Current and future treatment strategies

Dr. Mark Nelson

Chelsea & Westminster Hospital

Executive Committee of the British HIV Association (BHIVA)

GreenShoots FOUNDATION

“Support needing populations through medical assistance and the transfer of knowledge to local medical practitioners.”

Our vision for the

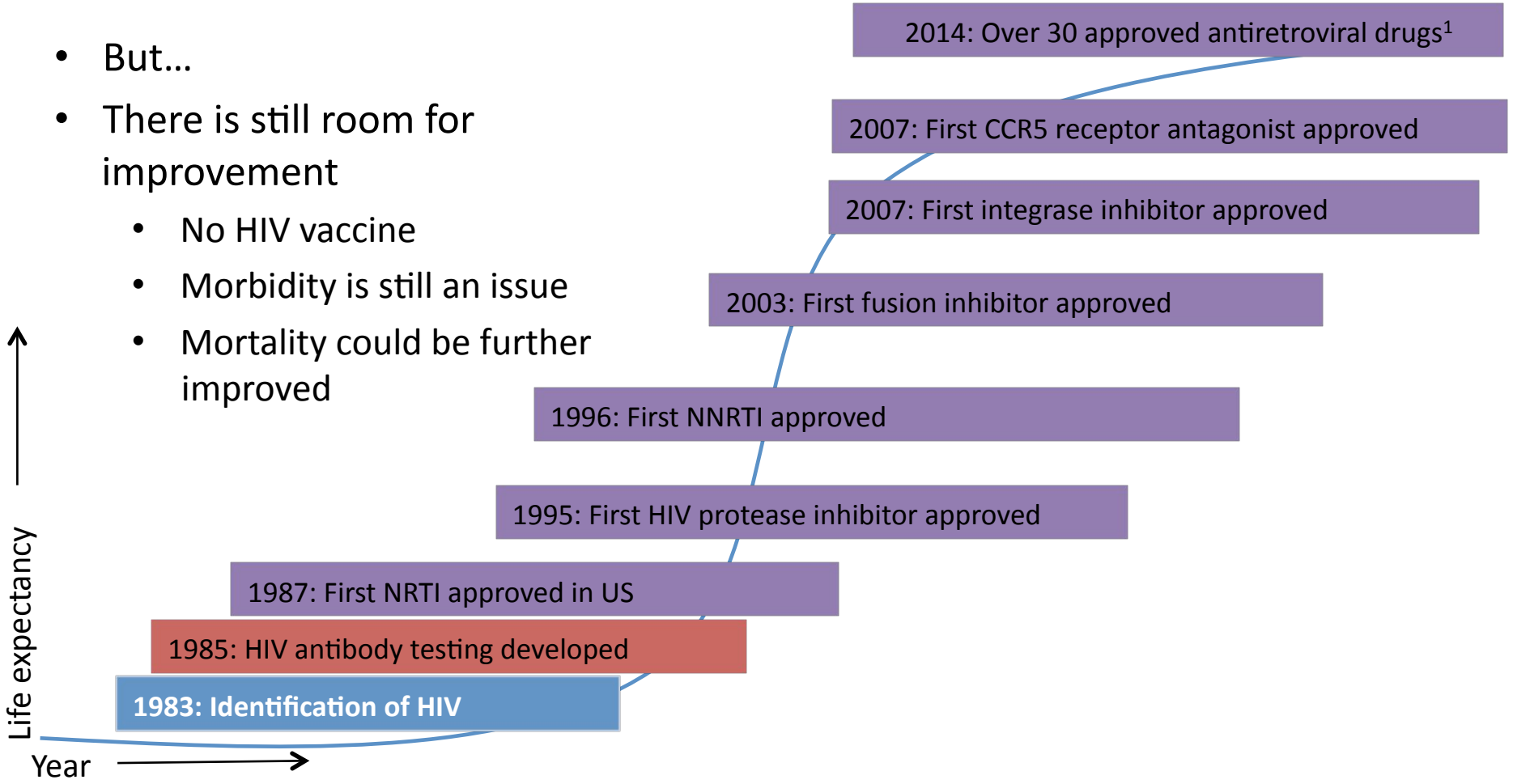
Medical Assistance & Medical Education (MAME) Programs

GreenShoots FOUNDATION


Lamborghini
Lamborghini
CLASSIC DRIVER
CARLOS DE JESUS

30 years of HIV drug development

- But…
- There is still room for improvement
  - No HIV vaccine
  - Morbidity is still an issue
  - Mortality could be further improved



Adapted from Palmisano L & Vella S. Ann Ist Super Sanita 2011;47:44–8.

1. FDA. Available at: http://www.fda.gov/ForConsumers/byAudience/ForPatientAdvocates/HIVandAIDSActivities/ucm118915.htm. Accessed 16 Sep 2013

PARTNERING FOR CURE

LES POTAGES, HORS D'OEUVRE ET OEUFS

Consommé riche de volaille tremblotant à l'estragon, et sa fondue de tomates aux poivrons

Tian de légumes provençaux aux senteurs des sous-bois et à l'huile d'olive aux herbes

Délicates feuilles de gnocchi de pommes de terre servies tièdes, méli-mélo d'asperges à la truffe écrasée et son coulis d'artichauts

Terrine de foie gras au blanc de volaille enrobé de pistaches, accompagnée de grains de raisins en ratafia

Oeufs pochés en feuilleté aux pointes d'asperges, sauce mousseline

Tartare de tomates au basilic, crémeux frais d'œufs brouillés et légumes du moment à la grecque

Indulgence d'esturgeon, de saumon fumé et de caviar Sevruga sur blinis au froment et grains de maïs

LES CRUSTACES ET COQUILLAGES

Tourteau et queues de langoustines au naturel, servis sur une crème onctueuse à la pêche, croquants de concombre

Tronçonnettes de homard poêlées minute au Porto blanc

Noix de Saint-Jacques poêlées sur coussin d'algues marines, salade de fines herbes confondues et de petits chipirons, vinaigrette safranée

LES DESSERTS

Crème brûlée à la pistache, glace vanille

Farandole de glaces et sorbets de saison, quelques pétales candis de roses du jardin

Dôme de rhubarbe en gelée de Bonnezeaux et sorbet aux framboises

Crémeux de chocolat, coulant d'abricot et son sorbet à l'infusion de verveine

Spoom à la fraise et son coulis, petites larmes de meringue, tutti frutti de fruits d 'été mentholé

You Choose for Me

Escargots?

Cuisses de Grenouilles?

Guideline recommendations for first-line treatment of adult treatment-naive patients

		IAS[1]	DHHS[2,3]	EACS[4]	BHIVA[5]	WHO[6]
NRTI	TDF/FTC or 3TC	✓	✓	✓	✓	✓
	ABC/3TC	✓	✓* ●	✓	●	✓
	ZDV/3TC	✗	✗	●	✗	✗
NNRTI	EFV	✓	✓	✓	✓	✓
	NVP	●	✗	●	✗	●
	RPV	●	●	✓	●	✗
PI	ATV/r	✓	✓	✓	✓	●
	DRV/r	✓	✓	✓	✓	●
	LPV/r	●	●	●	●	●
II	RAL	✓	✓	✓	✓	✗
	EVG/c	●	✓	●	✓	✗
	DTG	✗	✓	✓	✗	✗

✓ Recommended/preferred

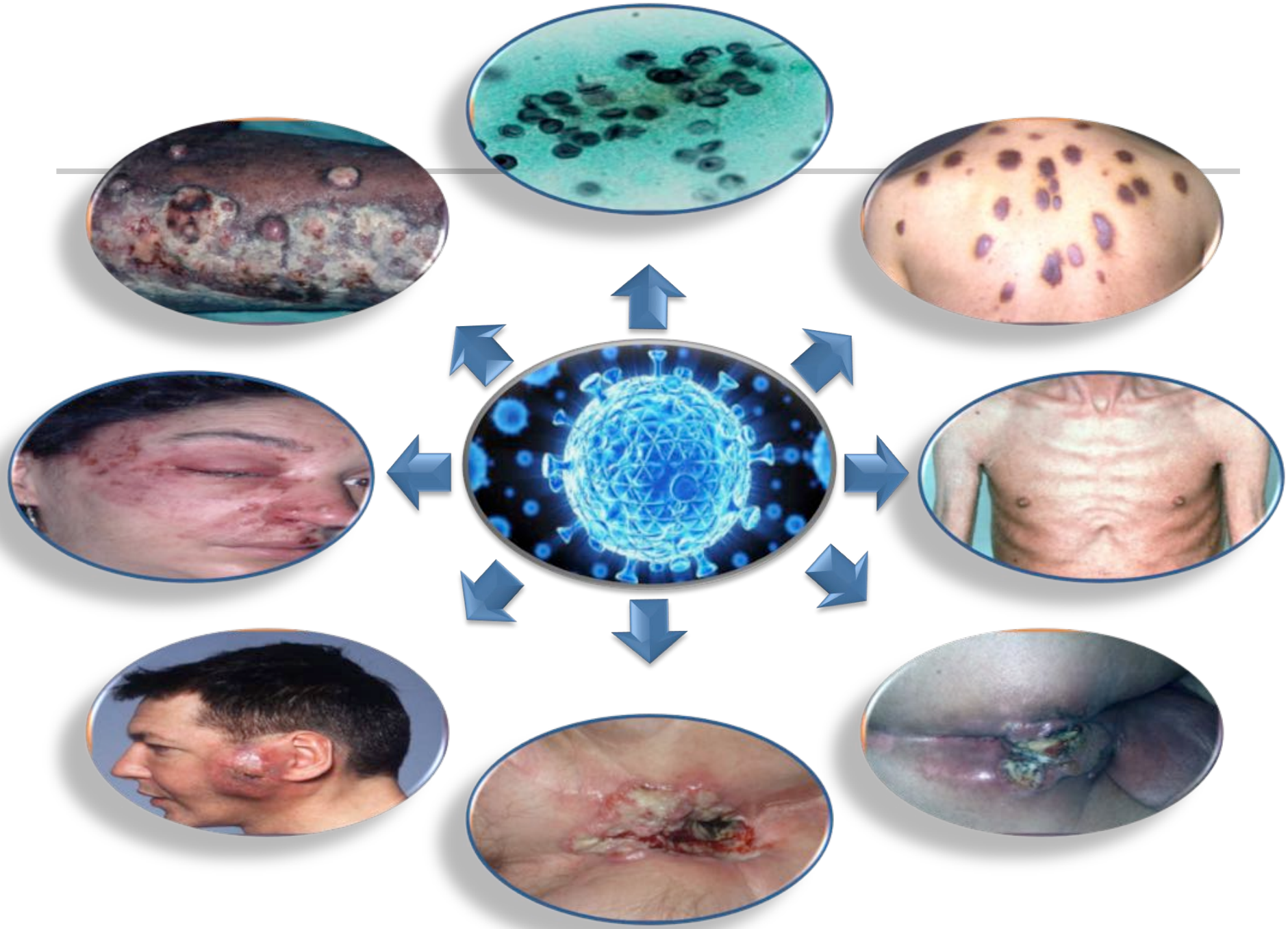
● Alternative

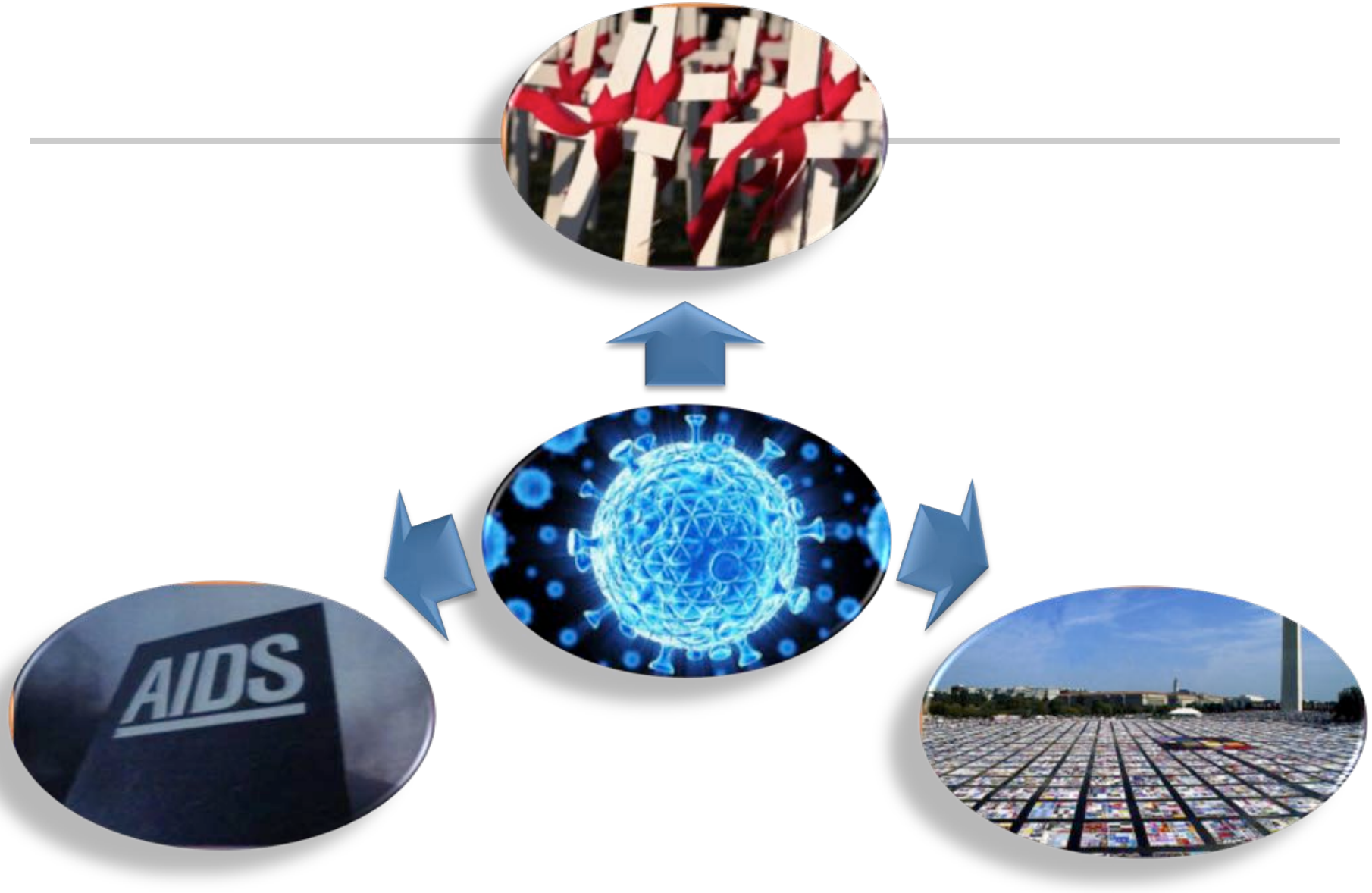
● Acceptable but less so than recommended/ preferred or alternative; may be some cautions

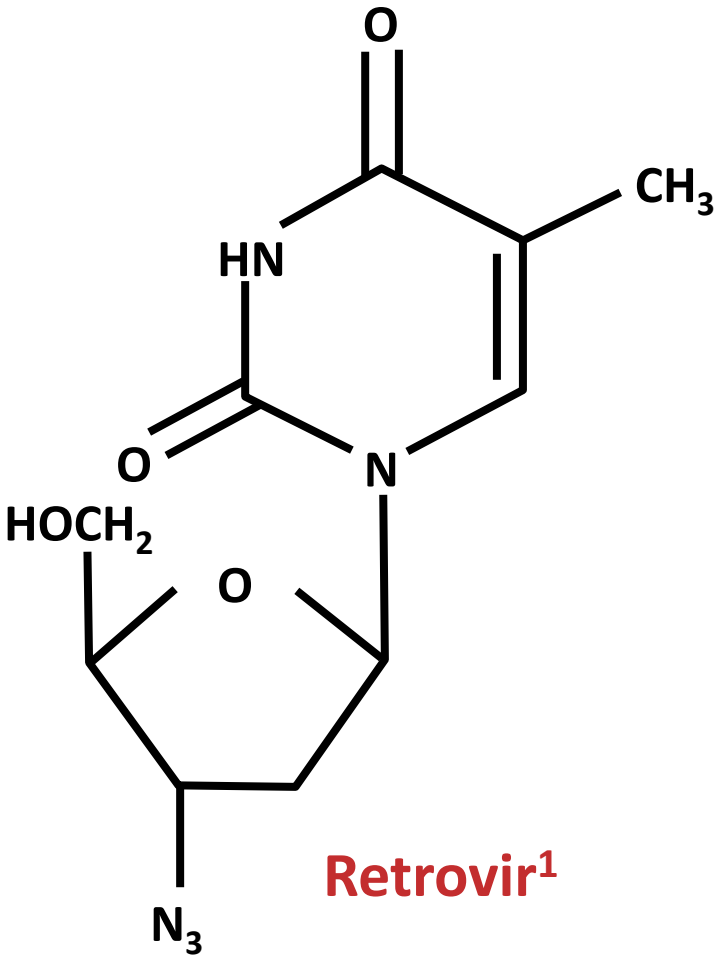
✗ Not recommended

1. Thompson M, et al. JAMA 2012;308:387–402. 2. http://aidsinfo.nih.gov/contentfiles/lvguidelines/adultandadolescentgl.pdf. Accessed 25 Nov 2013.
3. http://aidsinfo.nih.gov/news/1392/hhs-panel-on-antiretroviral-guidelines-for-adults-and-adolescents-updates-recommendations-on-preferred-insti-based-regimens-for-art-naive-individual. Accessed 26 Feb 2014. 4. EACS guidelines 2013 v7.0. Available at: http://www.eacsociety.org/Portals/0/Guidelines_Online_131014.pdf. Accessed 14 Nov 2013. 5. BHIVA ART guidelines 2012. Available at: http://www.bhiva.org/documents/Guidelines/Treatment/2012/hiv1029_2.pdf. Accessed 13 Nov 2013. 6. WHO ART guidelines 2013. Available at: http://apps.who.int/iris/bitstream/10665/85321/1/9789241505727_eng.pdf. Accessed 25 Nov 2013.
*ABC/3TC only preferred for use with DTG in HLA B*5701-negative patients.

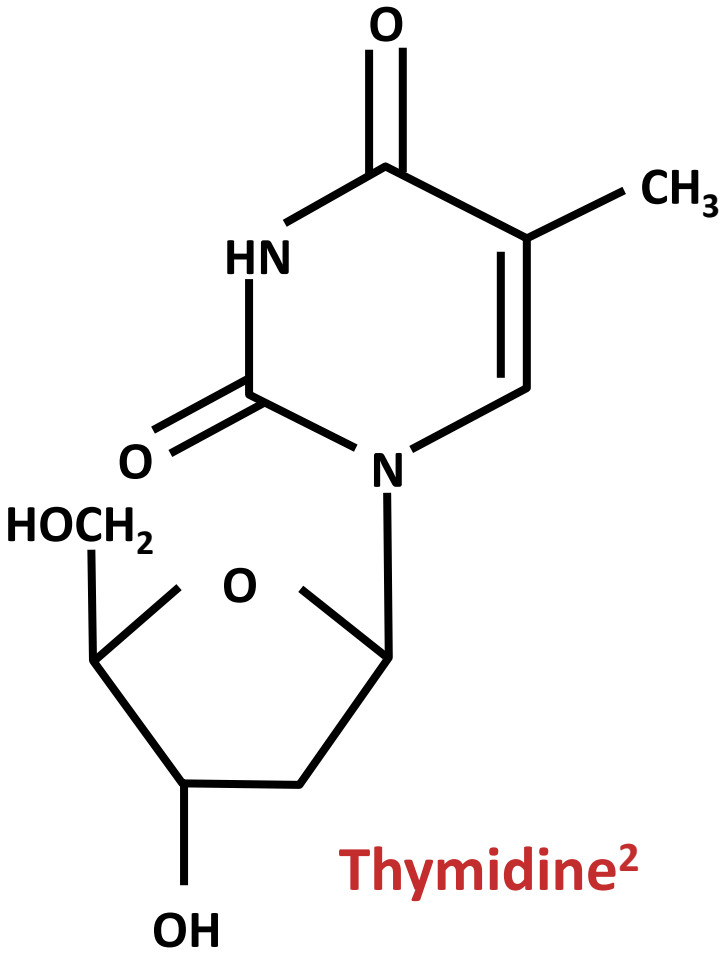

Survival
Efficacy
Tolerability




AIDS

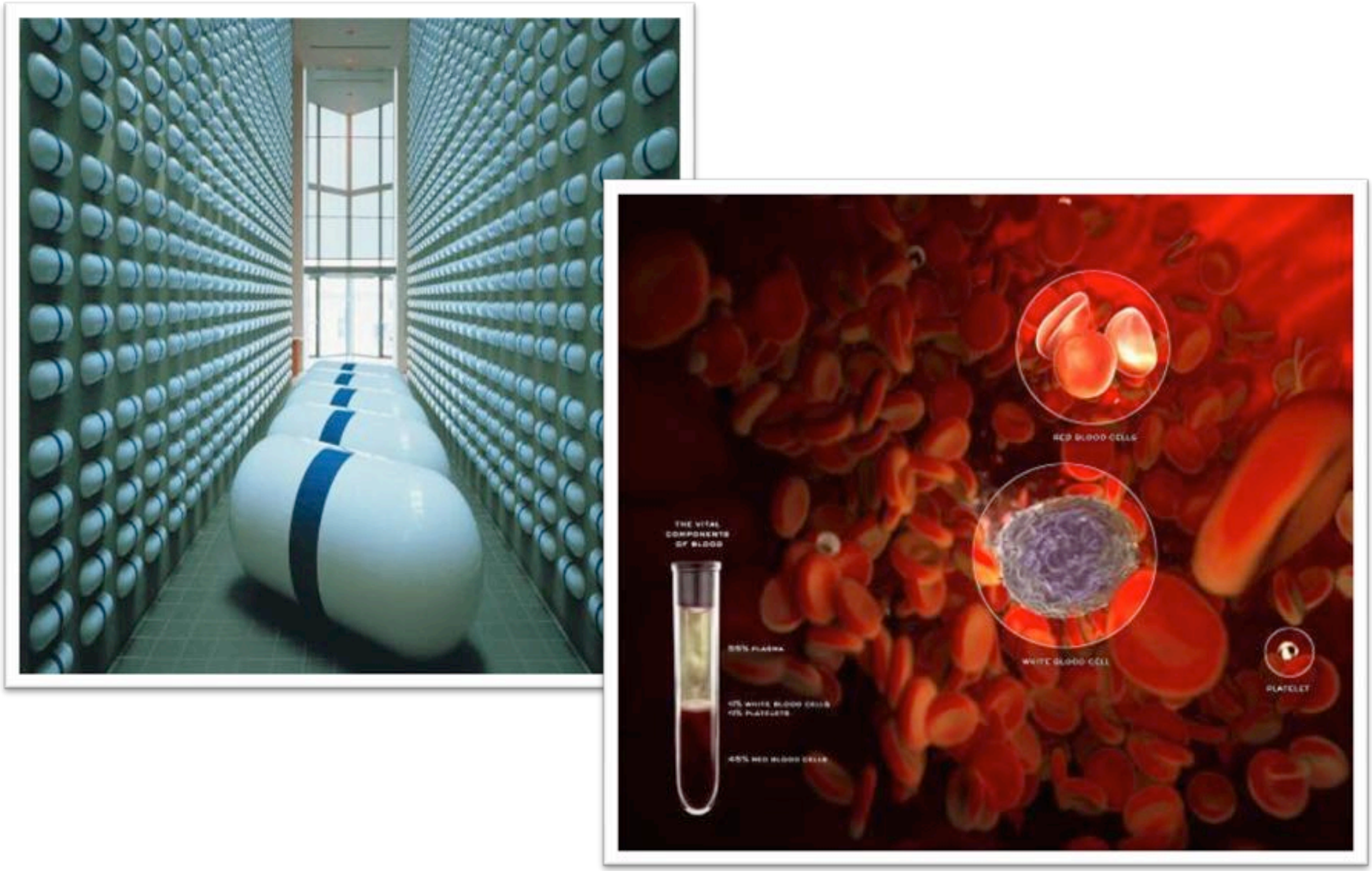


Retrovir[1]

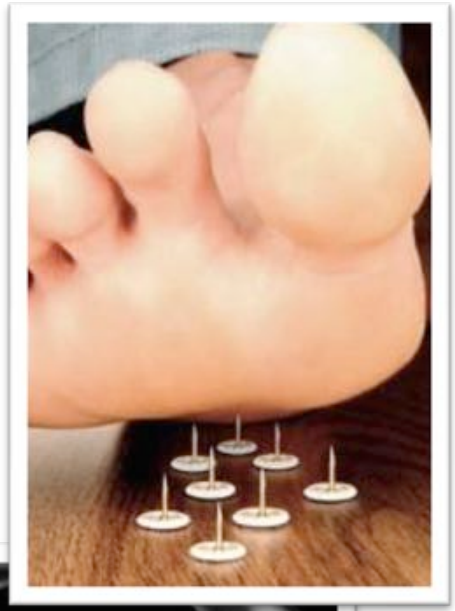


Thymidine[2]

1. US Retrovir Prescribing Information. Revised Sep 2010; 2. Levene PA and Tipson RS. *Science* 1935;81(2091):623–630

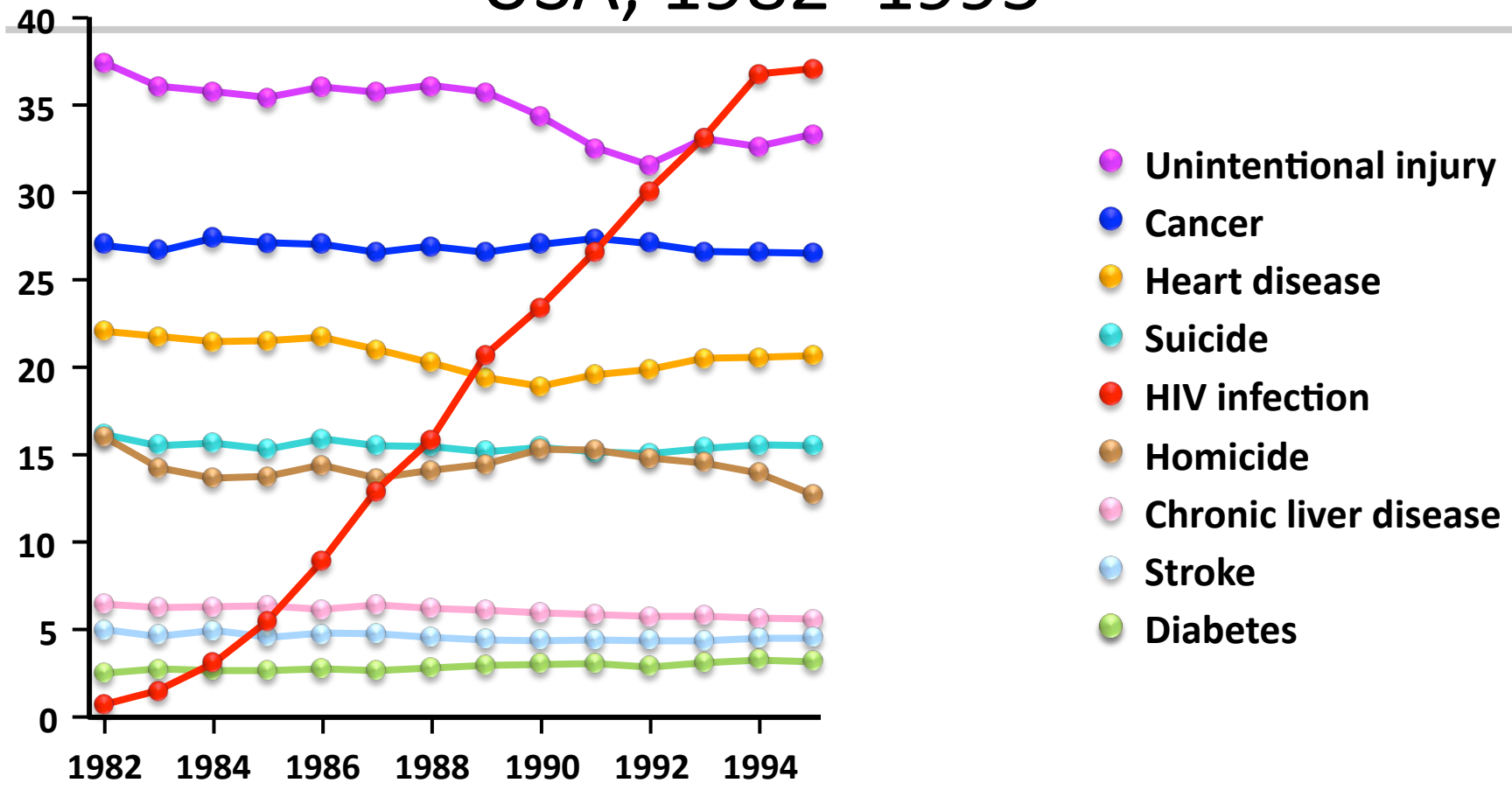

THE VITAL
COMPONENTS
OF BLOOD
RED BLOOD CELLS
WHITE BLOOD CELL
PLATELET


ROCHE
HIVID
0.750



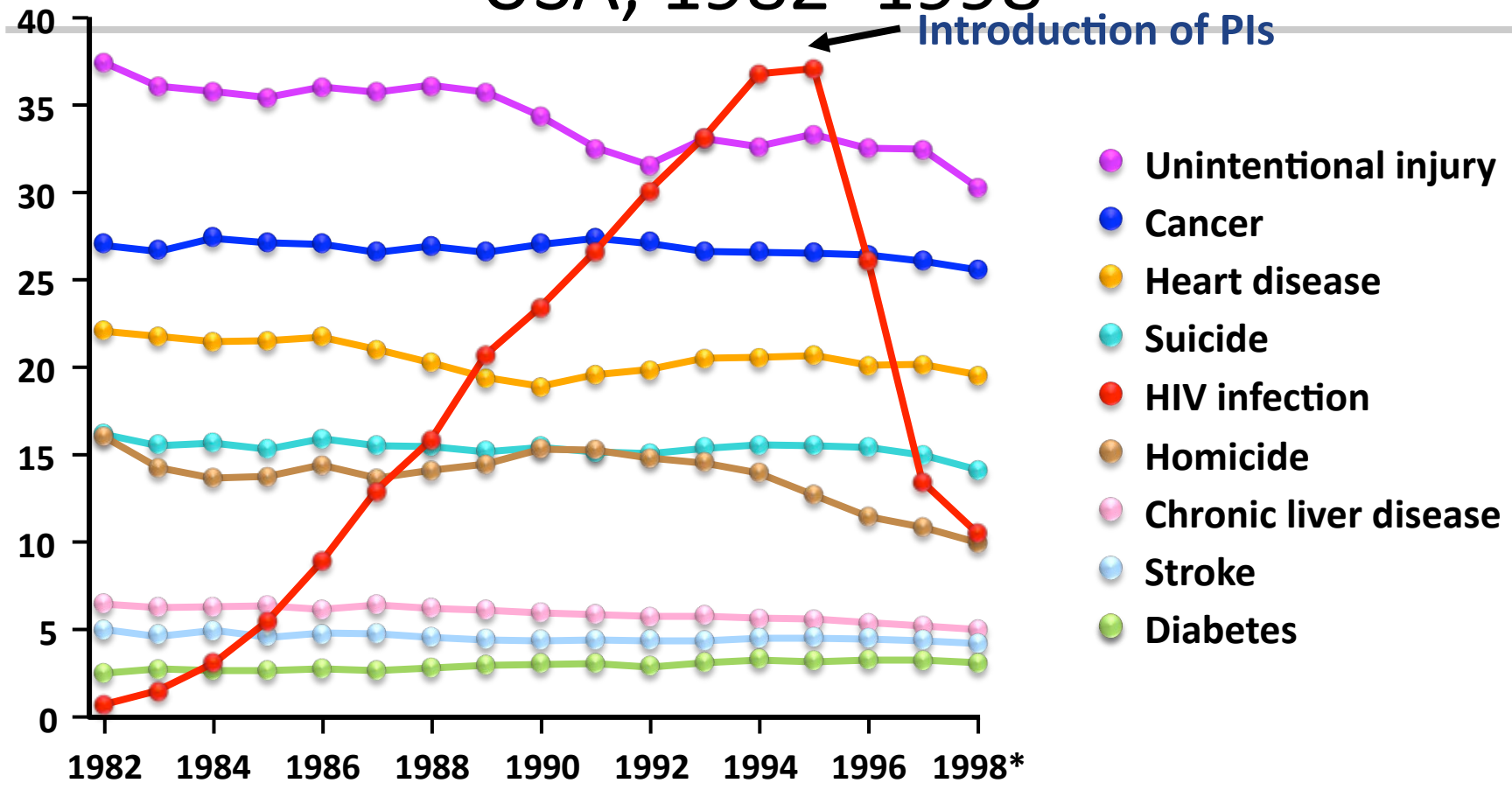

CHILD-RESISTANT PACKAGING
USE SCISSORS TO OPEN
SINGLE-DOSE PACKET
VIDEX®
(didanosine)
Buffered Powder For Oral Solution
CAUTION: FEDERAL LAW PROHIBITS DISPENSING WITHOUT PRESCRIPTION
See accompanying circular for indications and dosage schedules.
BRISTOL-MYERS SQUIBB
Immunology

Mortality among persons 25–44 years old, USA, 1982–1995



Centers for Disease Control HIV Mortality (through 2005). Available at: http://www.cdc.gov/hiv/topics/surveillance/resources/slides/mortality/index.htm. Accessed June 10, 2009

Mortality among persons 25–44 years old, USA, 1982–1998

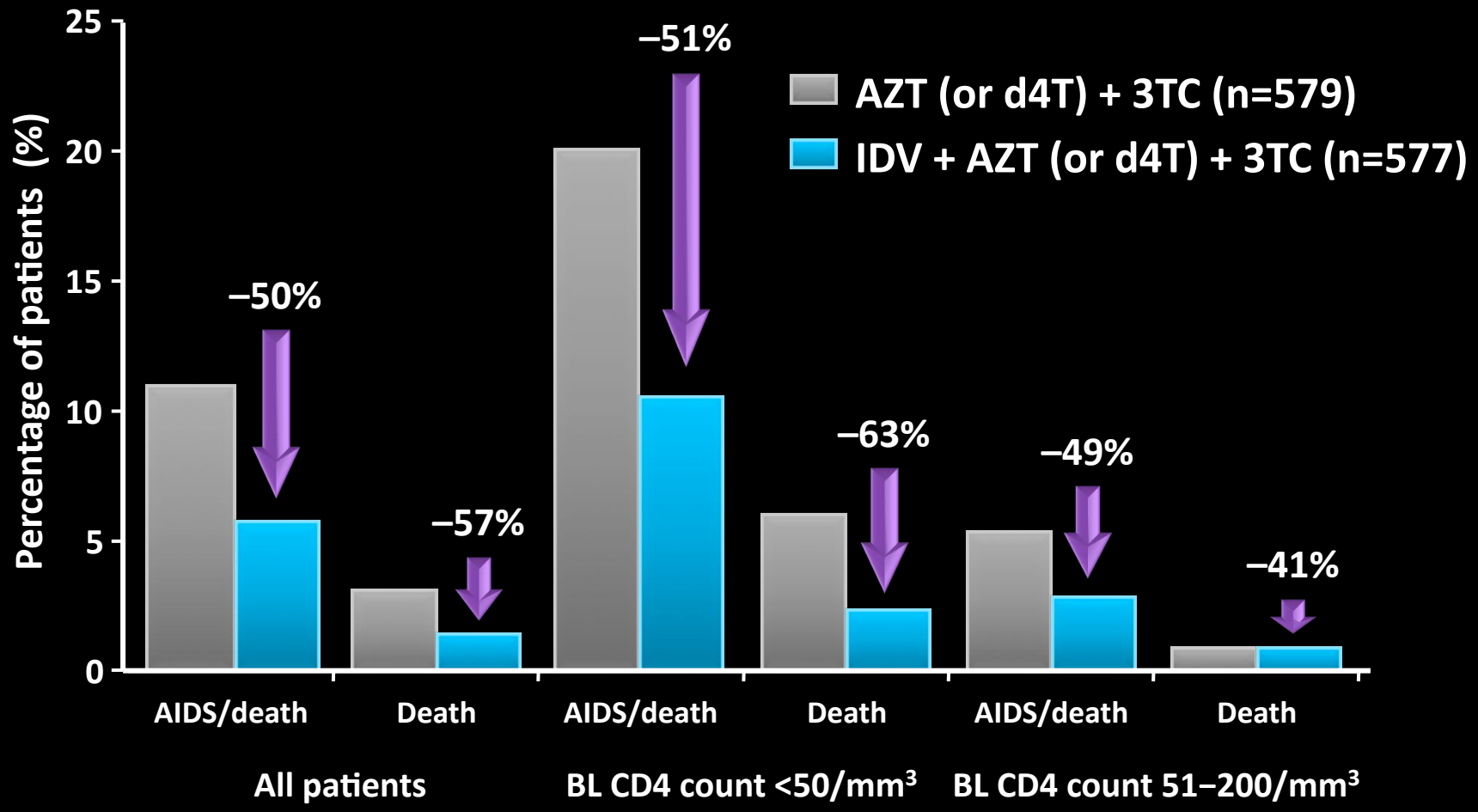


* Preliminary 1998 data

Centers for Disease Control HIV Mortality (through 2005). Available at: http://www.cdc.gov/hiv/topics/surveillance/resources/slides/mortality/index.htm. Accessed June 10, 2009

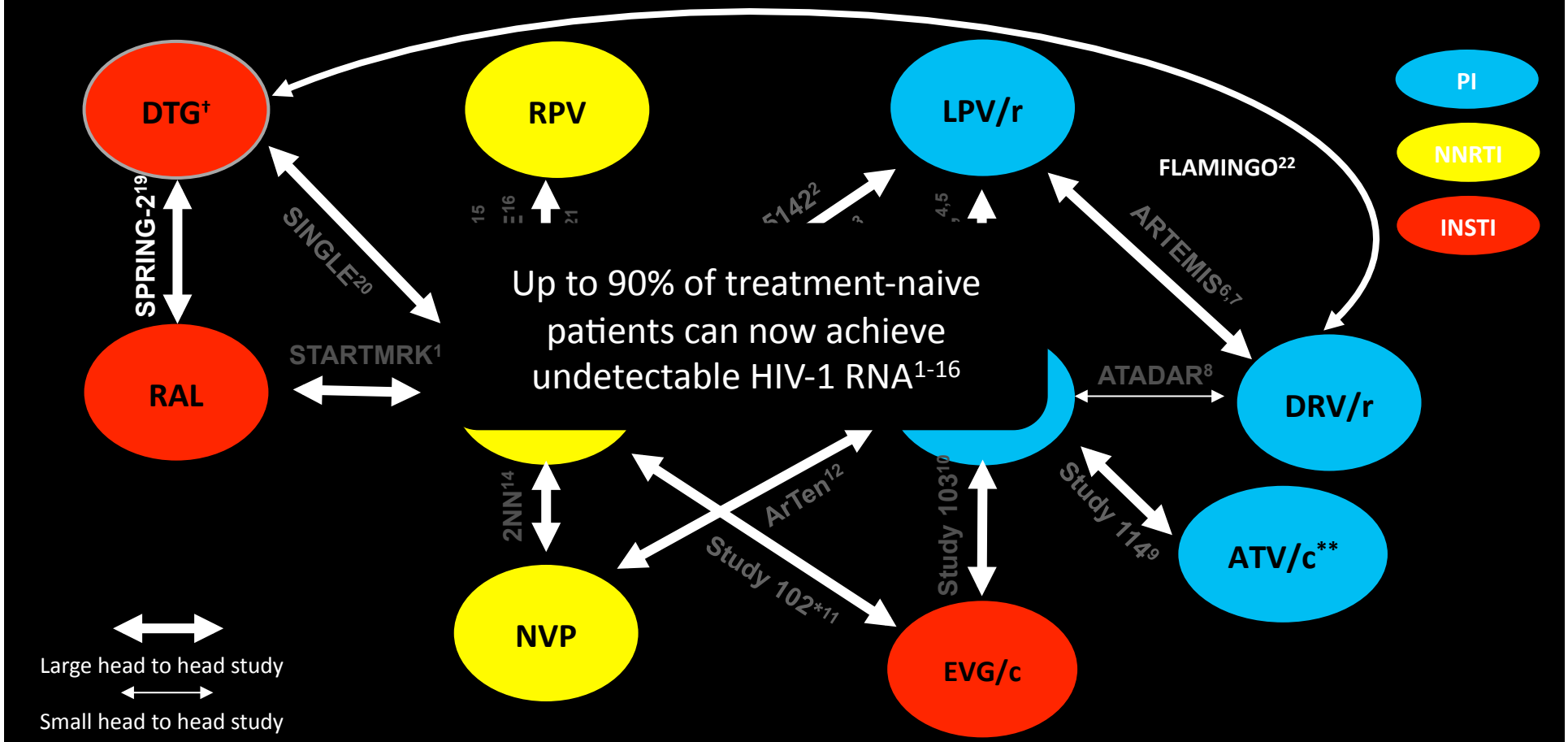

Survival
Efficacy
Tolerability

Improved clinical outcomes: ACTG 320



Adapted from Hammer SM *et al. NEJM* 1997;337:725–33

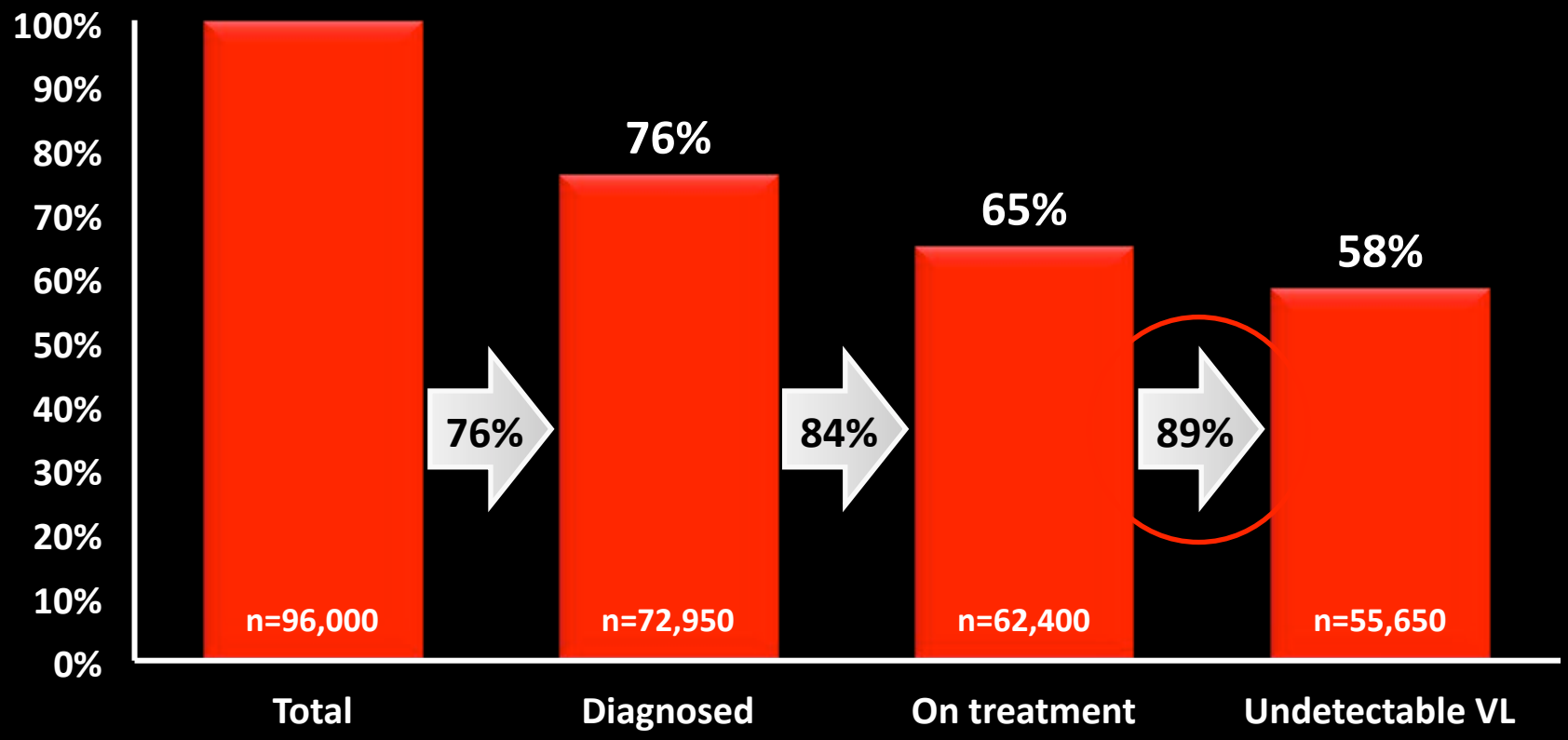
…a potent armamentarium



O425. URL: http://natap.org/2012/interHIV/InterHIV_15.htm. 22.

21. Cohen C et al. HIV11 2012. Oral presentation

Continuum of care
Persons living with HIV in the UK 2011



HIV and AIDS Reporting System
HIV and STI Department, Health Protection Agency - Colindale


THE MARLOWE PLAYERS
present
Charles Dickens
A Tale of Two Cities
Adapted by
Mark Fitzgibbons
At Derby Playhouse, Studio Theatre
March 28th – April 1st 2000
Time 7.45pm
Tickets £6.00 (£5.00 concessions)
BOX OFFICE 01332 363275
an amateur production


HIV VOLUNTARY
COUNSELING AND
TESTING CENTER

HAART teams

	Chelsea and Westminster	Zewiditu, Ethiopia
Doctors	32	5
Nurses	14	5+8
Pharmacists	4	1

HAART teams

	Chelsea and Westminster	Zewiditu, Ethiopia
Doctors	32	5
Nurses	14	5+8
Pharmacists	4	1
Patients	4210	9122
On-treatment	3117	3045

Available Antiretrovirals 2010

NRTIs

- Abacavir
- Didanosine
- Emtricitabine
- Lamivudine
- Stavudine
- Tenofovir
- Zidovudine

NNRTIs

- Efavirenz
- Nevirapine
- Etravirine

Protease Inhibitors

- Atazanavir
- Darunavir
- Fos-Amprenavir
- Indinavir
- Lopinavir
- Nelfinavir
- Ritonavir
- Saquinavir
- Tipranavir

New Classes

Fusion Inhibitors

- Enfuvirtide

R5 Inhibitors

- Maraviroc

Integrase Inhibitors

- Raltegravir

www.emea.europa.eu

Available Antiretrovirals -Ethiopia

NRTIs

- Didanosine
- Lamivudine
- Stavudine
- Zidovudine

NNRTIs

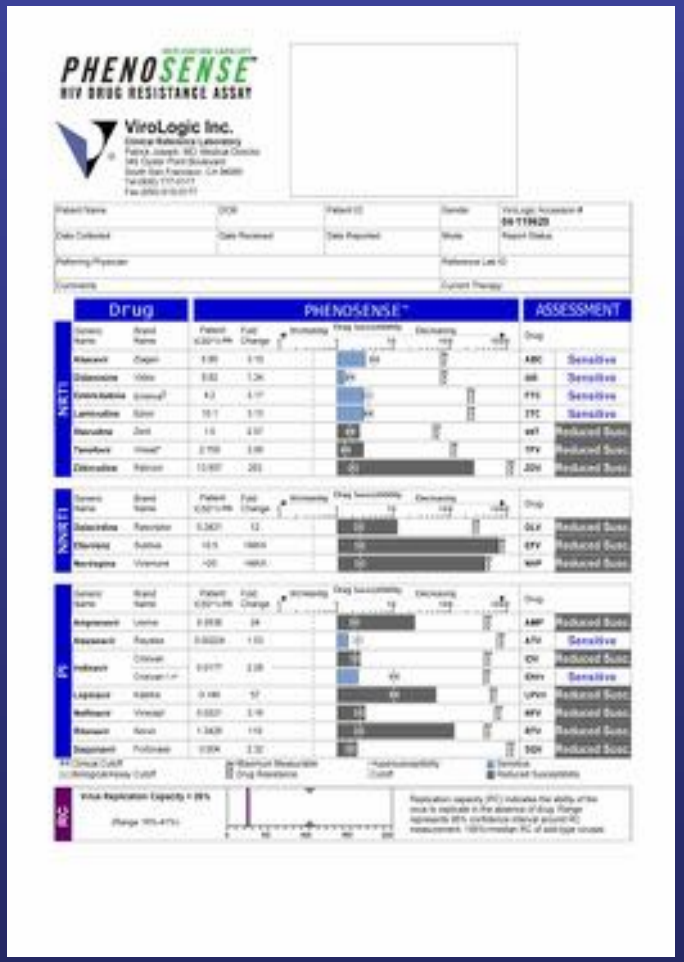
- Efavirenz
- Nevirapine

Protease Inhibitors

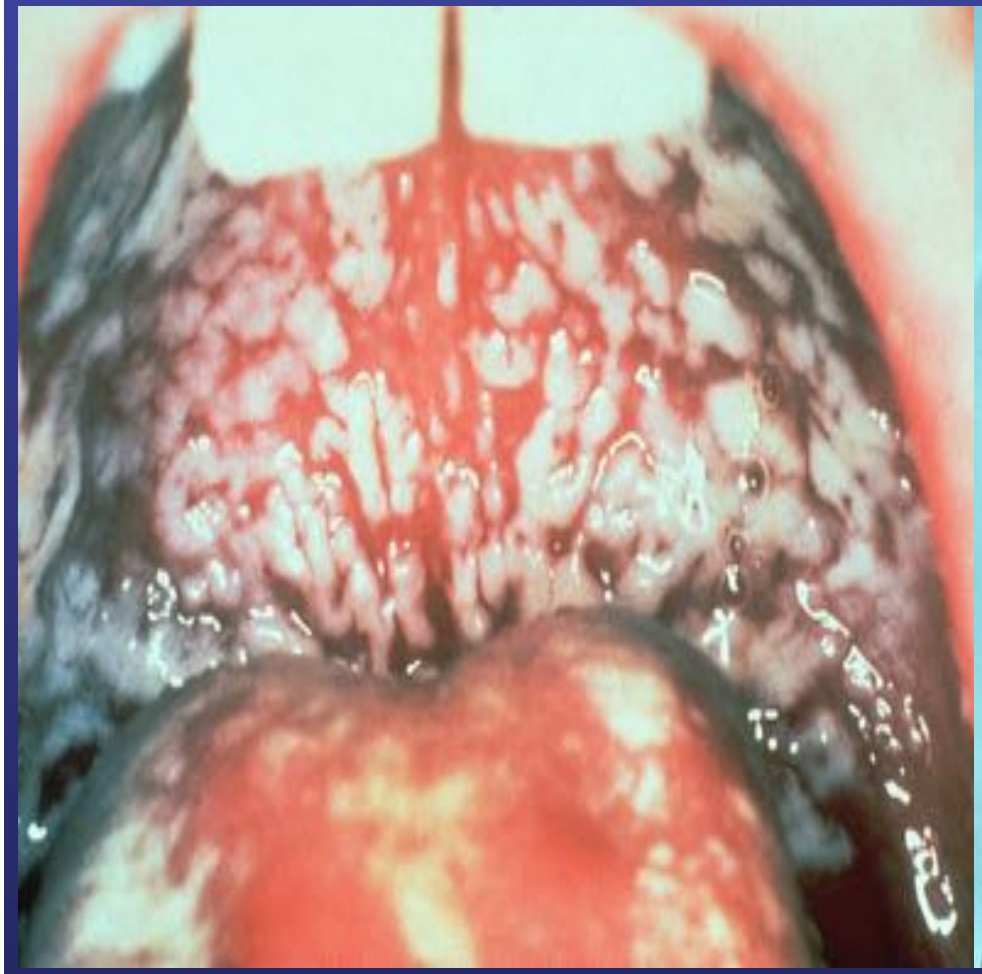
- Lopinavir
- Nelfinavir

New Classes

Monitoring at Chelsea and Westminster

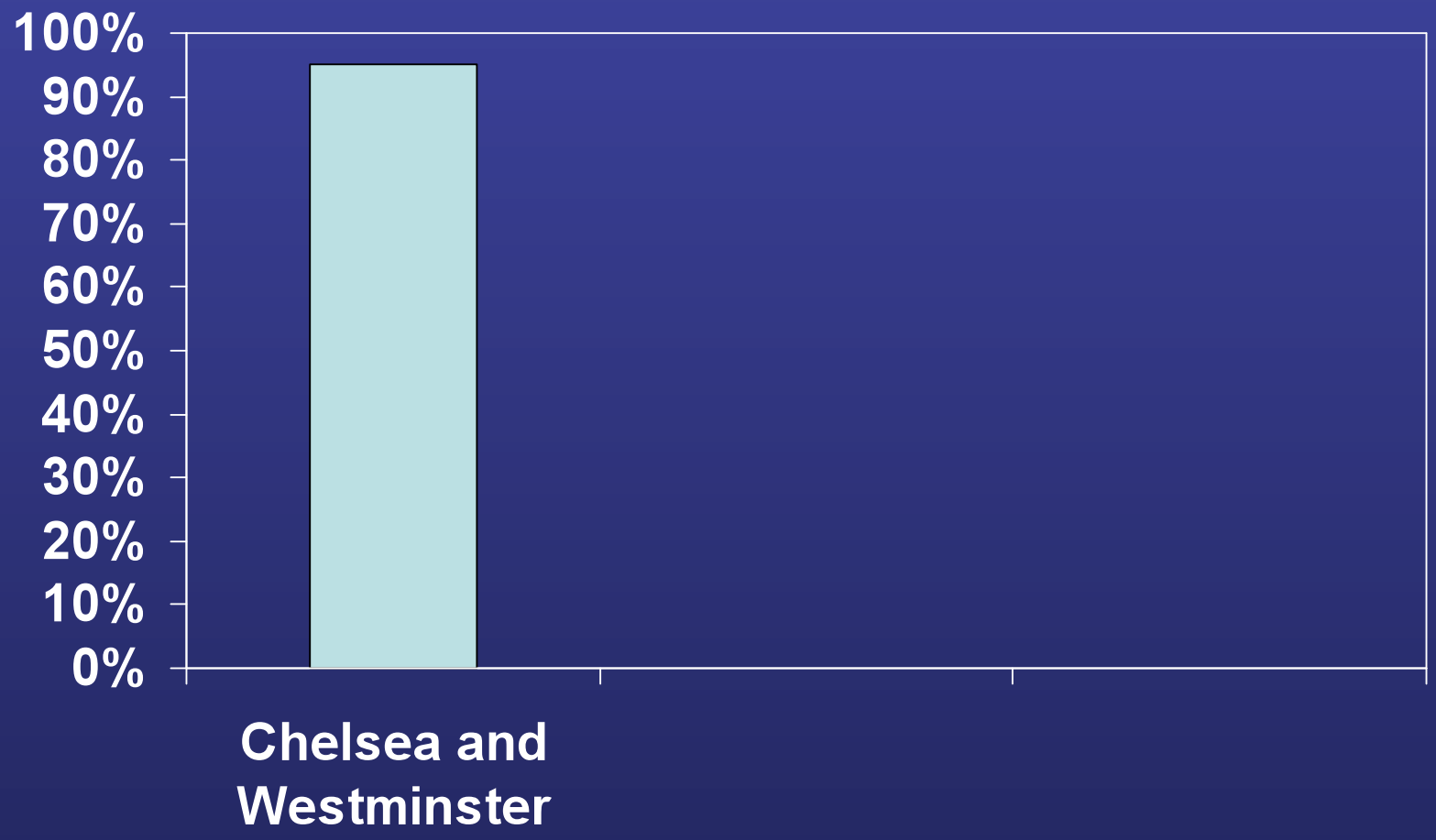


Monitoring in Ethiopia




HIV VOLUNTARY
COUNSELING AND
TESTING CENTER

Naïve patients undetectable viral load at 6 months



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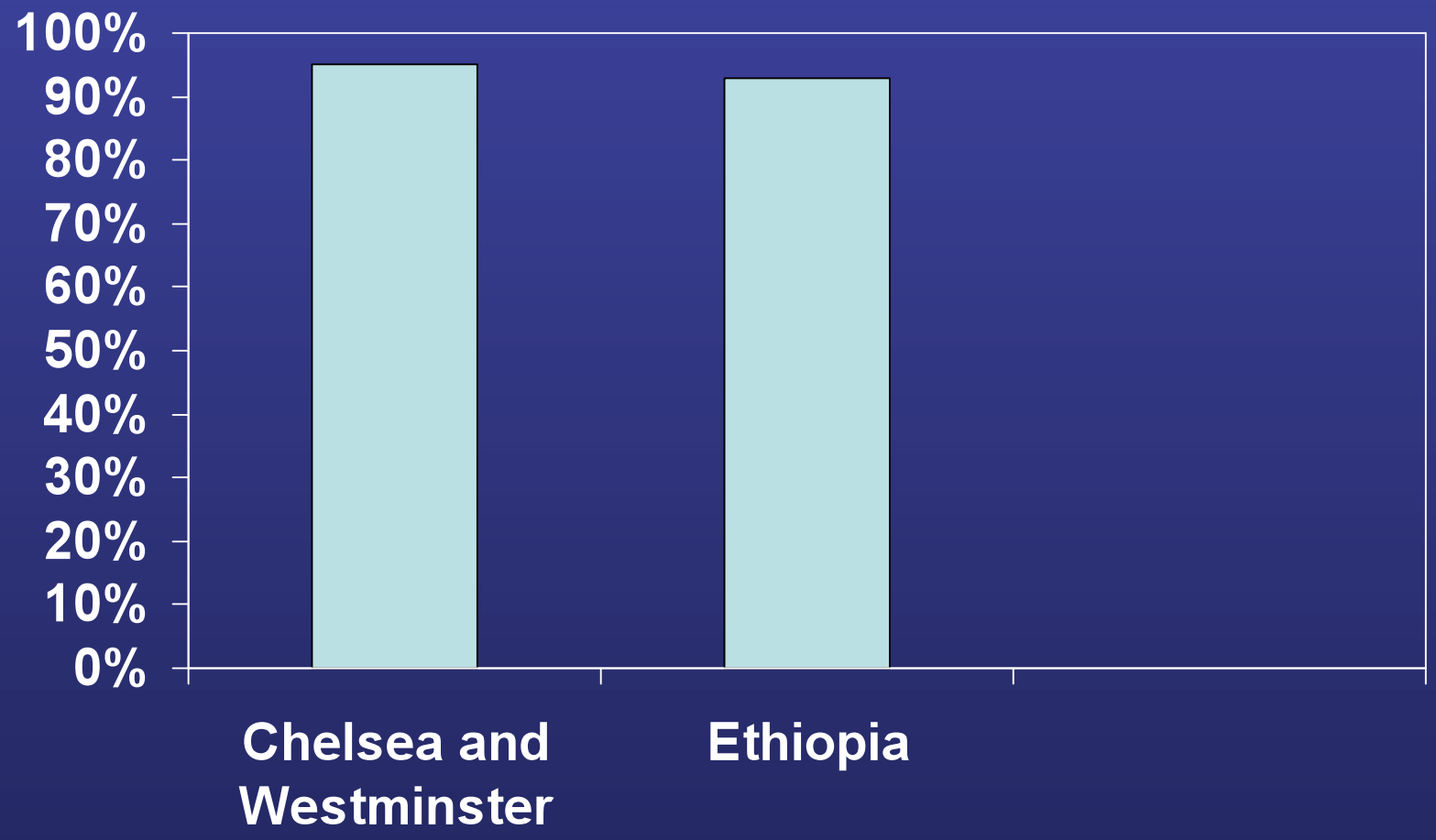

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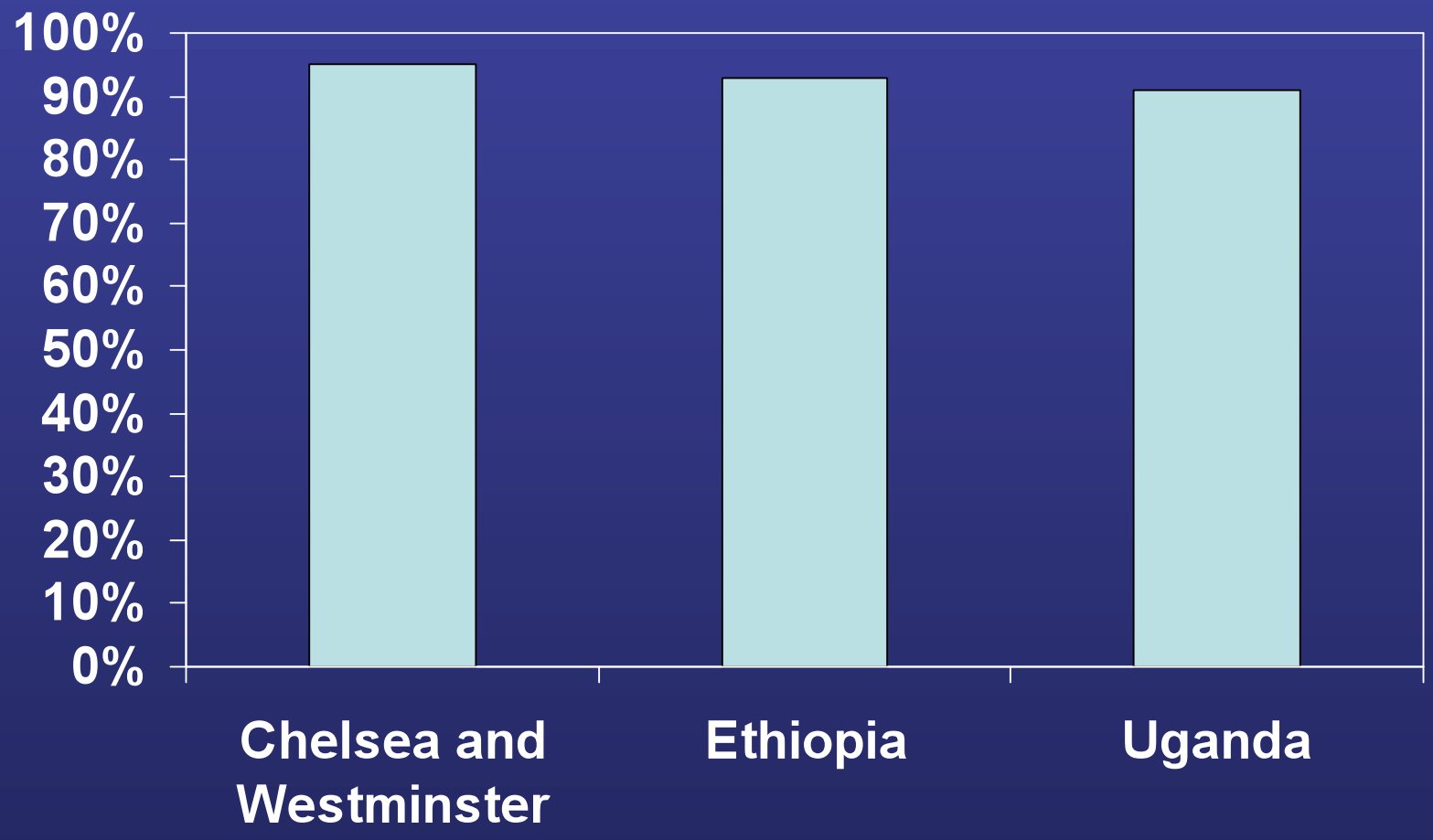
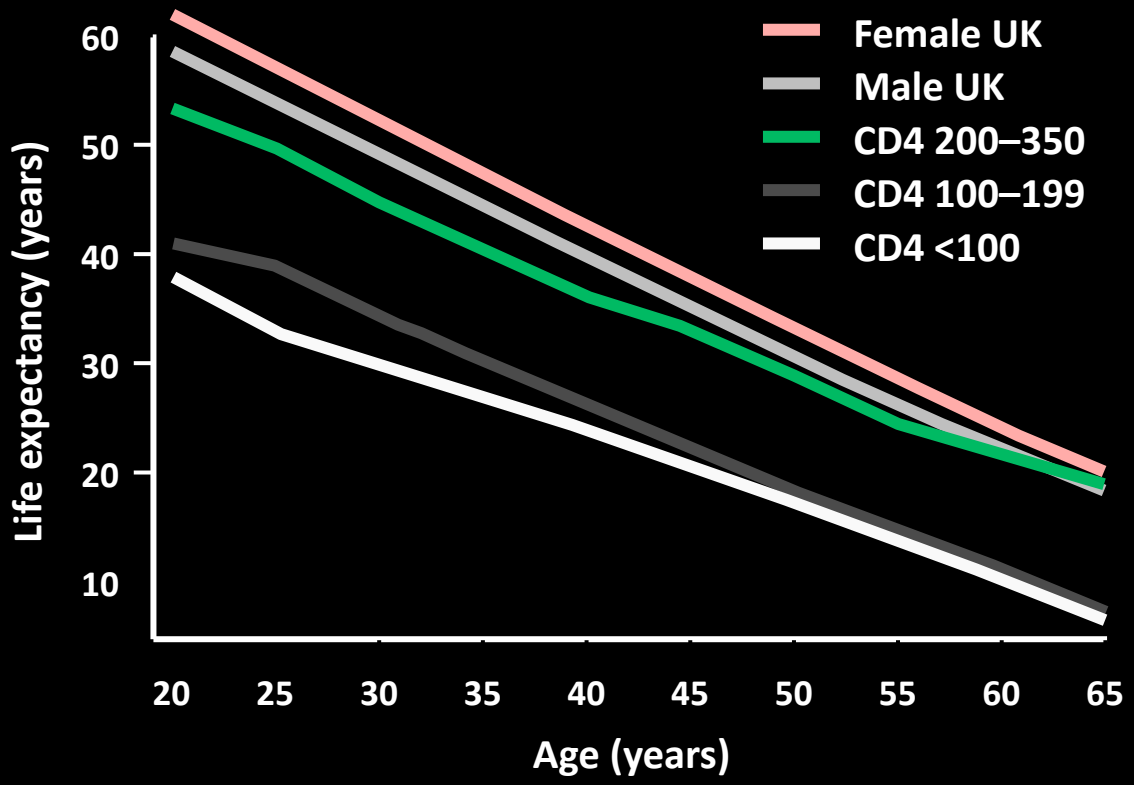


UK CHIC – Life expectancy

Life expectancy by CD4 count compared with UK population



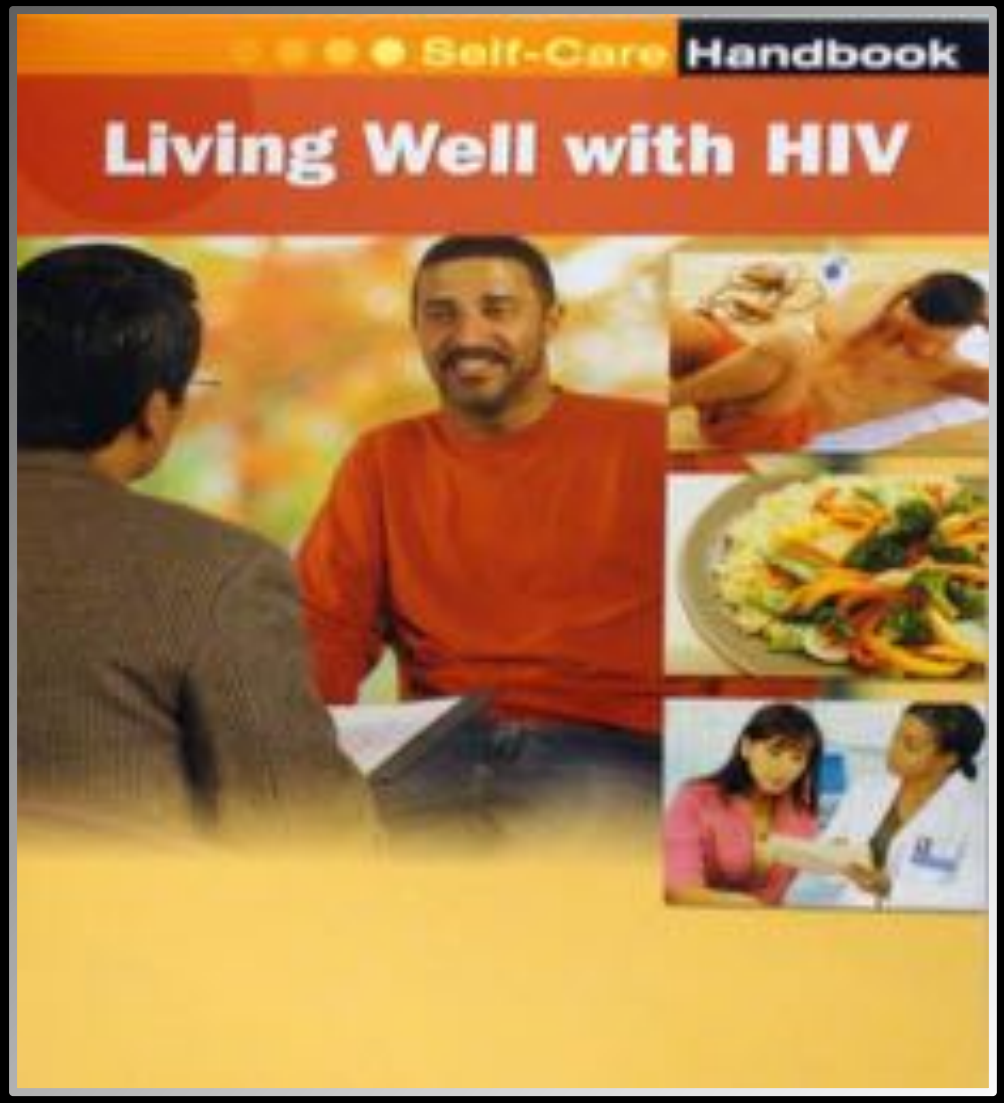
LE at exact age 20 years:
1996- 2008

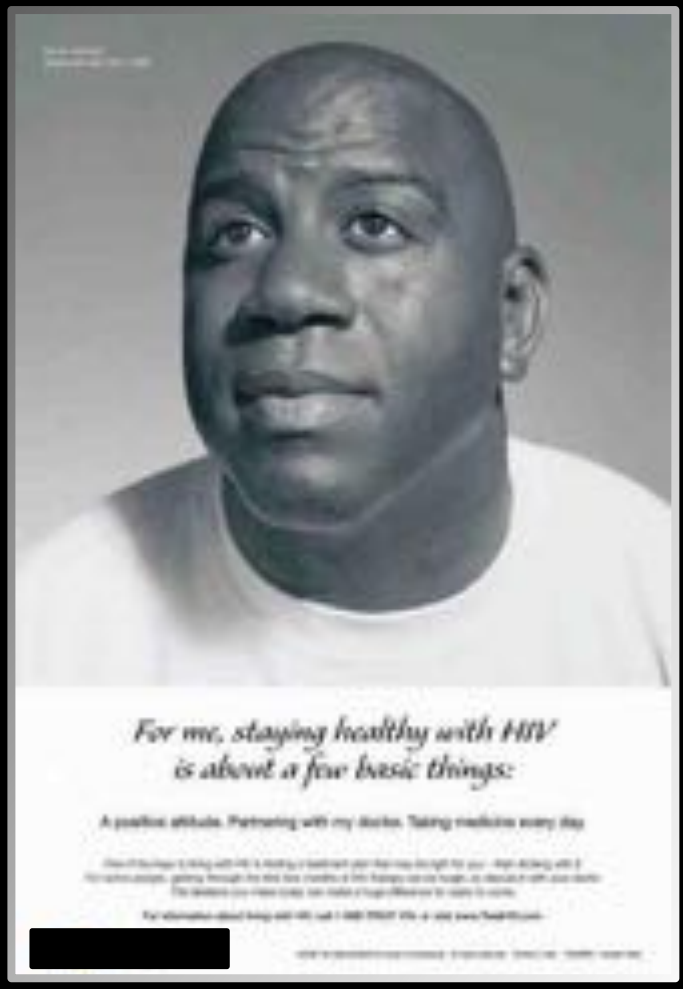
UK women	61.6 yrs
UK men	57.8 yrs
HIV+ women	50.2 yrs
HIV+ men	39.5 yrs
1996–99 HIV+	30.0 yrs
2006–08 HIV+	45.8 yrs

Start triple ART post 2000

CD4 200–350	53.4 yrs
CD4 100–199	41.0 yrs
CD4 <100	37.9 yrs

Impact on life expectancy of late diagnosis and treatment of HIV-1 infected individuals:
UK CHIC M May, M Gompels, C Sabin for UK CHIC. HIV10 Glasgow abstract 1629596

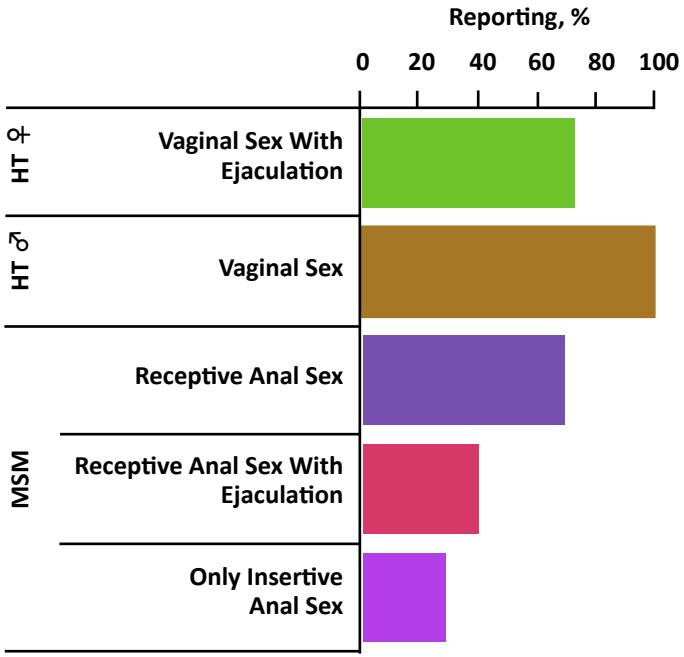

Self-Care Handbook
Living Well with HIV


For me, staying healthy with HIV
is about a few basic things:
A positive attitude. Partnering with my doctor. Taking medicine every day.

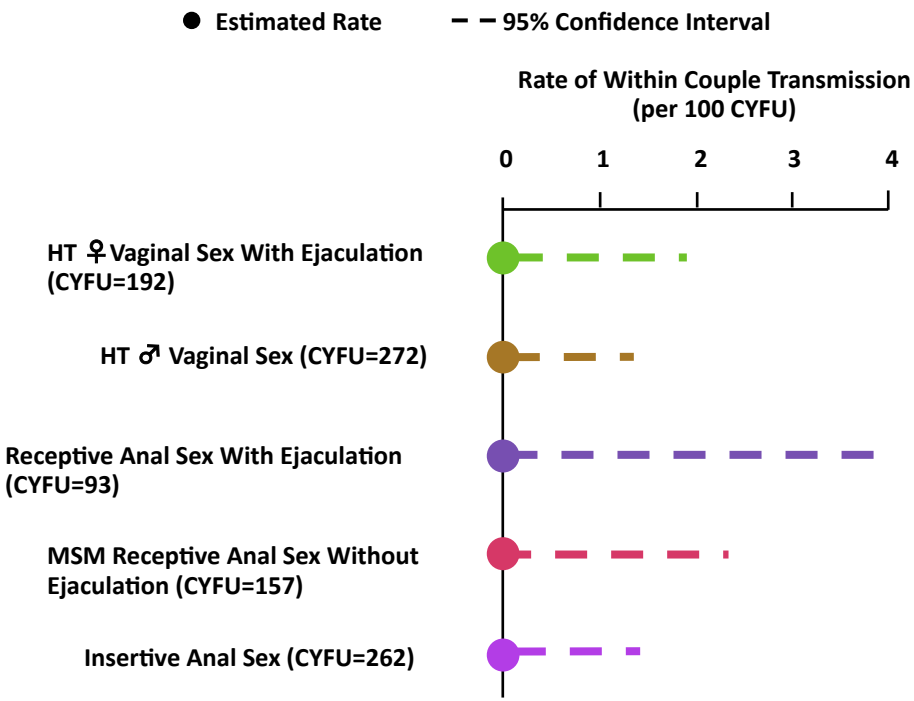
PARTNER Study

Condomless Sex Acts and Rate of HIV Transmission by Sexual Behaviour

HIV-Negative Partners Reporting Penetrative Sex Acts



Rate of HIV Transmission by Behaviour of HIV-Negative Partner



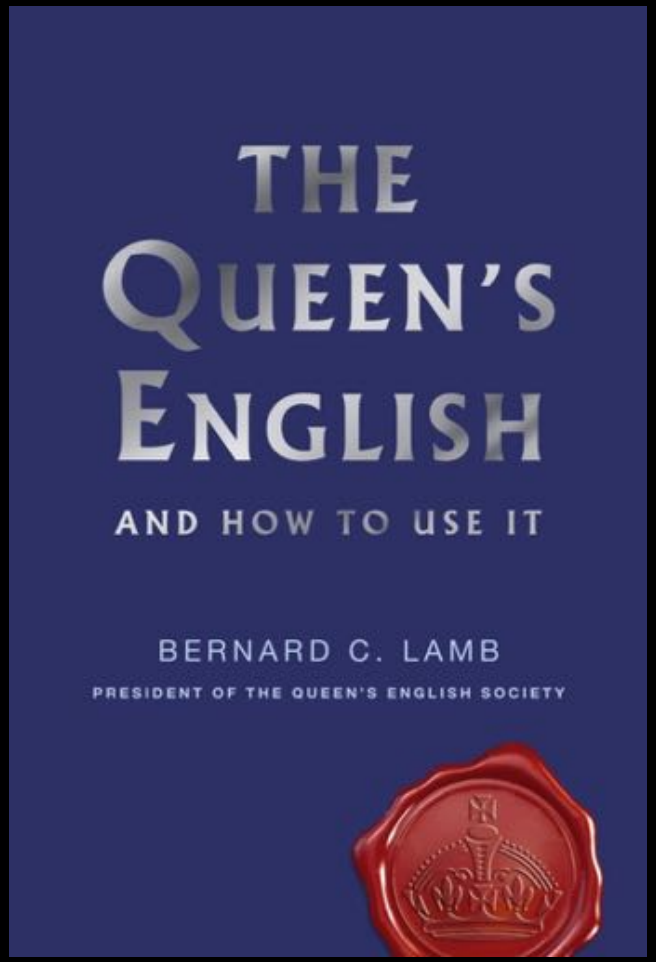
Suppressive ART resulted in zero linked transmissions to HIV-negative partners with condomless sex, despite a substantial number of sex acts. Unlinked transmissions did occur. Additional follow-up in MSM is forthcoming in the PARTNER2 study.

Rodger A, et al. CROI 2014; Boston. #153LB


Survival
Efficacy
Tolerability

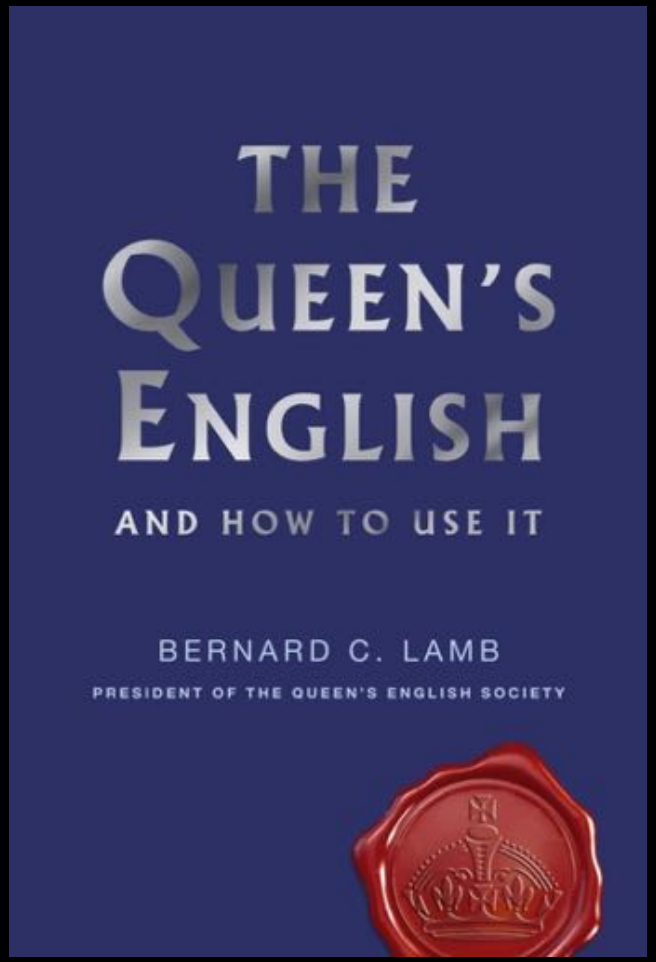

QUALITY
QUANTITY

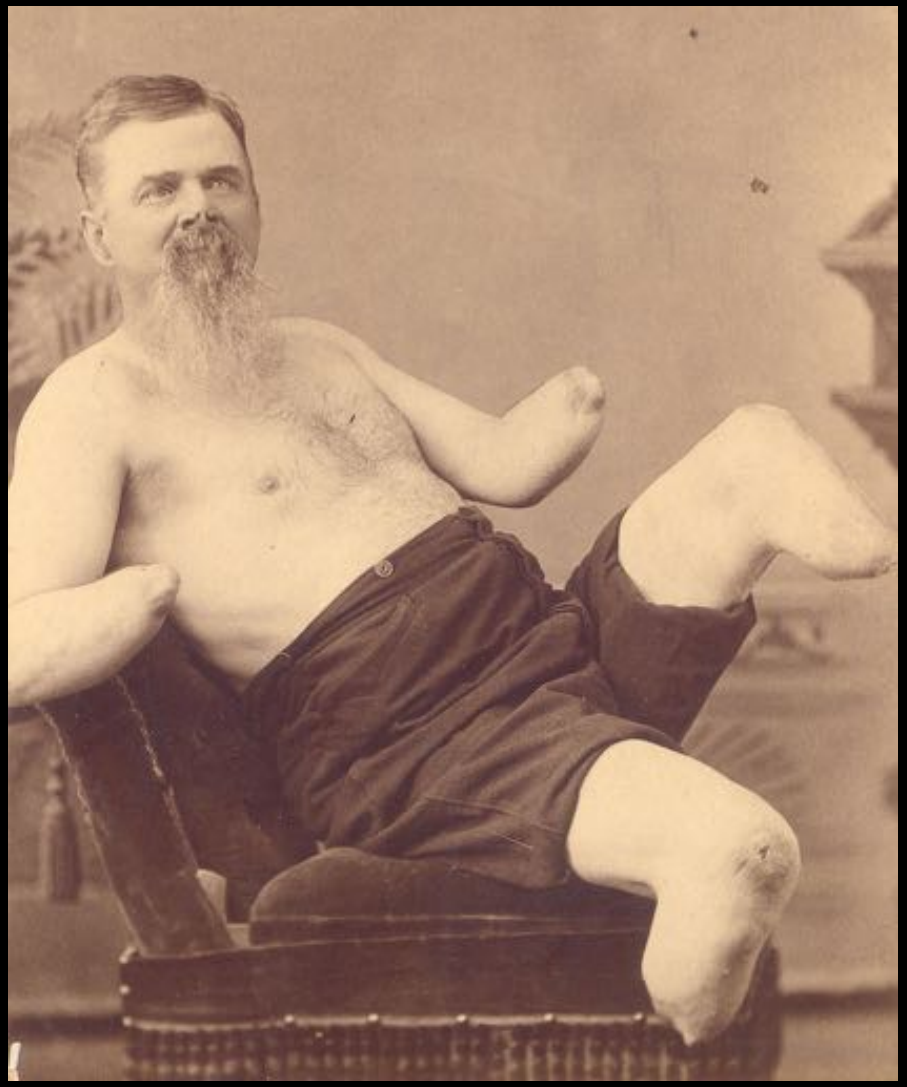
To Tolerate


THE
QUEEN'S
ENGLISH
AND HOW TO USE IT
BERNARD C. LAMB
PRESIDENT OF THE QUEEN'S ENGLISH SOCIETY

To Tolerate

- To endure





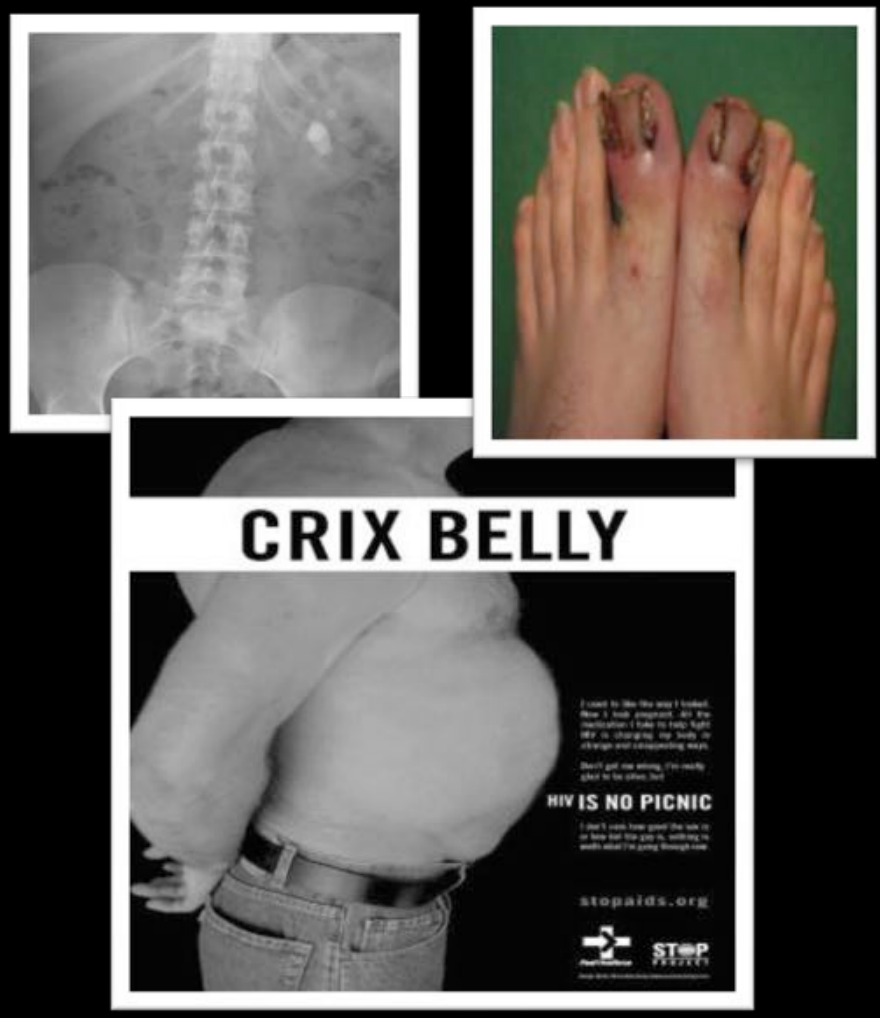

Bruce in New Zealand

06_15368 © Th Martinez /BILBAO, SPAIN. 22 October 2008


QUALITY
QUANTITY

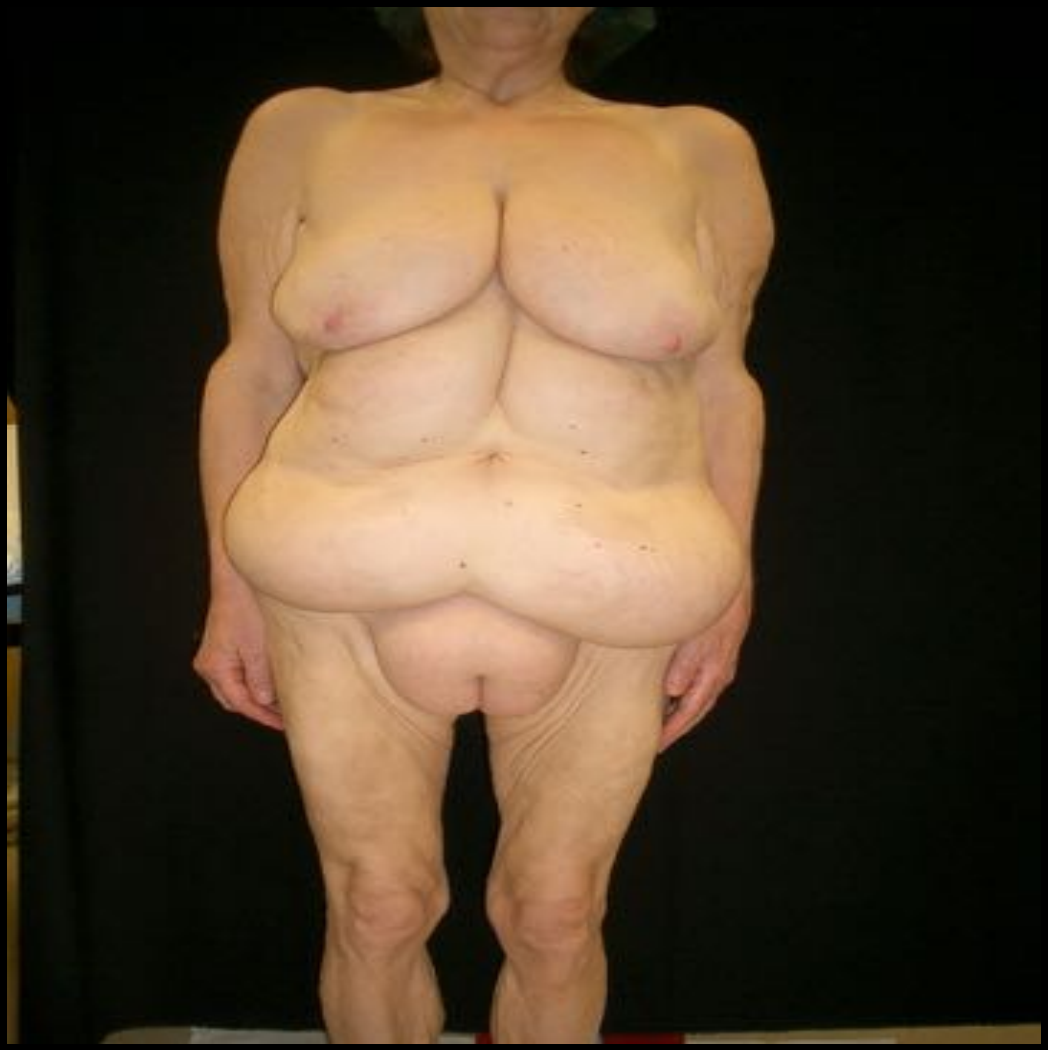
Toxicity of first generation PIs

- Nausea
- Diarrhoea
- Metabolic disturbances
- Body shape changes
- Paraesthesia
- Dysgeusia

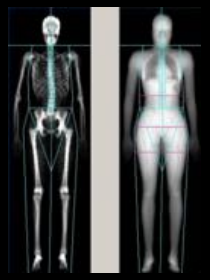


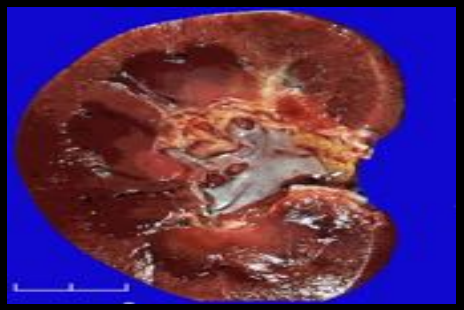
And nucleosides were associated with.....

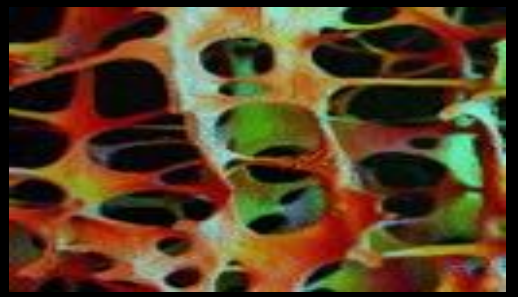
Resulting in.....

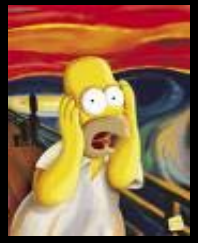


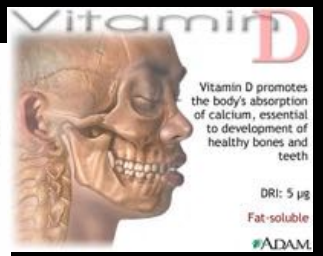

Lipemic










Vitamin D
Vitamin D promotes the body's absorption of calcium, essential to development of healthy bones and teeth
DRI: 5 µg
Fat-soluble
ADAM.

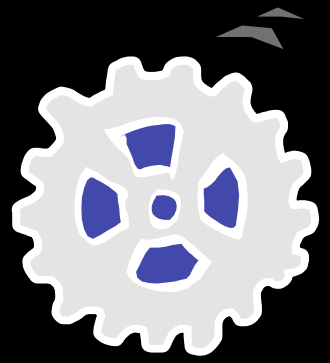
Toxicities: delayed recognition

Drug / class	FDA approval	Toxicity	Strong signal	Delay (years)
Zidovudine	1987	lipoatrophy	1999	12
Stavudine	1994	lipoatrophy	1999	5
Nevirapine	1996	hepatitis / rash at higher CD4	2005	9
PIs	1996-	heart attack	2003	7
Efavirenz	1998	suicidality	2013	15
Abacavir	1998	heart attack	2008	10
Tenofovir	2001	kidney disease	2006	5
Tenofovir	2001	fracture	2013	12
Raltegravir	2007	myopathy	2012	5

Saint-Marc et al, AIDS 1999; Lundgren et al, NEJM 2003; D:A:D Study Group, Lancet 2008
Cooper et al, Clin Infect Dis 2010; Bedimo et al, AIDS 2012; Lee et al, JAIDS 2013; Mollan et al, IDSA 2013


NICOLAS SARKOZY
L'ÉTÉ AMÉRICAIN

Tolerability drives adherence, which drives efficacy



Tolerability

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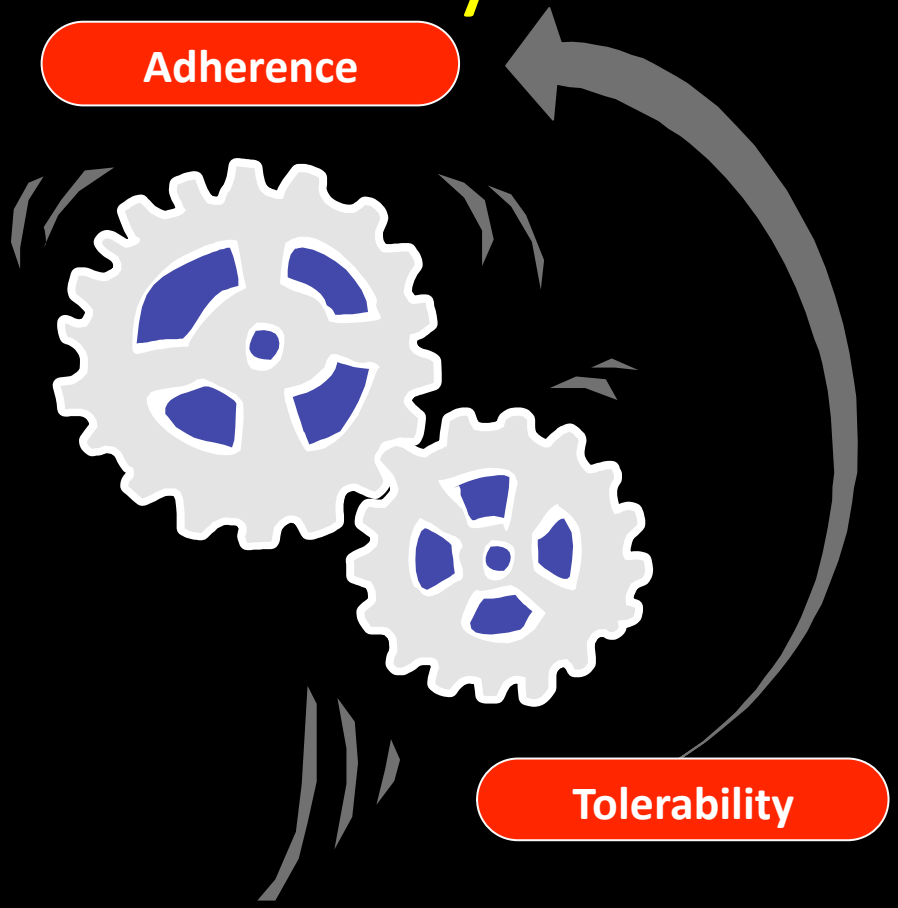

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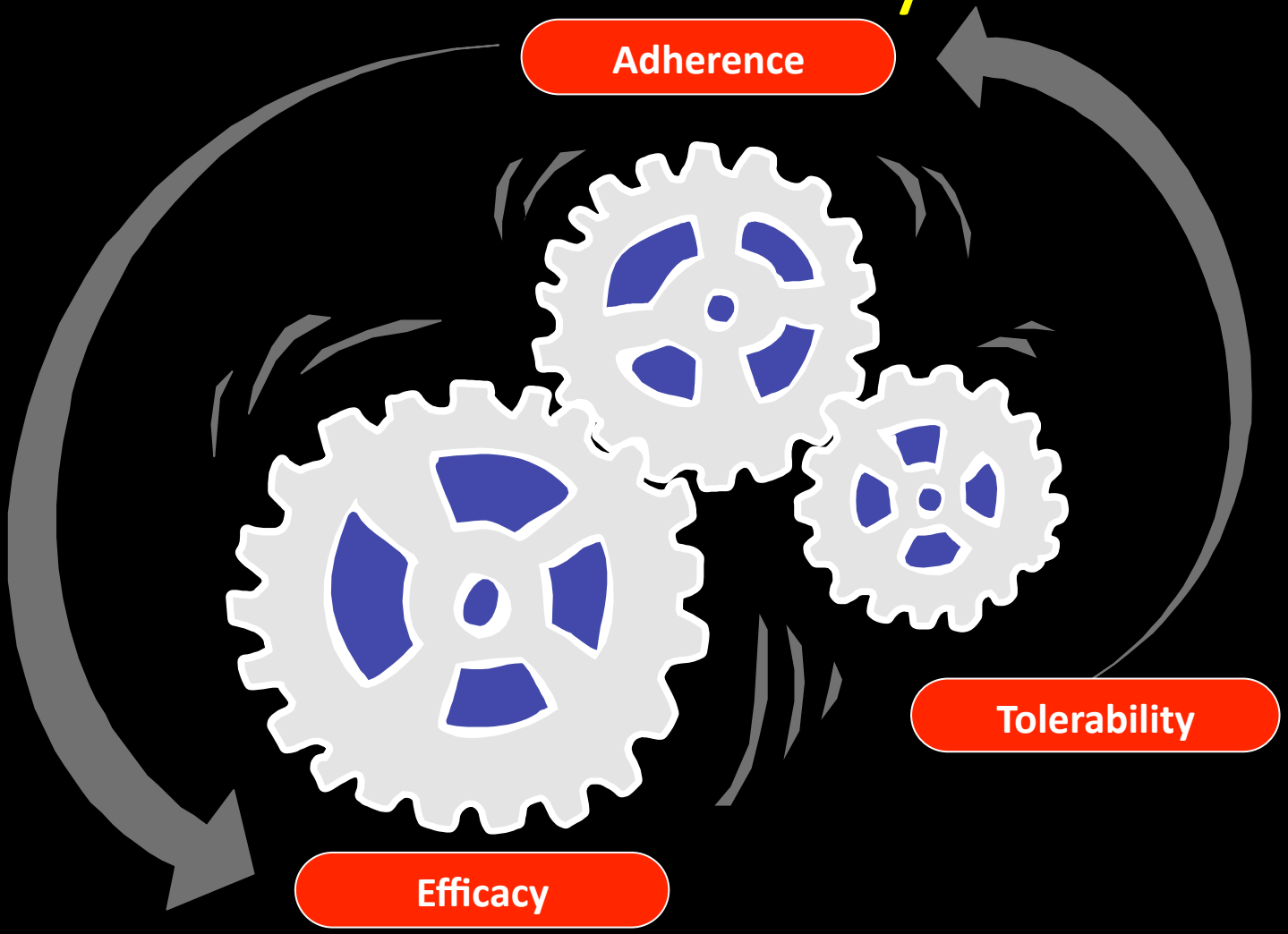
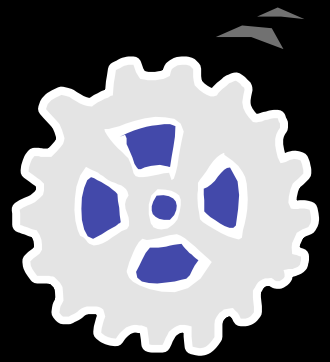
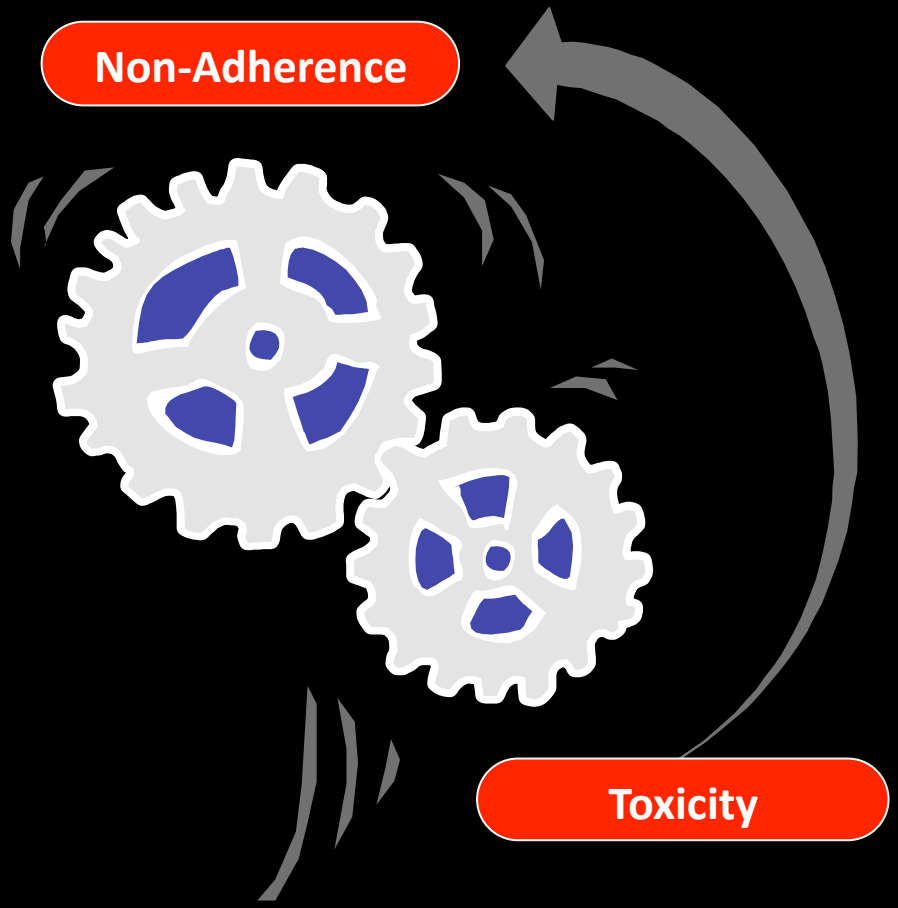


Toxicity drives non-adherence, which drives failure

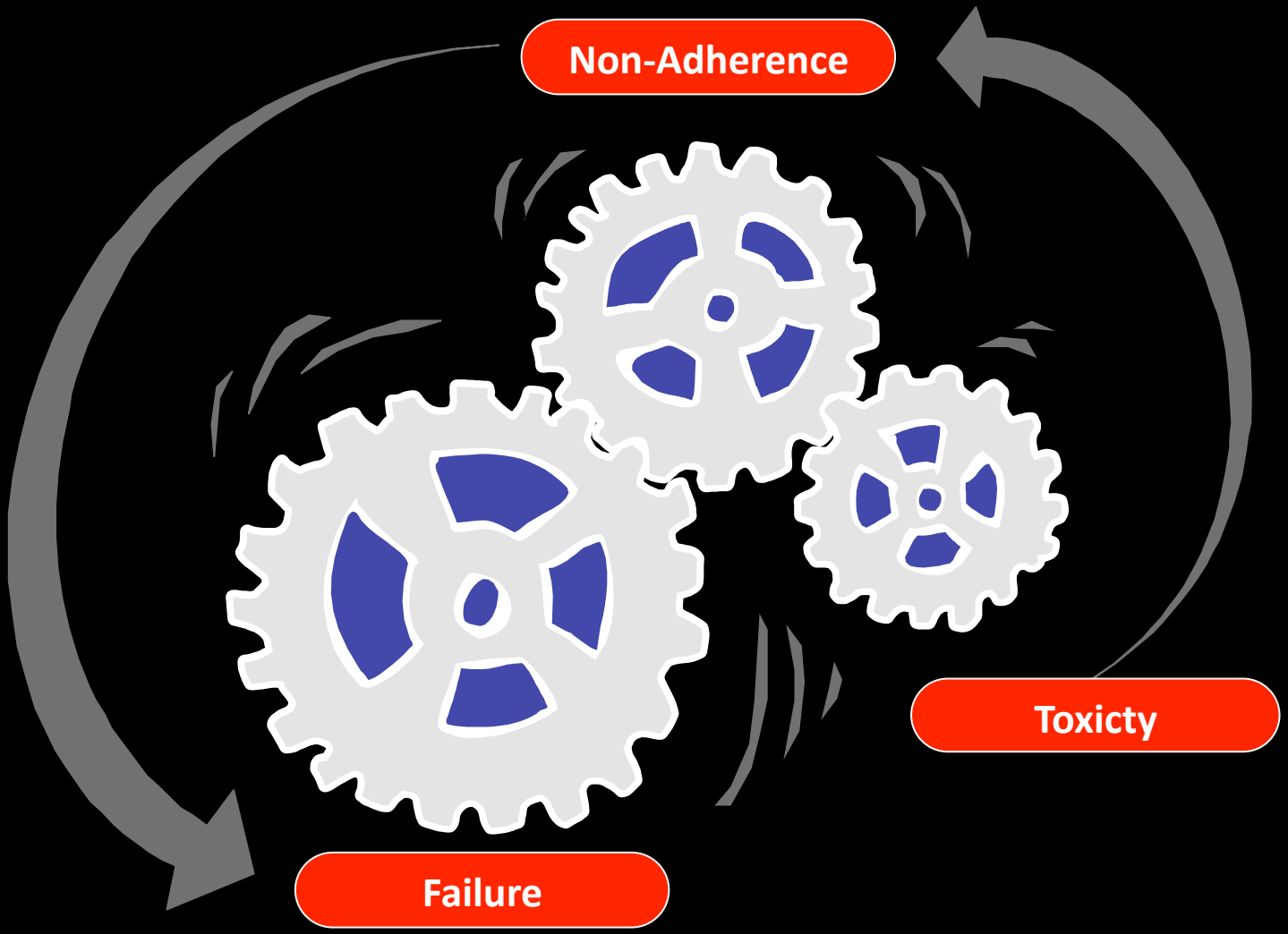


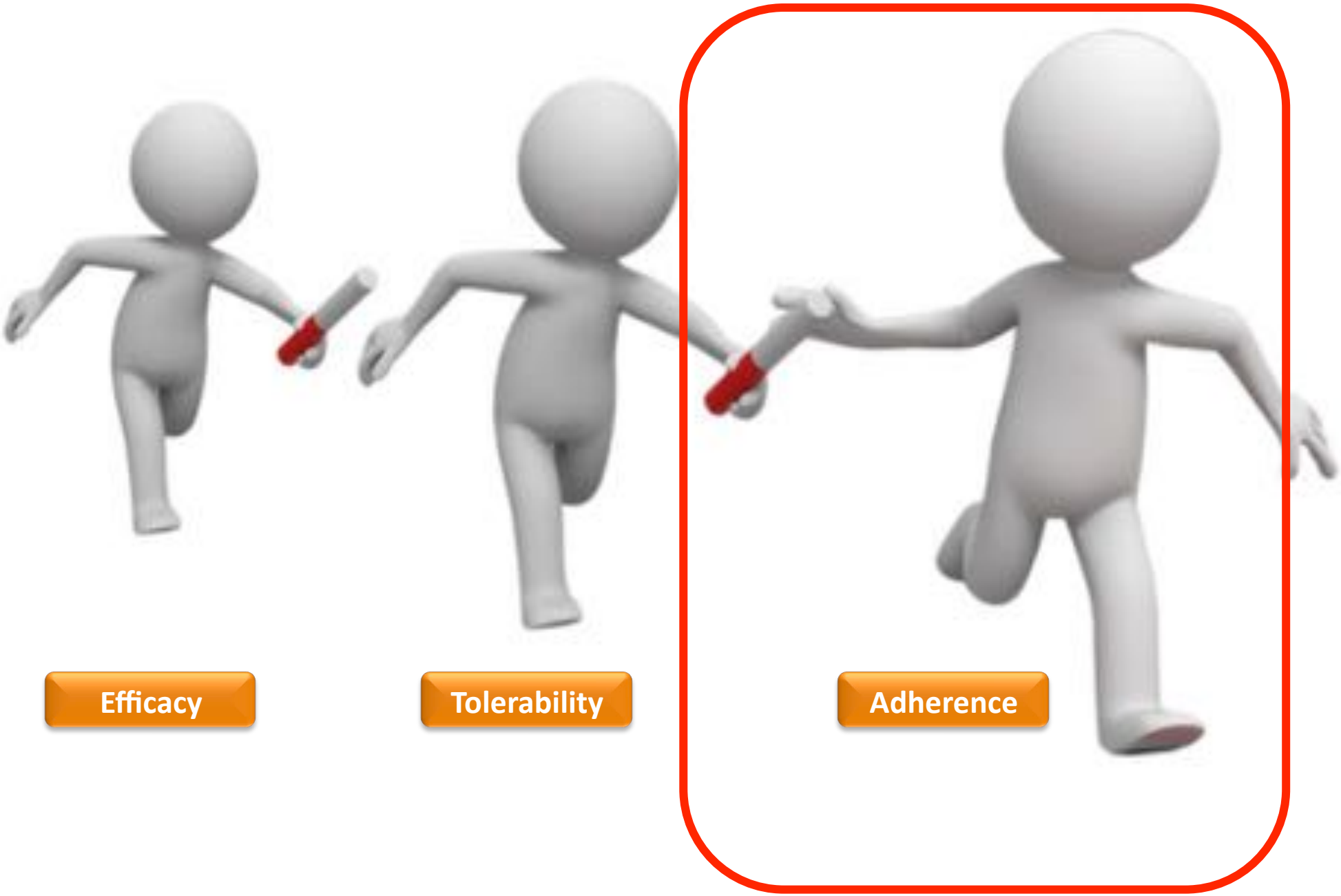
Toxicty

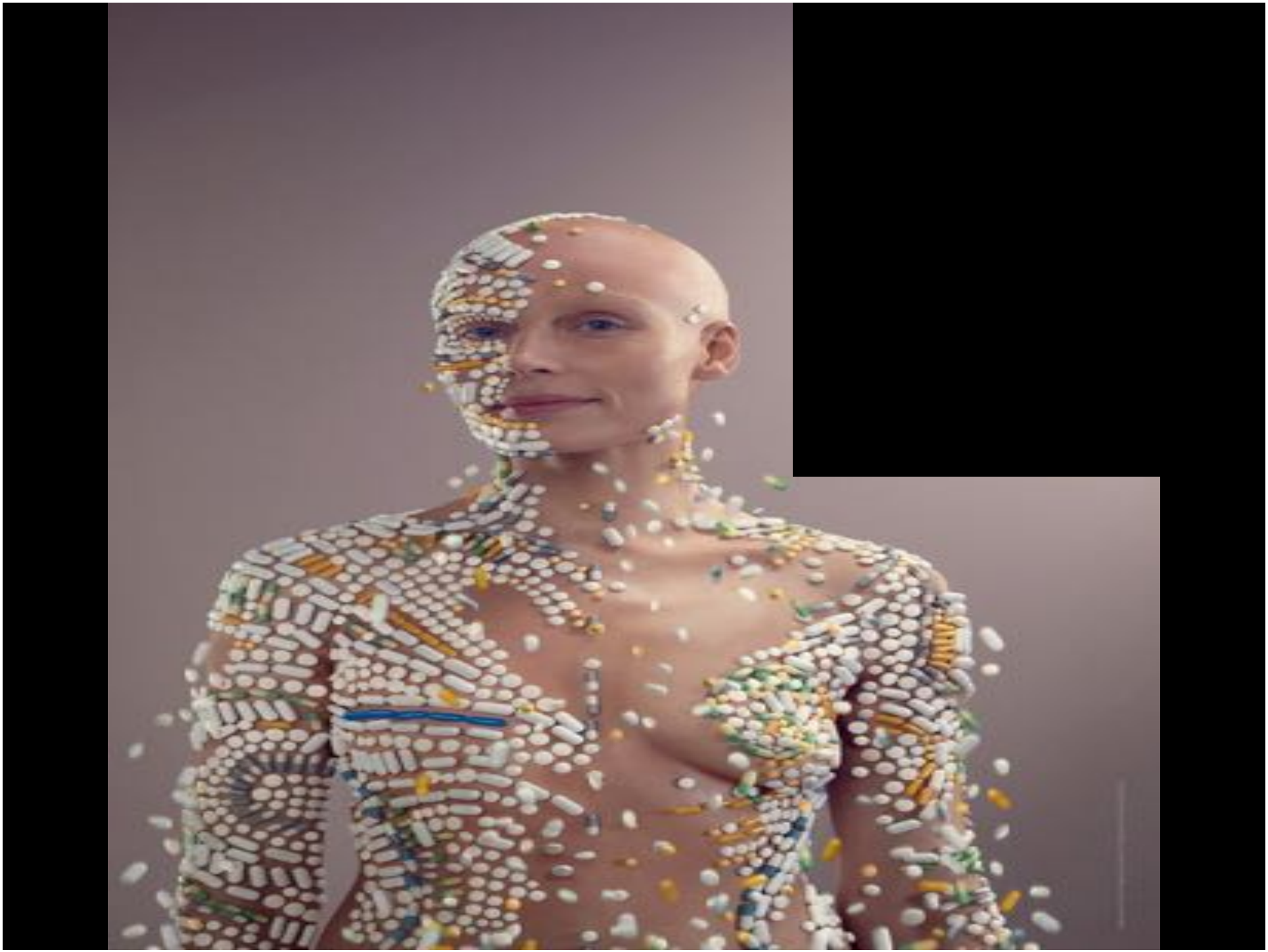
Toxicity drives non-adherence, which drives failure



Toxicity drives non-adherence, which drives failure




Efficacy
Tolerability
Adherence



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

Former US Surgeon General C. Everett Koop

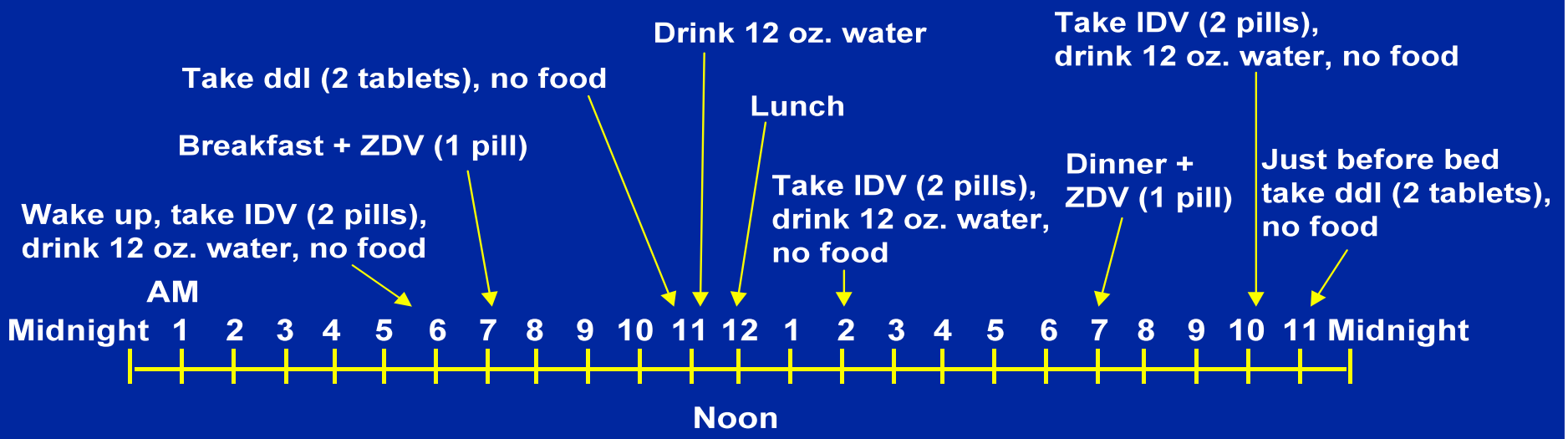
- ***"Drugs do work if people do take them"***

Mark R. Nelson

UK Surgeon General

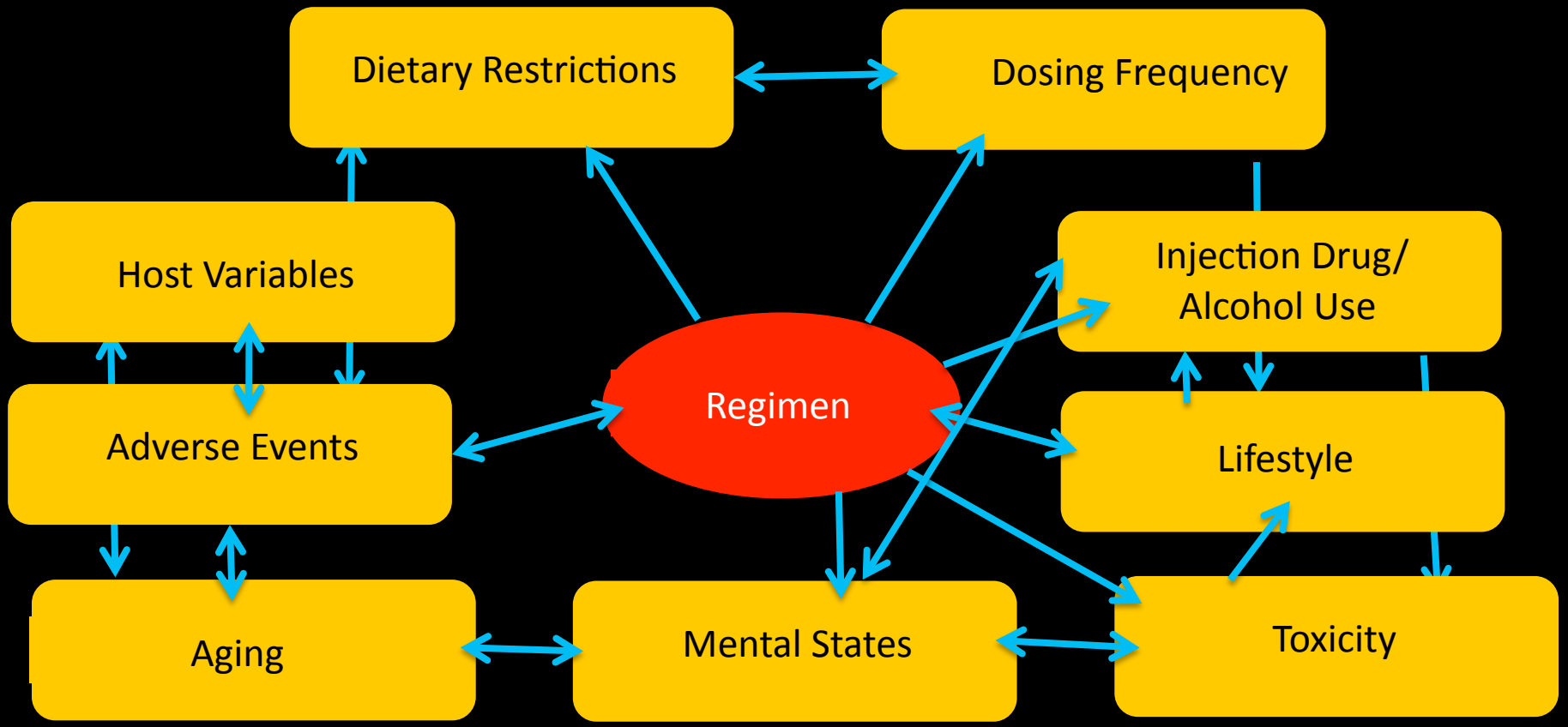
Complexity of Regimens

Adherence Issues: ZDV + ddI + IDV



Source: *Physicians' Desk Reference®*. Medical Economics Co; 1997.

The Complexity of Adherence



‡

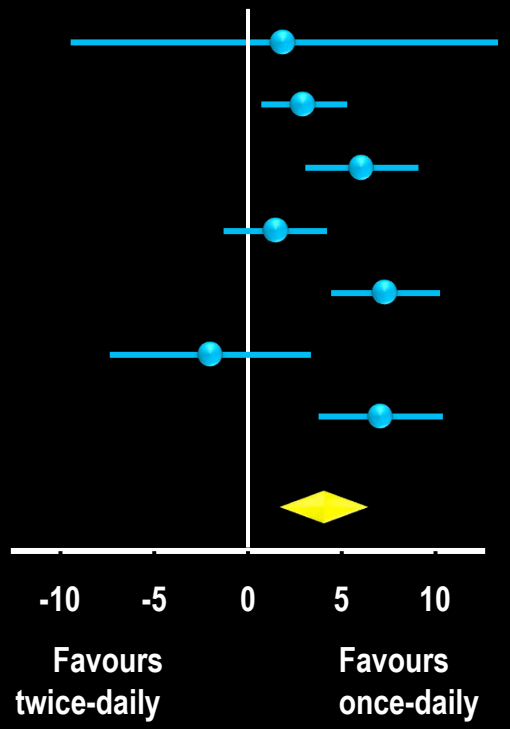
twicedaily

RAL

Pooled adherence ART-naïve patients

Study or subgroup	Once-daily Mean	SD	Total	Twice-daily Mean	SD	Total	Weight	Mean difference IV, Random, 95% CI
Eron 2004 [48]	94	18.3	19	92	17.2	19	3.5%	2.00 [-9.25, 13.29]
Gallant 2006 [49]	90	11.7	244	87	14	243	18.9%	3.00 [0.71, 5.29]
Gonzalez-Garcia 2010 [15]	99	9.9	333	93	25.5	331	16.8%	6.00 [3.05,8.95]
Kubota 2006 [50]	94.3	15.8	411	92.9	15.7	195	17.7%	1.40 [-1.28, 4.08]
Molina 2007 [54]	99.8	11	115	92.6	9.4	75	16.9%	7.20 [4.27, 10.13]
Molina 2008 [53]	82	38.4	401	84	36.7	378	10.5%	-2.00 [-7.27, 3.27]
Podsadecki 2008 [56]	90.8	20.7	310	83.8	20.7	296	15.7%	7.00 [3.70, 10.30]
Total (95% CI)			1833			1537	100.0%	4.00 [1.70, 6.31]

Heterogeneity: Tau^2=5.96; Chi^2=18.93, df=6 (p=0.004); I^2=68%
Test for overall effect: Z=3.40 (p=0.0007)



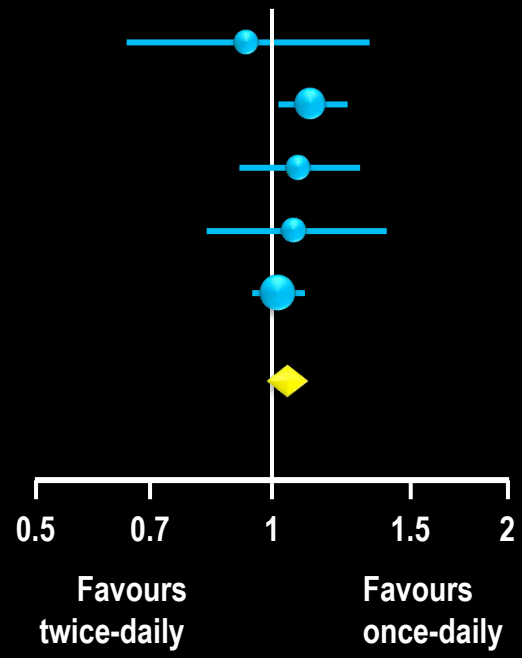
Nachega J *et al.* EACS 2013. Abstr PS4/5

Pooled virologic suppression in ART-naïve patients

‡

Study or subgroup	Once-daily Events	Once-daily Total	Twice-daily Events	Twice-daily Total	Weight	Risk ratio M-H, Random, 95% CI
Eron 2004 [48]	14	19	15	19	2.3%	0.93 [0.65, 1.33]
Gallant 2006 [49]	194	244	171	243	27.3%	1.13 [1.02, 1.25]
Gathe 2008 [60]	145	310	128	296	9.4%	1.08 [0.91, 1.29]
Molina 2007 [54]	66	115	40	75	4.2%	1.08 [0.83, 1.40]
Molina 2008 [53]	343	440	338	443	56.7%	1.02 [0.95, 1.10]
Total (95% CI)		1128		1076	100.0%	1.06 [1.00, 1.11]
Total events	762		692			

Heterogeneity: $Tau^2=0.00$; $Chi^2=3.04$, df=4 ($p=0.55$); $I^2=0\%$
Test for overall effect: $Z=1.97$ ($p=0.05$)



Nachega J *et al.* EACS 2013. Abstr PS4/5

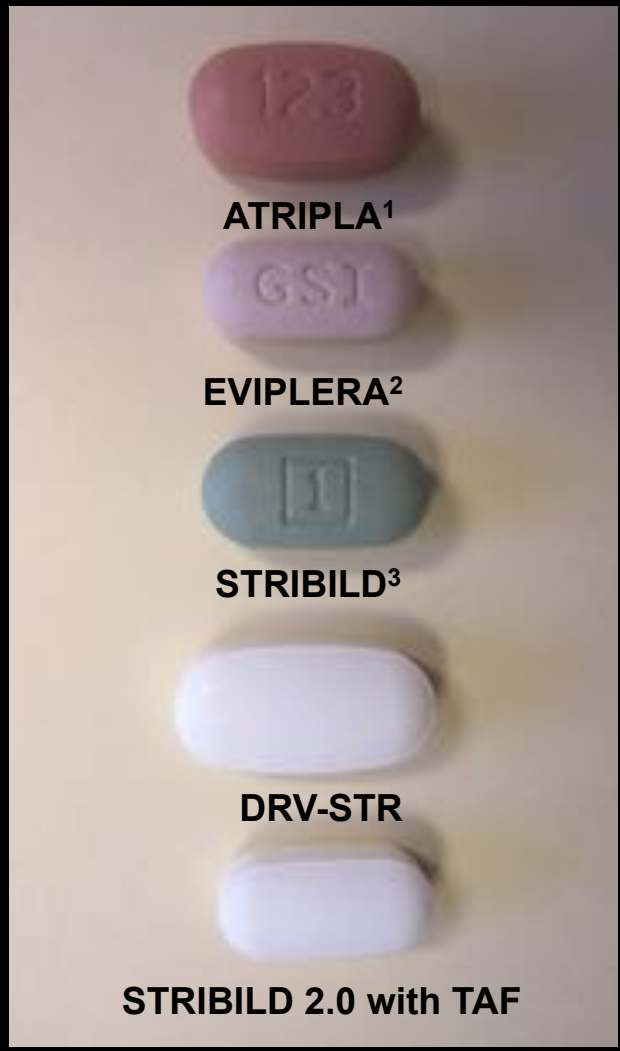
Single Tablet Regimens (STRs)

Current

- **ATRIPLA (1550 mg)**
- **EVIPLERA (1150 mg)**
- **STRIBILD (1350 mg)**

Future

- **DRV-STR (1550 mg)**
  - DRV/COBI/FTC/TAF
- **STRIBILD 2.0 (1050mg)**
- **DOLUTEGRAVIR/ ABACAVIR/LAMIVUDINE**



1. Mathias AA, et al. JAIDS;2007;46(2):167-73
2. Mathias AA, et al. IAC 2010; Vienna. THLBPE17
3. German P, et al. JAIDS 2010;55:323–329

Rationale for STRs

STRs can have a positive impact on treatment outcomes of interest

- Adherence[1–2]
  - Improved quality of life
  - No refill misalignment
  - Simultaneous dosing of all ARVs
- Health outcomes & healthcare costs[3–7]
  - Improved virologic outcomes
  - Few discontinuations
  - Remain undetectable longer, potentially reducing transmission
  - Longer duration of therapy
  - Lower risk of hospitalisation
  - Lower healthcare costs
  - Lower pharmacy costs
- Patient convenience
  - Simple[1]
  - Single co-pay

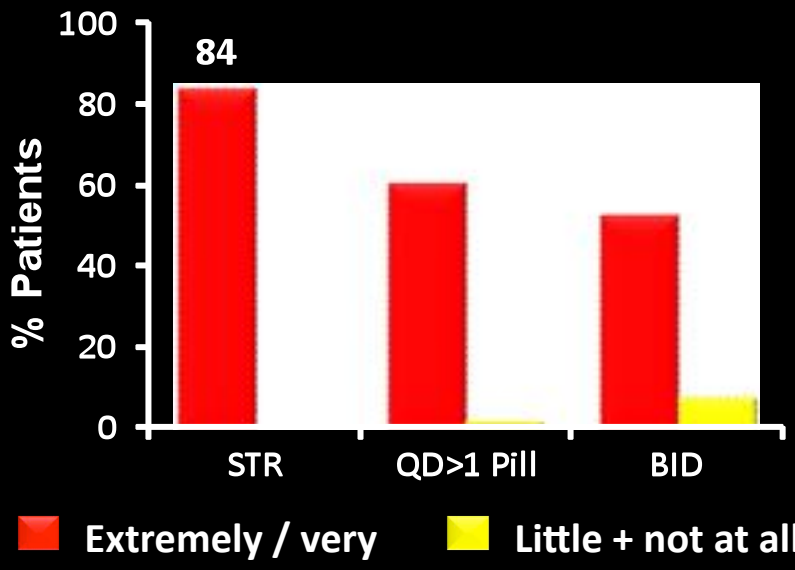
1. Airoldi M, *et al. Patient Preference Adherence* 2010;4:115-125
2. DeJesus E, *et al. JAIDS* 2009; 51:163-174
3. Bangsberg D, *et al. AIDS* 2010;24(18):2835-40
4. Juday T, *et al.* EACS 2009. Cologne. Poster #PE10.1/9
5. Taneja C, *et al.* EACS 2011. Belgrade, Serbia. #PE10.1/2
6. Sax P, *et al.* HIV10 2010. Glasgow. Oral #113
7. Cohen C, *et al.* EACS 2011. Belgrade, Serbia. #PE7.5/7

Patient reported outcomes STR enhances patients' acceptability of HAART and self-reported adherence

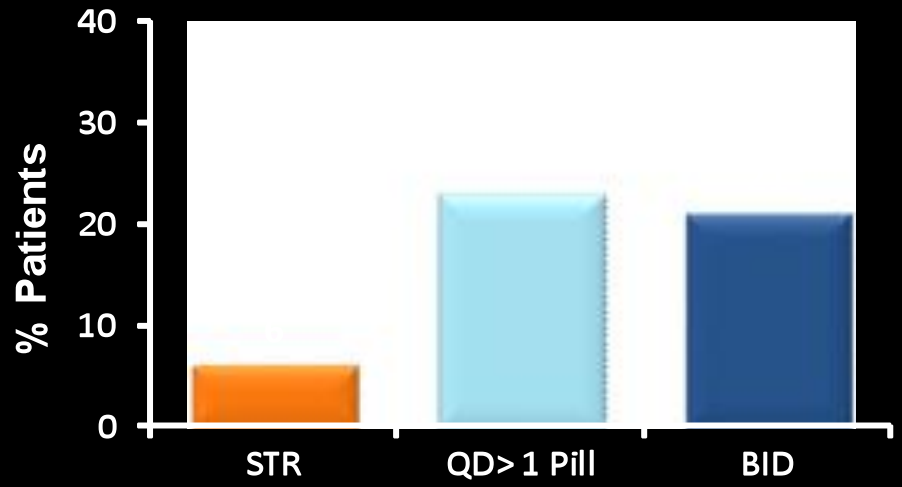
‡

230 patients on stable HAART completed questionnaires on their attitude towards HAART, adherence level and the acceptability of their regimen[1,2]

Patient reported acceptability of current HAART regimen[1]



Self-reported non-adherence[2]



Suboptimal adherence defined as self-reporting having missed at least one dose during the past week

Patients receiving a STR reported a higher acceptability of their regimen and better adherence compared with those receiving more complex regimens

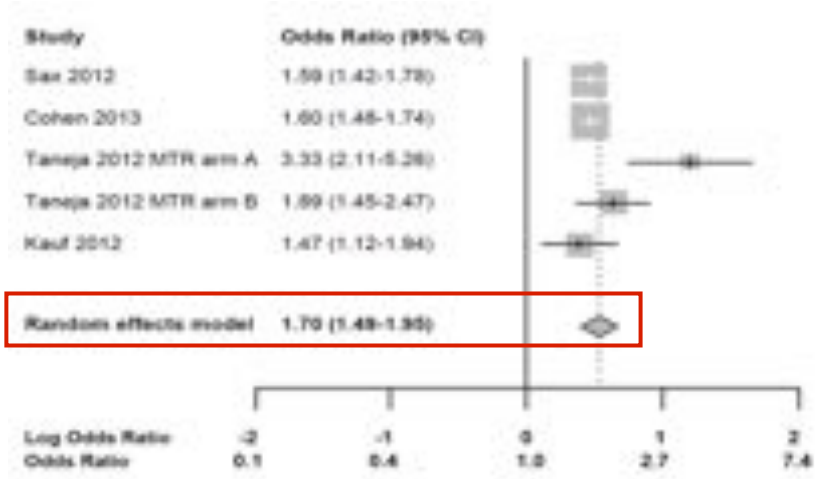
1. Maggiolo F, *et al.* HIV-11 2012. Glasgow. P18;
2. Murri R, *et al*. HIV-11 2012. Glasgow. P16

STR vs. MTR: Systematic Review and Meta-Analysis of Real World Adherence

Real world adherence and association between adherence and viral outcomes

Evaluation of published associations among use of STR vs. MTR, ART adherence and treatment efficacy/effectiveness

Meta-analysis: odds of achieving ≥95% real-world adherence with STR vs. MTR



Association between adherence and viral outcomes

Studies	N	Viral Failure Rate¥		P-value
		High Adherence	Low Adherence	
Cohen et al., 2013*				
Rilpivirine+2NRTIs	639	19%	44%	<0.001
Efavirenz+2NRTIs	599	16%	35%	0.001
Martin et al., 2008†				
NNRTI-based regimen	662	1.4%	6.2% (a) 31.4% (b) 51.7% (c)	<0.05 for each comparison

*High adherence, >95%; low adherence, ≤95%
†High adherence, ≥90%; low adherence, (a) 80-89%, (b) 70-79%, (c) <70%
¥ The drug efficacy/effectiveness was measured as viral load (RNA level), viral suppression rate, viral failure rate, or undetectable RNA level

- **In comparative real-world studies, patients receiving STRs vs. MTRs had a 70% greater odds of achieving ≥95% adherence**
- **Available evidence supports a positive and clinically significant association between higher adherence and viral suppression**


CHELSEA
FOOTBALL CLUB
JOSÉ
MOURINHO
"I AM A SPECIAL ONE"


Fly
Emirates
chelsea fc


SAMSUNG
mobile


CHELSEA FC
CHELSEA
FOOTBALL CLUB
BARCLAYS
FOOTBALL-WALLPAPERS.com

"I wouldn't say I was the best manager in the business. But I was definitely in the top one."

— Brian Clough


quaestio quaestio qo ? ? ? ?


HOW LOW CAN YOU GO?
THE AIM IS TO KEEP YOUR VIRAL LOAD UNDER 50, WHAT WE CALL UNDETECTABLE


HIV
AIDS

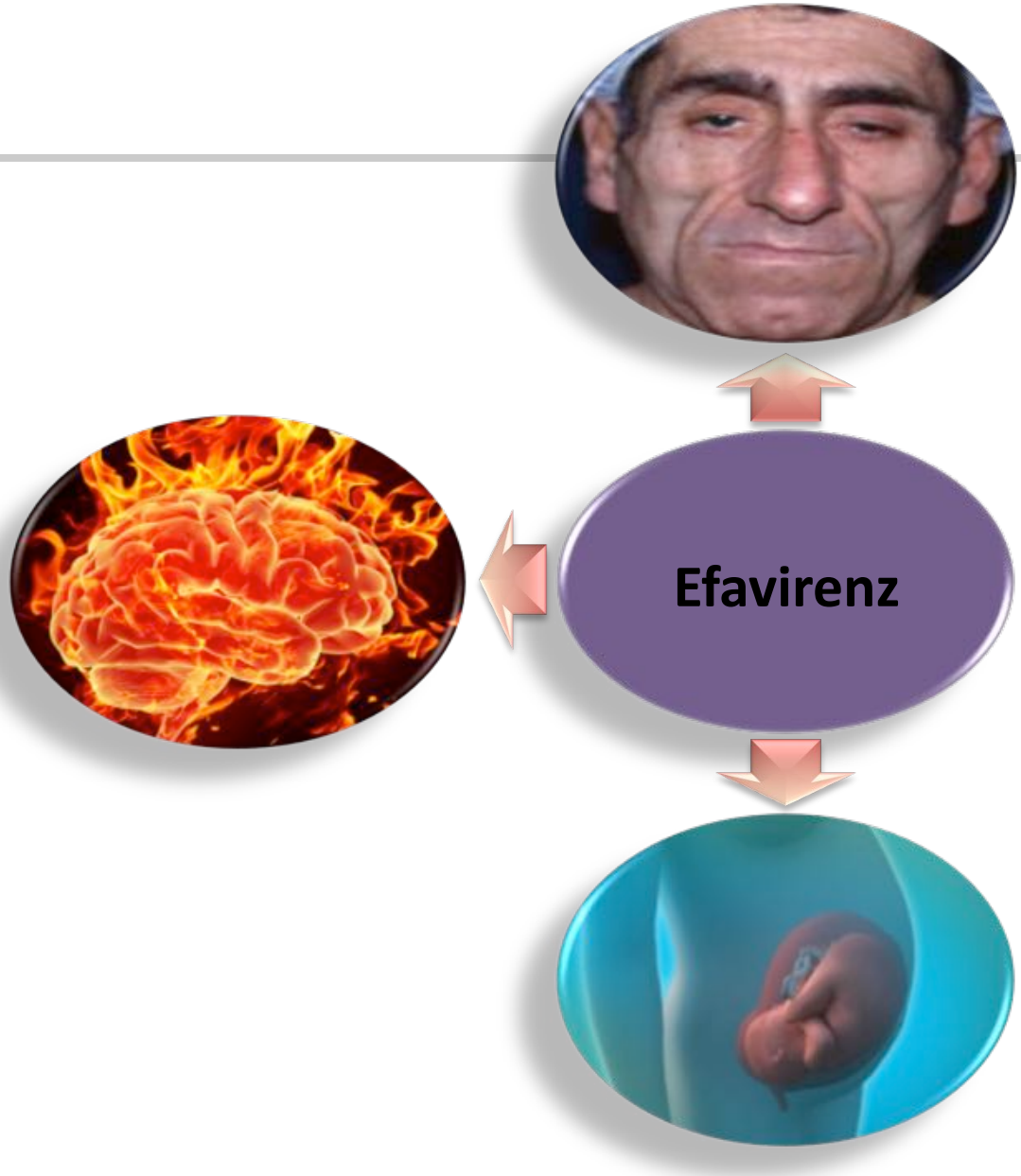

TOXIC

Drug resistance


©Vincent Desjardins 2009
MILK MILK
inter actions

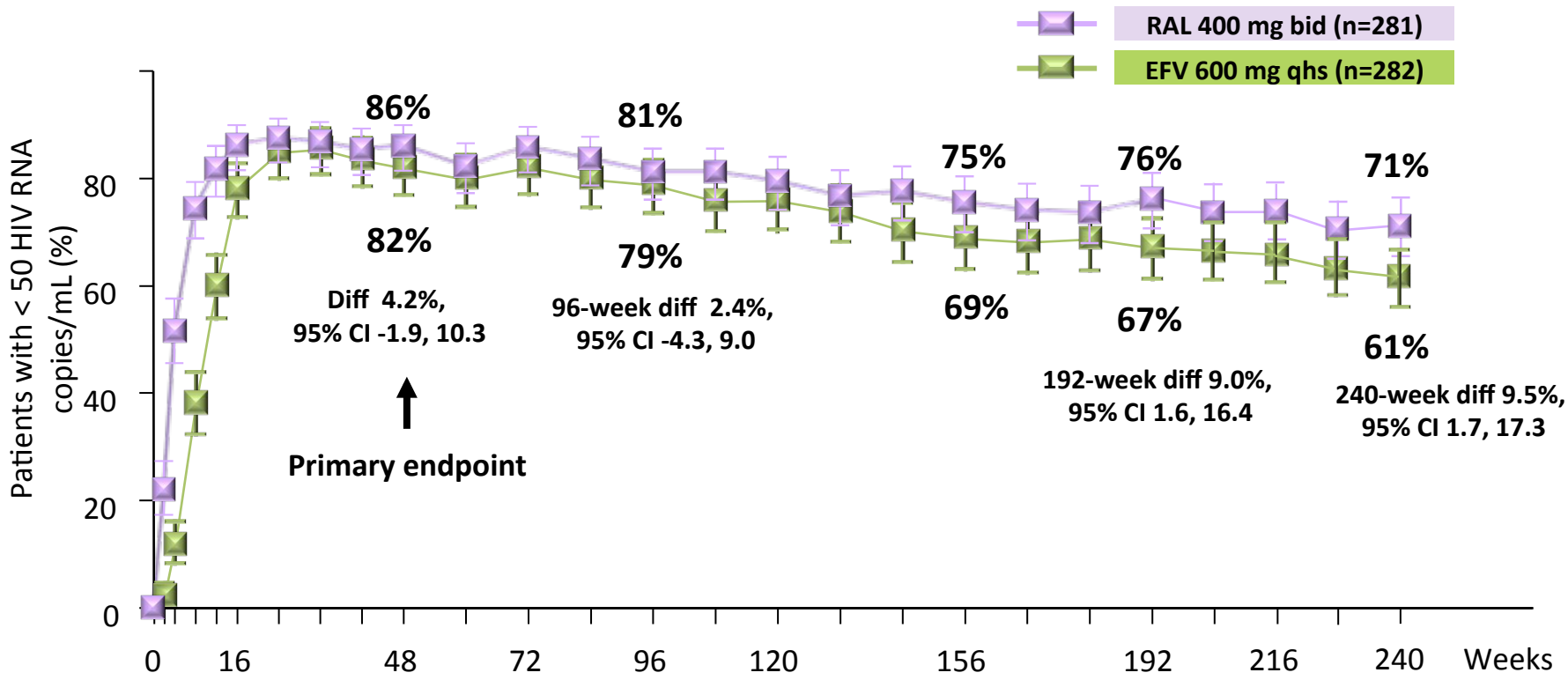

CLOSE TIGHTLY
PUSH DOWN AND UNSCREW
VHS


Efavirenz


Efavirenz

Potency: STARTMRK

RAL vs EFV in naive patients to 240 weeks



bid, twice-daily; qhs, every night before bedtime.

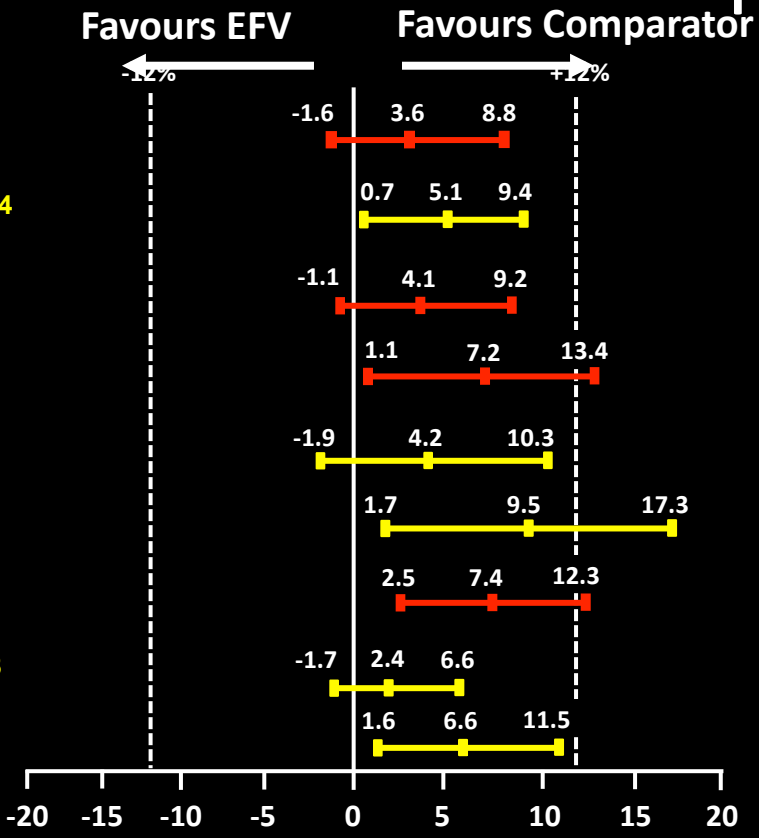
Adapted from Rockstroh JK, et al. AIDS 2012. Poster LBE19.

Available at http://pag.aids2012.org/EPosterHandler.axd?aid=21410. Accessed August 2013.

A new era in HIV treatment

Efficacy: newer treatments outperform EFV

‡



GS-102[1] (STB vs. ATR) N=700
88% vs. 84% (Snapshot)

Week 48: Non-inferiority shown

GS-102/103/104[2] (STB vs. ATR) N=1124
89% vs. 84% (Snapshot)

Week 48 (Pooled): Statistically significant higher VL response

STaR[3] (CPA vs. ATR) N=786
86% vs. 82% (Snapshot)

Week 48: Non-inferiority shown

89% vs. 82% (Snapshot)
BLVL ≤100,000 cpm

Week 48: Statistically significant higher VL response

STARTMRK[4] (RAL vs. EFV) N=566
86% vs. 82% (ITT, NC=F)

Week 48: Non-inferiority shown

71% vs. 61% (ITT, NC=F)

Week 240: Statistically significant higher VL response

SINGLE[5] (DTG vs. ATR) N=833
88% vs. 81% (Snapshot)

Week 48: Statistically significant superior VL response

ECHO/THRIVE[6] (RPV vs. ATR) N=1368
83% vs. 80% (Snapshot)

Week 48: Non-inferiority shown

90% vs. 84% (TLOVR)
BLVL ≤100,000 cpm

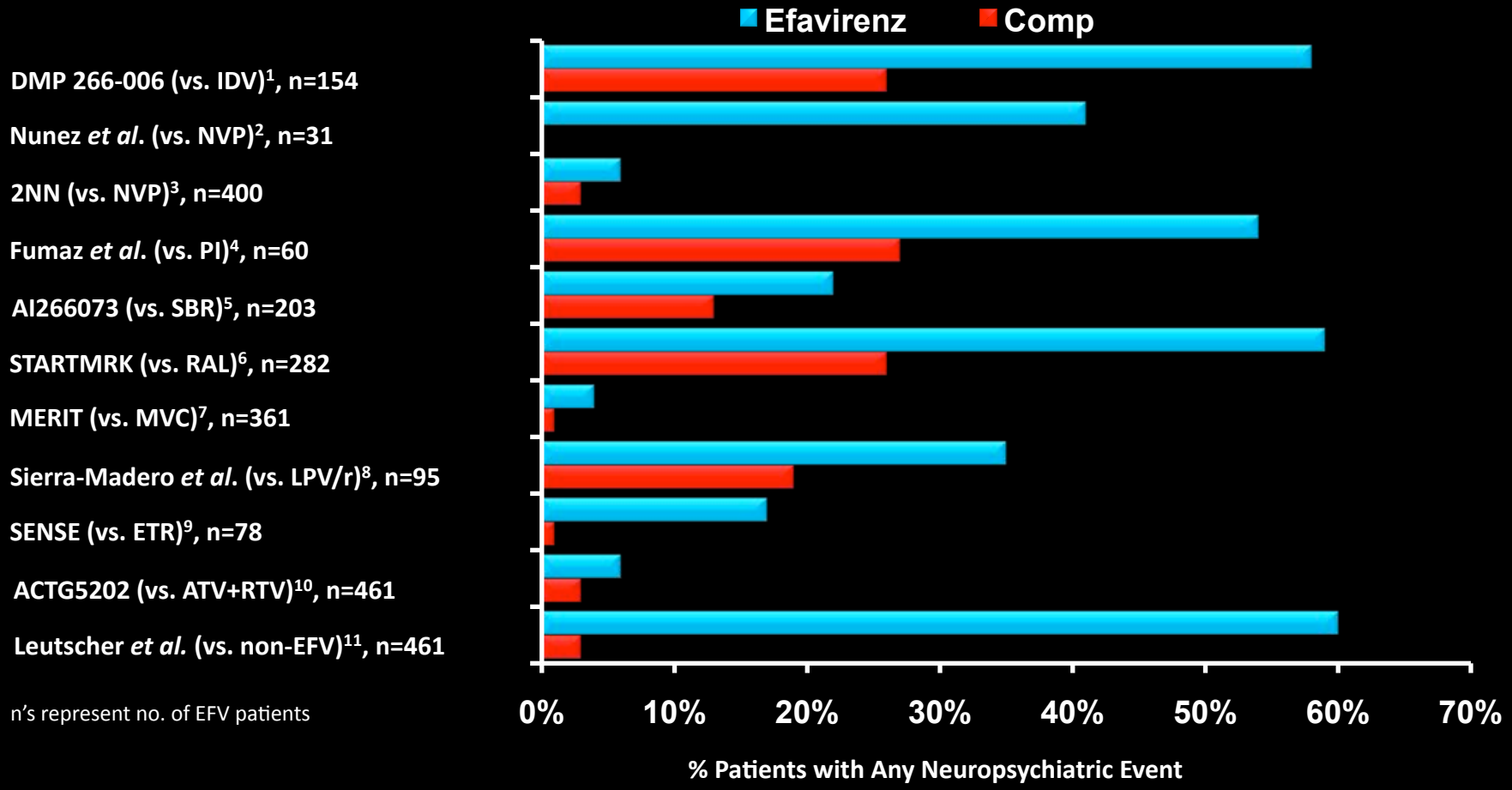
Week 48: Statistically significant higher VL response

Newer ARVs have demonstrated higher rates of virologic suppression compared to EFV-based regimens in HIV-1 infected ART-naïve patients

1. Sax P, et al. Lancet 2012;379:2429–38
2. Ward D, et al. ICAAC 2012; San Francisco, CA. Oral H-555
3. Cohen C, et al. HIV-11 2012; Glasgow. O425; Data on File
4. Rockstroh J, et al. IAC 2012; Washington, DC. LBPE019
5. Walmsley S, et al. ICAAC 2012; San Francisco, CA. Oral H-556b
6. Cohen C, et al. JAIDS 2012;60:33-42

EFV: Cross-study comparison of the overall incidence of neuropsychiatric adverse events

‡

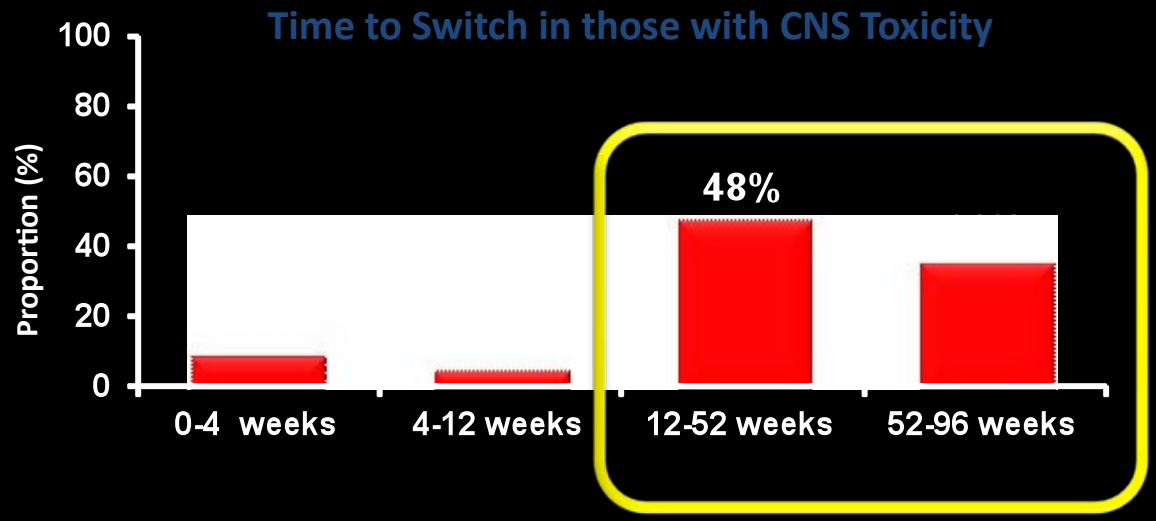


Post-approval, EFV-associated CNS toxicity has been consistently reported in both randomized clinical trials and cohort studies

Evolution of ARV therapy

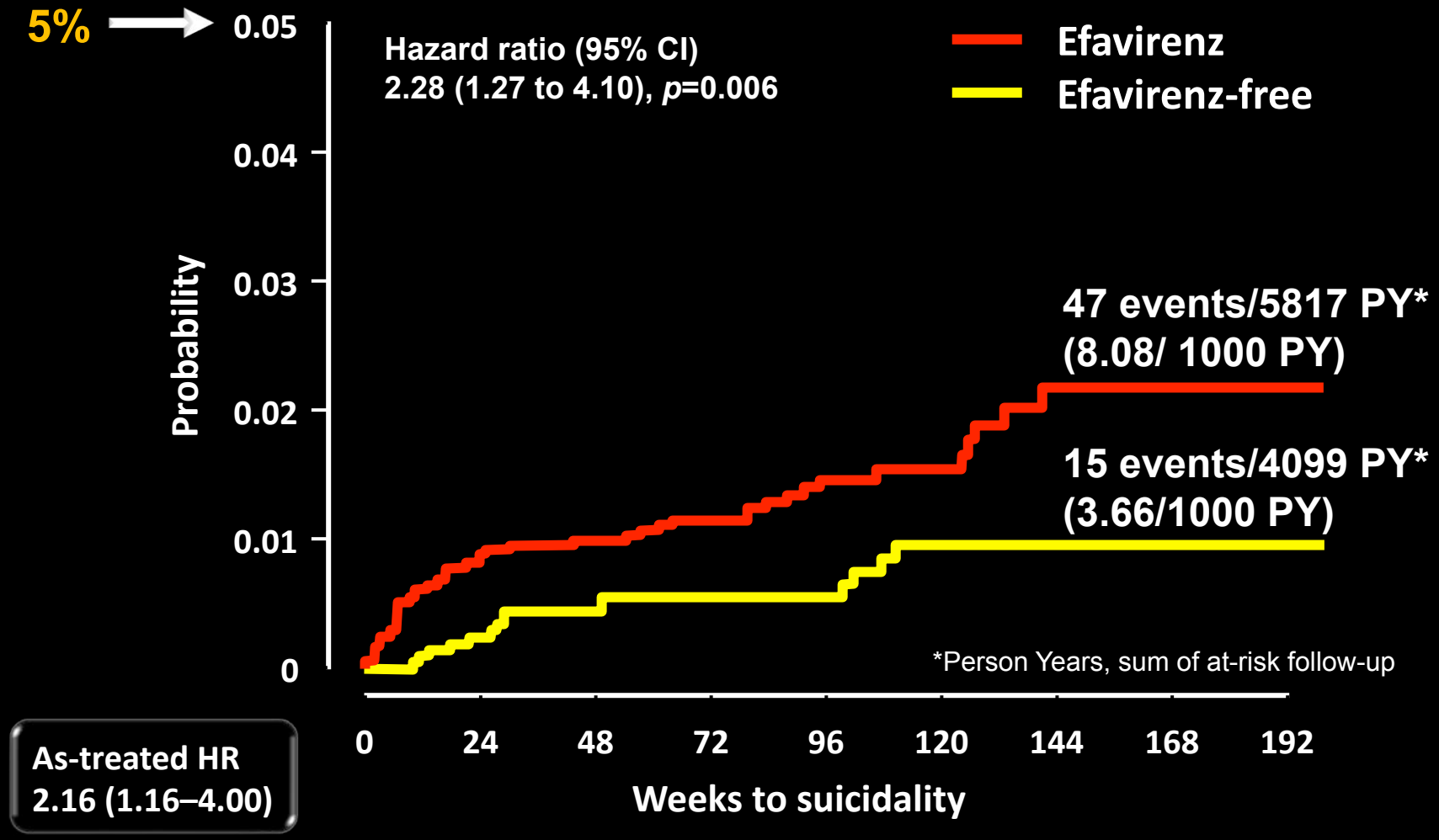
‡

Persistent neuropsychiatric AEs lead to late discontinuation of EFV/FTC/TDF STR



The majority of cases of CNS toxicity leading to treatment modification occurred after having been established on EFV/FTC/TDF STR for more than 3 months

Time to suicidality, primary analysis



As-treated HR
2.16 (1.16–4.00)

Scourfield A, *et al. AIDS*, 2012;26:1399-1401

‡

Tolerability: Newer ARVs outperform EFV

Incidence of specific AEs of interest (%)

Study	Comparator	EFV Pts, n	Dizziness		Insomnia		Abnormal Dreams		Rash		FU Weeks
			EFV	Comp	EFV	Comp	EFV	Comp	EFV	Comp	
GS-102[1]	EVG/COBI	352	24	7	14	9	27	15	12	6	48
STaR[2]	RPV	392	22	7	14	10	25	6	12	6	48
STARTMRK[3]	RAL	284	35	8	8	8	13	7	8	1	240
SINGLE[4]	DTG	419	35	9	10	15	17	7	14	3	48
ECHO/THRIVE[5,6]	RPV	682	28	10	8	8	13	9	14	3	48

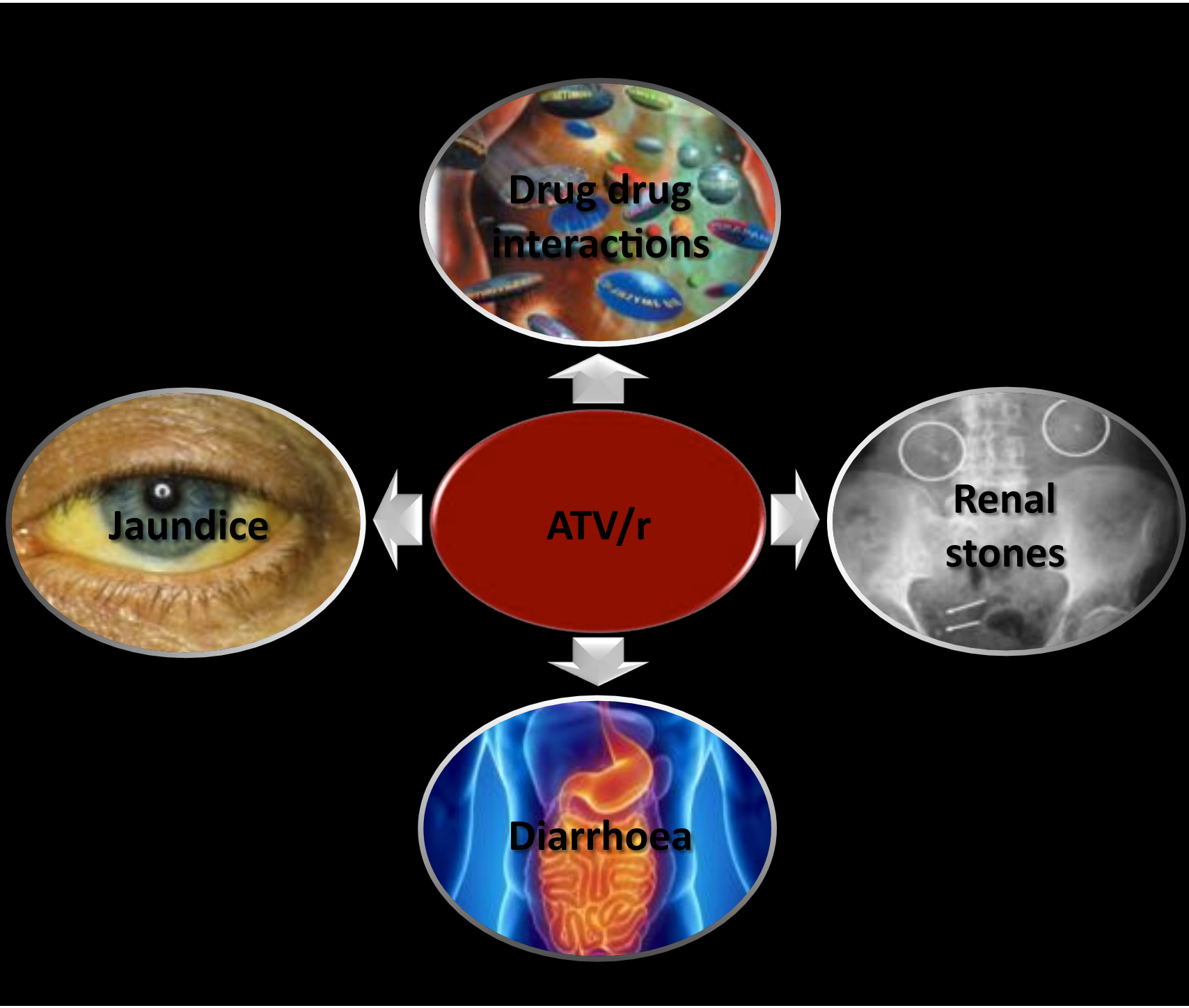
Randomized, controlled trials in ART-naïve patients have shown newer ARVs to be associated with a lower incidence of neuropsychiatric symptoms and rash compared with EFV

Table 2. Subjects with Resistance-Associated Mutations at Baseline

Resistance Category	Clinical Study Number		
	903	934	104 & 111 Combined
Enrollment Year	2000	2003	2013
NNRTI-R	0.5%	4.2%	8.7% *
K103N	0.3%	3.2%	5.9%
Y181C	0	0	1.1%
NRTI-R	3.2%	2.6%	2.6%
TAMs	2.8%	2.6%	2.2%
M184V/I	0.2%	0.2%	0.1%
K65R	0	0	0.1%
PI-R	1.2%	2.4%	2.9% *
INSTI-R	1%	0	1.4%
T66I	0	0	0.07%
T97A polymorphism	1%	0	1.3%

a. Increases in NNRTI-R from 2000 to 2003, 2000 to 2013, and 2003 to 2013 were statistically significant (p-value: <0.0001, <0.0001, and 0.0008, respectively). Increase in PI-R from 2000 to 2013 was statistically significant (p-value: 0.03). All other comparisons were not statistically significant. Fisher's exact and Chi-square tests.

‡

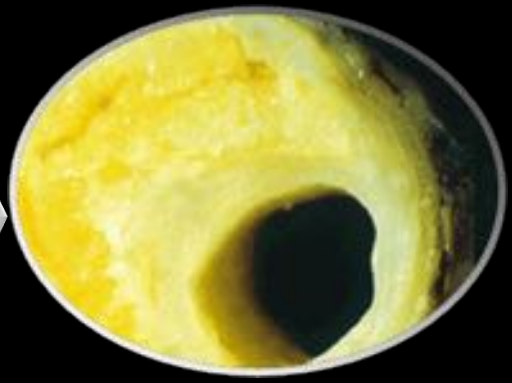

Drug drug interactions
Jaundice
ATV/r
Renal stones
Diarrhoea

‡

DRV/r

‡

LOP/r

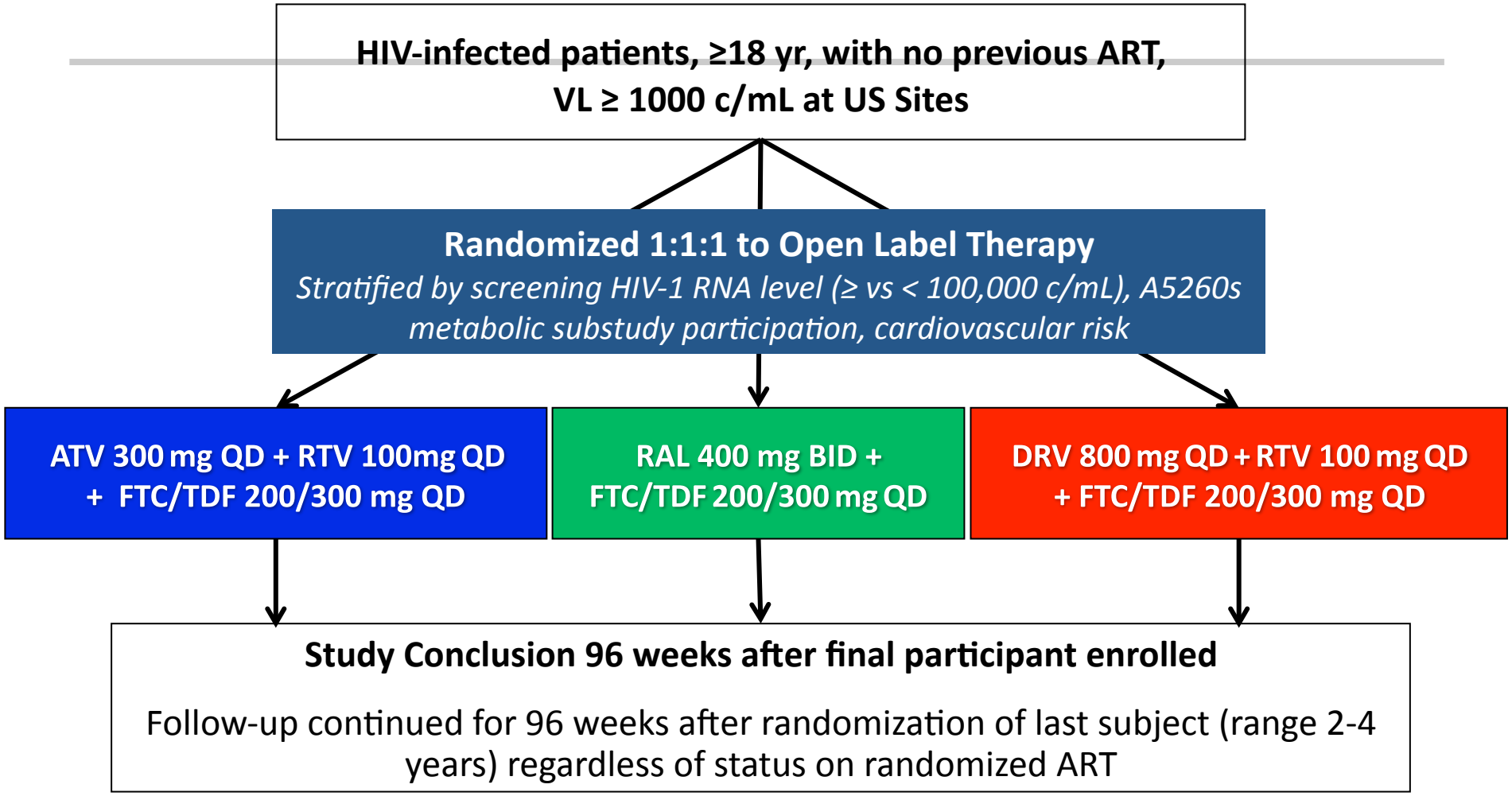


‡

twicedaily

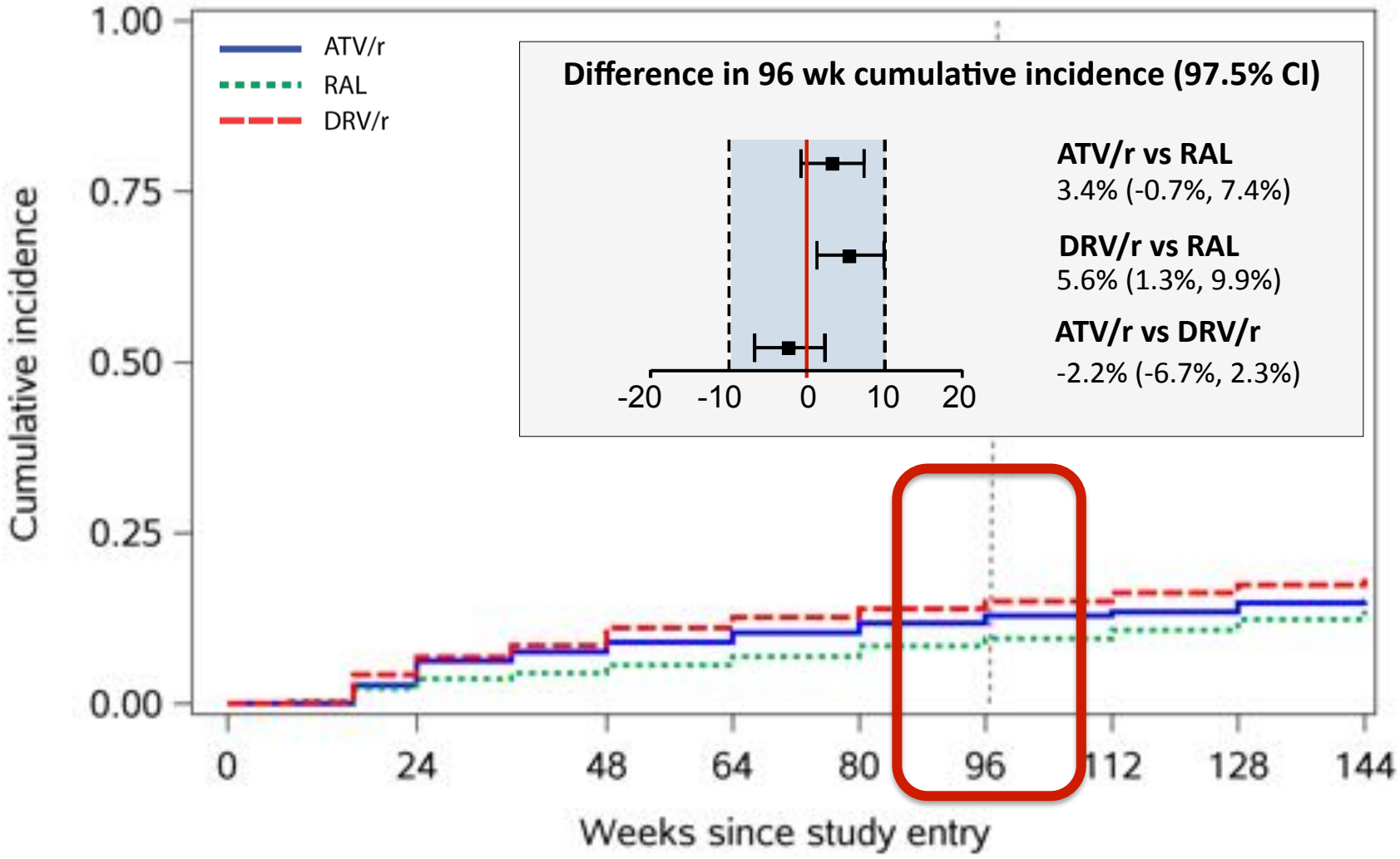
RAL

A5257 Study Design*

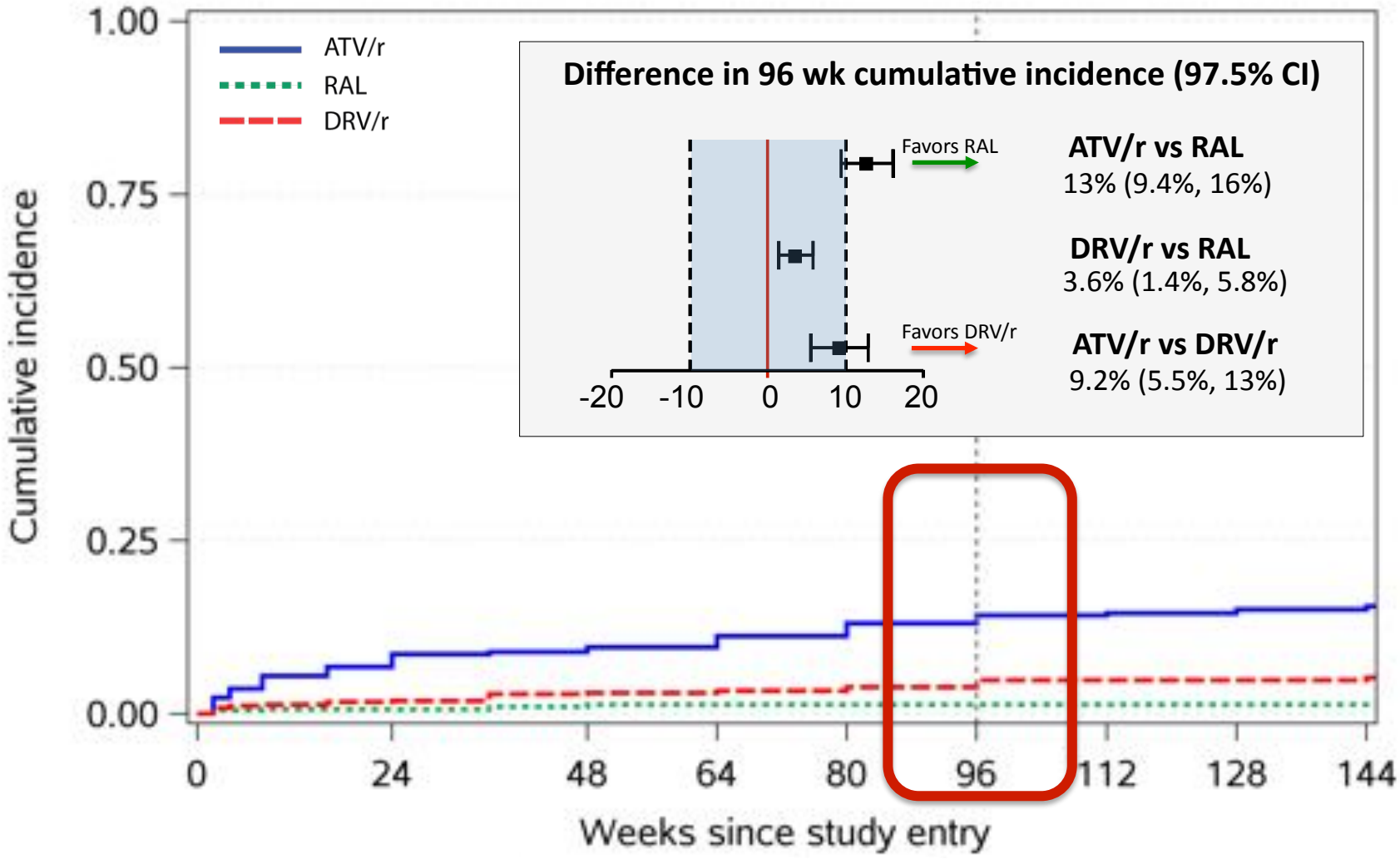


*With the exception of RTV, all ART drugs were provided by the study

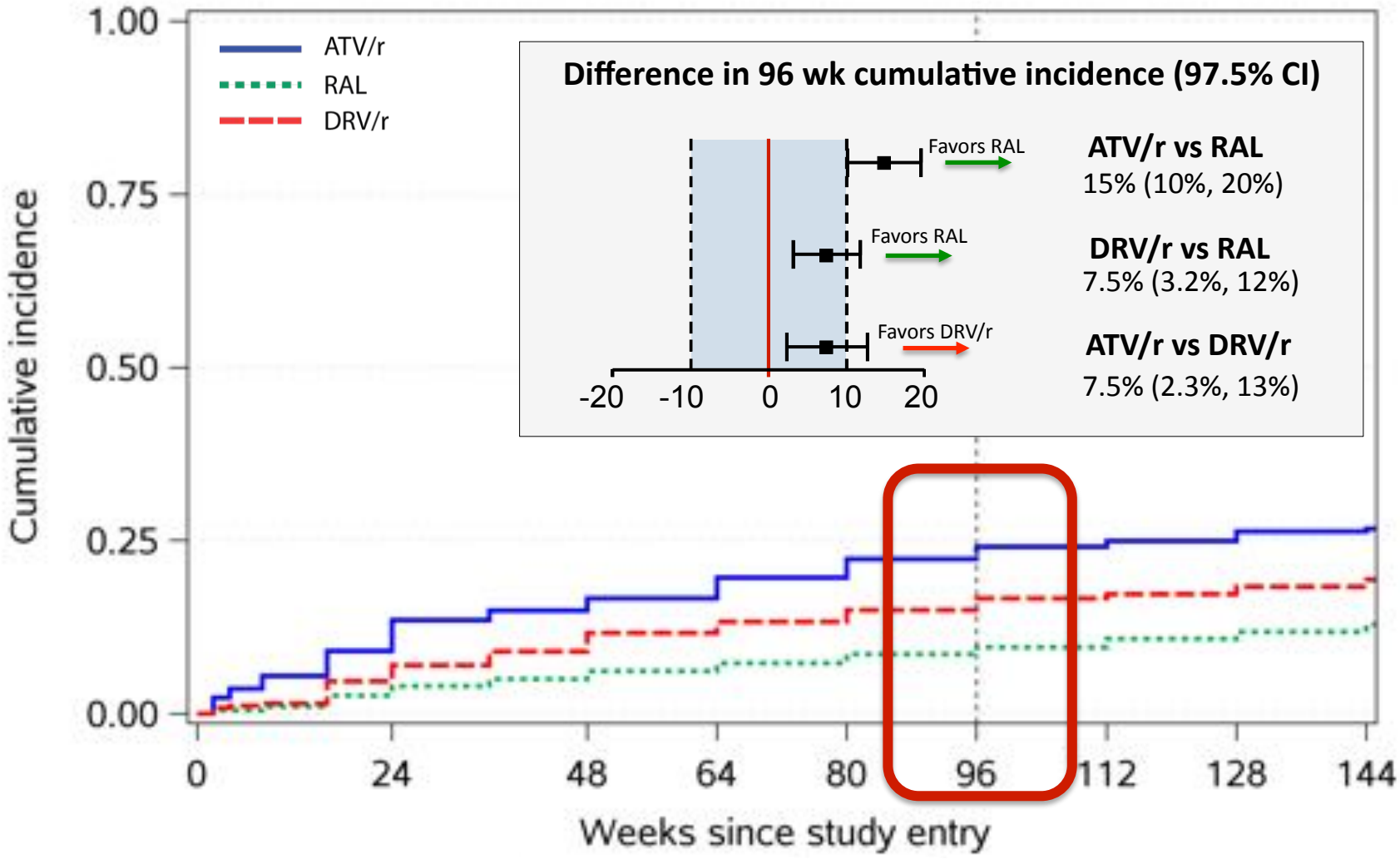
Cumulative Incidence of Virologic Failure



Cumulative Incidence of Tolerability Failure



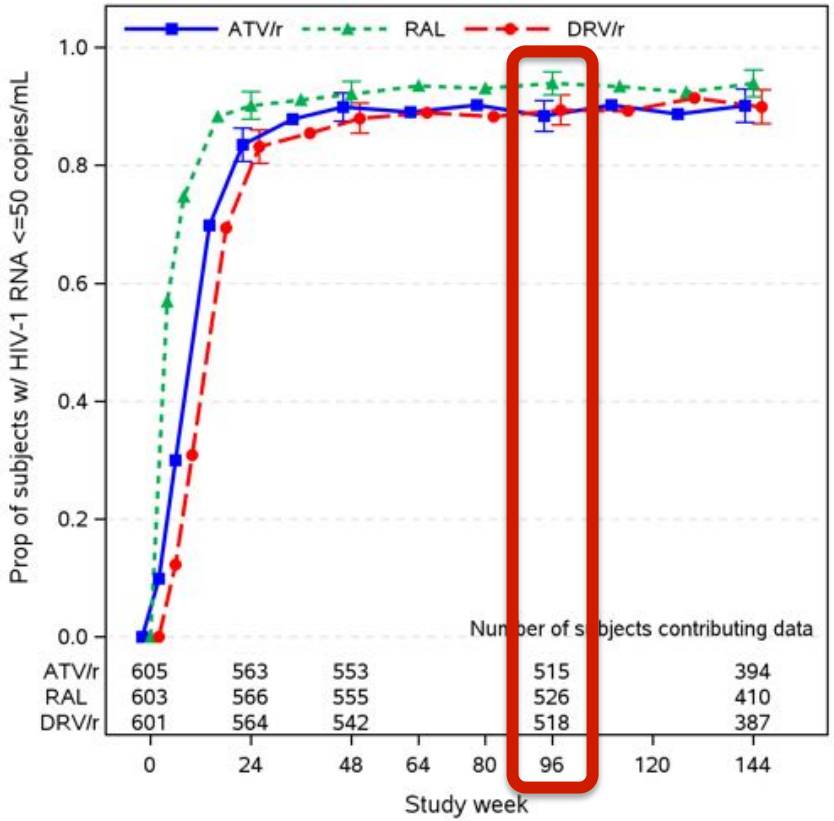
Cumulative Incidence of Virologic or Tolerability Failure



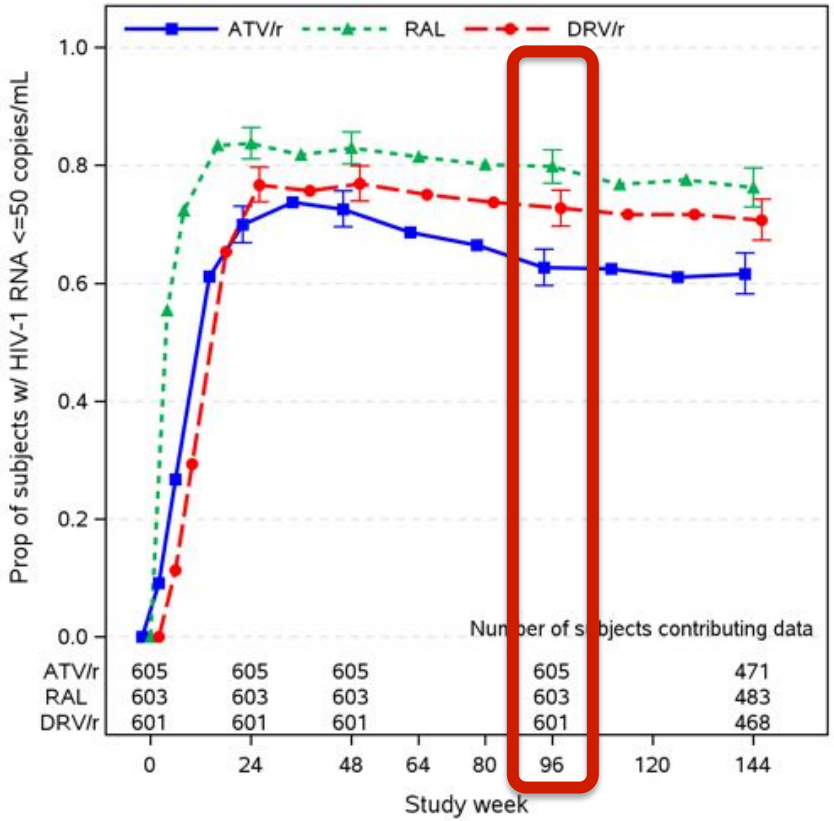
**Consistent results seen with TLOVR at a 200 copies/ml threshold*

Proportion VL ≤50 copies/mL

ITT, regardless of ART change

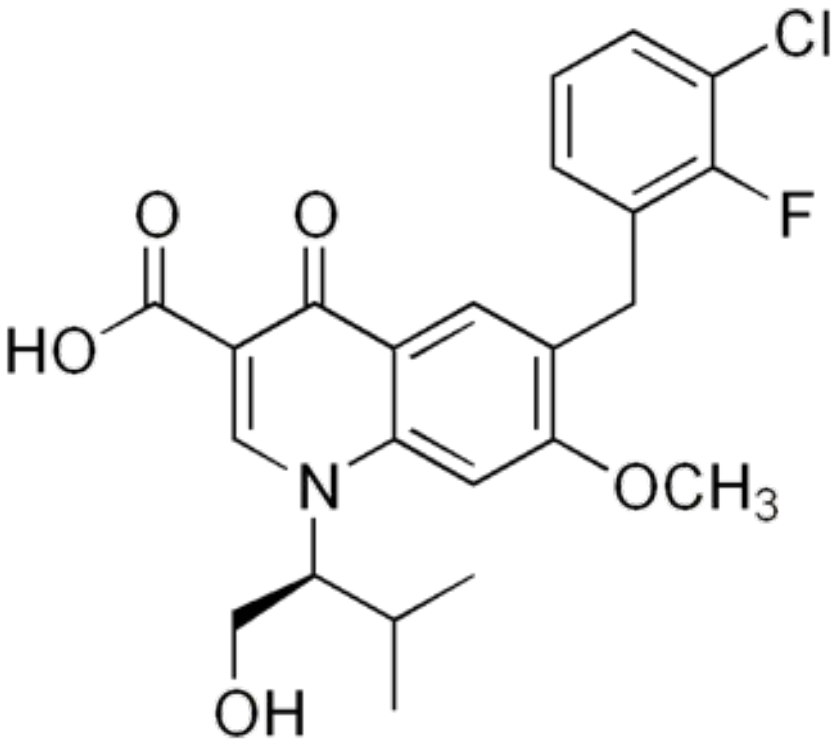


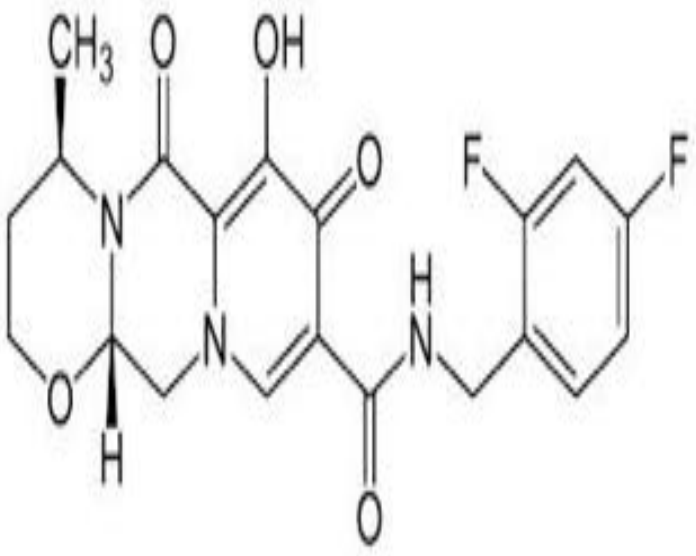
ITT, off-ART=failure (SNAPSHOT)



	24	48	96	144
ATV/r	83%	90%	**88%**	90%
RAL	90%	92%	**94%**	94%
DRV/r	83%	88%	**89%**	90%

	24	48	96	144
ATV/r	70%	73%	**63%**	62%
RAL	84%	83%	**80%**	76%
DRV/r	77%	77%	**73%**	71%

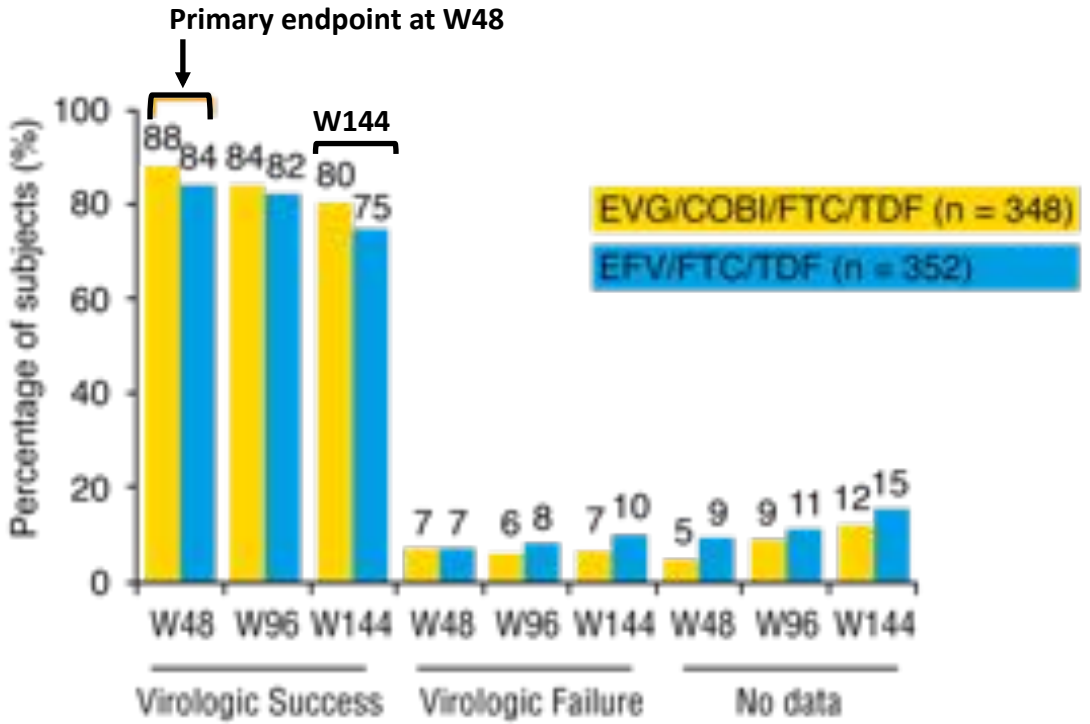

Cl
F
O
O
HO
N
OCH3
OH


CH3
O
OH
O
F
F
N
H
N
O
H
O

Potency: Study 102

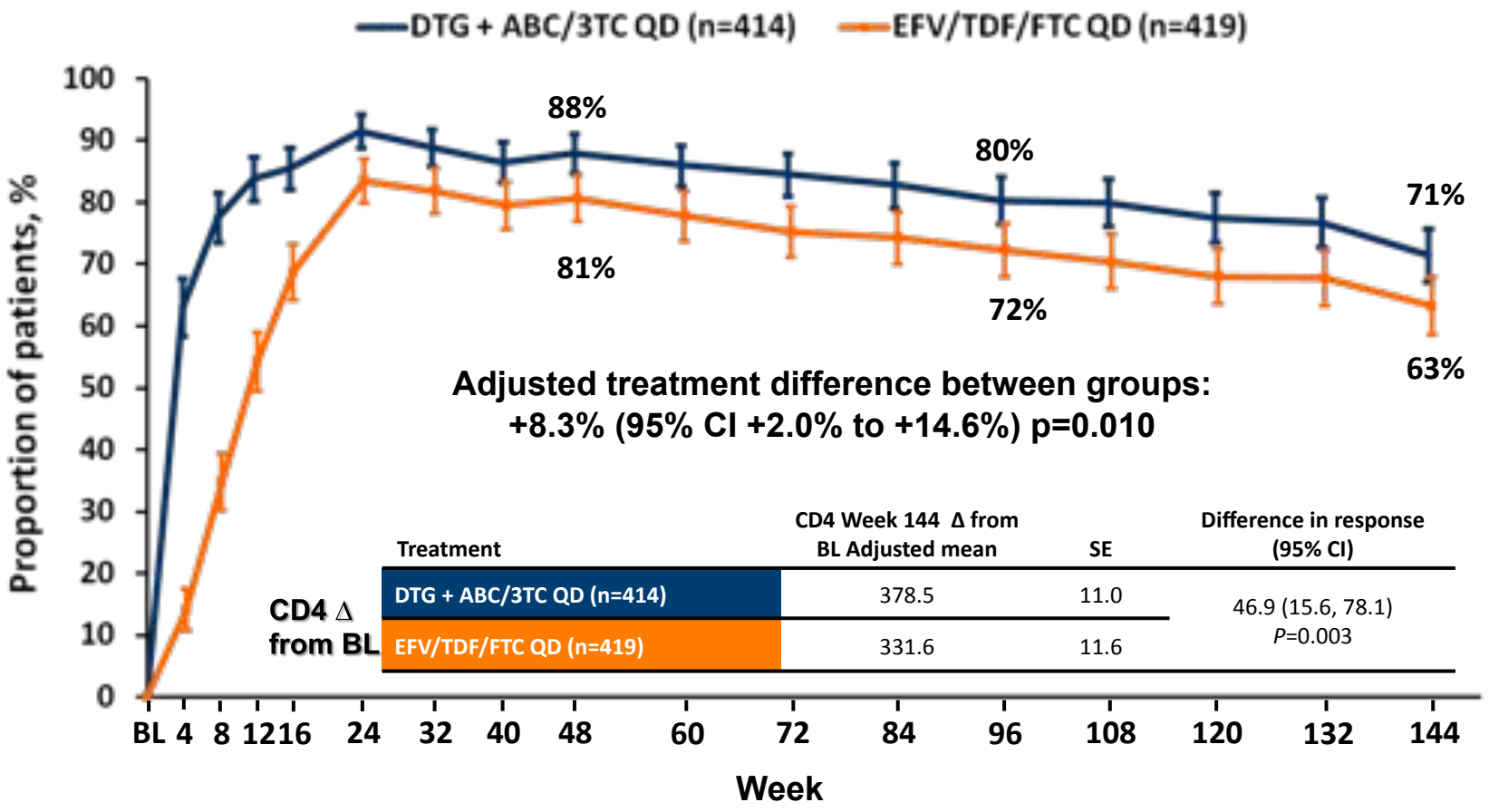
EVG vs EFV in naive patients to 144 weeks

- EVG/COBI/FTC/TDF showed durable, high rates of virologic success through to Week 144 in Study 102 (80% vs 75% for EFV/FTC/TDF)
  - Treatment difference at W144: 4.9% (95% CI: -1.3% to 11.1%)



Wohl D, et al. ICCAC 2013; oral presentation H-672a.

Proportion <50 c/mL (95% CI) and CD4 Change from Baseline



CD4 Δ from BL

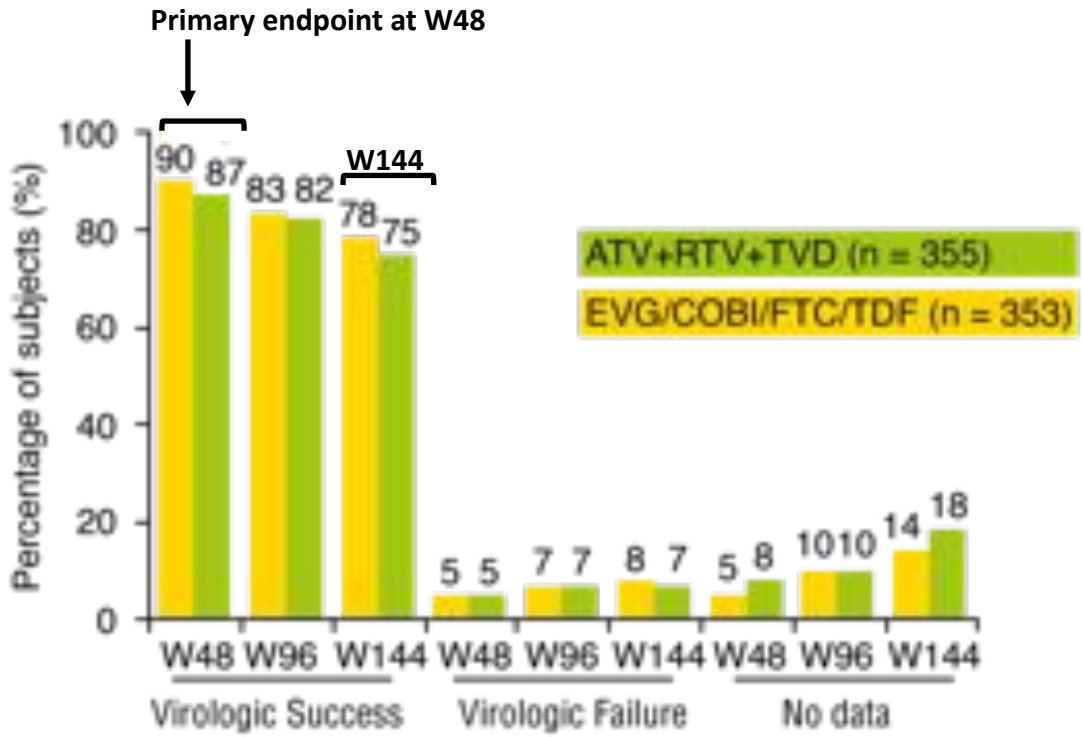
Treatment	CD4 Week 144 Δ from BL Adjusted mean	SE	Difference in response (95% CI)
DTG + ABC/3TC QD (n=414)	378.5	11.0	46.9 (15.6, 78.1) *P*=0.003
EFV/TDF/FTC QD (n=419)	331.6	11.6	

Pappa et al. ICAAC 2014; Washington, DC. H-647a.

Potency: Study 103

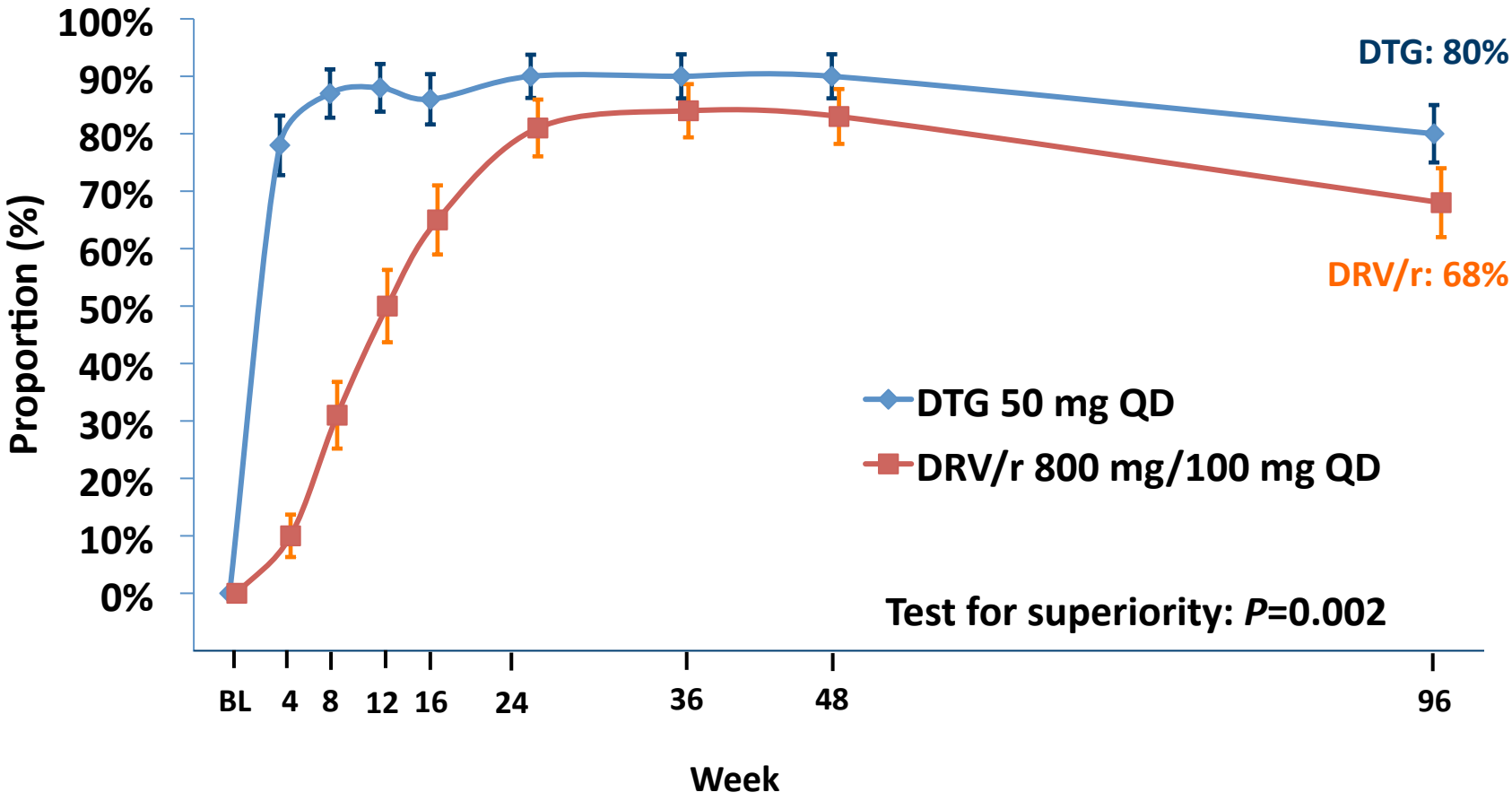
ATV vs EVG in naive patients to 144 weeks

- In study 103, EVG/COBI/FTC/TDF maintained high rates of virologic success (78% vs 75%) through to W144 (78% vs 75% with ATV/r/FTC/TDF)
  - Treatment difference at W144 3.1% (95% CI: -3.2% to 9.4%)



Clumeck N, et al. EACS 2013, abstract LBPS7/2.

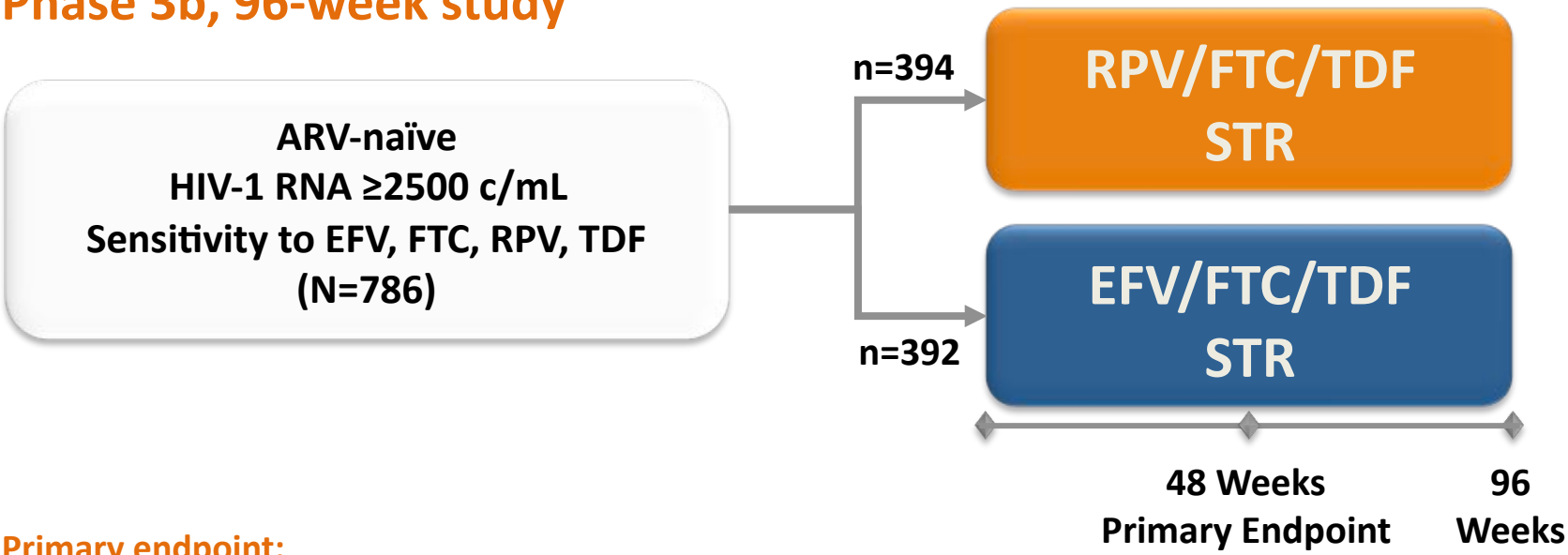
Proportion (95% CI) of Individuals With HIV-1 RNA <50 c/mL Over Time – Snapshot



Molina et al. HIV Drug Therapy Glasgow 2014; Glasgow, UK. Slides O153.

STaR – Study design

Multicenter, international, randomised, open-label, Phase 3b, 96-week study



Primary endpoint:

- **Efficacy of the 2 STRs by proportion with HIV-1 RNA <50 c/mL at Week 48 (Snapshot analysis); non-inferiority margin of 12%**

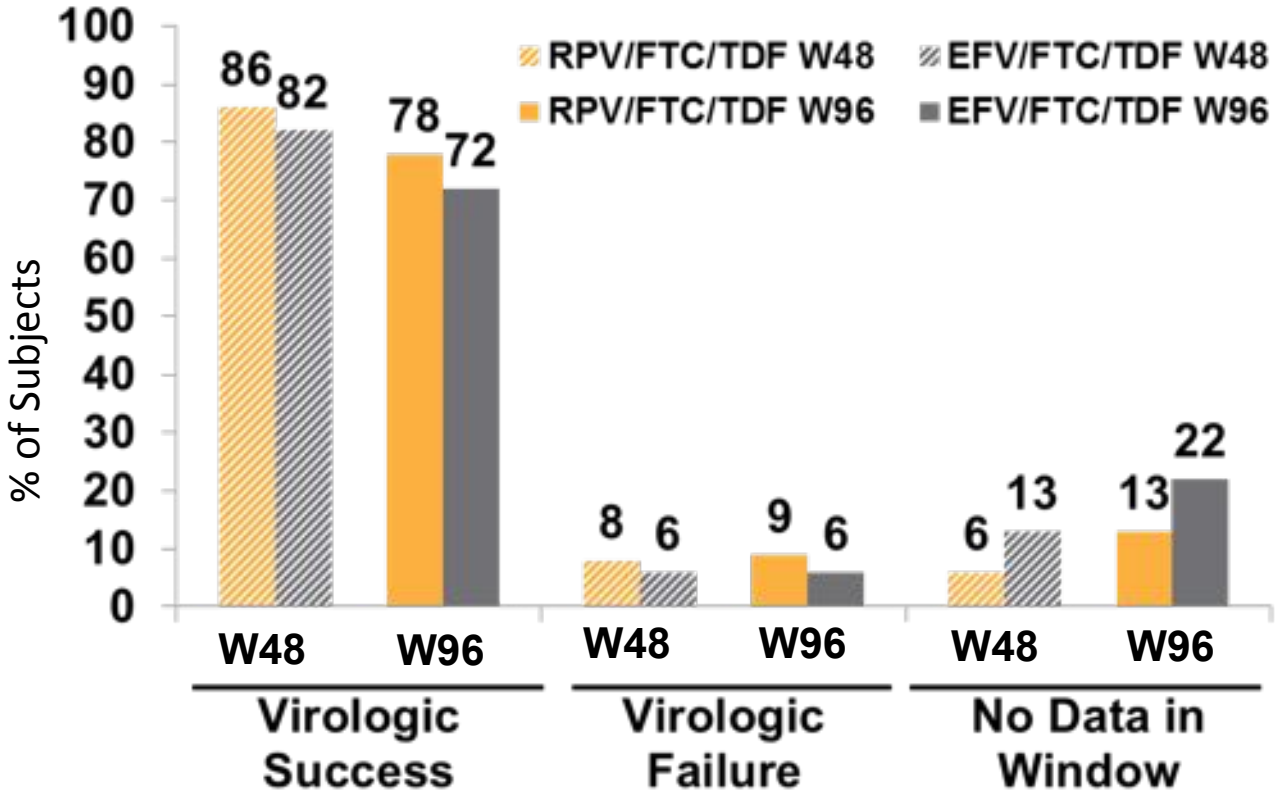
Secondary endpoints:

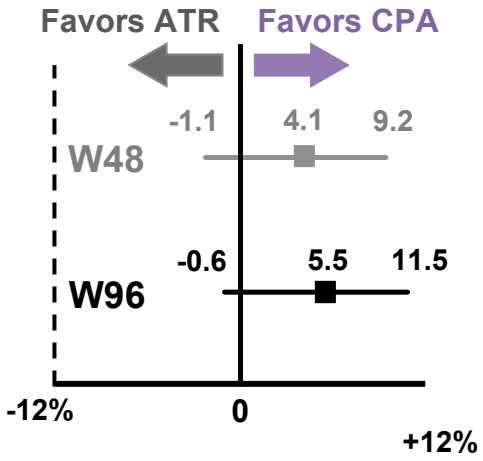
- **Safety and efficacy of the 2 STRs by proportion with HIV-1 RNA <50 c/mL at Week 96 (Snapshot analysis)**
- **Change in CD4 cell count at Weeks 48 and 96**
- **Genotype/phenotype resistance at time of virologic failure**

Cohen C *et al*. EACS 2013, Brussels, Belgium - abstract PE7/13

STaR Study: 96 Week Safety Analysis

Virologic Outcomes by Snapshot Analysis and CD4 Changes





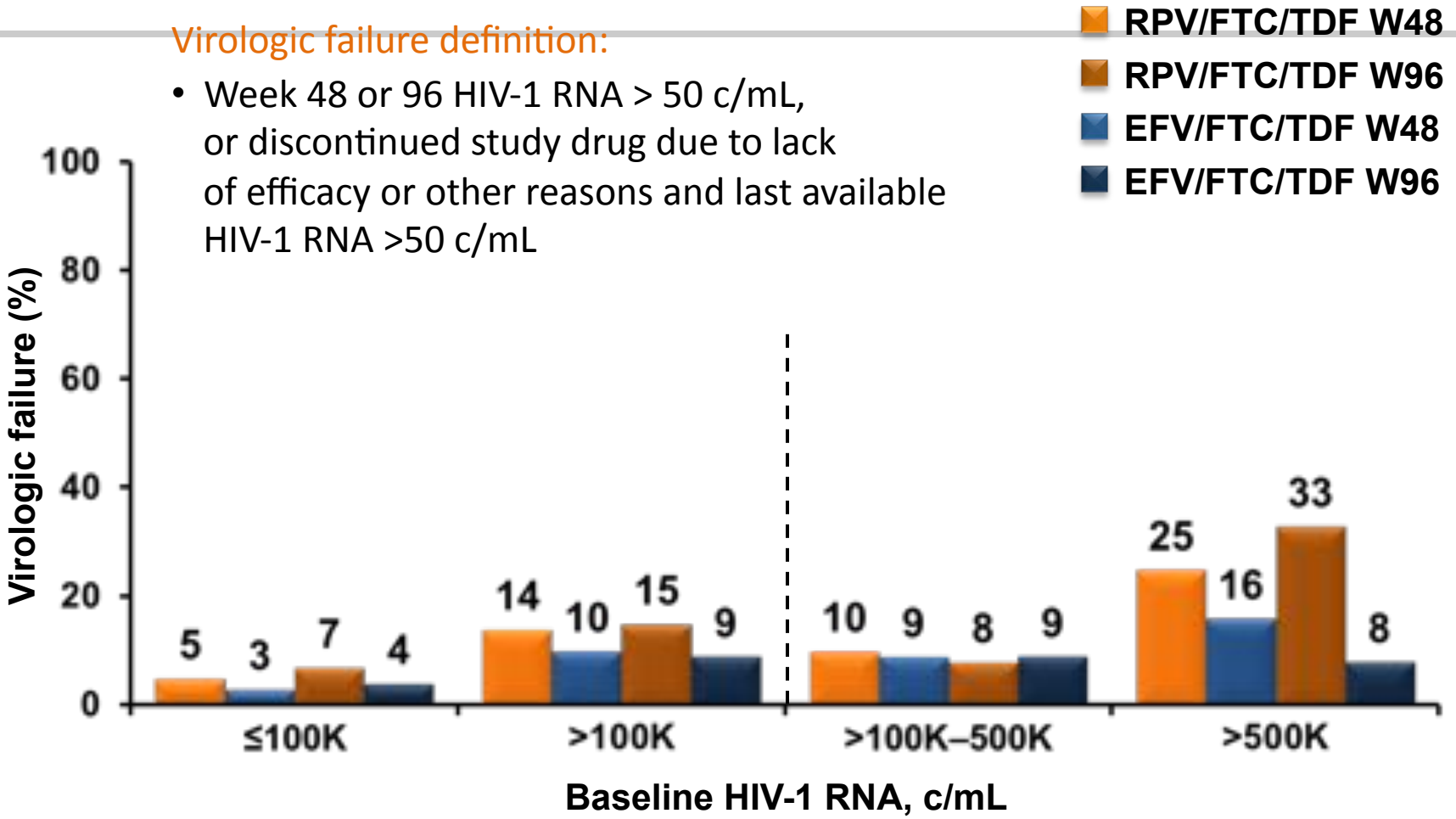
- **Mean CD4 count change (cells/mm^3):**
  - **Week 48: CPA +200 vs. ATR +191 (p=0.37)**
  - **Week 96: CPA +278 vs. ATR +259 (p=0.17)**

STaR – Virologic failure at Weeks 48 & 96 stratified by baseline HIV-1 RNA – snapshot analysis

‡

Virologic failure definition:

- Week 48 or 96 HIV-1 RNA > 50 c/mL, or discontinued study drug due to lack of efficacy or other reasons and last available HIV-1 RNA >50 c/mL



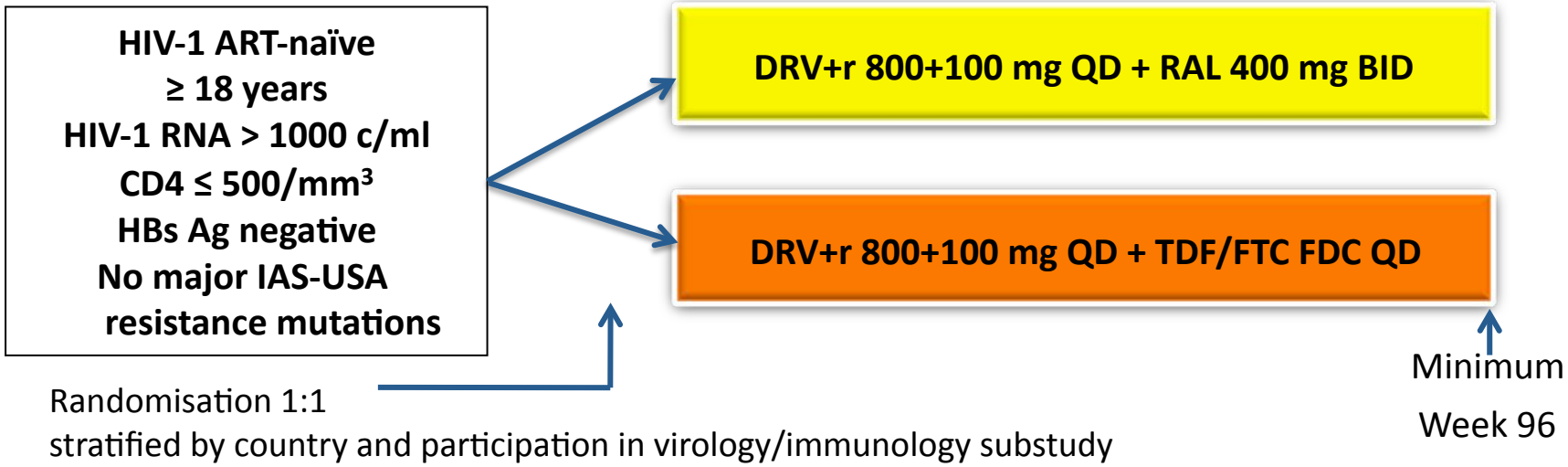
* Post hoc analyses; analyses for non-inferiority only pre-specified for ≤100,000 c/mL and >100,000 c/mL

Cohen C *et al*. EACS 2013. Brussels, Belgium - abstract PE7/13

Changing Preferences

NEAT 001/ANRS 143 study design

- Phase III, randomised, open-label, multicenter, parallel-group, non-inferiority, strategic trial
- 78 sites, 15 countries (Austria, Belgium, Denmark, France, Germany, Great Britain, Greece, Hungary, Ireland, Italy, Netherlands, Poland, Portugal, Spain, Sweden)



- Composite virological and clinical primary endpoint (6 components)

Raffi F et al. CROI 2014 oral 84LB

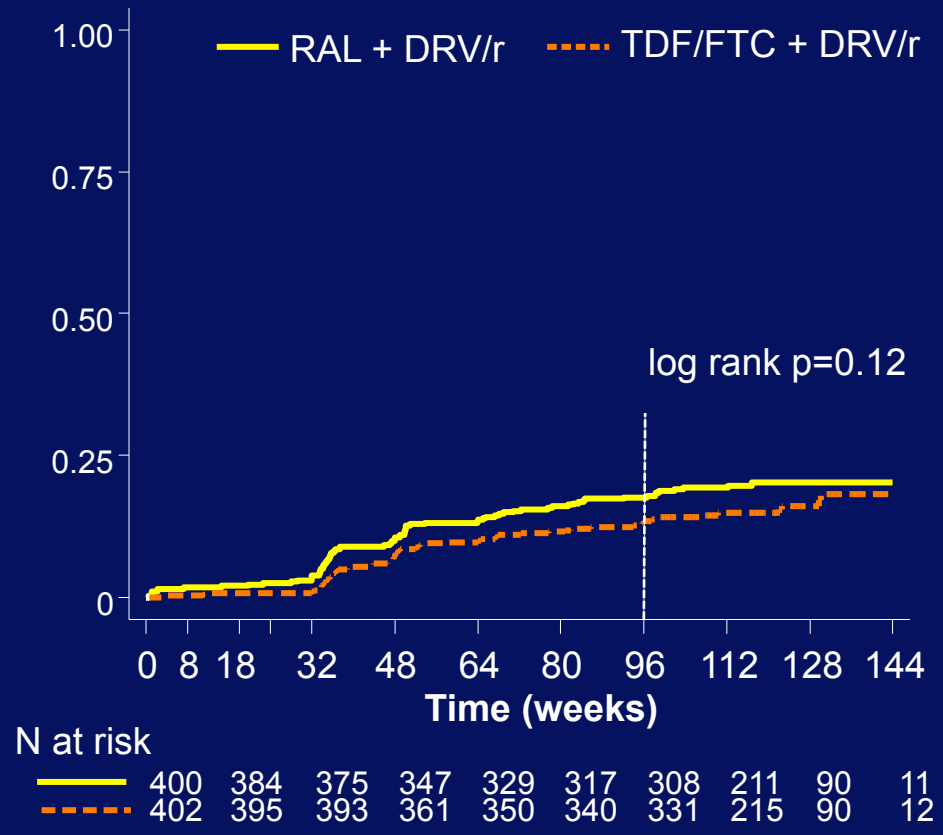
Primary analysis: time from randomisation to primary endpoint

Primary endpoint

	RAL + DRV/r	TDF/FTC + DRV/r
N	401	404
N with primary endpoint	76 (19%)	61 (15%)
V1. Regimen change for insufficient response		
< 1 log_{10} c/ml HIV RNA reduction W18*	1	0
HIV RNA ≥ 400 c/ml W24*	1	0
V2. HIV RNA ≥ 50 c/ml at W32*	27	28
V3. HIV RNA ≥ 50 c/ml after W32*	32	22
C1. Death	3	1
C2. AIDS event	5	3
C3. SNAIDS event	7	7

** confirmed by a subsequent measurement*

Probability of reaching primary endpoint

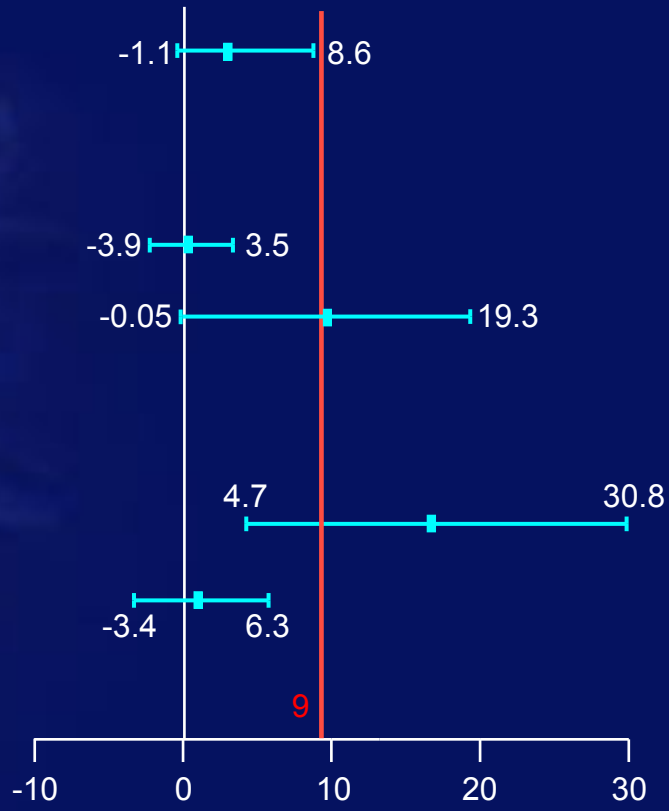


Estimated proportion reaching primary endpoint at W96
RAL: 17.4% vs TDF/FTC: 13.7%
Adjusted difference: 3.7% (95% CI: -1.1, 8.6%)

Primary endpoint at W96 by baseline characteristics

Overall analysis: RAL + DRV/r non inferior to TDF/FTC + DRV/r

		RAL + DRV/r	TDF/FTC + DRV/r
Overall	n = 805	17.4 %	13.7 %
Baseline HIV-1 RNA			
< 100,000 c/ml	n = 530	7 %	7 %
≥ 100,000 c/ml	n = 275	36 %	27 %
			p = 0.09*
Baseline CD4+			
< 200/mm^3	n = 123	39.0 %	21.3 %
≥ 200/mm^3	n = 682	13.6 %	12.2 %
			p = 0.02*

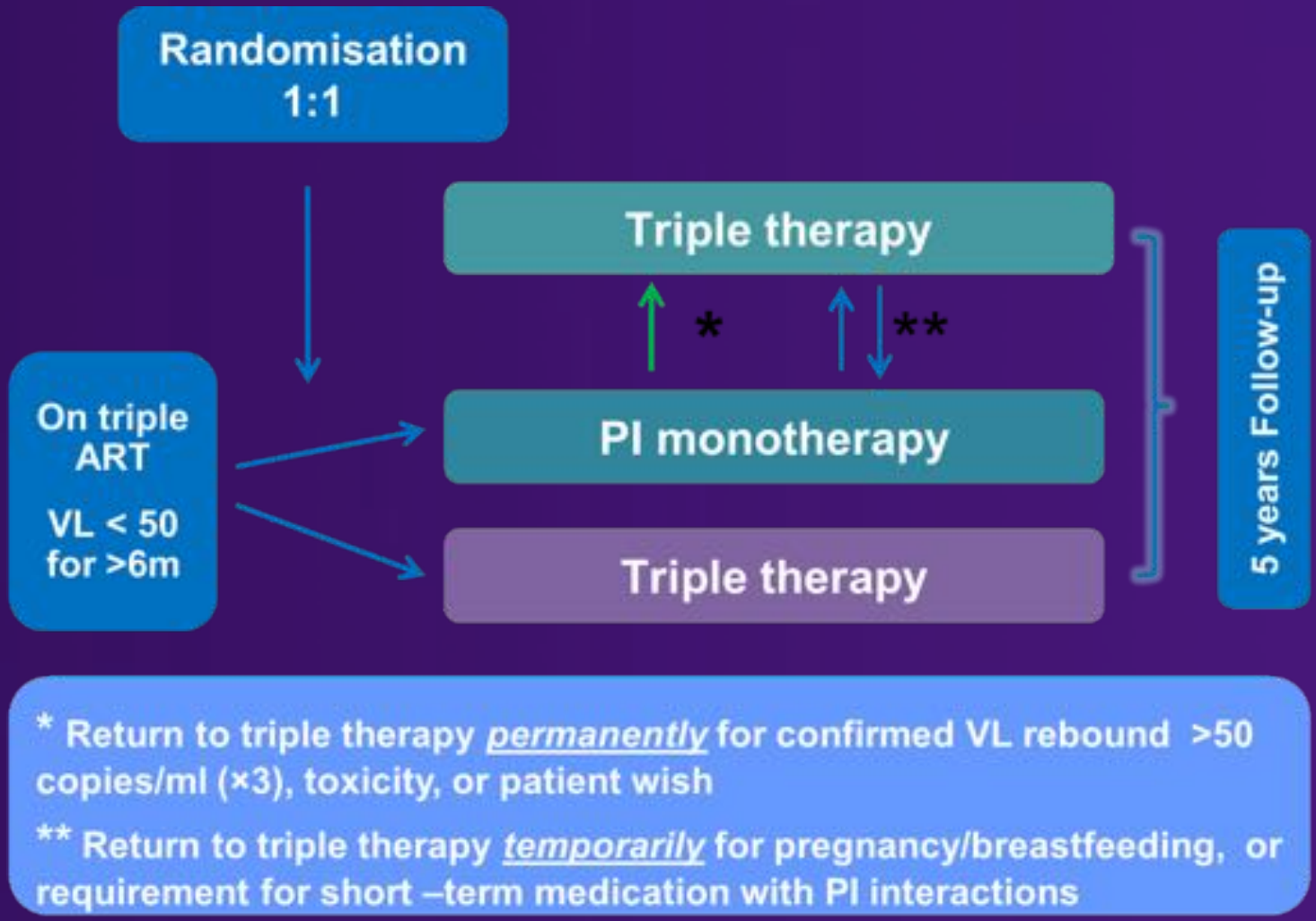


Difference in estimated proportion (95% CI) RAL – TDF/FTC; adjusted

* Test for homogeneity

PIVOT

Design



- Primary Endpoint: Loss of future drug options, defined as: new intermediate/high level resistance to ≥1 drug to which the patient's virus was considered to be sensitive at trial entry

Patton et al. CROI 2014 poster 550

PIVOT

Outcomes

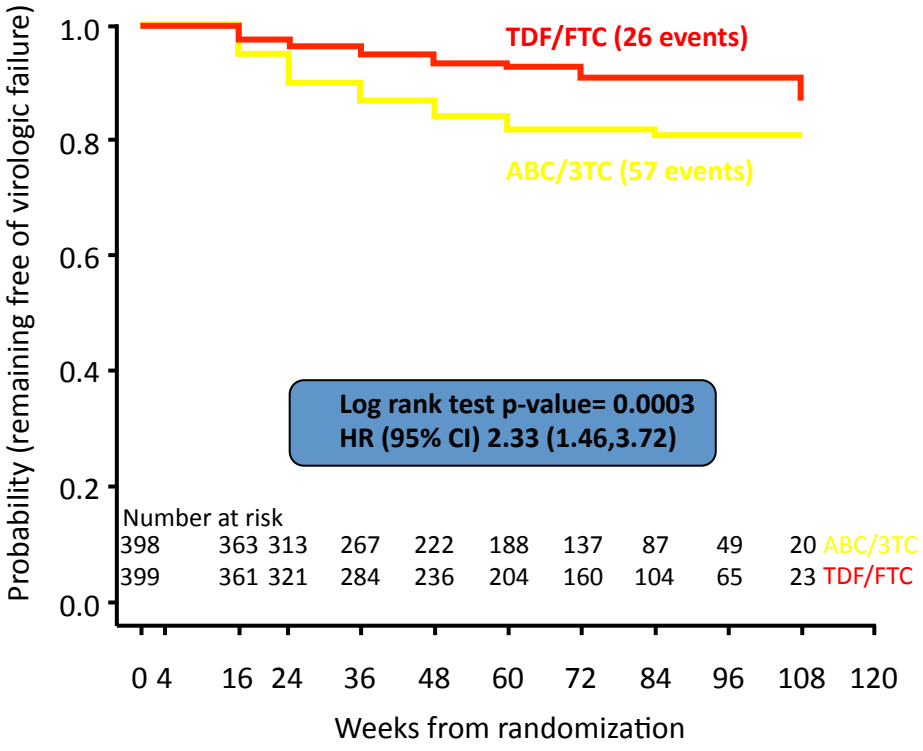
Characteristic	OTT (n=291)	PIm (n=296)	Difference PIm–OTT (95% CI)	p-value
VL rebound ≥ 50 copies/ml, confirmed - n (%) [1]	8 (3.2%)	95(35.0 %)	31.8% (24.6 to 39.0%)	<0.001
Loss of future drug options [by 36 months] - n (%) [2]	2 (0.7%)	6 (2.1%)	1.4% (-0.4 to 3.4%)	0.15
Loss of future drug options [by end of trial] - n (%) [2]	4 (1.8%)	6 (2.1%)	0.2% (-2.5 to 2.6%)	0.85
By drug class – n				
NRTI	3	1	-	-
NNRTI	3	2	-	-
PI	1	3	-	-
CD4 change, cells/mm^3 mean (SE) [3]	+91 (9)	+108 (9)	+17 (-10 to +43)	0.21
Serious disease complication n (%)	8 (2.8%)	15 (5.1%)	2.3% (-0.8% to 5.4%)	0.15
Grade 3/4 adverse event n (%) [5]	159 (55%)	137 (46%)	-8.4% (-16.4% to 0.3%)	0.043
Neurocognitive function [NPZ-5] change -mean (SE)[3]	+0.51 (0.04)	+0.50 (0.04)	-0.01 (-0.11 to +0.09)	0.86
Cost of ART drugs, £ mean (SE)[4]	30,230 (860)	21,260 (700)	-8970 (-6,790 to -11,160)	–

Patton et al. CROI 2014 poster 550

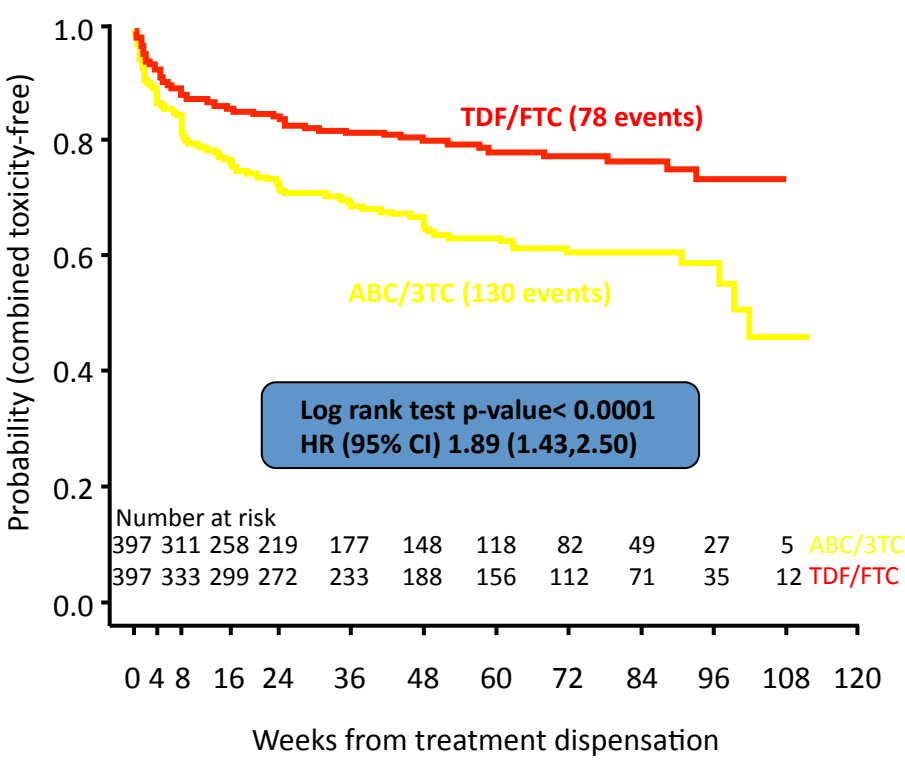
Primary virologic and safety endpoints (high viral load stratum at DSMB action)

N=797; median (25th, 75th) follow-up = 60 weeks (28, 84)

Time to virologic failure



Time to safety endpoint



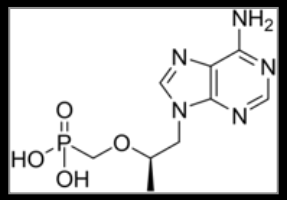
Sax PE *et al.* *NEJM* 2009; 361:2230-2240. Randomized, blinded equivalence study comparing four once-daily ARV regimens. N=1858.

TDF

ABC

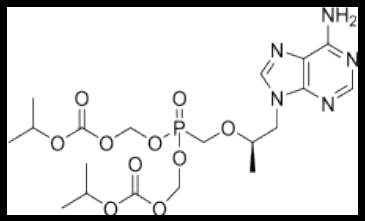
Tenofovir Alafenamide (TAF)

Next Generation Prodrug of Tenofovir-increased liver, lymph concentration



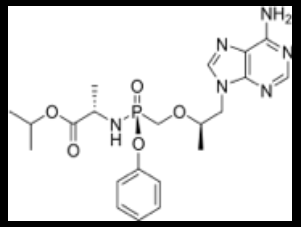
TFV

Tenofovir



TDF

Tenofovir Disoproxil Fumarate

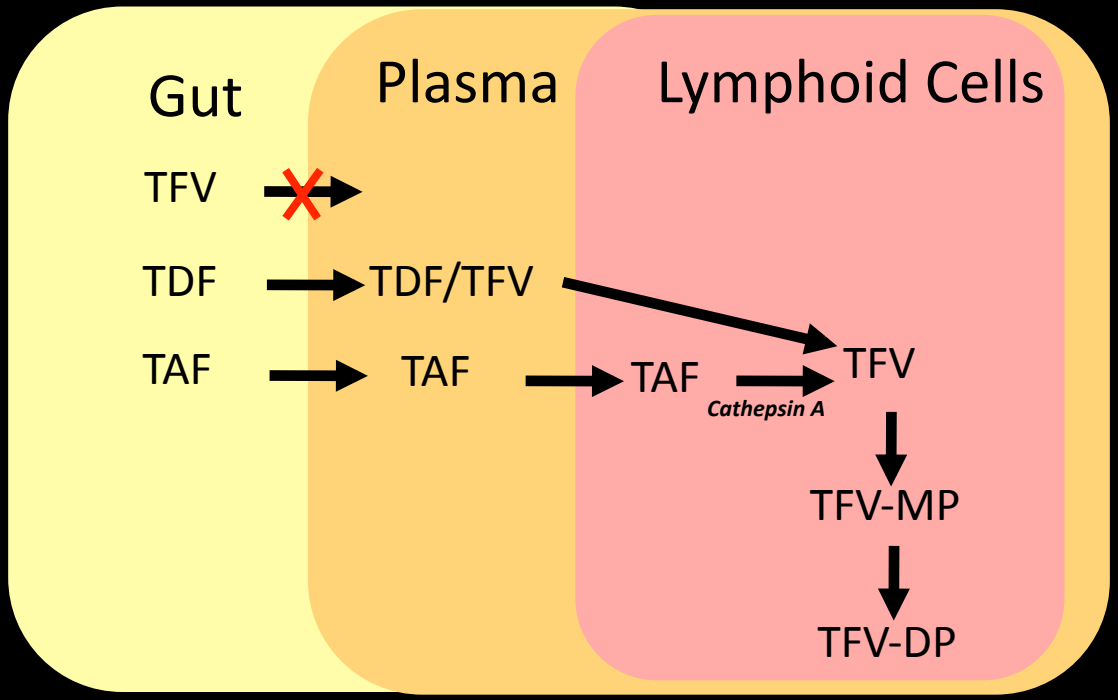


TAF

Tenofovir Alafenamide

TAF 10mg in E/C/F/TAF has PK comparable to TAF 25mg alone[2]

- COBI ↑ TAF levels ~2.2-fold



Relative to TDF 300 mg, TAF 25 mg has[1]:

- Increased anti-HIV-1 activity in Phase 1
- Increased intracellular TFV-DP levels by ~7-fold
- Decreased circulating plasma TFV levels by ~90%
- Lower levels of TFV in kidney and bone tissue expected

[1]P Ruane, et al. CROI 2012; Paper # 103

[2]S Ramanathan, et al. IWCPHT 2012; Abstract O_13

Virologic response (M=F, ITT)

GS-US-292-0102 – Week 24 Analysis

Resistance

3 subjects met protocol-specified criteria for resistance analysis

Confirmed >400 copies/mL of HIV-1 RNA at Week 24 or the discontinuation visit

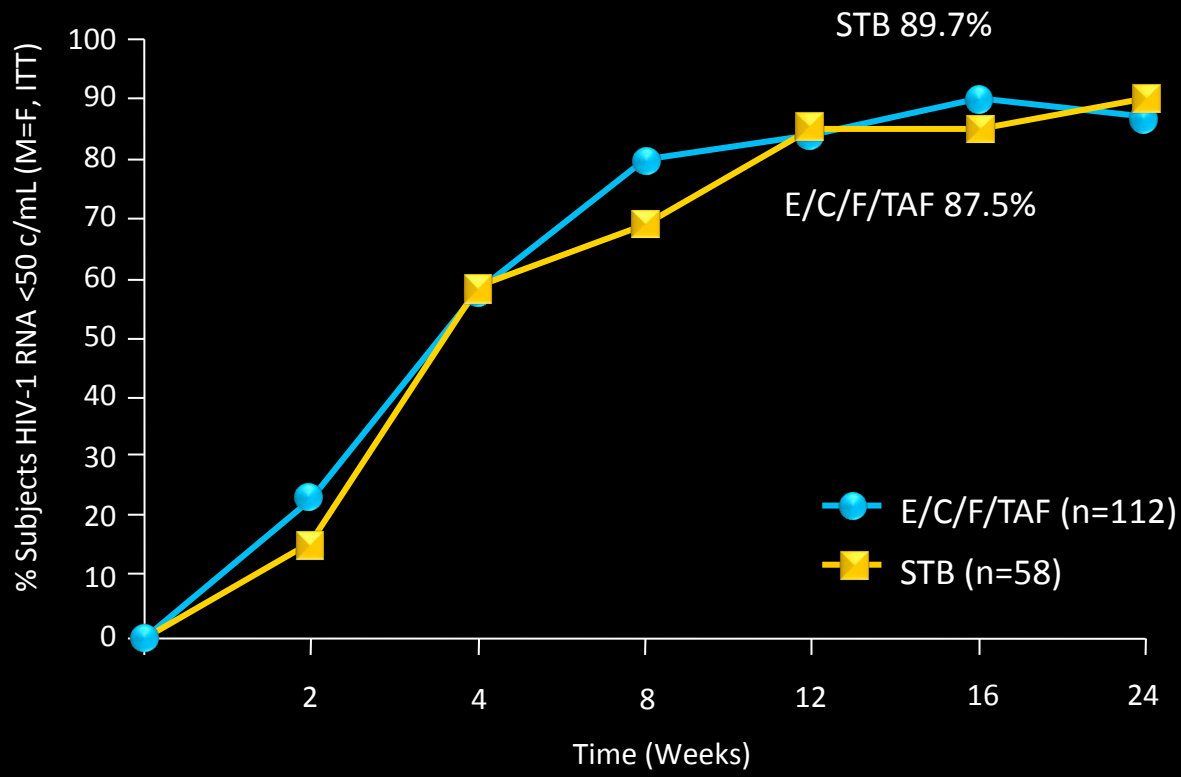
E/C/F/TAF arm (n=1)

- **1 subject with Week 24 rebound**

No resistance detected

STB arm (n=2)

- **1 subject with persistent viremia**
  - **NRTI resistance (M184V + K70E)**
  - **No EVG resistance**
- **1 subject with late rebound**
  - **No resistance detected**

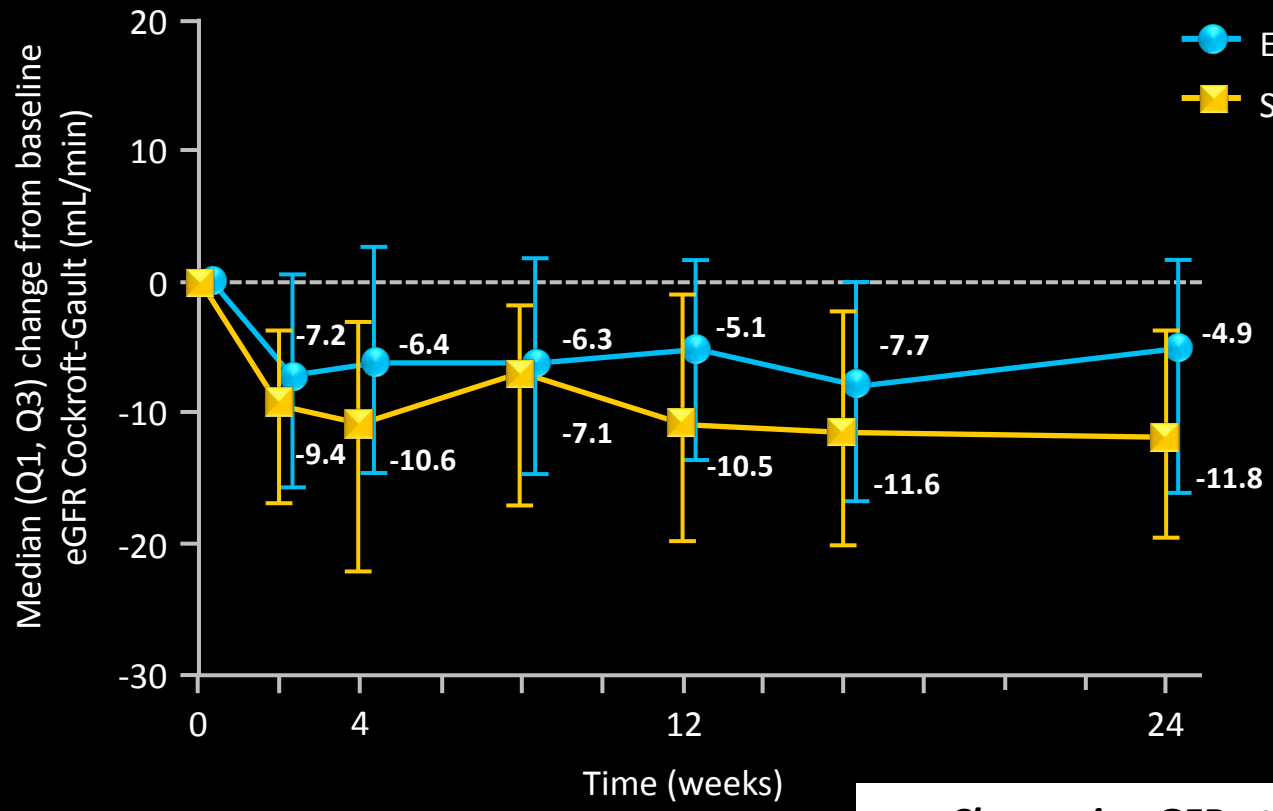


- **Mean change from baseline CD4+ cell count:**
  - **E/C/F/TAF, +163 cells/µL**
  - **STB, +177 cells/µL (p = 0.76)**

A Zolopa *et al., CROI* 2013; Paper # 99LB. Randomized, placebo-controlled, double-blind study. N=150.

Median estimated GFR (Cockcroft-Gault)

GS-US-292-0102 – Week 24 Analysis



- ***Change in eGFR at Week 24***
  - ***E/C/F/TAF: -4.8 mL/min***
  - ***STB: -11.8 mL/min (p=0.04)***

A Zolopa *et al., CROI* 2013; Paper # 99LB. Randomized, placebo-controlled, double-blind study. N=150.


.Real life is overrated.

Moving forward with cART – what's the target?

- Potent viral suppression
- Improved tolerability
- Regimen simplicity
- Durability of response

- Optimal immune restoration
- Minimal inflammation/activation

Andrieux-Meyer I, et al. J Int AIDS Soc 2012;15:17986.
Palmisano L & Vella S. Ann Ist Super Sanita 2011;47:44–8.


Trust Me, I'm a Doctor

ARV therapy – Do doctors and patients think alike?

Rank	Patient (N=114)	HCP (N=32)
1 (most important)	Efficacy	Efficacy
2	CD4 rise	Low toxicity
3	Protecting others	CD4 rise
4	Low toxicity	Once daily dosing
5	Resistance if fails	STR
6	Drug interactions	Low tablet load
7	Once daily dosing	Protecting others
8	Low tablet load	Drug interactions
9	STR	Resistance if fails
10 (least important)	Cost	Cost

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Thank you

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