Antiretroviral Drugs

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Disclosures

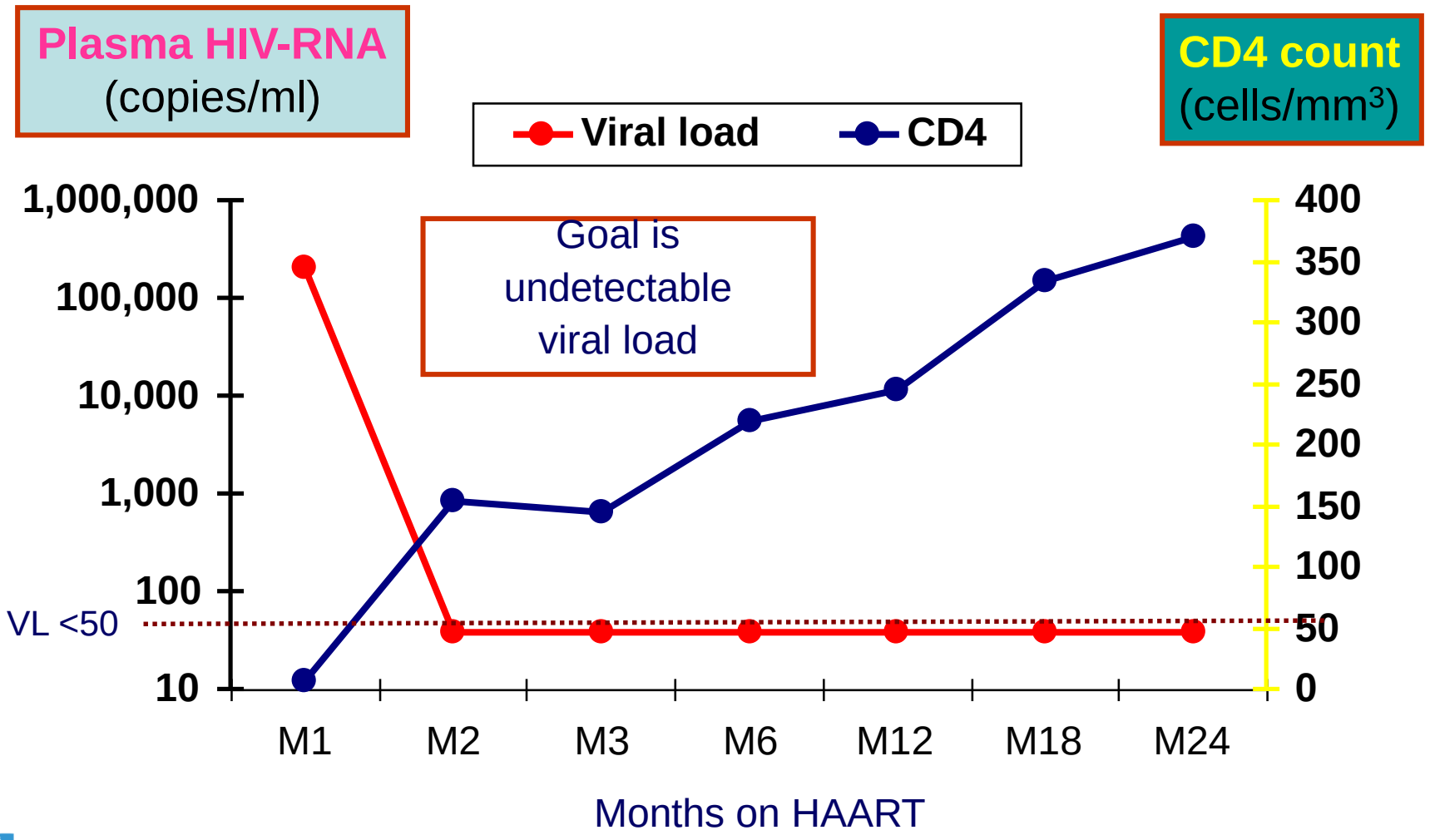
Speaker Bureau / Honoraria:

ViiV Healthcare, Merck Sharpe and Dohme, Gilead, Janssen Cilag (Tibotec), Bristol Myers Squibb

Research funding / educational grants:

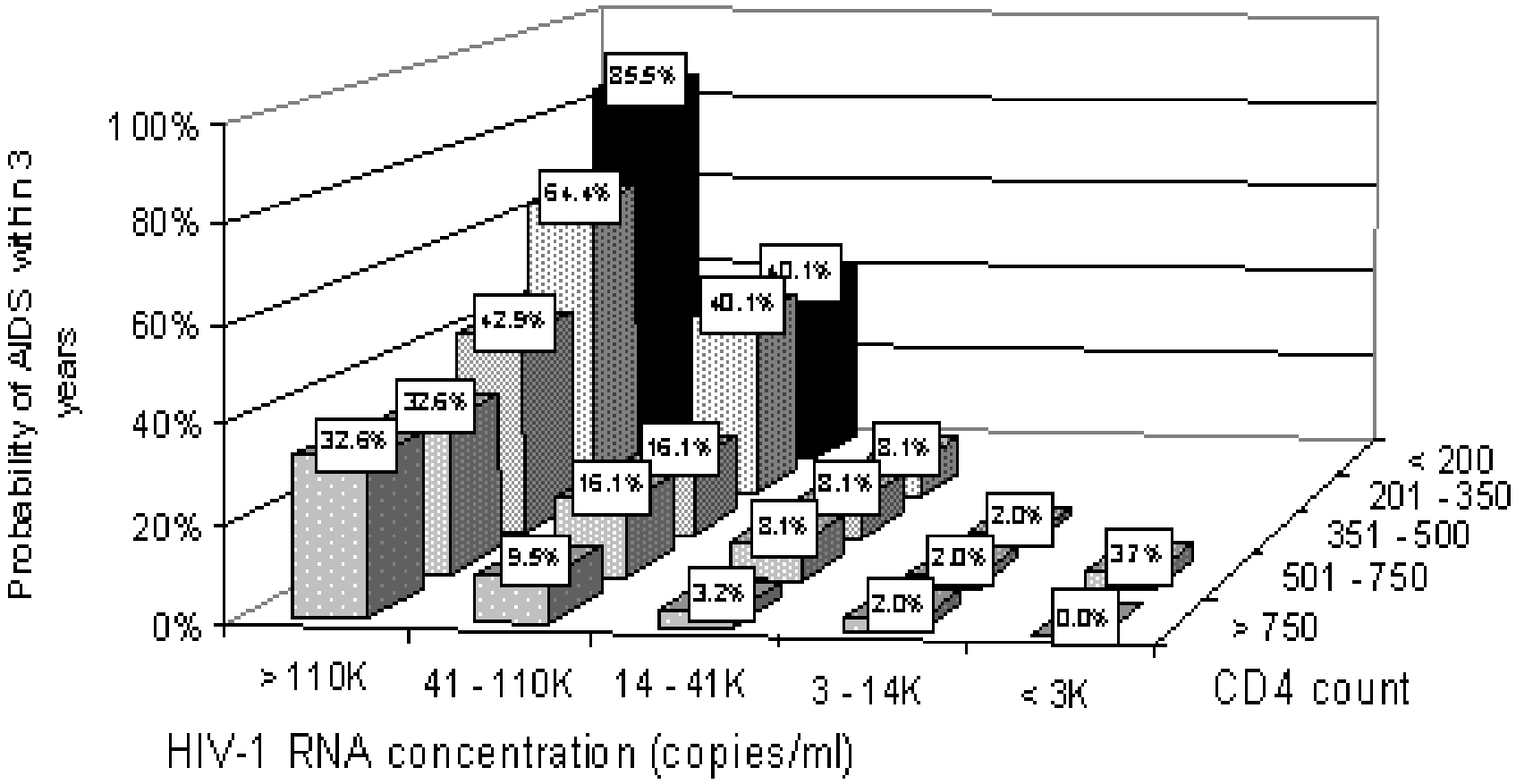
- Science Foundation Ireland
- Health Research Board (Ireland)
- Molecular Medicine Ireland
- GlaxoSmithKline
- Gilead Sciences
- Bristol Myers Squibb
- Janssen Cilag (Tibotec)
- Merck Sharpe and Dohme

Goals of antiretroviral therapy ART



What effect does ART have?

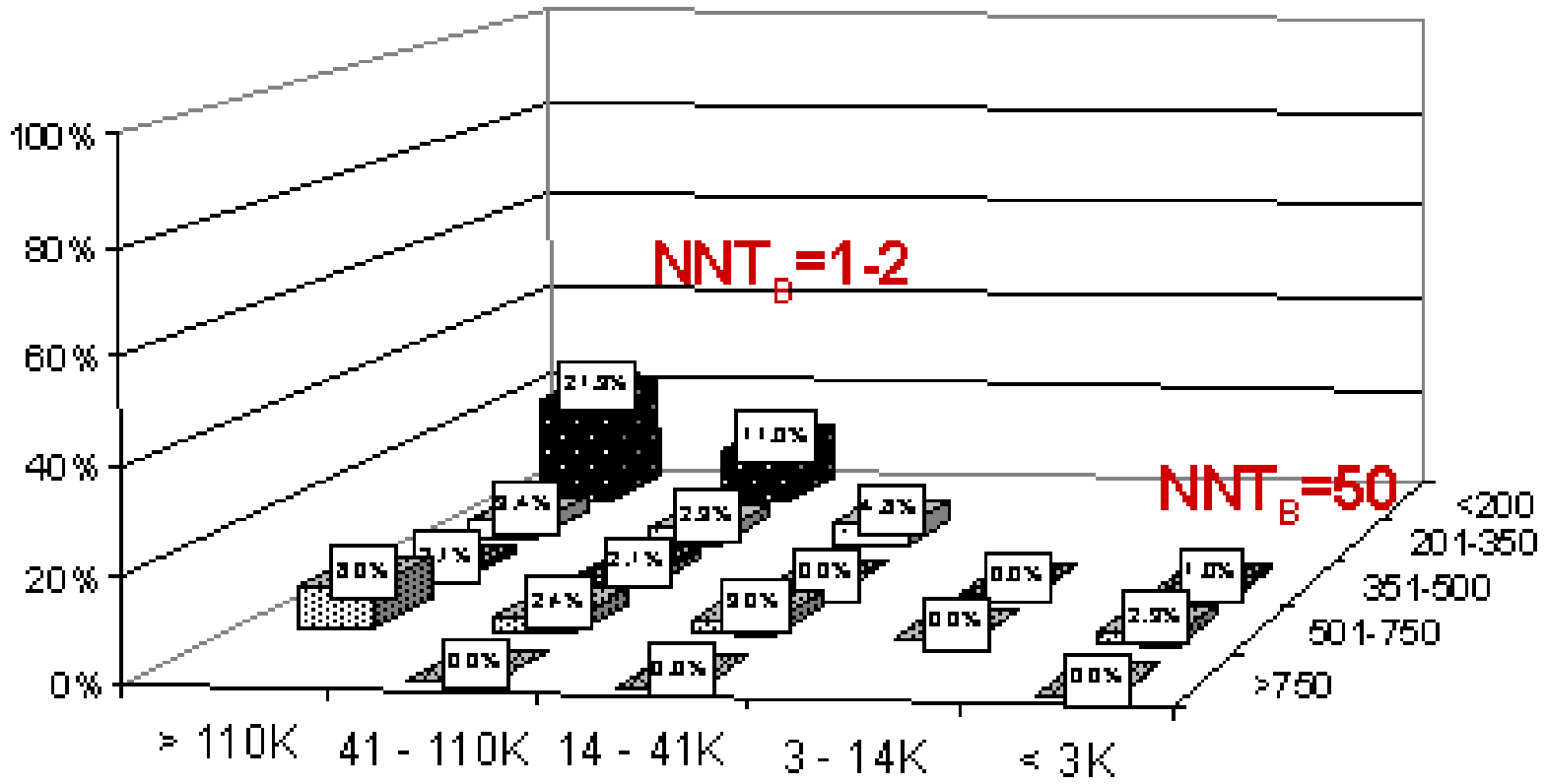
3 year risk of AIDS without treatment



Egger et al. *AIDS* 2001

What effect does ART have?

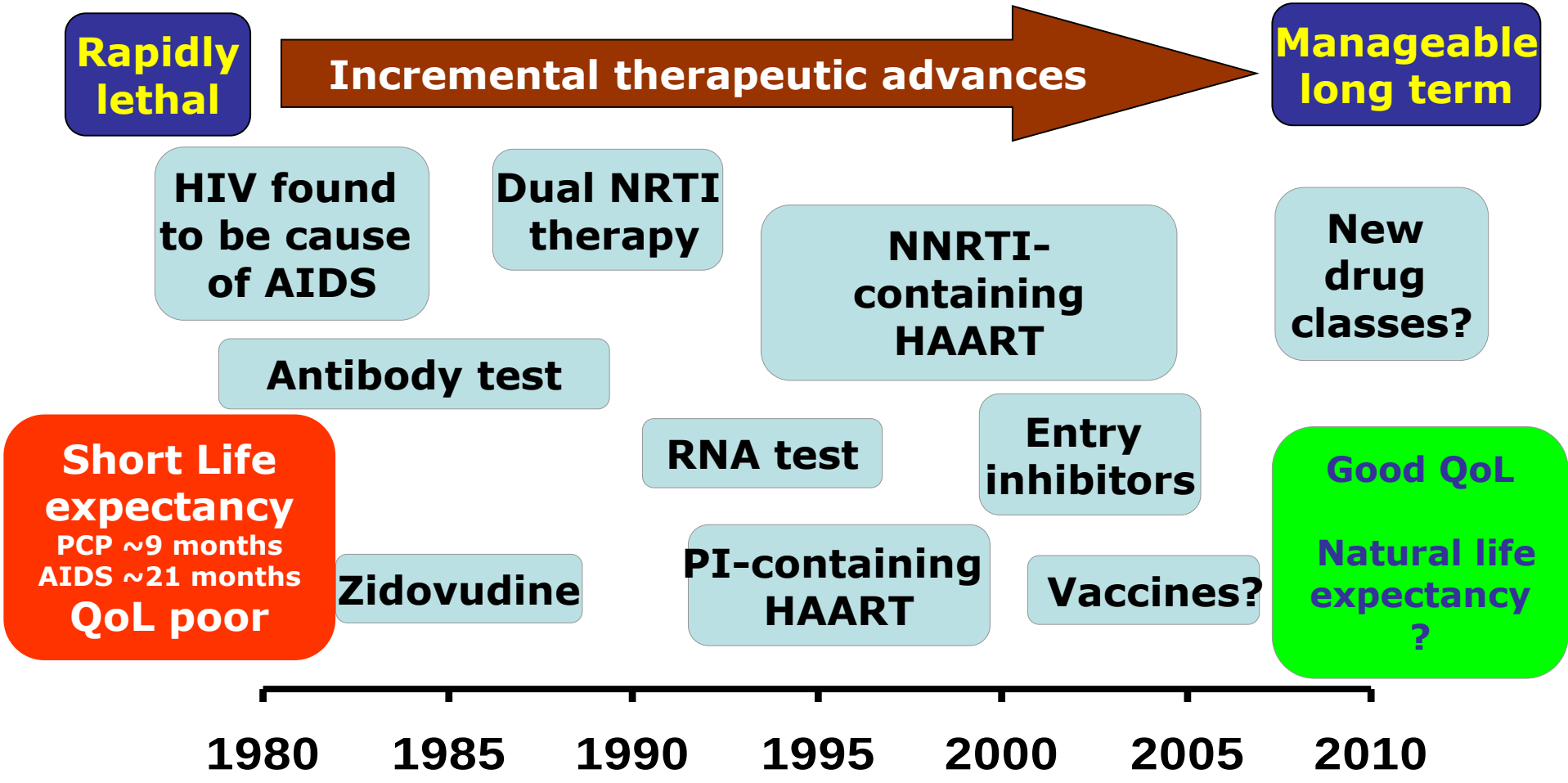
3 year risk of AIDS with HAART



Egger et al. *AIDS* 2001

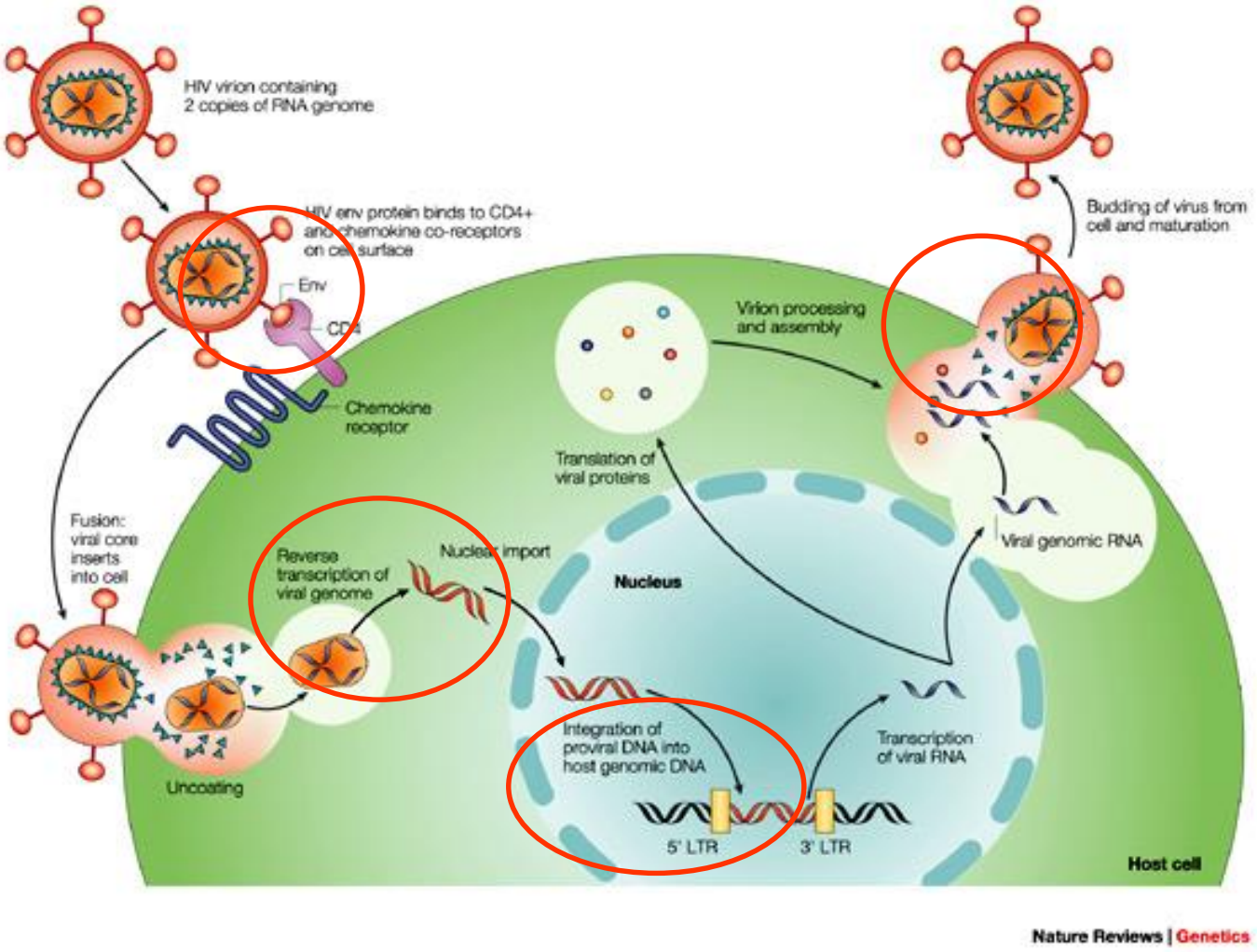
Evolution of treatment for HIV infection

From mortality to long-term manageability

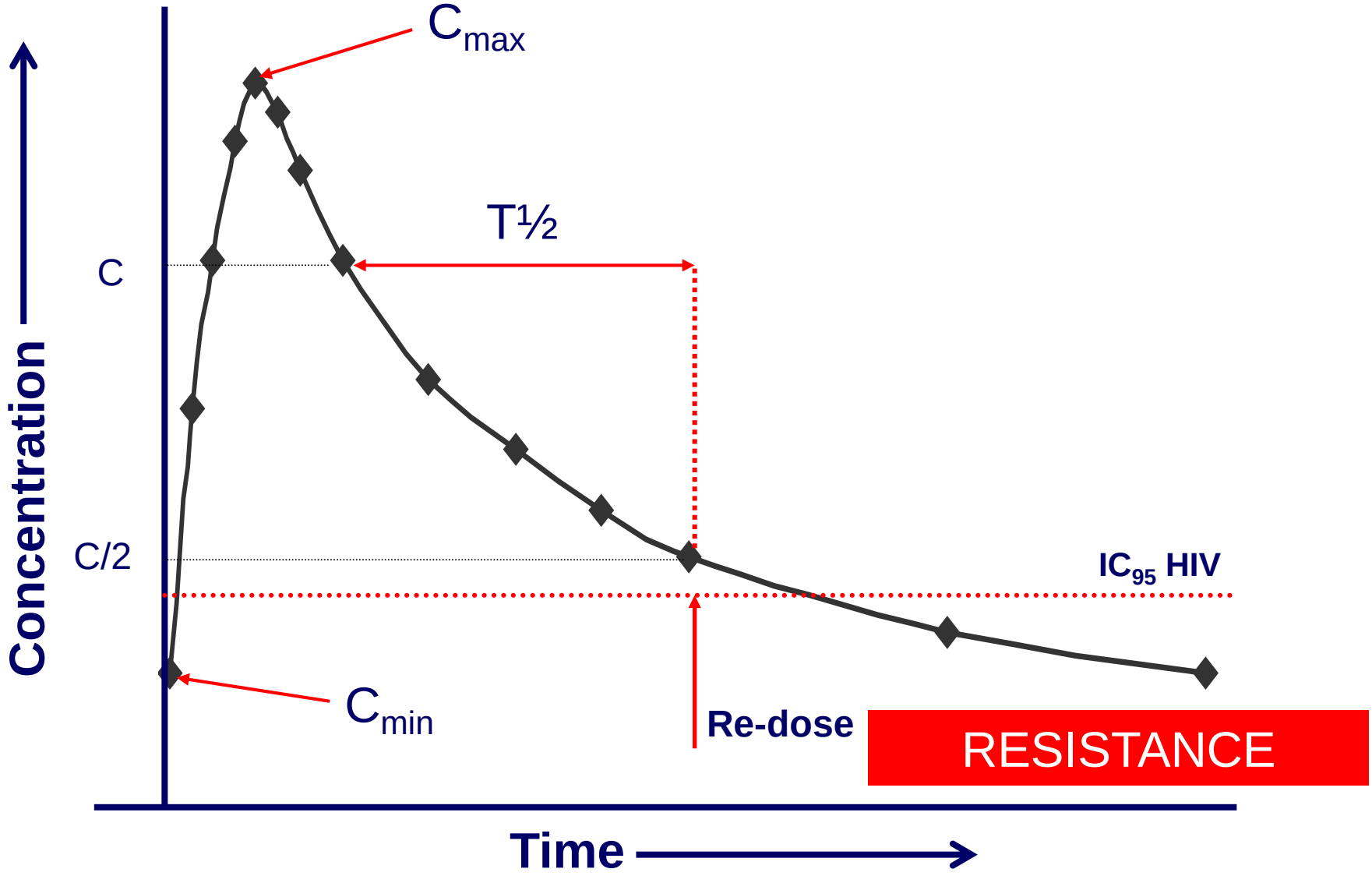


Concept of ART

- Inhibit HIV replication
- Target replication at >1 target



Basic pharmacology of ART



Principal antiretroviral drug classes

- Nucleoside reverse transcriptase inhibitors (NRTI)
- Non-nucleoside reverse transcriptase inhibitors (NNRTI)
- Protease inhibitors
- Integrase inhibitors
- Attachment inhibitors

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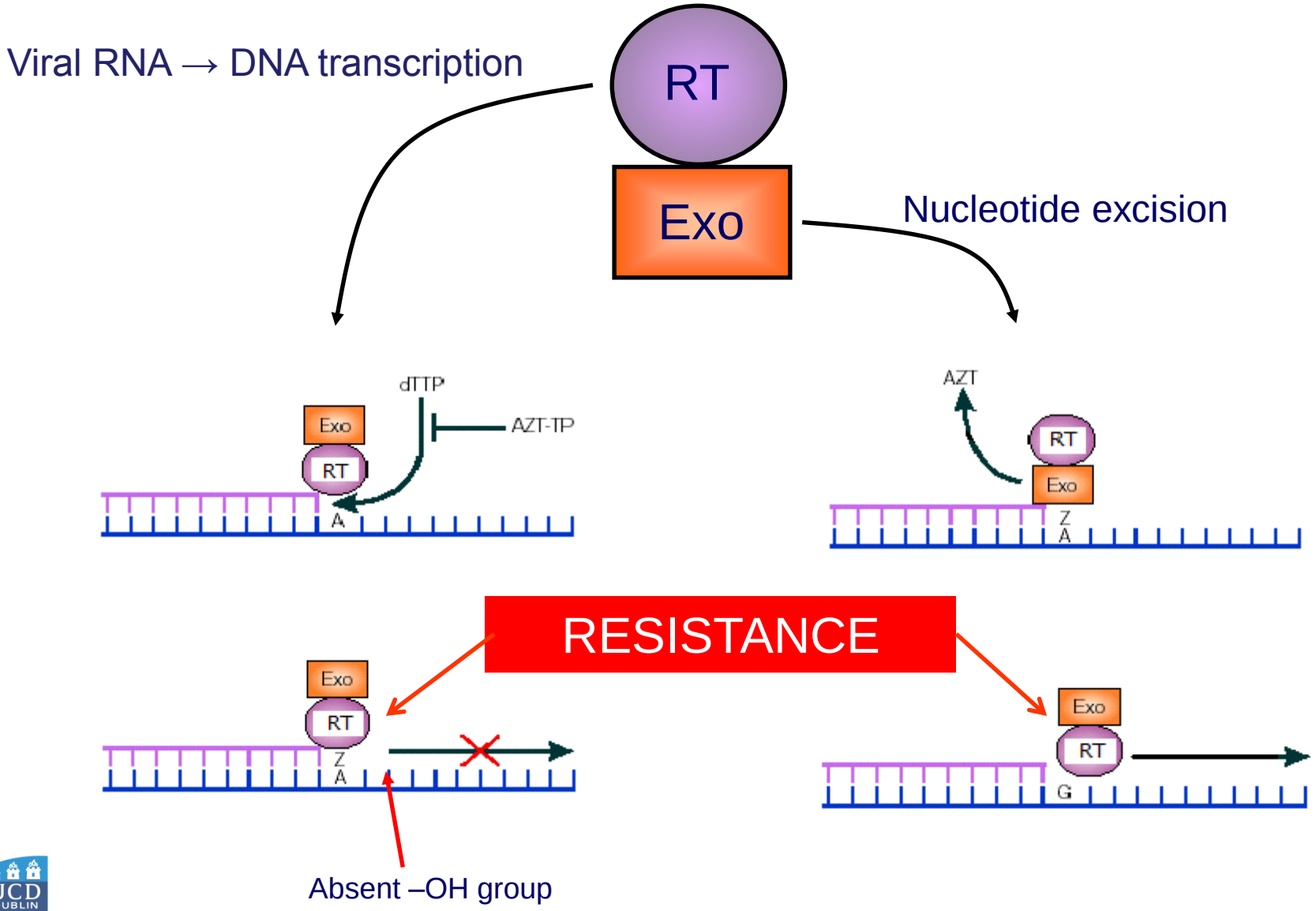
NRTI - mechanisms



Nucleoside Reverse Transcriptase Inhibitors

Class	Purine		Pyrimidine	
Endogenous nucleotide	adenosine	guanosine	cytosine	thymidine
Synthetic NRTI analogues	didanosine (ddI)	abacavir (ABC) (carbovir)	zalcitabine (ddC)	zidovudine (AZT)
	adefovir (PMEA)		lamivudine (3TC)	stavudine (d4T)
	tenofovir disoproxil fumarate (TDF)		emtricitabine (FTC)	

Kivexa®

Truvada®

NRTI resistance

- Signature mutations
  - Lamivudine / emtricitabine – M184V
    - Affects viral fitness
  - Tenofovir DF – K65R

- Thymidine-associated mutations (TAMS)
  - Accumulate with continued exposure to failing regimes
  - Can result in cross-class resistance

NRTI tolerability / toxicity

Abacavir

- Associated with hypersensitivity reaction
- Occurs in 4-8% subjects mostly within 6-12 weeks
- Fever, rash, abnormal LFT, abdominal symptoms
- Reduced by pre-screening HLAB*5701

- Association with CVD (RR approx 1.8)

Tenofovir DF

- Associated with renal / bone abnormalities
- Loss of BMD with initiation / switch
- Associations with fractures
- Renal tubular dysfunction (proteinuria / low PO4)
- Renal failure (rare)

Principal antiretroviral drug classes

- Nucleoside reverse transcriptase inhibitors (NRTI)
- Non-nucleoside reverse transcriptase inhibitors (NNRTI)
- Protease inhibitors
- Integrase inhibitors
- Attachment inhibitors

NNRTI – 1st generation

- Bind directly to the HIV reverse transcriptase active site
- Long half lives – QD dosing
- Low genetic barrier to resistance
- High levels of cross class resistance

Efavirenz

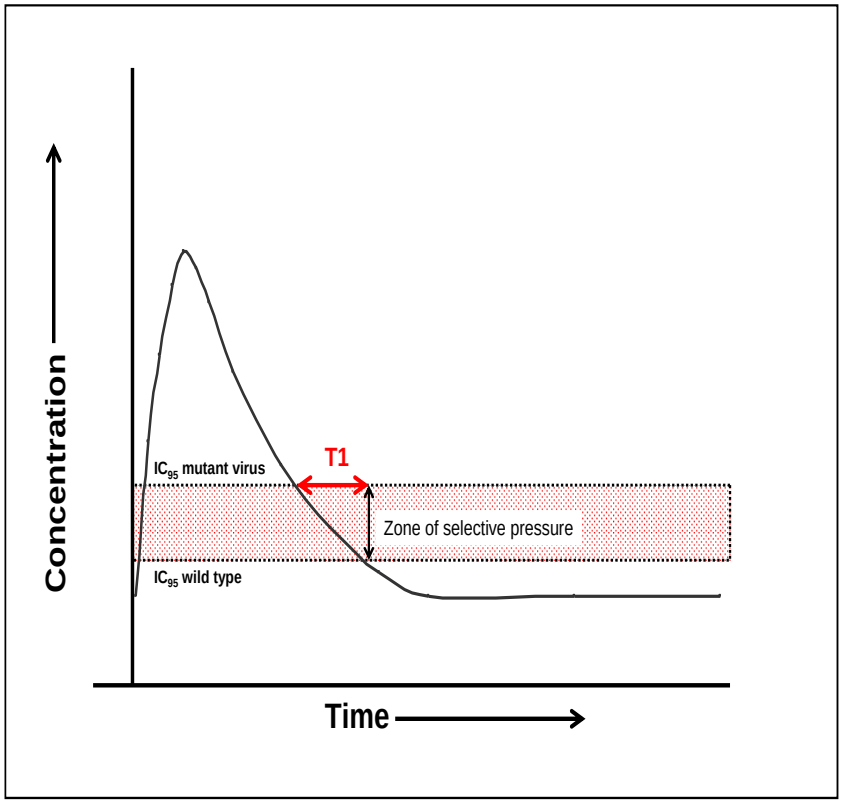
- Single tablet
- CNS side effects – treatment limiting in 5%
- Combined with Truvada – Atripla®

Nevirapine

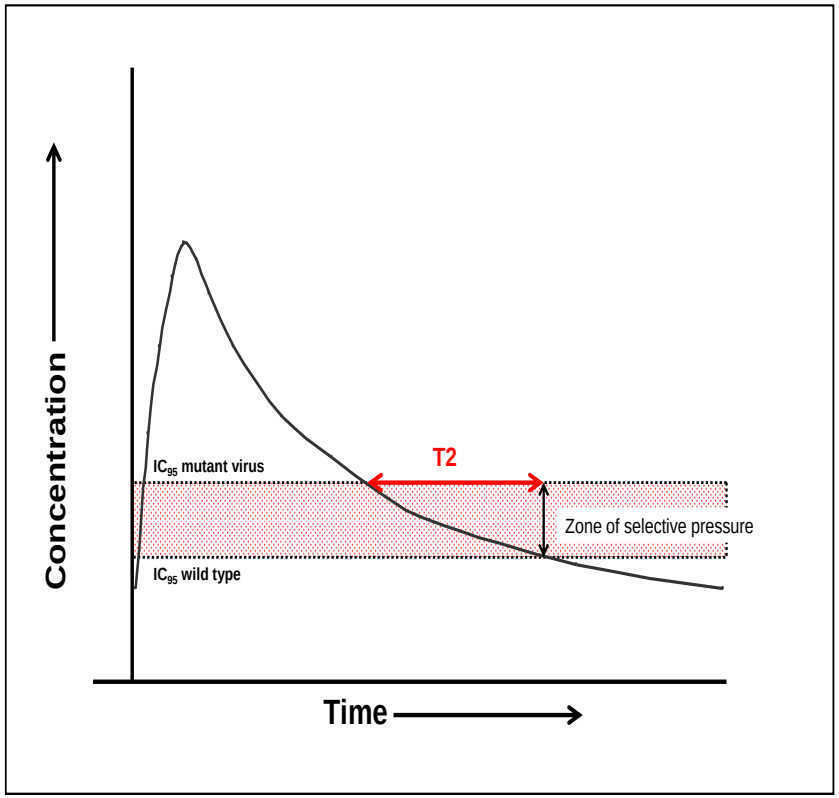
- BD / QD (new formulation)
- Concerns re liver toxicity
- Hypersensitivity – not recommended in high CD4+ / women

NNRTI - resistance

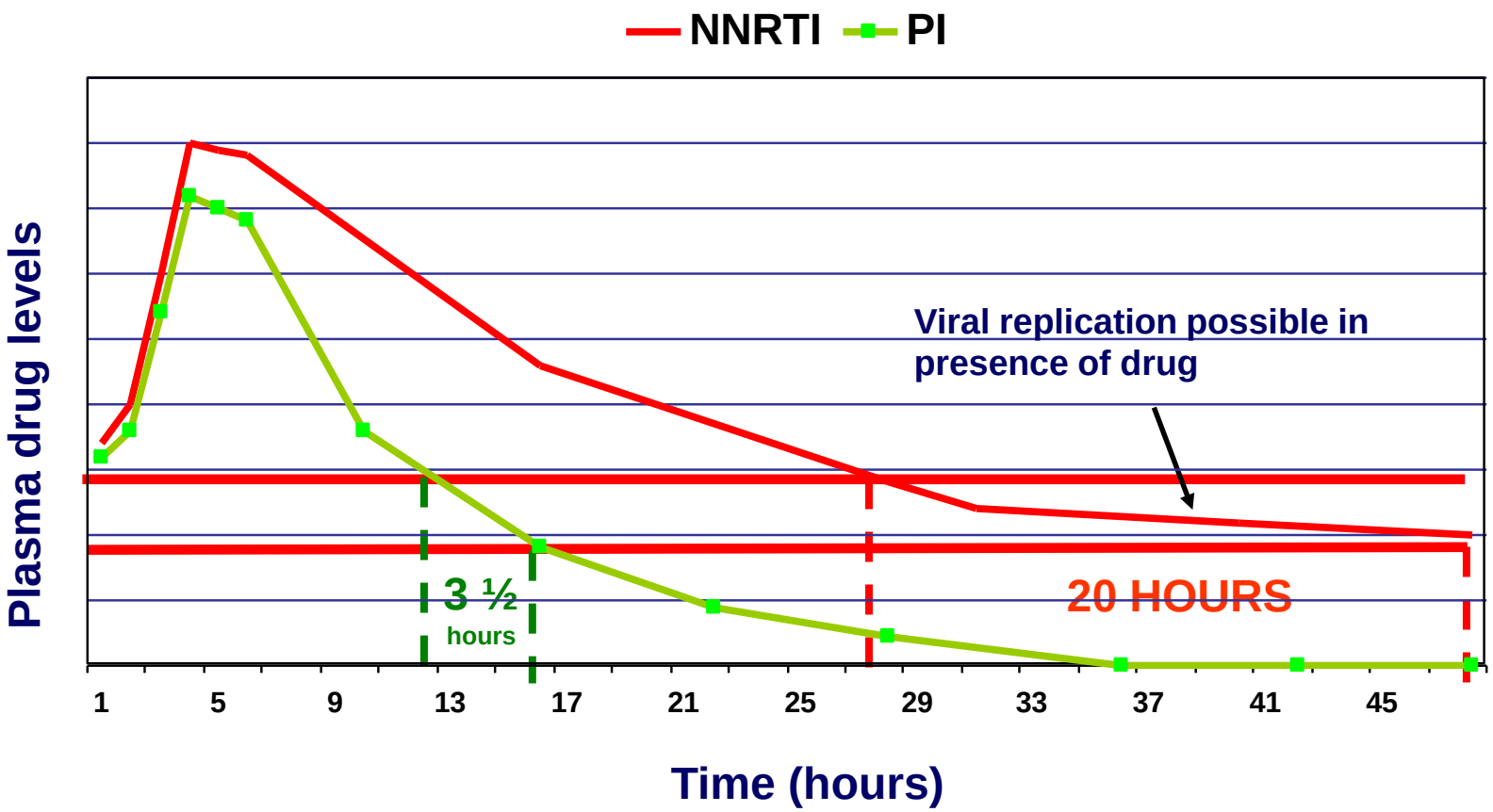
Short T½ (SQVr)



Long T½ (EFV)



NNRTI - resistance



Low genetic barrier to resistance
EFV – K103N, V108I, G190A
NVP – Y181C

Cross-class resistance common
Not '**forgiving**'!

NNRTI – 2nd generation

Less CNS side effects
Less hepatotoxicity
Effective in some resistance settings

Etravirine

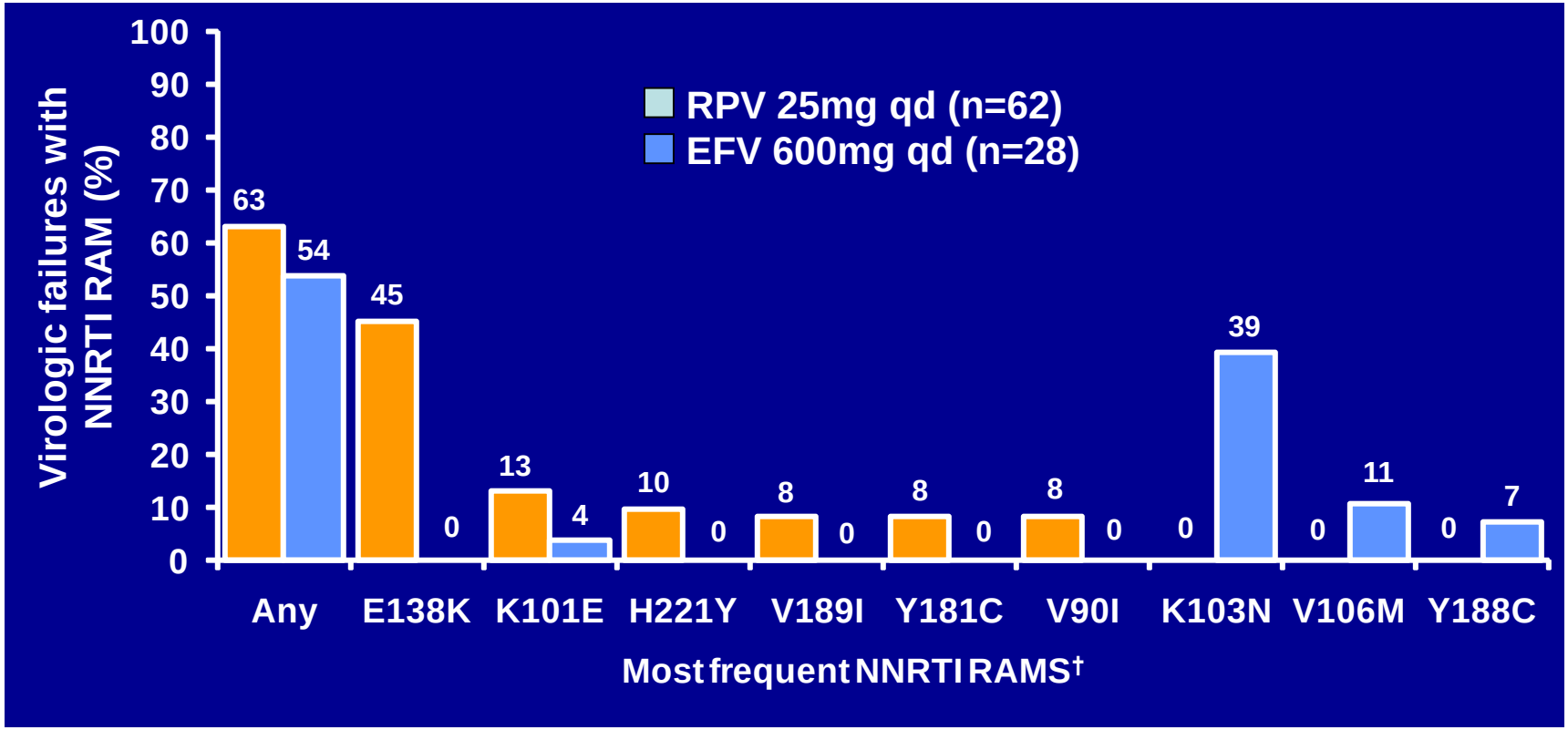
- Effective in setting of K103N
- Decreased susceptibility with Y181C

Rilpivirine

- Only use if HIVRNA <100,000cps/ml
- Requires food (significantly decreased exposure)
- Co-formulated with Truvada – Eviplera®

NNRTI – 2nd generation

Treatment-emergent NNRTI RAMs



- **Among RPV VFs with emerging NNRTI RAMs, 46%, 31% and 23% had 1, 2, or 3 NNRTI RAMs, respectively, at failure**

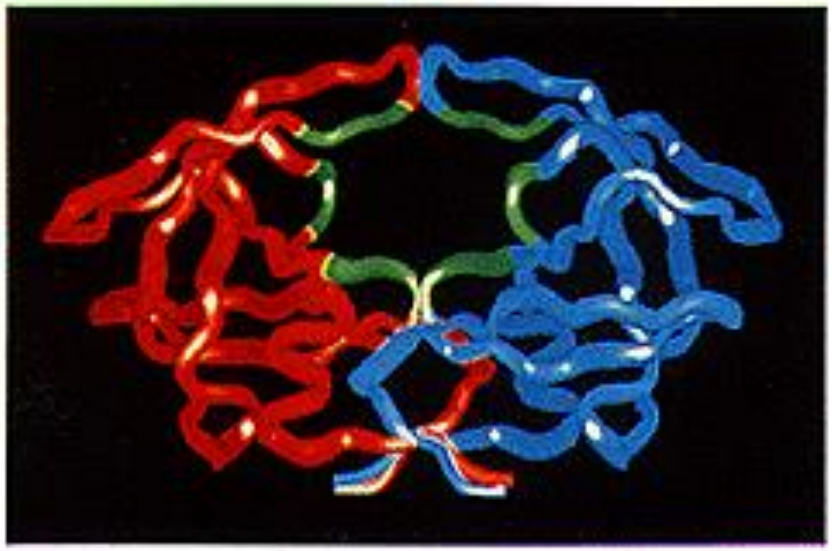
Eron J, et al. ICAAC 2010; Boston. Abstract H-1810

Principal antiretroviral drug classes

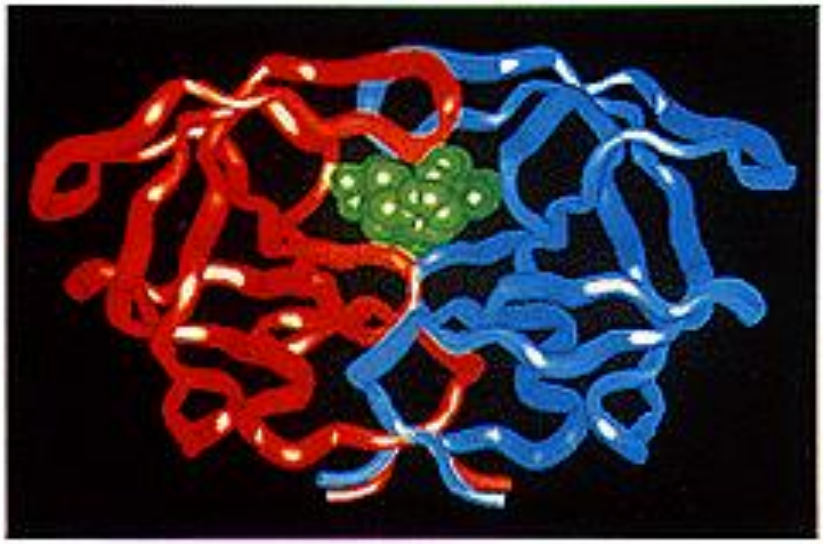
- Nucleoside reverse transcriptase inhibitors (NRTI)
- Non-nucleoside reverse transcriptase inhibitors (NNRTI)
- Protease inhibitors
- Integrase inhibitors
- Attachment inhibitors

Protease inhibitors (PI)

HIV protease



With PI



PI and 'boosting'

Ritonavir (RTV) is a potent inhibitor of CYP3A4
Beneficial Pharmacological Enhancement

$$\frac{C_{min}}{IC_{95}} > 1$$

IDV	3.7
IDV & RTV	28.2

Lopinavir	Saquinavir
Fosamprenavir	Tipranavir
Indinavir	Atazanavir
Darunavir	*nelfinavir*

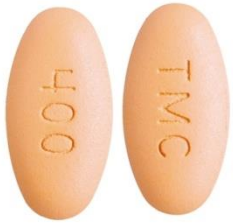
Cobicistat new pharmacological booster

Condra et al, *JID* 2001

Common PI

atazanavir

Evotaz®



darunavir

Prezcobix®

Kaletra®

PI - tolerability

GI intolerance common

atazanavir

Hyperbilirubinaemia
Renal calcuil

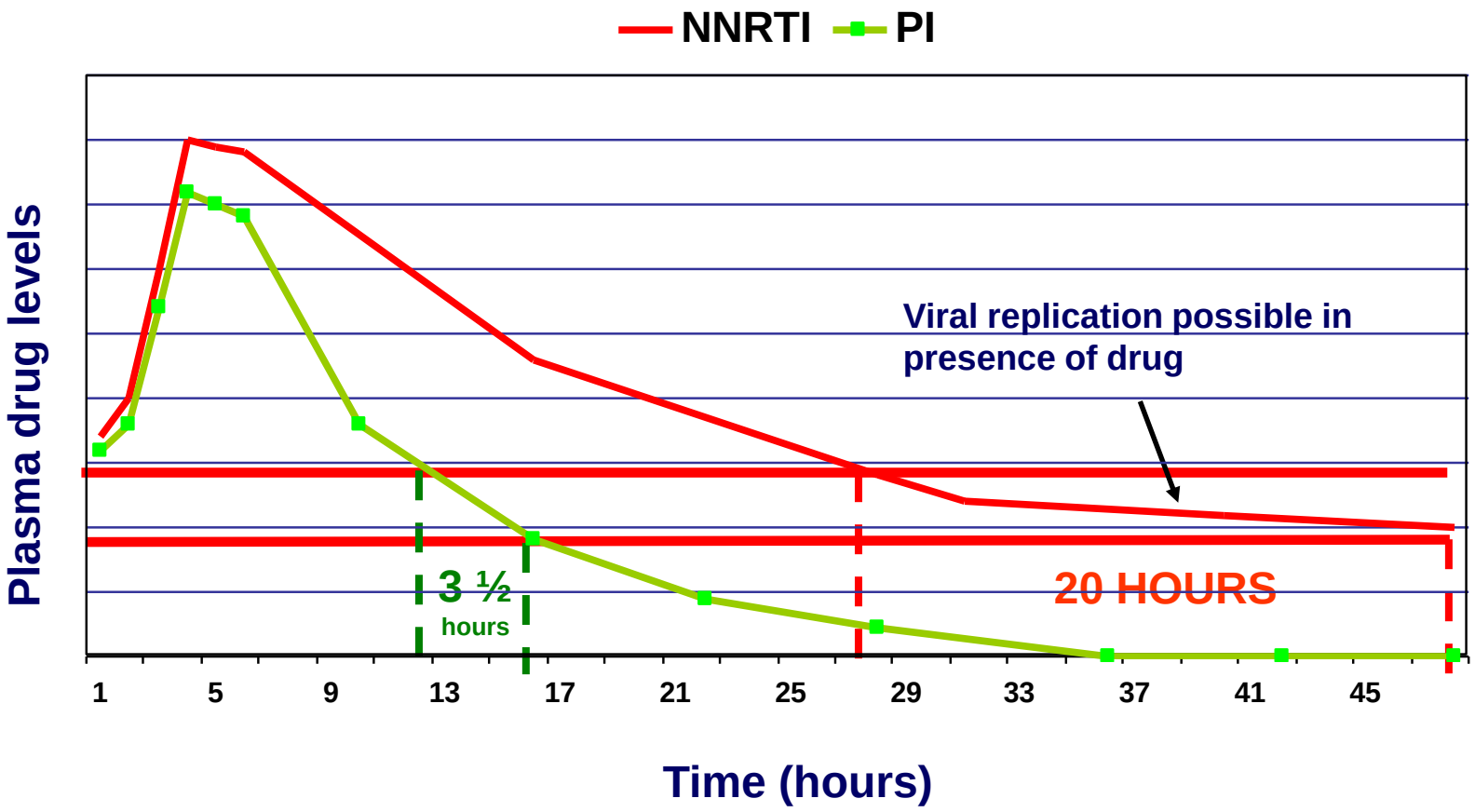
darunavir

Rash
Renal calcuil

Kaletra®

Diarrhoea
Perioral parasthesia

PI - resistance



PI resistance – relatively rare with 1st line failure

'Forgiving' drug class

Mix of signature and accumulated resistance

PI - resistance

Combined Study GS-102 and -103 – Week 96

Mutation, n (%)	STB (combined, n=701) Wk 48	STB (combined, n=701) Wk 48–96	Mutation	EFV/FTC/TDF (n=352) Wk 48	EFV/FTC/TDF (n=352) Wk 48–96	ATV+RTV+FTC/TDF (n=355) Wk 48	ATV+RTV+FTC/TDF (n=355) Wk 48–96
Resistance analysis population at Week 96		36 (5.1%)			23 (5.1%)		16 (4.5%)
Any emergent resistance	13 (1.9%)	+3 (+0.4%)		8 (2.3%)	+2 (+0.6%)	0	0
Any primary integrase resistance	11 (1.6%)	+3 (+0.4%)	Any NNRTI resistance	8 (2.3%)	+2 (+0.6%)	0	0
E92Q	8	+1	K103N	7	+2		
N155H	3	+2	K101E	0	+3		
Q148R	3	0	V108I	2	0		
T66I	2	0	Y188F/H/L	1	+1		
			M230L	0	+2		
			V90I	0	+1		
			G190A	1	0		
			P225H	0	+1		
Any primary NRTI resistance	12 (1.7%)	+3 (+0.4%)		2 (0.6%)	+1 (+0.3%)	0	0
M184V/I	12	+3		2	+1	0	0
K65R	4	+1		2	+1	0	0

Zolopa A. Presented at CROI 2013, poster 553

Principal antiretroviral drug classes

- Nucleoside reverse transcriptase inhibitors (NRTI)
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- Attachment inhibitors

Integrase inhibitors

- Integrase strand transfer inhibitors (InSTI)
- Very potent antiretrovirals
- Generally well tolerated – no real signature side effects
- Intra-class differences in resistance

Raltegravir (RAL) - BID

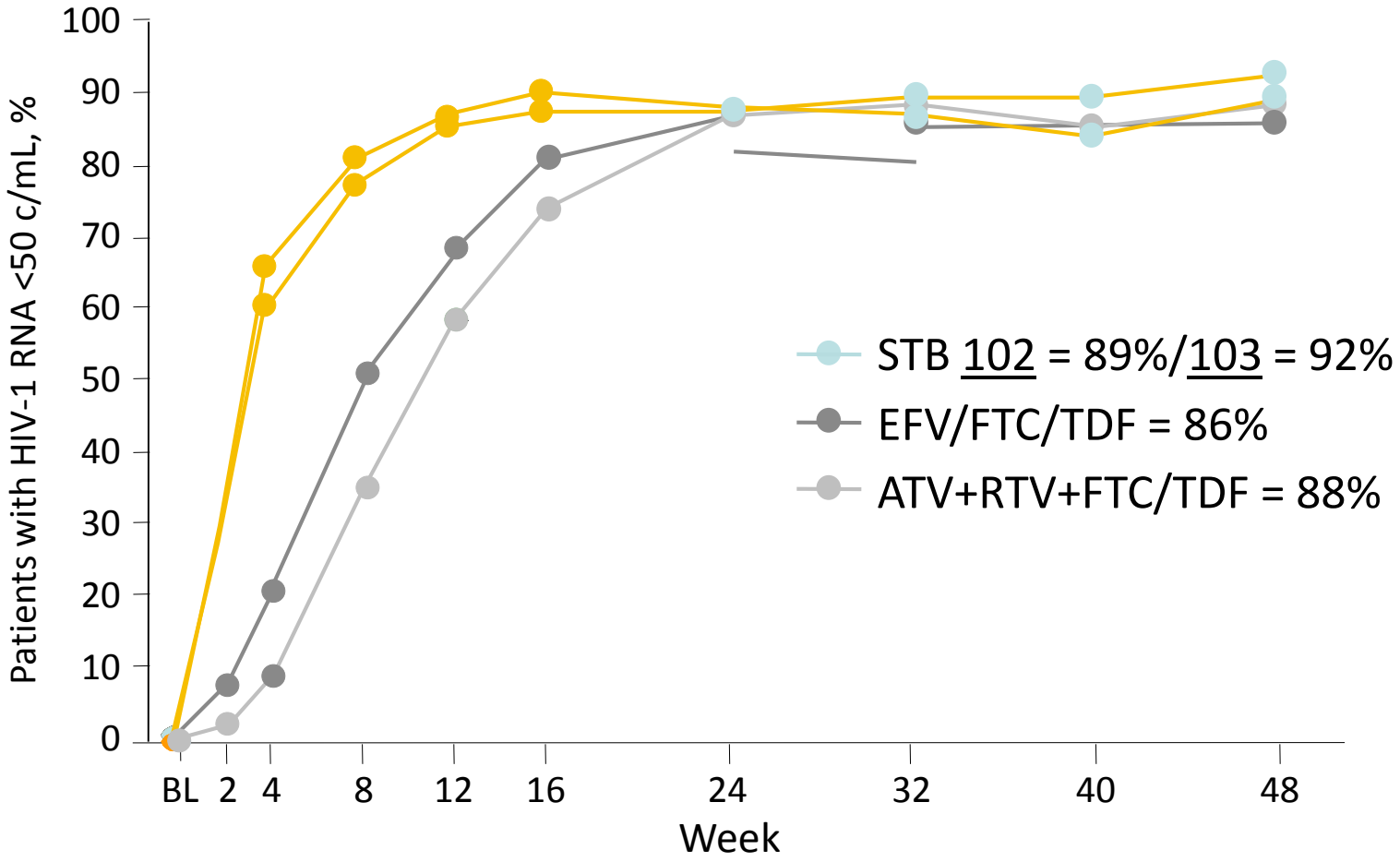
Stribild® - Elvitegravir / Cobi / TDF / FTC

Dolutegravir

Triumeq® - Dolutegravir / ABC / 3TC

Integrase inhibitors

Subjects HIV-1 RNA <50 copies/mL (ITT M = F) Phase 3 GS-102 and -103:

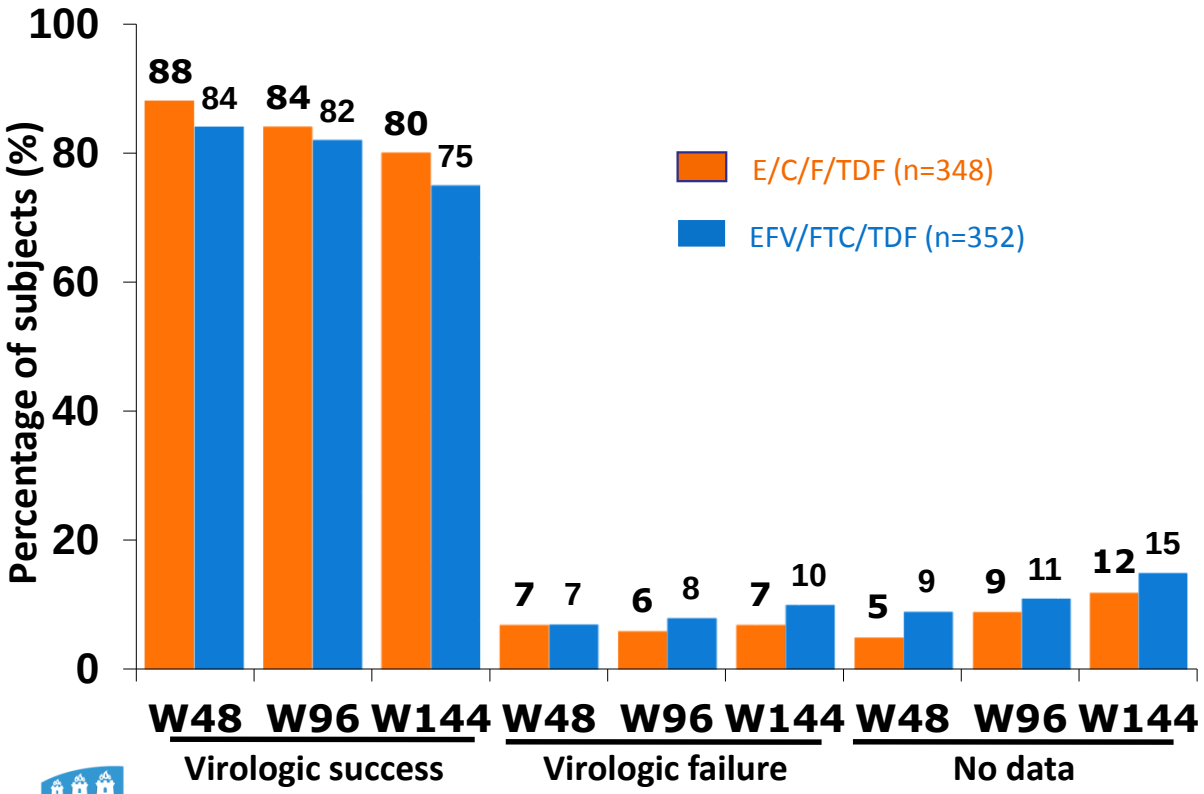


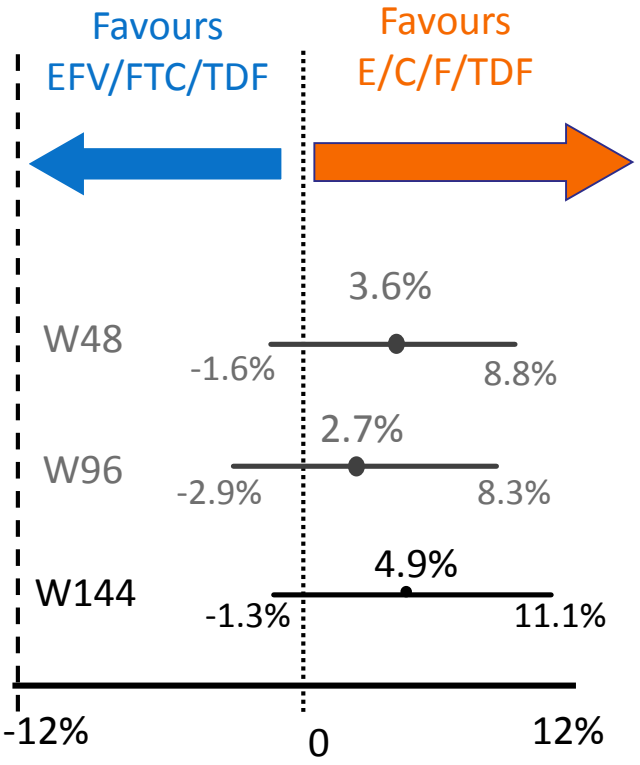
Sax P et al. Lancet 2012; 379: 2439–48
DeJesus E et al. Lancet 2012; 379: 2429–38

InSTI - efficacy

Studies 102 (E/C/F/TDF vs EFV/FTC/TDF – virological outcomes

Virologic success (HIV-1 RNA <50 copies/mL) as defined by FDA Snapshot algorithm





Wohl DA et al. *JAIDS* 2014;65(3):e118–121

InSTI resistance - raltegravir

NEAT 001/ANRS 143

	RAL + DRV/r	TDF/FTC + DRV/r
N pts meeting criteria for genotypic testing	69	58
N pts undergoing genotypic testing (at least one amplified gene)	61	49
Pts with ≥1 major IAS resistance mutation	17*	0
Reverse transcriptase**	3/53 (5.7%)	0
Protease	1/57 (1.8%)	0
Integrase	14/55 (25.5%)	0

* 1 patient had 2 major IAS resistance mutations (1 NRTI + 1 IN)
** only NRTI , not NNRTI

VL at time of testing was not significantly different in pts who failed with or without an IN mutation: median 615 c/ml (IQR: 192, 14864) *vs*. 361 c/ml (IQR: 137, 990); p=0.27

InSTI – resistance - elvitegravir

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Zolopa A. Presented at CROI 2013, poster 553

InSTI – resistance - dolutegravir

- Very effective in ART-naïve – few failures
- Little or no InSTI resistance observed with dolutegravir in ART naïve studies
- Likely high genetic barrier AND forgiving
- SPRING1 vs EFV

Outcome	DTG 10mg (N=53)	DTG 25mg (N=51)	DTG 50mg (N=51)	EFV 600mg (N=50)
Protocol-defined Virologic Failure	**2 ***	**1 ***	**0**	**1****
Genotype/phenotype Determinable	**2**	**0**	**0**	**1**
INI Mutations Present	**0**	**0**	**0**	**0**
NNRTI Mutations Present	**0**	**0**	**0**	**0**
NRTI Mutations Present	**M184V (1)**	**0**	**0**	**0**

PDVF = confirmed HIV-1 RNA >400 c/mL OR < 1.0 $\log_{10}$ c/mL decrease by Week 4
Amongst DTG-treated subjects (N=155), no integrase mutations were detected through Week 96
No subjects in 50 mg arm had confirmed VL ≥400 c/mL through Wk 96

*Non-adherence in DTG 10mg (n=1) and DTG 25mg subjects by report/pill count at time of PDVF
**<1.0 $\log_{10}$ decrease by Wk 4

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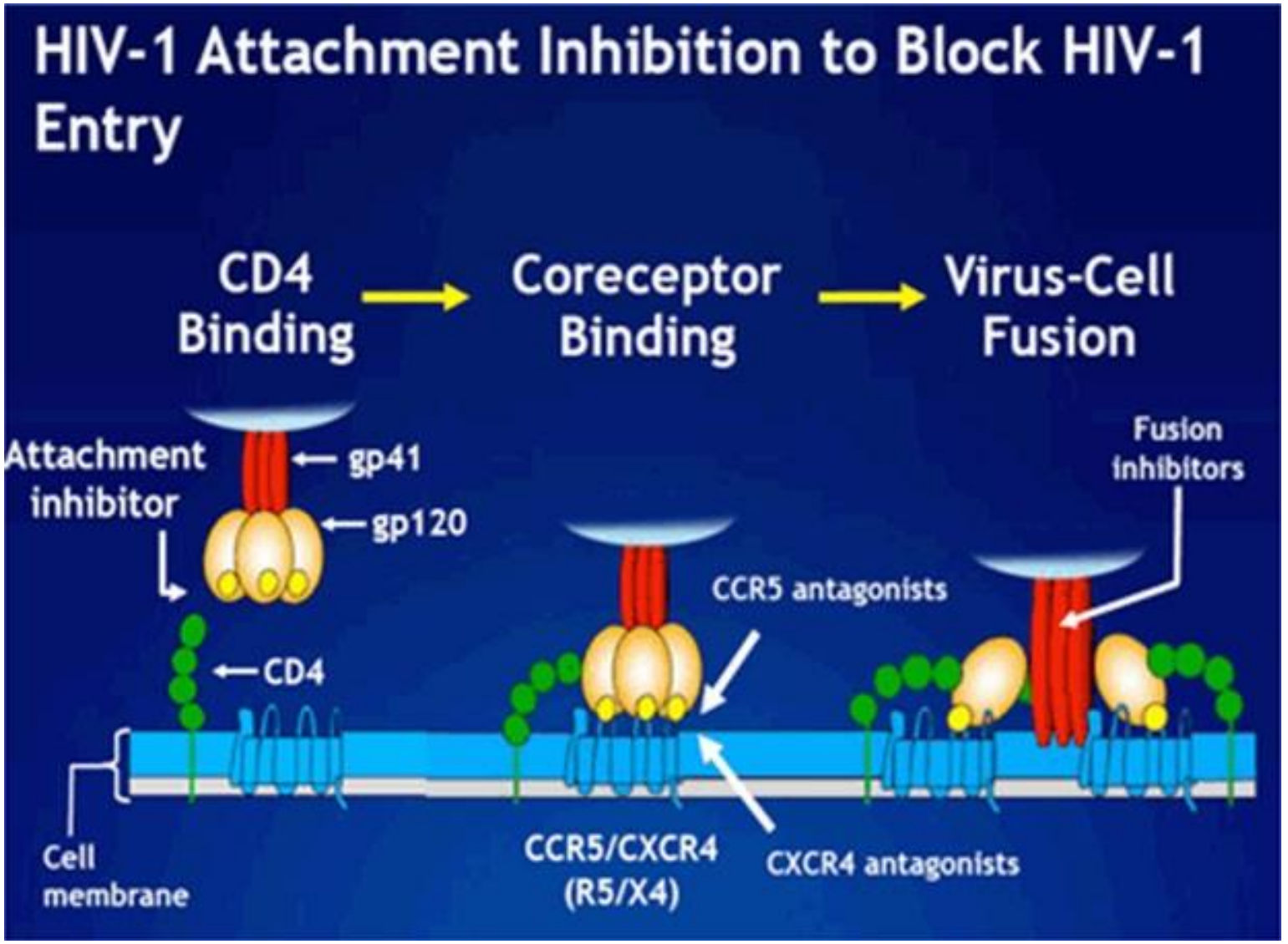
Attachment Inhibitors



Attachment Inhibitors

Figure 1. Conversion of BMS-663068 to BMS- 626529

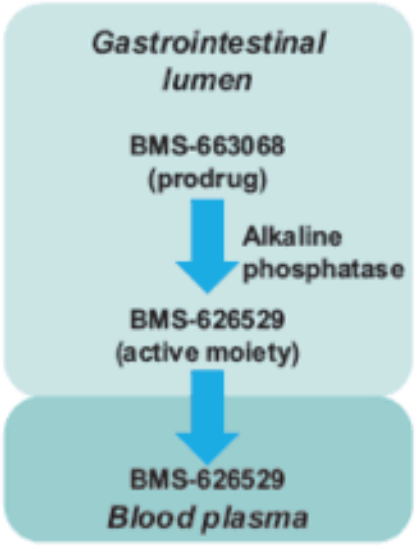
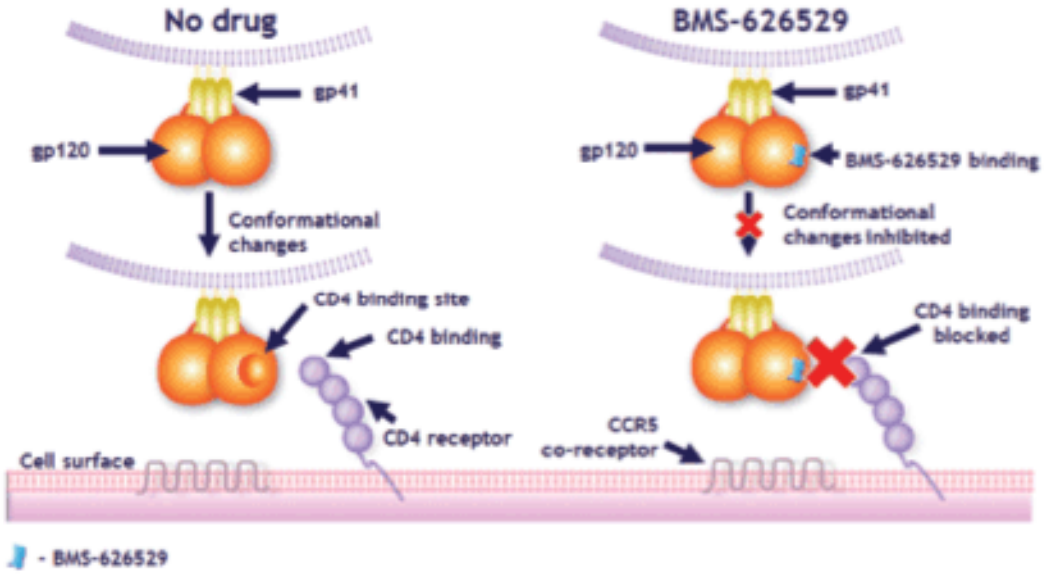


Figure 2. BMS-626529 attachment inhibitor: Proposed mechanism of action



ART and drug interactions

	Non-ARV drugs	ATV/r	DRV/c	DRV/r	LPV/r	EFV	ETV	NVP	RPV	MVC	DTG	EVG/c	RAL	ABC	FTC	3TC	TDF	ZDV
Cardiovascular drugs	atorvastatin	↑	↑	↑	↑490%	↓43%	↓37%	↓	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔
	fluvastatin	↔	↑	↔	↔	↑	↑	↔	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔
	pravastatin	↔	↑	↑81%	↔	↓44%	↓	↔	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔
	rosuvastatin	↑213%	↑	↑48%	↑107%	↔	↑	↔	↔	↔	↔	↑38%	↔	↔	↔	↔	↔	↔
	simvastatin	↑	↑	↑	↑	↓68%	↓	↓	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔
	amlodipine	↑[iii]	↑	↑	↑[iii]	↓	↓	↓	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔
	diltiazem	↑[iii]	↑	↑	↑[iii]	↓69%	↓E	↓	E	E	↔	↑	↔	↔	↔	↔	↔	↔
	metoprolol	↑[iii]	↑	↑	↑[iii]	↔	↔	↔	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔
	verapamil	↑[iii]	↑	↑	↑[iii]	↓	↓E	↓	E	E	↔	↑	↔	↔	↔	↔	↔	↔
	warfarin	↑ or ↓	↑	↓	↓	↑ or ↓	↑	↑ or ↓	↔	↔	↔	↑ or ↓	↔	↔	↔	↔	↔	↔
CNS drugs	diazepam	↑	↑	↑	↑	↓	↑	↓	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔
	midazolam (oral)	↑	↑	↑	↑	↓	↓	↓	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔
	triazolam	↑	↑	↑	↑	↓	↓	↓	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔
	citalopram	↑[iii]	↑	↑	↑[iii]	↓	↓	↓	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔
	mirtazapine	↑	↑	↑	↑	↓	↓	↓	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔
	paroxetine	↑↓?	↑↓?	↓39%	↑↓?	↔	↔	↔	↔	↔	↔	↑↓?	↔	↔	↔	↔	↔	↔
	sertraline	↓	↑	↓49%	↓	↓39%	↓	↓	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔
	bupropion	↓	↔	↓	↓57%	↓55%	↔	↓	↔	↔	↔	↑?	↔	↔	↔	↔	↔	↔
	pimozide	↑[iii]	↑	↑	↑[iii]	↑	↓	↓	↔[iv]	↔	↔	↑	↔	↔	↔	↔	↔	↔
	carbamazepine	↑D	↑D	↑	↑D	↓27%D36%	D	↓D	D	D	D	D	D	↑	↔	↔	↔	↑[ix]
	lamotrigine	↓32%[ii]	↔	↓[ii]	↓50%	↓	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	phenytoin	↓D	D	↓D	↓D	↓D	D	↓D	D	D	D	D	D	D	↔	↔	↔	↓

Rifampicin – decreases exposure to PI - use NNRTI / InSTI

DDIs – ART and hormonal contraception

NNRTIs:

ARV Drug	Recommendation for Combined Hormonal Methods and Progestin-Only Pills	Recommendation for DMPA	Recommendation for Etonogestrel Implants
EFV	Use alternative or additional contraception	No additional contraceptive needed	Use alternative or additional contraception
ETR	No additional contraceptive needed	No additional contraceptive needed	No additional contraceptive needed
NVP	Consider alternative contraceptive, or barrier + oral hormonal methods	No additional contraceptive needed	Consider alternative contraceptive, or barrier + implant
RPV	No additional contraceptive needed	No additional contraceptive needed	No additional contraceptive needed

http://aidsinfo.nih.gov/guidelines/html/3/perinatal-guidelines/0. Accessed January 25th 2015

DDIs – ART and hormonal contraception

RTV-Boosted PIs:

ARV Drug	Recommendation for Combined Hormonal Methods and Progestin-Only Pills	Recommendation for DMPA	Recommendation for Etonogestrel Implants
ATV/r	Use alternative or additional contraception	No additional contraceptive needed	Consider alternative contraceptive, or barrier + implant
DRV/r	Use alternative or additional contraception	No additional contraceptive needed	No additional contraceptive needed
FPV/r	Use alternative or additional contraception	No additional contraceptive needed	Consider alternative contraceptive, or barrier + implant
LPV/r	Use alternative or additional contraception	No additional contraceptive needed	Consider alternative contraceptive, or barrier + implant

http://aidsinfo.nih.gov/guidelines/html/3/perinatal-guidelines/0. Accessed January 25th 2015

How to use ART

Conventional HAART:

- 3 drugs from 2 drug classes
- Normally 2 X NRTI coupled with '3rd' agent

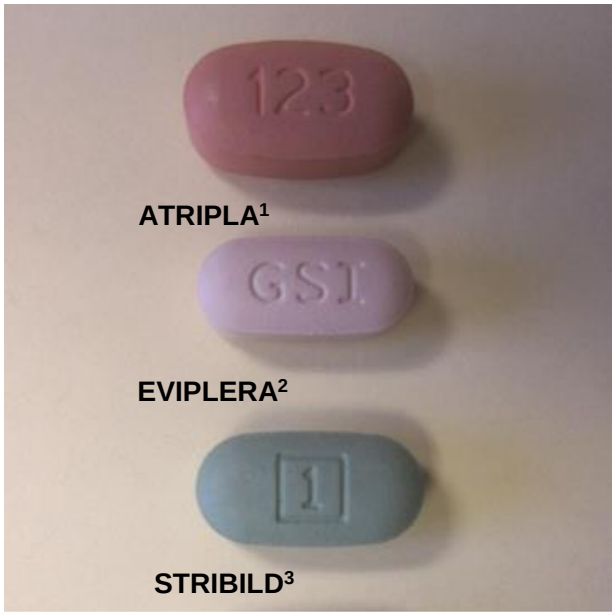
Characteristics of durable ART regimen:

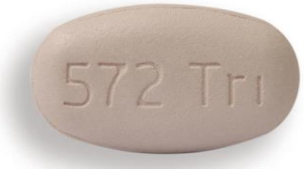
- Single tablet
- Once daily
- Well tolerated

Single tablet regimens (STR)

Current

- **EFV/FTC/TDF (ATRIPLA®)**
- **RPV/FTC/TDF (EVIPLERA®)**
- **EVG/C/FTC/TDF (STRIBILD®)**
- **DTG/3TC/ABC (TRIUMEQ®)**





TRIUMEQ[4]

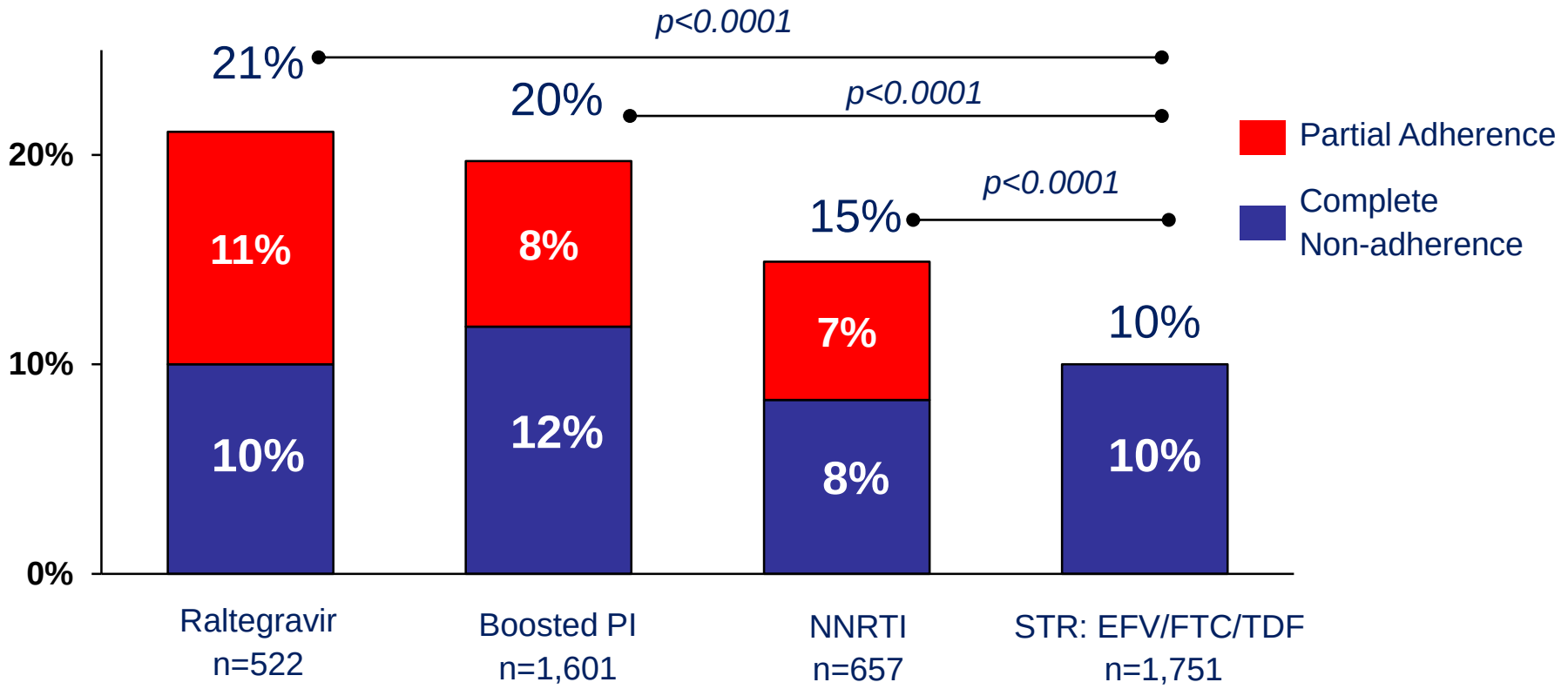
EFV= efavirenz, FTC=emtricitabine, TDF=tenofovir Disoproxil Fumarate, RPV= rilpivirine, EVG/C= elvitegravir/cobicistat, DTG= dolutegravir, 3TC=lamivudine, ABC= abacavir

1. Atripla SmPC, Dec 2014
2. Eviplera SmPC, Sep 2014
3. Stribild SmPC, Jul 2014
4. Triumeq SmPC

STR 'relative' worth - adherence

LifeLink Database

Retrospective analysis of US healthcare claims for commercially insured population (n=4,588) receiving 2 NRTIs plus NNRTI or PI or INSTI based ART (2009 – 2011)



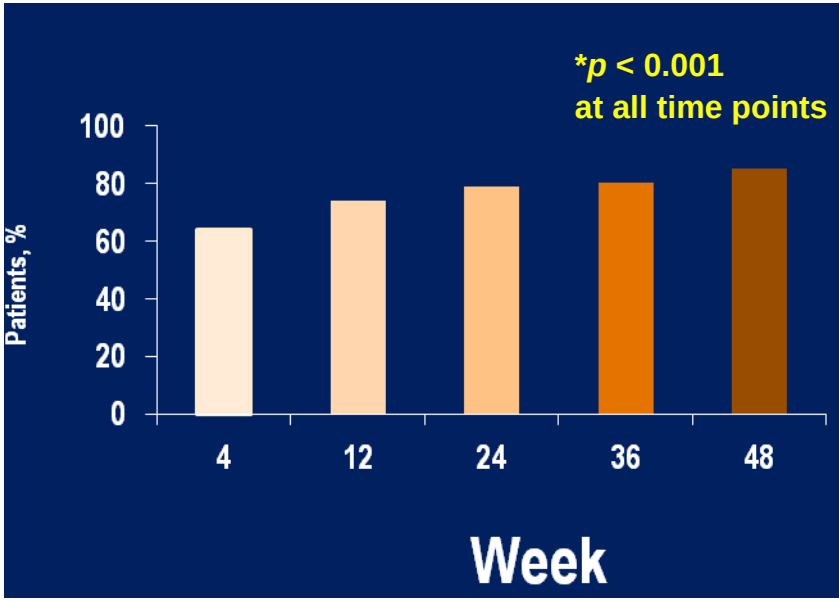
STR - significantly more days with a complete regimen

Cohen C, et al. ICAAC 2012; San Francisco, CA. #H-211

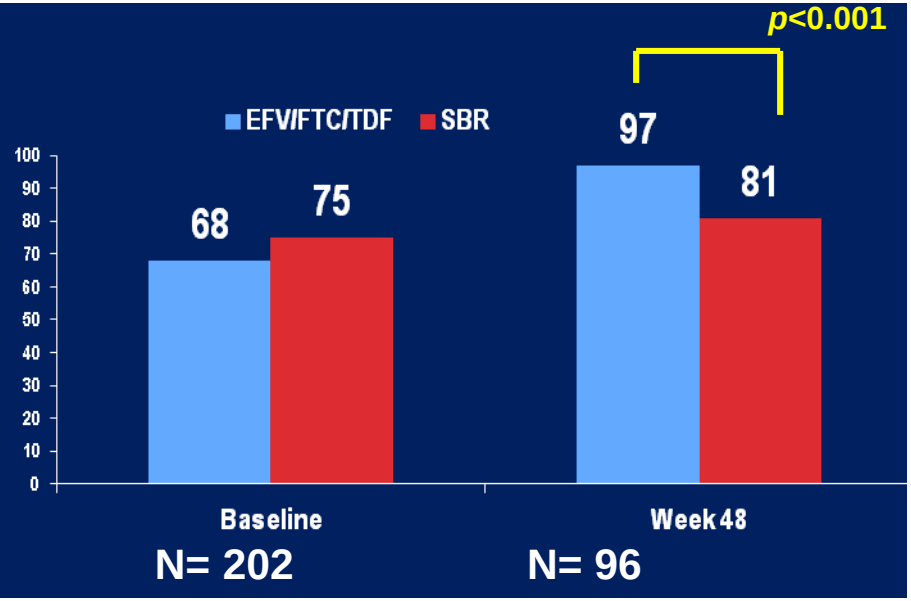
What is the '*value*' of patient preference?

Study 073: Patient Reported Outcomes

The proportion of patients describing EFV/FTC/TDF as "much better"*



Percentage of patients who found their regimen "very easy to take"



There was a significant increase in patients preferring EFV/FTC/TDF to their prior regimen at all time points ($p<0.001$) for overall study population, prior PI strata, and prior NNRTI strata

Date of preparation: May 2013
001/UK/13-04/NMAR/1063j

DeJesus E, et al. JAIDS 2009; 51:163-174

HIV treatment guidelines

DHHS 2014 Guidelines Recommend First-line ARV Regimens in Naive Adults

Recommended first line regimens			
Integrase inhibitor	RAL (BID) +	TDF/FTC	
	DTG +	TDF/FTC	
		ABC/3TC	Only for patients who are HLA-B*5701- negative
	DTG/ABC/3TC (FDC)		Only for patients who are HLA-B*5701- negative
	EVG/c/TDF/FTC		Only for patients with pre-ART CrCl >70mL/min
Boosted PI	DRV + RTV +	TDF/FTC	
Only for patients with pre-ART plasma HIV RNA <100,000 copies/mL			
NNRTI NNRTI	RPV/TDF/FTC		Only for patients with HIVRNA<100,000 cps/ml and CD4 count >200 cells/mm^3
	EFV +	ABC/3TC	Only for patients who are HLA-B*5701-negative
	EFV/FTC/TDF (ATR)		
Boosted PI	ATV + RTV +	TDF/FTC	
	ATV + c +	TDF/FTC	
	DRV + RTV or c	ABC/3TC	Only for patients who are HLA-B*5701- negative
	DRV + c	TDF/FTC	Only for patients with pre-ART CrCl >70mL/min

DHHS Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents. May 1, 2014. Available at: https://aidsinfo.nih.gov/contentfiles/lvguidelines/AA_Tables.pdf

HIV treatment guidelines

Updated EACS 2014 Guidelines Recommend Components of Initial ART in Adults

RECOMMENDED (combine a drug from Column A with those listed in Column B)	Column A	Column B	Remarks
NNRTI	**EFV[a] RPV[b]**	**FTC/TDF *or* 3TC/ABC[c]**	**EFV/FTC/TDF, RPV/FTC/TDF, FTC/TDF and 3TC/ABC coformulated**
Boosted PI	**ATV + RTV[d] DRV + RTV[d]**	**FTC/TDF *or* 3TC/ABC[c]**	**ATV + RTV: 300 + 100mg QD DRV + RTV: 800 + 100mg QD**
InSTI	**RAL**	**FTC/TDF *or* 3TC/ABC**	**RAL: 400mg BID**
	EVG/COBI	**FTC/TDF**	**EVG/COBI + FTC/TDF coformulated[e]**

[a] EFV: not recommended to be initiated in pregnant women or women with no reliable and consistent contraception; continuation is possible if EFV is already started before pregnancy; not active against HIV-2 and HIV-1 group O strains

[b] RPV: only if HIV-VL <100,000 copies/mL; PPI contraindicated, H2 antagonists to be taken 12h before or 4h after RPV

[c] ABC contraindicated if HLA B*5701-positive. Even if HLA B*5701-negative, counselling on HSR risk still mandatory. ABC should be used with caution in persons with a high CVD risk and/or persons with a VL >100,000 copies/mL

[d] Castle study (LPV/r vs ATV/r) showed better tolerability of ATV/r. Coadministration with PPI is contraindicated for treatment-experienced persons. If coadministration is judged unavoidable, close clinical monitoring is recommended and doses of PPI comparable to omeprazole 20mg should not be exceeded and must be taken approximately 12h prior to the ATV/r. Artemis study (LPV/r vs DRV/r) showed better efficacy and tolerability of DRV/r

[e] Should not be initiated in persons with eGFR <70mL/min. It is recommended that E/C/F/TDF not be initiated in persons with eGFR <90mL/min unless this is the preferred treatment

Adapted from EACS Guidelines for the Clinical Management and Treatment of HIV Infected Adults in Europe, Update June 2014

HMRG
HIV Molecular Research Group

QUESTIONS?

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UCD DUBLIN