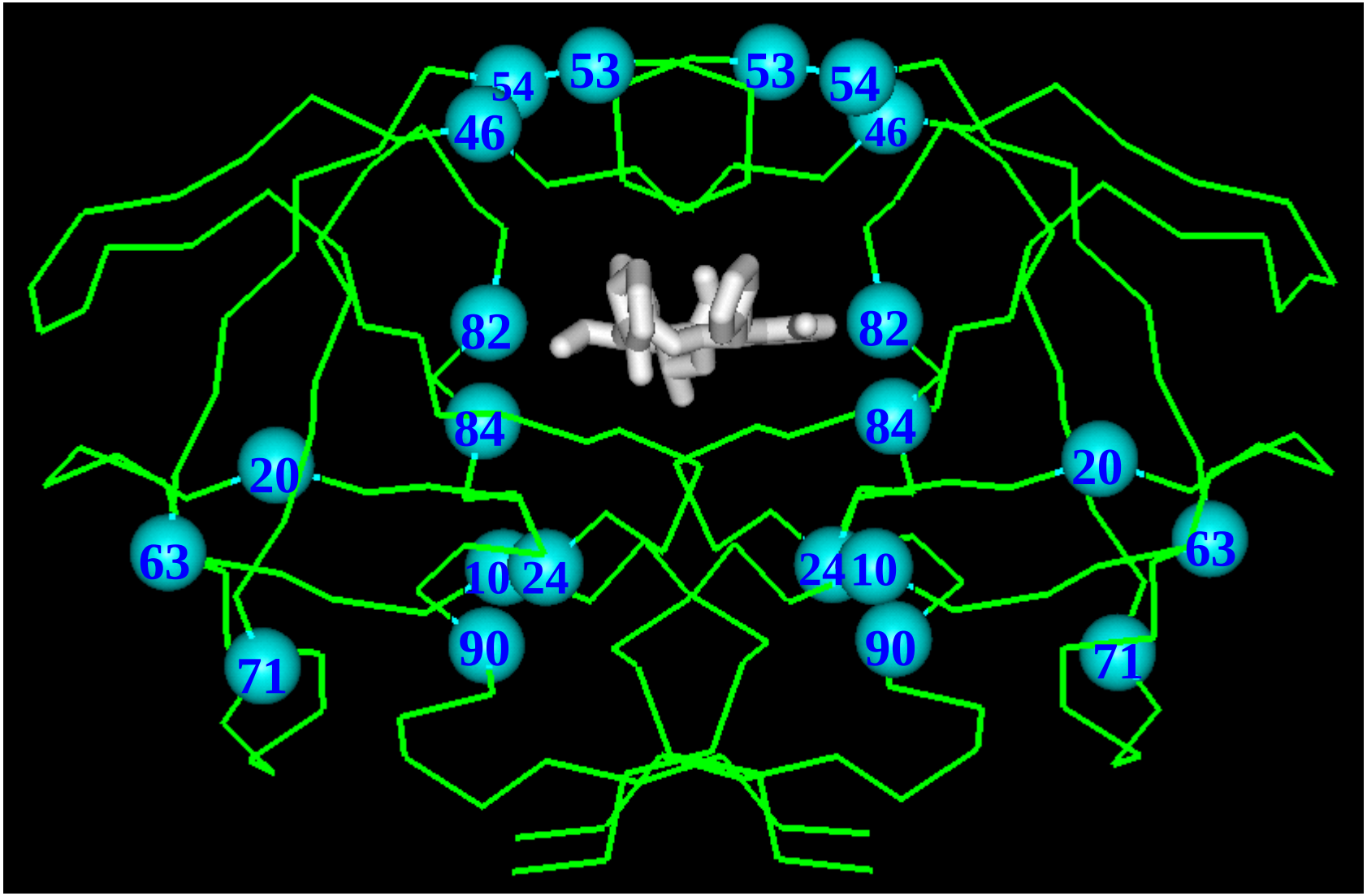
*Data from EVG (125 mg) patients after addition of a PI were excluded

Zolopa A, et al. 14th CROI, Los Angeles, CA, February 25-28, 2007. Abst. 143LB.

HIV-1 Lifecycle and Mechanisms of Action of Antiretroviral Agents



Protease Inhibitors are Competitive Inhibitors of the Protease

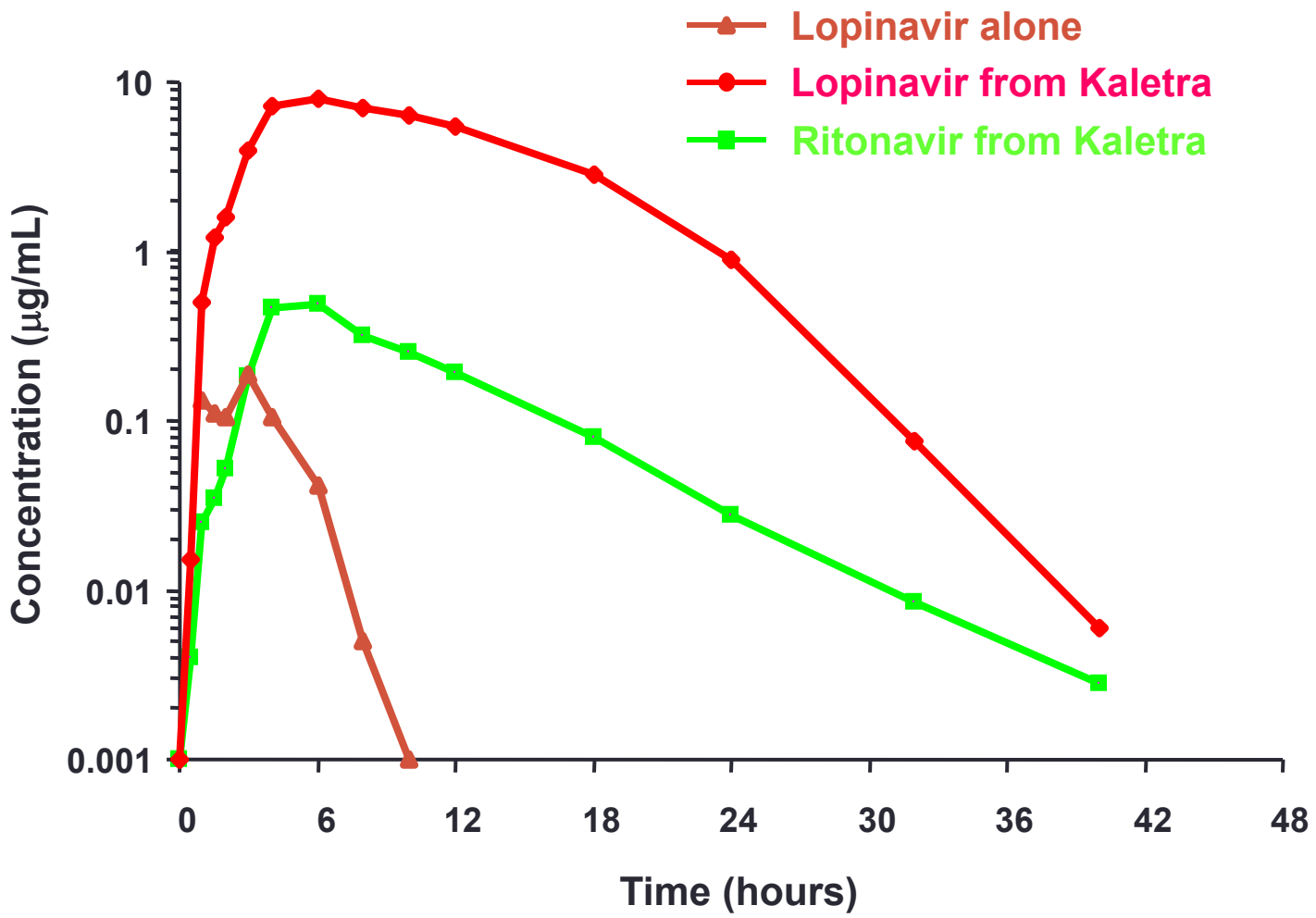


Kempf D, et al. Abstract 129, First IAS Conference on HIV Pathogenesis and Treatment, July 8-11, 2001.

Currently Approved Protease Inhibitors in the U.S.

Drug	Other Name	Year Approved
Saquinavir	(Invirase)	1995
Ritonavir	(Norvir)	1996
Indinavir	(Crixivan)	1996
Nelfinavir	(Viracept)	1997
Amprenavir	(Agenerase)	1999
Lopinavir/ritonavir	(ABT378, Kaletra)	2001
Atazanavir	(BMS232632,Reyataz)	2003
fosAmprenavir	(GW433908, Lexiva)	2003
Tipranavir	(Aptivus)	2005
Darunavir	(TMC-114, Prezista)	2006

Lopinavir and Lopinavir/r single dose pharmacokinetics in humans

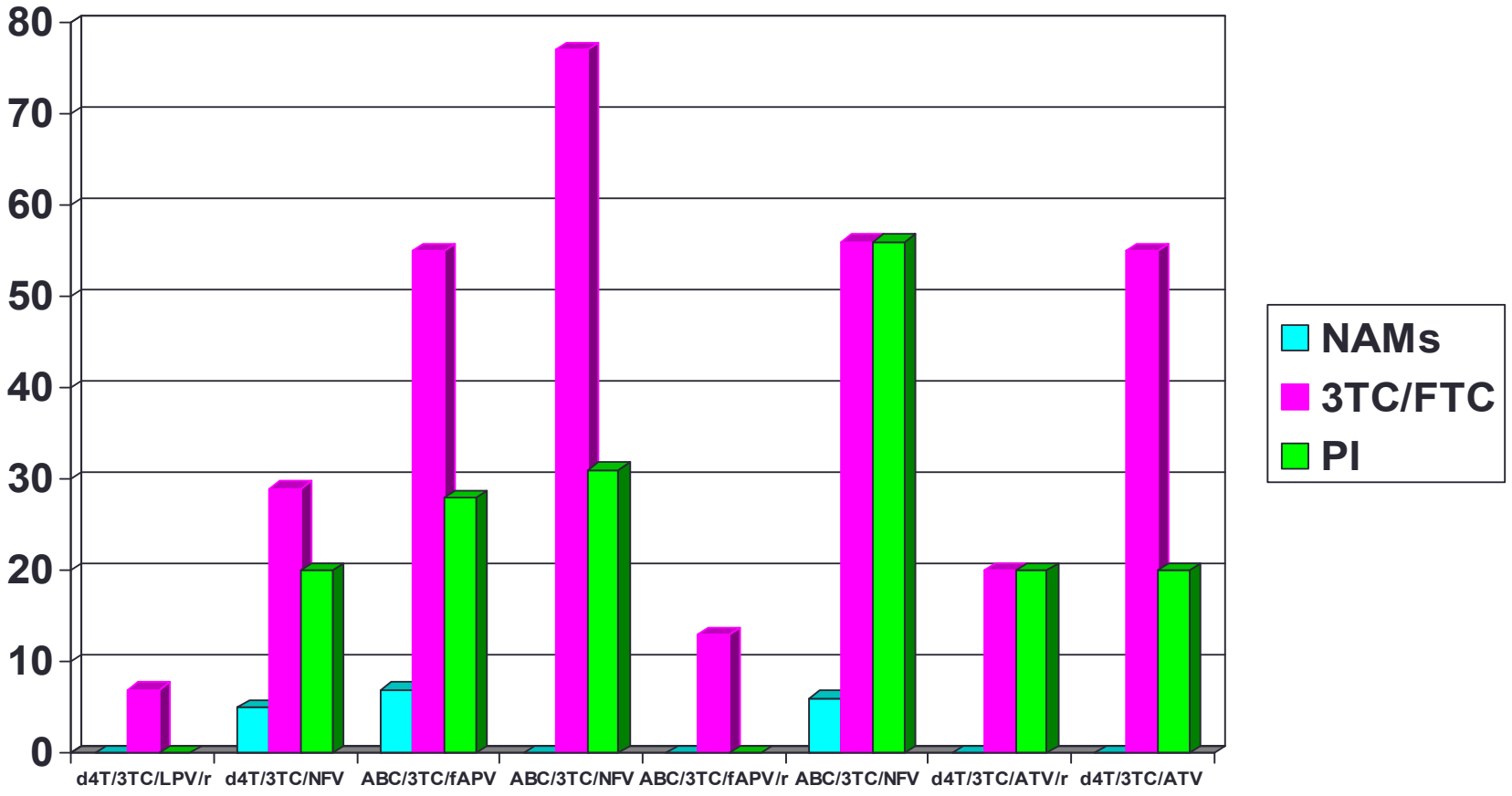


Reasons to Use a Boosted PI

- Potency
- High Barrier to Resistance
  - May also protect other agents in combination regimen
- Pharmacokinetics
- Durability
- May protect against apoptosis
- May decrease immune activation

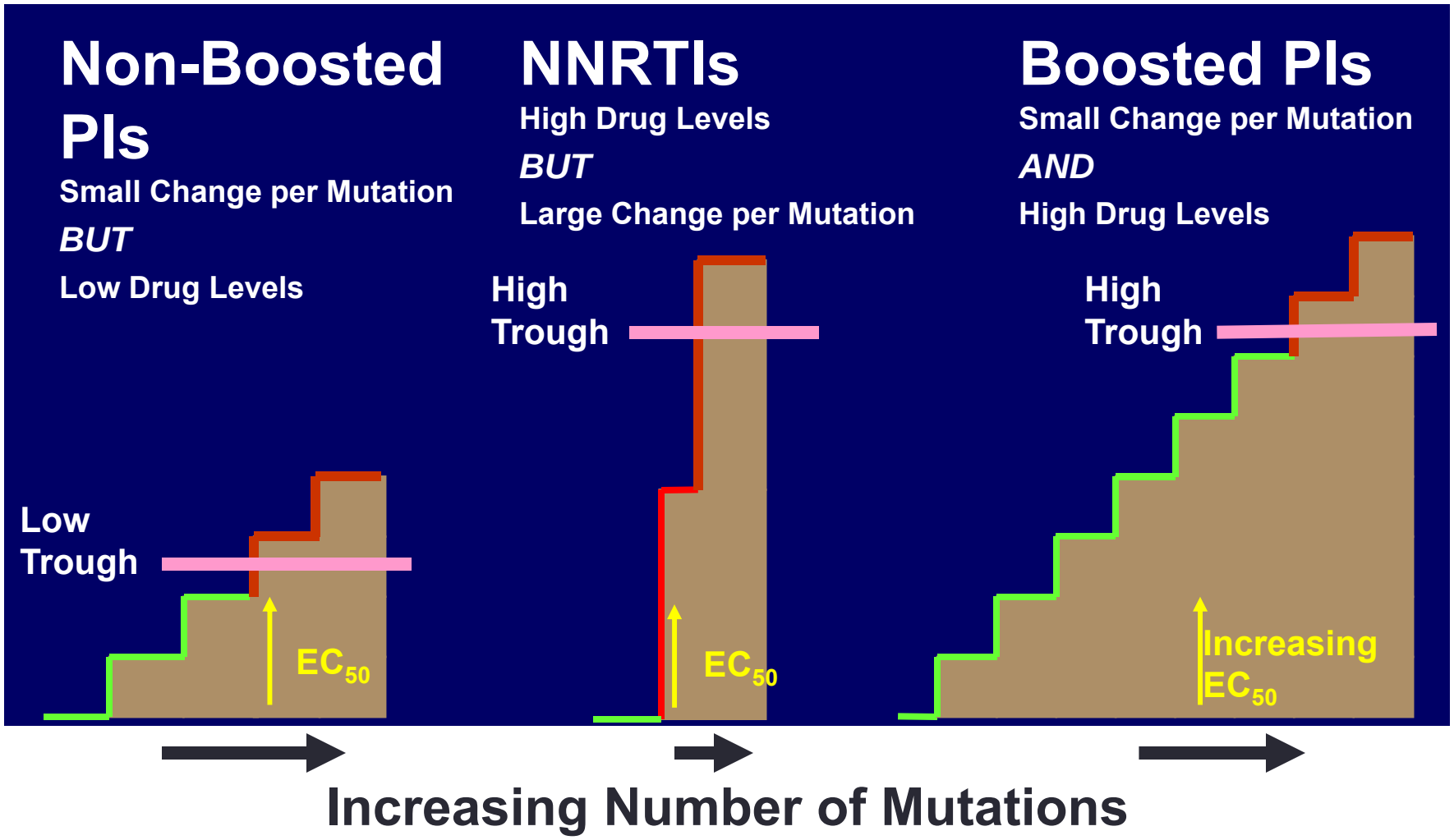
Mutations Acquired with Virologic Failure in Boosted vs. Non-boosted PIs

% Virologic Failures with Resistance



Kempf, et al, 10th CROI, Abstract 600, Macmanus, et al, 10th CROI, Abstract 598, Malan N, et al. IAS 2007. Abstract WEPEB024

Pharmacokinetic and Genetic Barriers to Resistance



Boosted vs. Unboosted PIs?

Desirable Factors	**Boosted**	**Unboosted**
Potency	x	
Durability	x	
Prevent Resistance	x	
High Drug Levels	x	
Once Daily in Naives*	x	x (ATV)
RTV(↓apoptosis/Immun Act)	x	
Undesirable Factors		
RTV (side effects/toxicities)	x	
Drug-drug Interactions	xx	x

* Applies to LPV/r, fAPV/r, SQV/r; No data with ATV/r in naives. ATV only unboosted QD PI

Medications That Interact with Protease Inhibitors

- Meperidine, Piroxicam
- Clarithromycin, Erythromycin, Flagyl
- Coumadin
- Phenytoin, Phenobarbital
- Azoles (i.e., fluconazole)
- Astemizole, Terfenadine
- Clofibrate
- Isoniazid, Rifampin, Rifabutin
- Anthracyclines, Tamoxifen
- Amiodarone,Amlodipine, Diltiazem, Flecainide, Nifedipine, Propafenone, Quinidine, Verapamil
- Corticosteroids (including some nasal steroids)
- Ergot alkaloids
- Estrogens
- Cimetidine, Cisapride
- Quinine
- Alfentanil, Fentanyl, Methadone
- Clozapine, Desipramine, Sertaline
- Alprazolam, Clorazepate, Diazepam, Flurazepam, Midazolam, Triazolam, Zolpidem
- Sildenafil, Tadalafil, Vardenafil

Drug-drug Interactions with Atazanavir

- Decreased ATV levels
  - Proton pump inhibitors
  - Antacids/H2 Blockers
  - Rifampin
  - St. John's Wort

  - Tenofovir
  - Didanosine
  - NVP, EFZ

- Increased Drug levels
  - Antiarrhythmics
  - Benzodiazepines
  - Calcium Channel Blockers
  - Cisapride
  - HMG CoA Reductase inhibitors
  - Pimozide
  - PDE5 Inhibitors
  - Tricyclic antidepressants
  - Warfarin

Nasal Steroid Metabolism

- P450 Metabolism
- RTV Contraindicated
  - Budesonide
  - Fluticasone
  - Mometasone
- Not P450 Metabolized
- Safe with RTV
  - Beclomethasone
  - Flunisolide
  - Triamcinolone

Case 2

- 32 y.o. African woman who was brought in by sisters for evaluation of HIV
- Diagnosed 3 years before with pregnancy
- CD4 390, RNA 194,000

- Started on ZDV/3TC, IDV, RTV
- RNA suppressed rapidly
- 1 year later
  - CD4 650, RNA < 50
  - Complains of clothes not fitting and changes in body appearance

Case 2

- Switched therapy to Trizivir (ZDV, ABC, 3TC)

- 2 years later
  - CD4 660, RNA < 50
  - Clothes size/appearance returned to baseline

Metabolic and Morphologic Complications of HIV and HAART

Wasting

Morphologic

- Fat accumulation
- Fat loss

Others

- Osteoporosis
- Osteopenia
- osteonecrosis

Metabolic

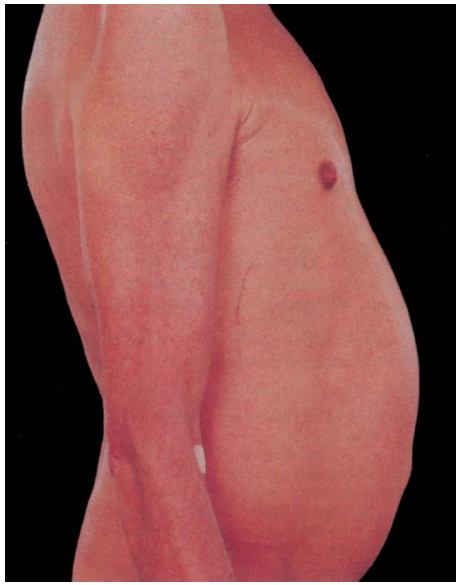
- Dyslipidemias

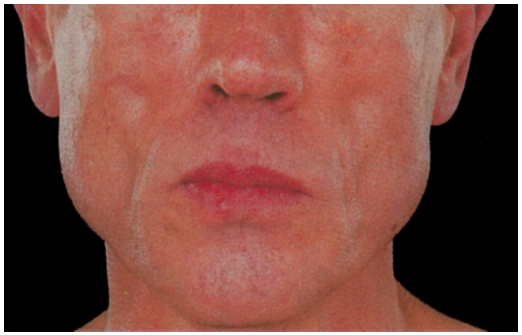
  -hypercholesteremia

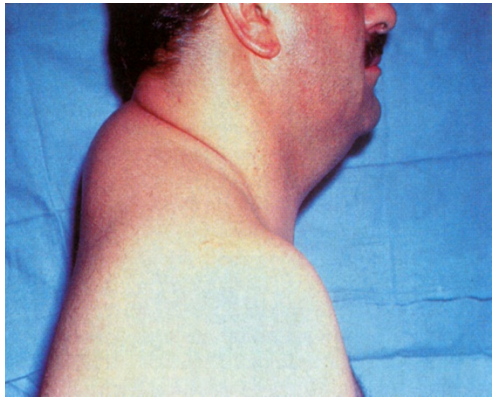
  -hyperlipidemia

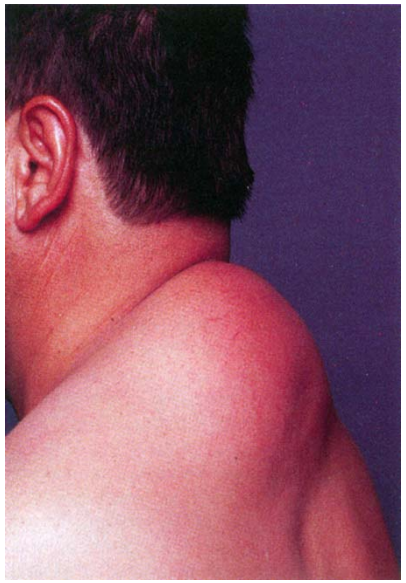
  -hypertriglyceridemia
- Impaired glucose tolerance/diabetes
- Lactic acidosis

Physical Manifestations of Lipodystrophy









Case 3

- 37 y.o. man who is an active duty soldier in the Army
- Recently diagnosed with HIV infection
- ARV naïve
- CD4 110, RNA 158,000

- Treated with d4T/3TC/IDV

- Wk 24: CD4 235, RNA <400

Case 3

- Patient is in the field on maneuvers frequently
- Begins experiencing a cramping flank pain, hematuria, and diarrhea
- Patient begins skipping second daily dose of d4T and IDV because of adverse events

- What is your diagnosis? What should you do?

IDV-associated genitourinary toxicity

- Patients with lower body mass index at greater risk for nephrolithiasis[1]
- Subclinical urinary abnormalities[2] (pyuria, hematuria, crystals) in 24/114 (21%) patients
  - abnormalities correlated with peak IDV levels; rate somewhat lower with IDV/RTV 400/400 mg BID dose
  - long-term significance unknown
- High rate (12% at 24 wks) of symptomatic nephrolithiasis with IDV/RTV 800/100 mg BID dose[3]

[1] Meraviglia P, *et al*. XIII IAC, Durban, 2000. Abstract 1312; [2] Dieleman J, *et al.* XIII IAC, Durban, 2000. Abstract 4264; [3] Gatell JM, *et al*. XIII IAC, Durban, 2000. Abstract 484

Research Letters

AIDS 2007, **21**:1207–1220

Atazanavir-associated nephrolithiasis: cases from the US Food and Drug Administration's Adverse Event Reporting System

Kirk M. Chan-Tack, Melissa M. Truffa, Kimberly A. Struble and Debra B. Birnkrant

The risk of nephrolithiasis associated with atazanavir is not well characterized. The US Food and Drug Administration's Adverse Event Reporting System was searched for reports of nephrolithiasis in HIV-infected patients taking an atazanavir-based regimen. Thirty cases were identified. Many patients required hospitalization for management, including lithotripsy, ureteral stent insertion, or endoscopic stone removal. Some cases of nephrolithiasis resulted in atazanavir discontinuation. Healthcare professionals and patients should be informed that nephrolithiasis is a possible adverse event with atazanavir.

ATV Nephrolithiasis

- December 2002 – January 2007
- 30 cases of nephrolithiasis in patients on ATV
- 21 men, 5 women, 4 not reported
- 5 had history of nephrolithiasis
- 5 with Hep B or C
- 14 with stone analysis; 12 had ATV in stone
- Median time on ATV 1.7 yrs (5 wks-6 yrs)
- 18 hospitalized
- 8 with procedure for stone removal

Other Adverse Effects of Protease Inhibitors

- Headache
- Insomnia
- Paresthesias
- Increased LFTs
  - Ritonavir
  - Tipranavir (Black Box warning)
- Diarrhea
  - Nelfinavir
- GI toxicities (anorexia, nausea, vomiting, abd pain)
- Intracranial Hemorrhage
  - Tipranavir (Black box warning)
- Rash
  - Fosamprenavir
  - Darunavir
  - Atazanavir
- Increased Bilirubin
  - Indinavir, Atazanavir
- Nephrolithiasis
  - Indinavir, Atazanavir

Protease Resistance Mutations

- Indinavir 10, 20, 24, 32, 36, 46, 54, 71, 73, 76, 77, 82, 84, 90
- Nelfinavir 10, 30, 36, 46, 71, 77, 82, 84, 88, 90
- Ritonavir 10, 20, 32, 33, 36, 46, 54, 71, 77, 82, 84, 90
- Saquinavir 10, 24, 48, 54, 62, 71, 73, 77, 82, 84, 90
- Fosamprenavir 10, 32, 46, 47, 50V, 54, 73, 76, 82, 84, 90
- Lopinavir/r 10, 20, 24, 32, 33, 46, 47, 50, 53, 54, 63, 71, 73, 76, 82,84, 90
- Atazanavir 10, 16, 20, 24, 32, 33, 34, 36, 46, 48, 50L, 53, 54, 60, 62, 64, 71, 73, 82, 84, 85, 88, 90, 93
- Tipranavir/r 10, 13, 20, 33, 35, 36, 43, 46, 47, 54, 58, 69,74, 82, 83, 84, 90
- Darunavir/r 11, 32, 33, 47, 50, 54, 74, 76, 84, 89

Pregnancy Risk

Category	Example	Description
A	**None**	**(Controlled studies…no risk in humans)**
B	**ddI, TDF, FTC, NFV DRV, RTV, SQV, ATV MVC, ETV, RPV, EVG Cobicistat, DTG**	**(Animal studies…no abnormalities but no human studies)**
C	**ZDV, ddC, d4T, 3TC ABC, NVP, DLV, IDV, APV, fAPV, LPV/r TPV, RAL**	**(Animal studies reveal fetal abnormalities but no human studies, use only if benefit > risk)**
D	**EFV Hydroxyurea**	**Human fetal risk but benefit > risk**

Summary

- Knowledge of how agents work can help understand their limitations/toxicities
- Some toxicities can occur across all classes
  - GI disturbances
  - Headache
  - Fatigue
- Careful choice of agents can minimize the impact of toxicities on adherence/treatment success