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Impact of Neuropsychiatric AEs associated with ART

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Impact of Neuropsychiatric AEs associated with ART

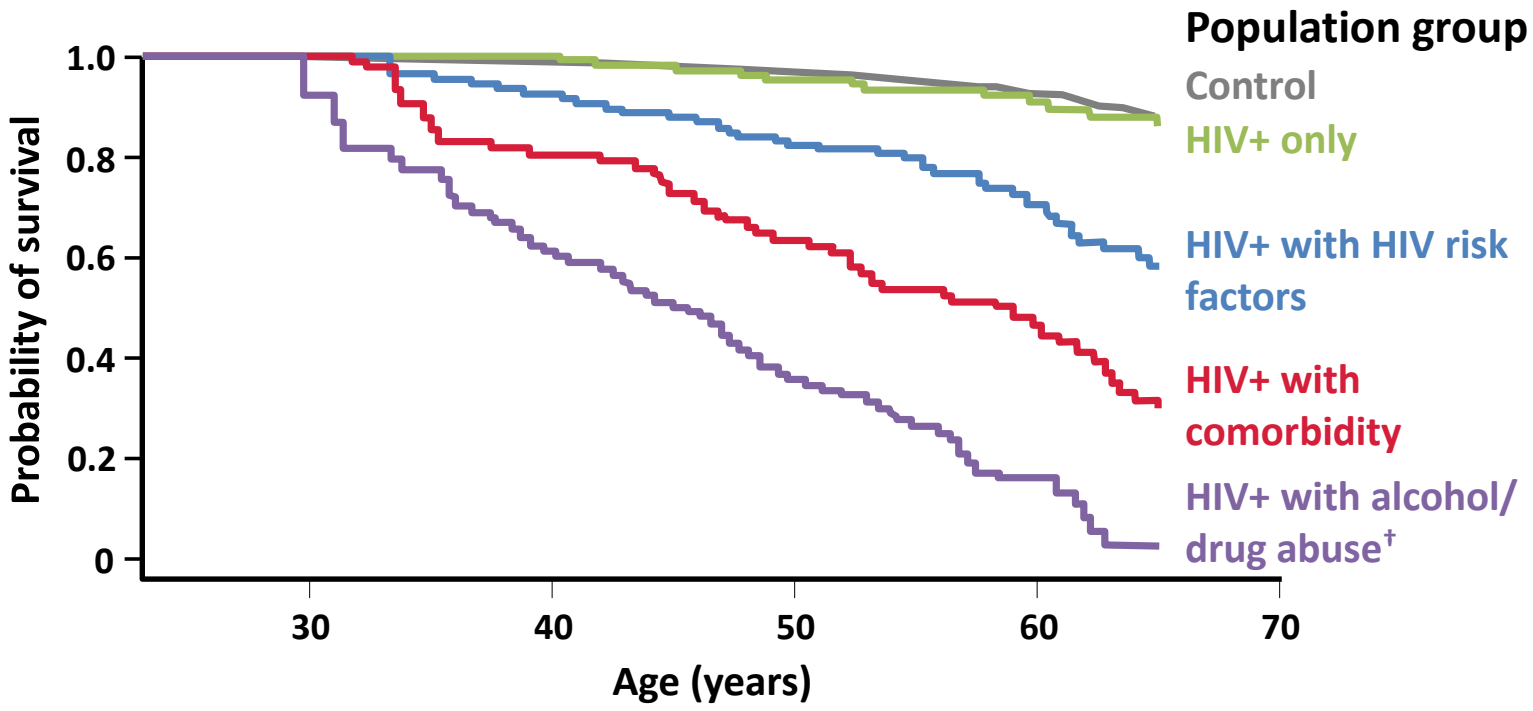
Conflict of interest:
Alan Winston has received speaker honoraria, participated in advisory boards or received investigator initiation study grants from AbbVie, BI, BMS, Gilead Sciences, GSK, Janssen, MSD and ViiV Healthcare.

Overview

- Where are we in 2014?
- How have we got here?
- Neuropsychiatric AEs
- Management strategies
- The future

Age at diagnosis, comorbidities and life expectancy

Cumulative survival for HIV-infected patients starting HAART and persons from the general population



Obel N, et al. PLoS ONE 2011;6:e22698

Our first question

Do we need new antiretroviral agents and treatment strategies?

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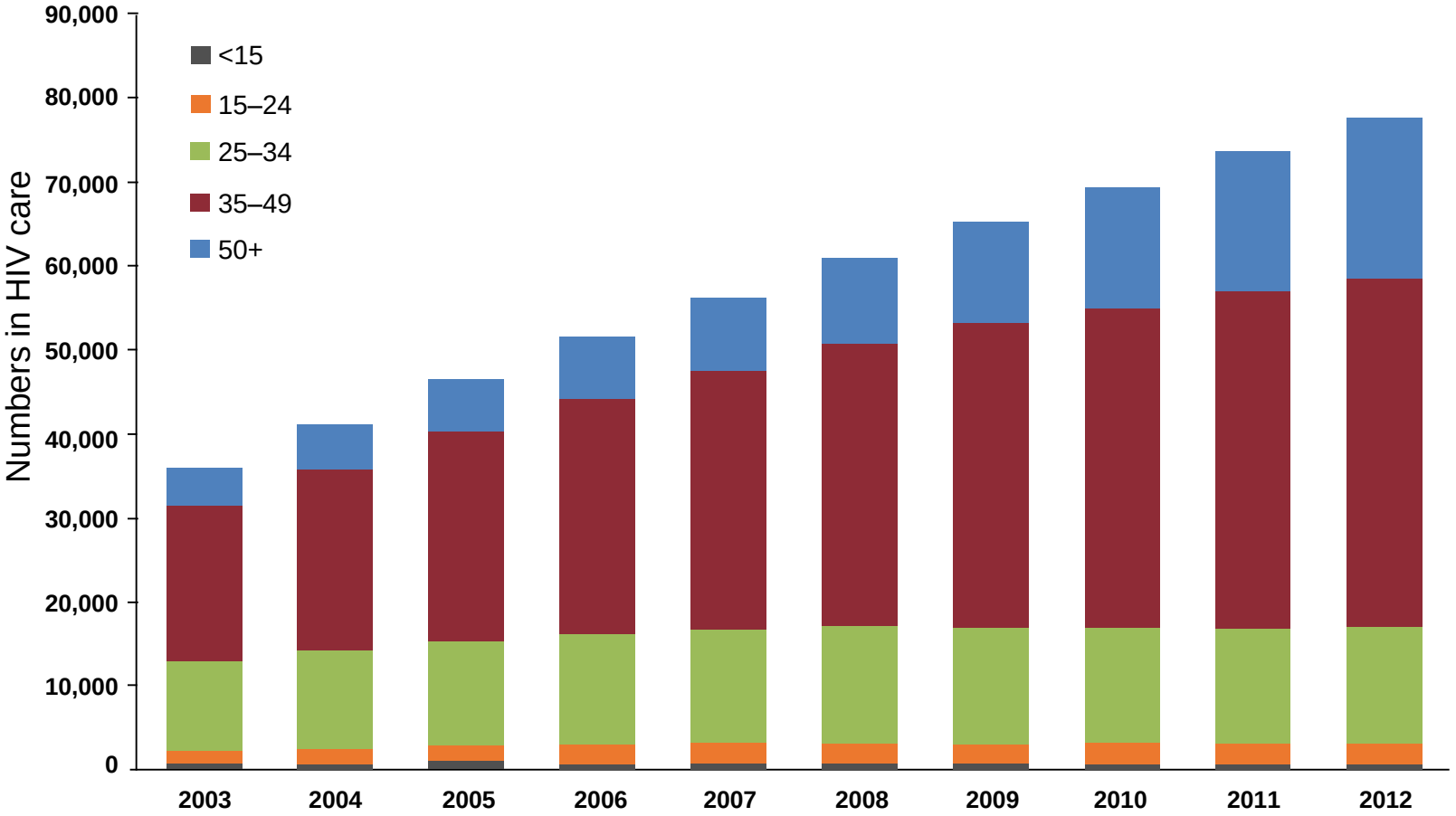
Diagnosis of HIV by age group : UK 2003 - 2012



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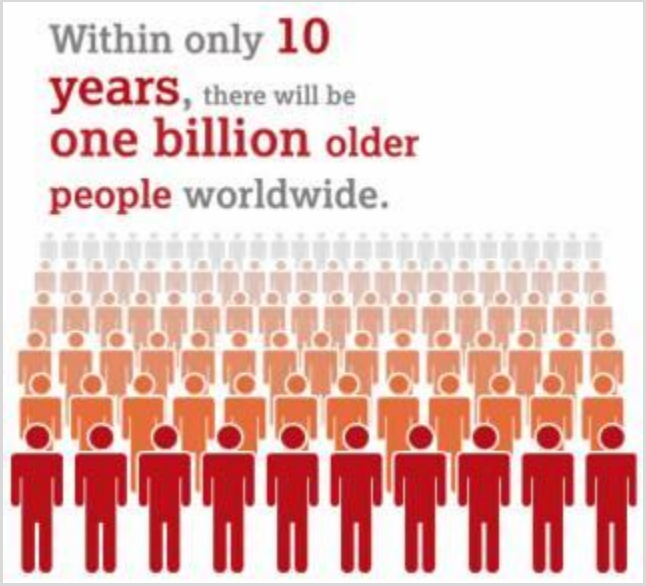
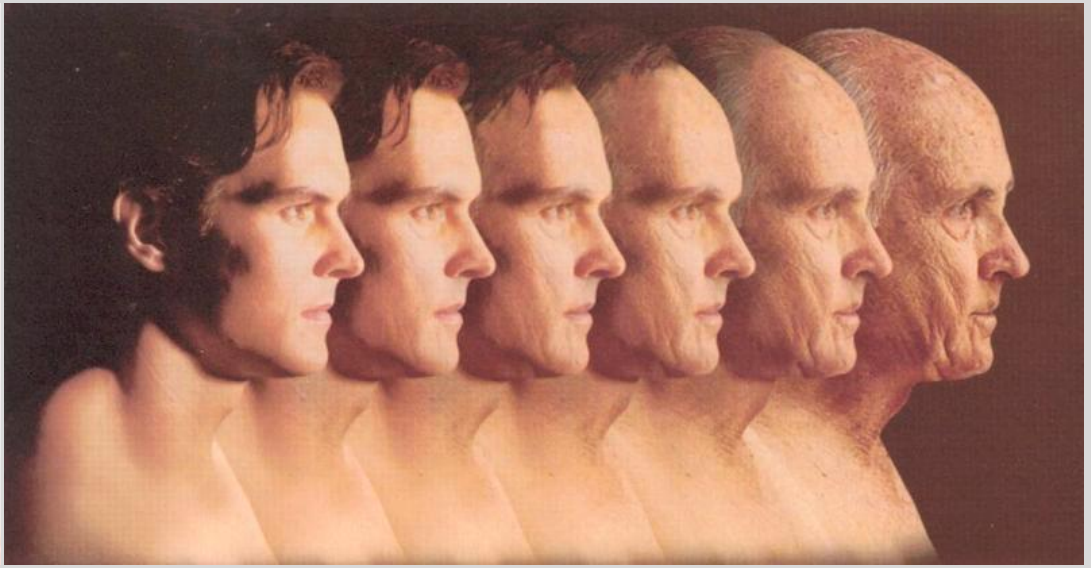
New infections in over 50s

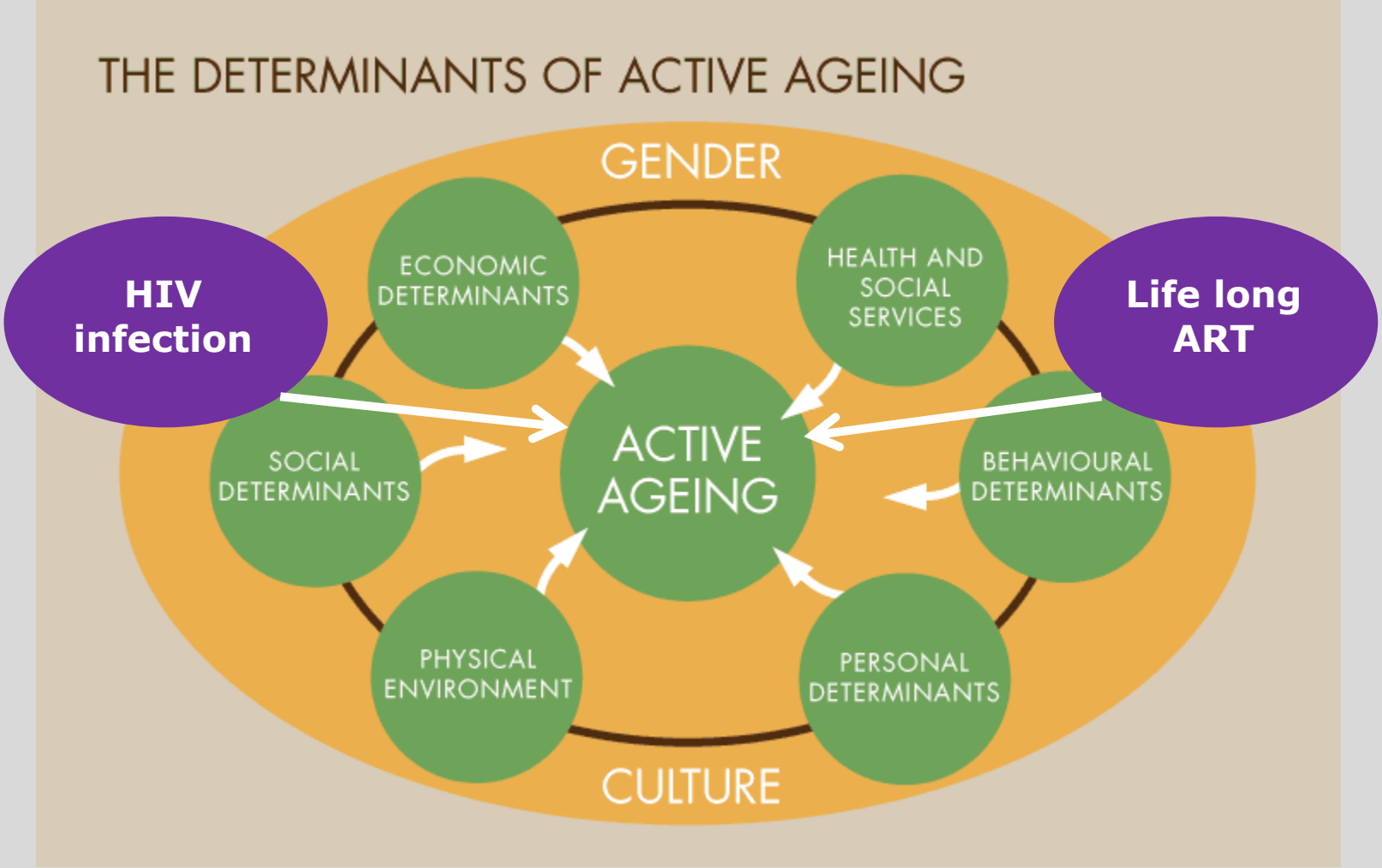
- This age group is the least likely to practice safe sex[1,2]
- Late-life changes in the reproductive tract and immune system may enhance their susceptibility to HIV acquisition[1]
- Physicians are less likely to recommend HIV testing to older patients[2–4]
- Asymptomatic, older, HIV-infected individuals are less likely to seek out testing and medical care[2,5]
- Symptomatic, older, HIV-infected individuals are more likely to attribute symptoms to other illnesses or to ageing[6]

1. High KP, et al. JAIDS 2012;60(Suppl 1):S1–S18; 2. Conde DM ,et al. Menopause 2009;16:199–213;
3. Mutevedzi PC, Newell M-L. Future Virol 2011;6:755–67; 4. Harawa MT, et al. Sex Transm Dis 2011;38:1110–7;
5. Cuzin L. Clin Infect Dis 2007;45:654–7; 6. Siegel K. AIDS Care 1999;11:525–35


Within only 10
years, there will be
one billion older
people worldwide.

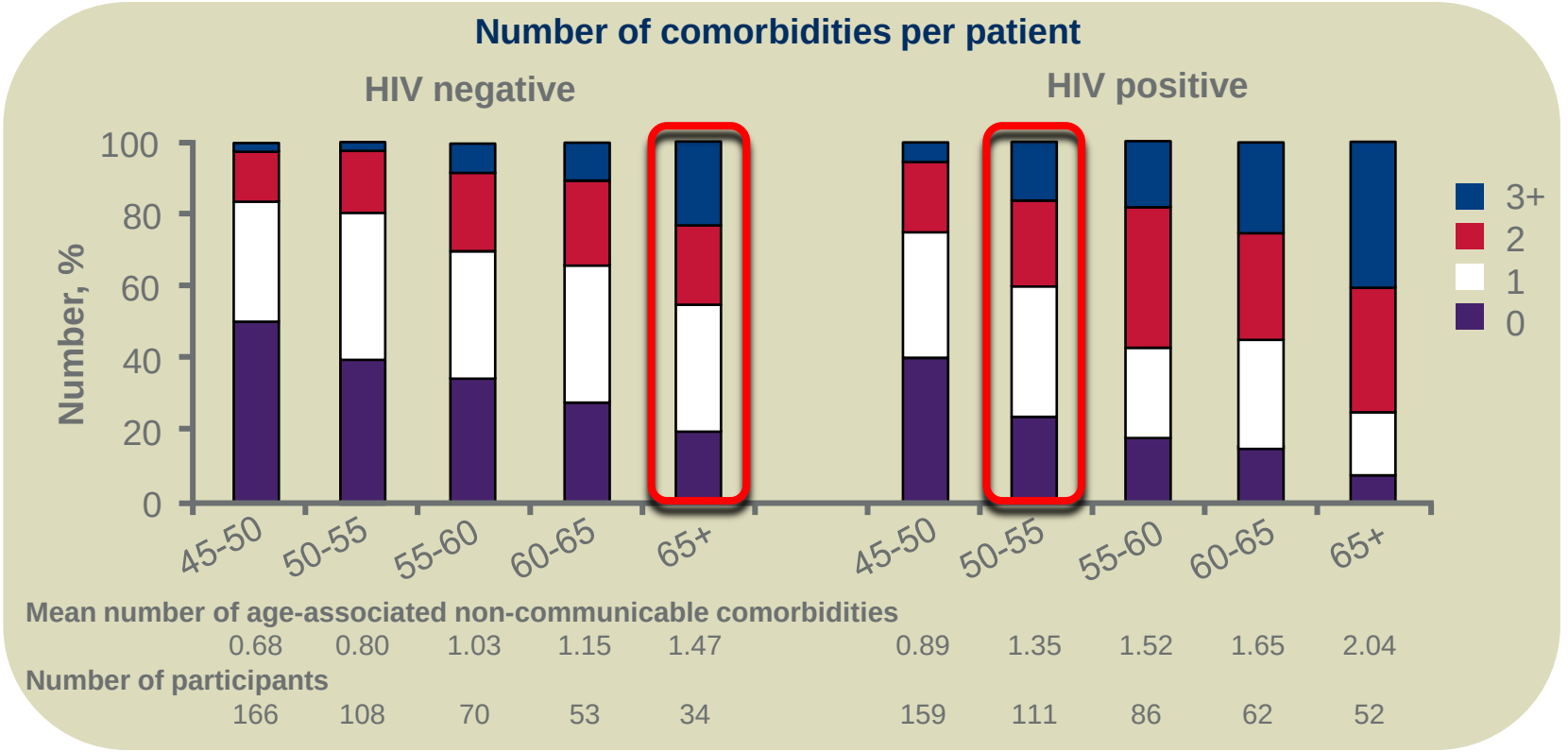


Healthy ageing



Comorbidities

- Cohort study of HIV and comorbidities in The Netherlands (N=452 HIV-negative and 489 HIV-positive persons)



Schouten J, et al. AIDS 2012. Abstract THAB0205

Intolerance to ART in older subjects

Discontinuation of cART in the first year for reasons other than virological failure

Age group, yrs	Relative Hazard	95% CI	p Value
<30	1.12	1.01–1.24	0.03
30–39	Reference	–	–
40–49	1.06	0.97–1.17	0.21
≥50	1.14	1.00–1.31	0.06

UK CHIC report:

- n=8,708 naïve patients initiating cART, 1998–2005
- 2,650 (30%) discontinued ≥1 drug during first year of therapy for reasons other than virological failure

Sabin CA, et al. HIV Medicine 2009;10:35–43

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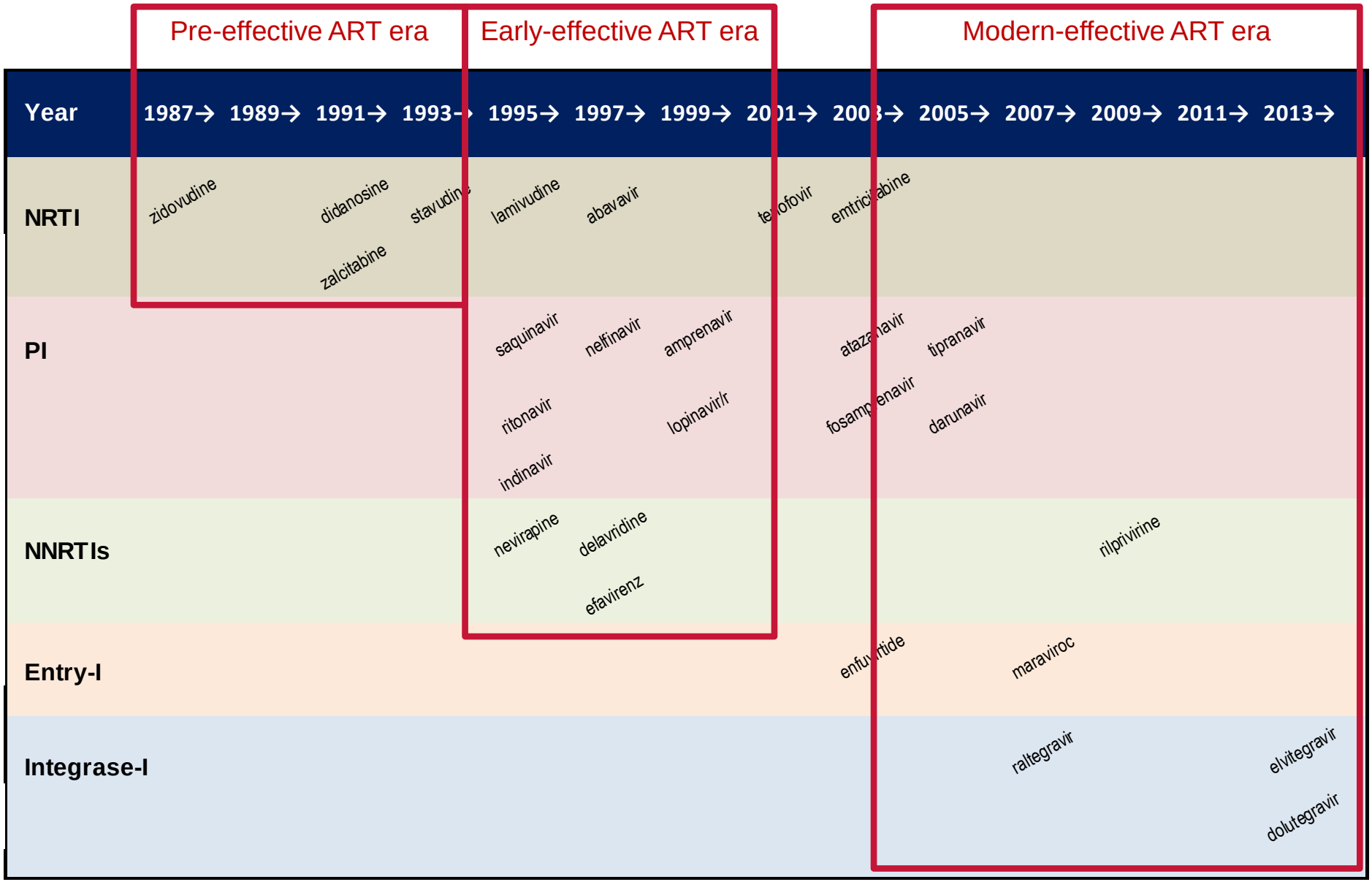
How has 'standard' ART evolved?



Current guidelines

NRTI backbone with either	1 NNRTI
	2 Boosted PI
	3 Integrase-I

Recommended Regimens(*)

A drug from column A should be combined with the drugs listed in column B(**)

A	B	Remarks
NNRTI	NRTI	
EFV(i) RPV(ii)	ABC/3TC(vii) or TDF/FTC	ABC/3TC co-formulated TDF/FTC co-formulated EFV/TDF/FTC co-formulated RPV/TDF/FTC co-formulated
PI/r		
ATV/r(iv) DRV/r(iv)	ABC/3TC(vii) or TDF/FTC	ATV/r: 300/100 mg qd DRV/r: 800/100 mg qd
INSTI		
RAL	TDF/FTC or ABC/3TC	RAL: 400 mg bd

Dynamics of regimen selection

Preferred ARVs

NRTIs
- ZDV
- DTG*
- d4T
- ddC
- 3TC
- TDF
- FTC
- RAL

INI

PIs
- IDV
- NFV
- RTV
- SAQ
- FPV
- LPV/r
- bATV
- bDRV

NNRTIs
- EFV

FDCs
- FTC/TDF
- ABC/3TC

STRs
- EFV/FTC/TDF

**With either FTC/TDF or ABC/3TC*

Alternative ARVs

STRs
- RPV/FTC/TDF
- EVG/COBI/FTC/TDF

FDCs
- ZDV/3TC

PIs

PIs
- IDV
- RTV
- SAQ
- NFV
- ATV

NRTIs
- ABC
- ddC
- ddI
- d4T

NNRTIs
- DLV
- NVP

FDCs

Efavirenz virological efficacy

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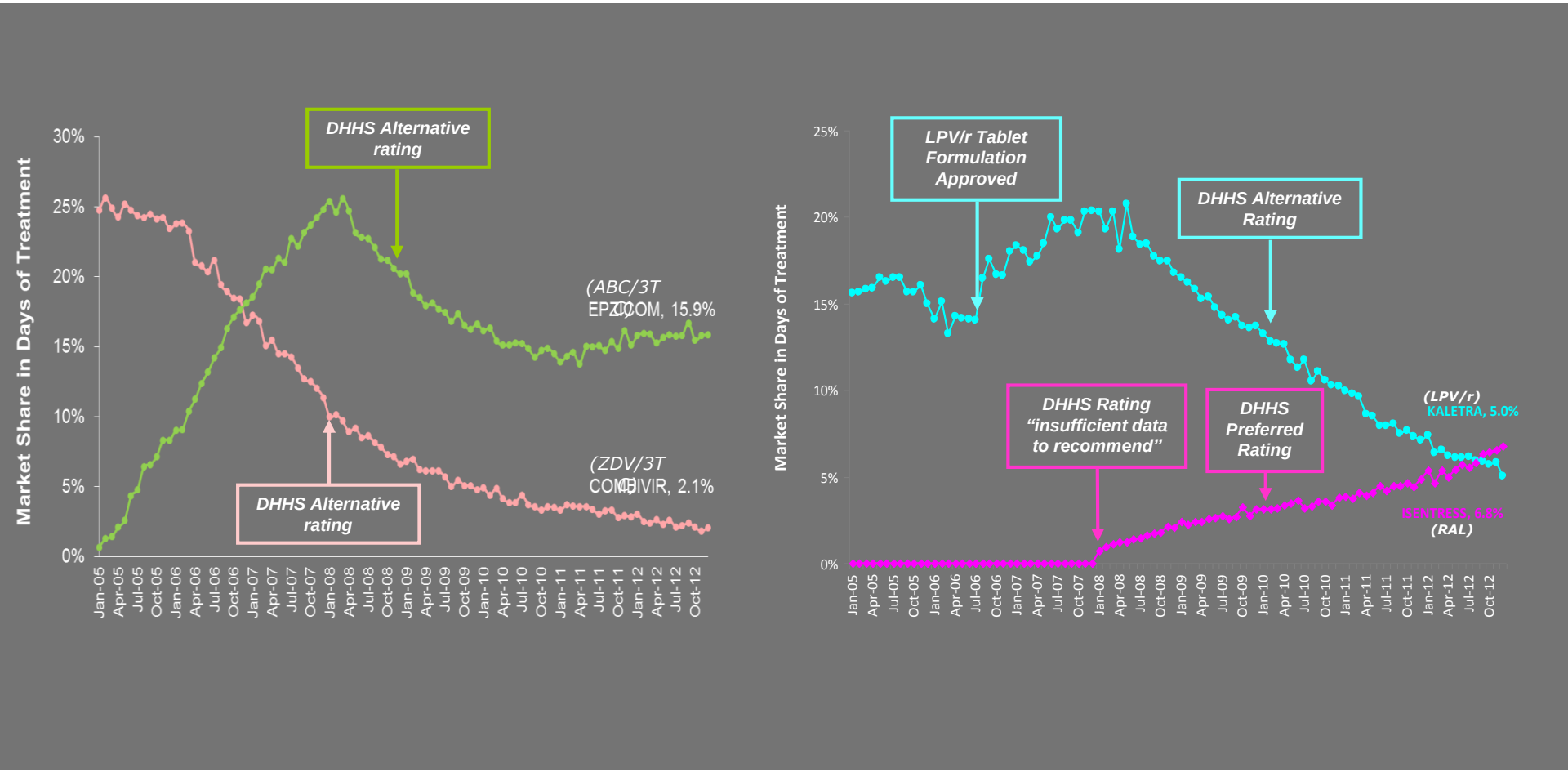
Key efficacy data over the last decade from randomized controlled trials and cohort studies

Study	Year	Comp.	EFV, n	% VL <50 c/mL		FU Weeks
				EFV	Comp	
				64		
Johns Hopkins[2]	2001	SAQ+RTV	64	72*	51*	48
Swiss HIV Cohort[3]	2001	PI-based	89	77	51	48
2NN[4]	2003	NVP	400	70	65	48
ACTG 5142[5]	2007	LPV/r	250	76	67	96
Sierra-Madero *et al*.[6]	2010	LPV/r	95	71	53	48

1. Staszewski S, et al. NEJM 1999;341:1865-1873
2. Lucas G, et al. AIDS 2001;15:1679-1686
3. Friedl A, et al. AIDS 2001;15:1793-1800
4. Van Leth, F et al. Lancet 2004;363:1253-1263
5. Riddler S, et al. NEJM 2008;358:2095-2106
6. Sierra-Madero, et al. JAIDS 2010;53:582-588

Guidelines and what we do!



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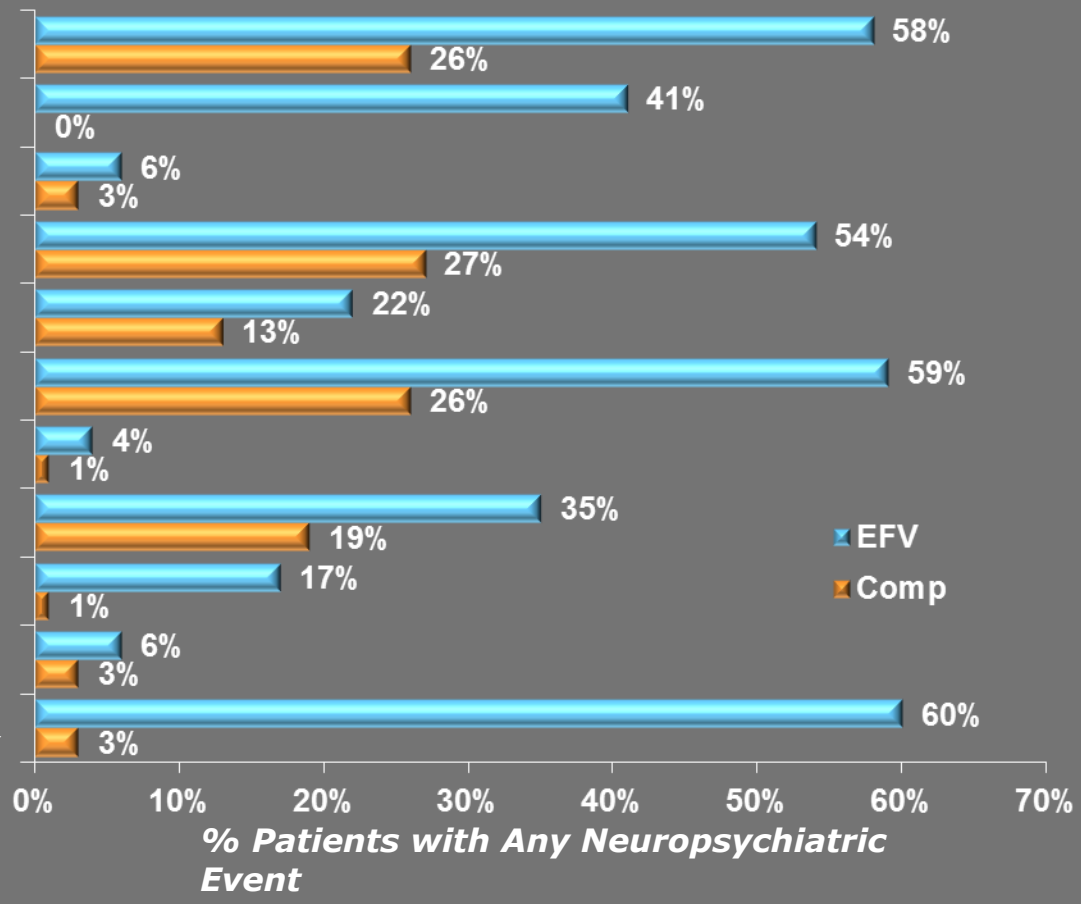
Neuropsychiatric Symptoms - historical

Treatment Emergent Neuropsychiatric AEs of Moderate or Severe Intensity Reported in Study DMP 266-006*

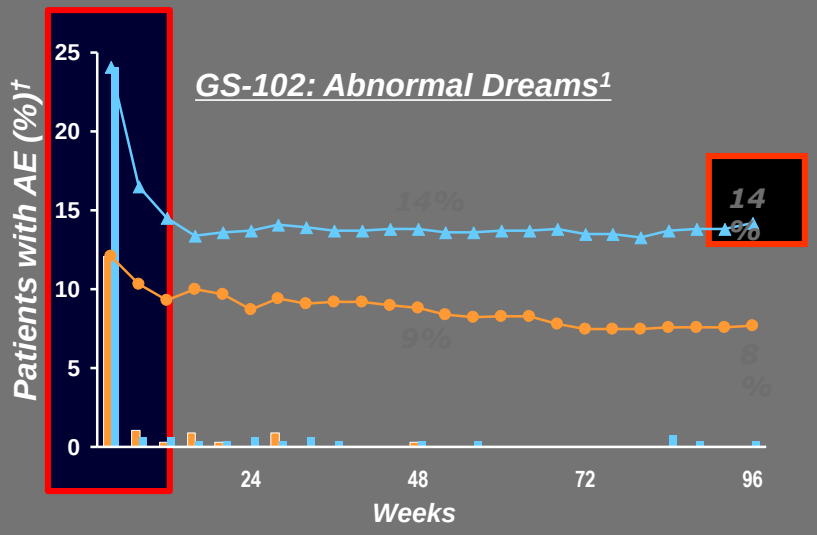
*AEs for the third treatment arm (EFV+LPV) are not presented	EFV+AZT+3TC (n=412)	IDV+AZT+3TC (n=401)
Central Nervous System		
Dizziness	9%	2%
Headache	8%	3%
Insomnia	7%	2%
Concentration impaired	5%	<1%
Abnormal dreams	3%	0%
Somnolence	2%	<1%
Anorexia	1%	<1%
Psychiatric		
Anxiety	2%	<1%
Depression	5%	<1%
Nervousness	2%	0%

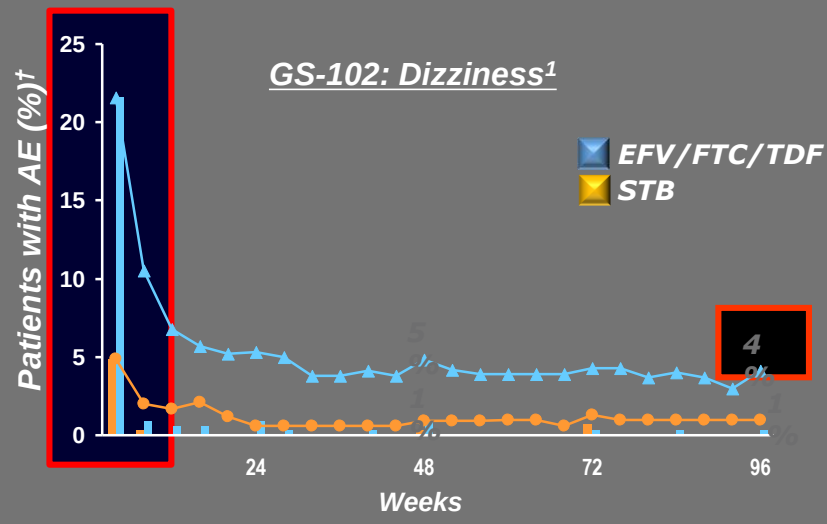
Neuropsychiatric Symptoms – comparison studies



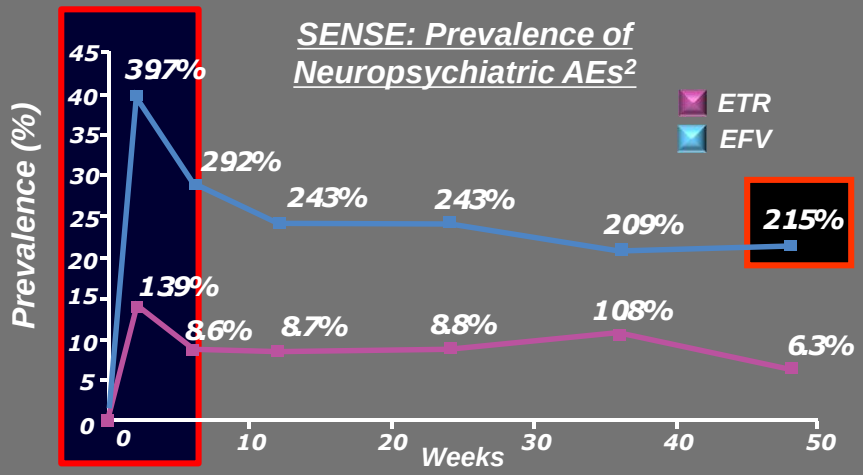
n's represent no. of EFV patients

Neuropsychiatric Symptoms – contemporary studies





† Bar (Incidence): New onset or worsening AEs
Line (Prevalence): Ongoing events

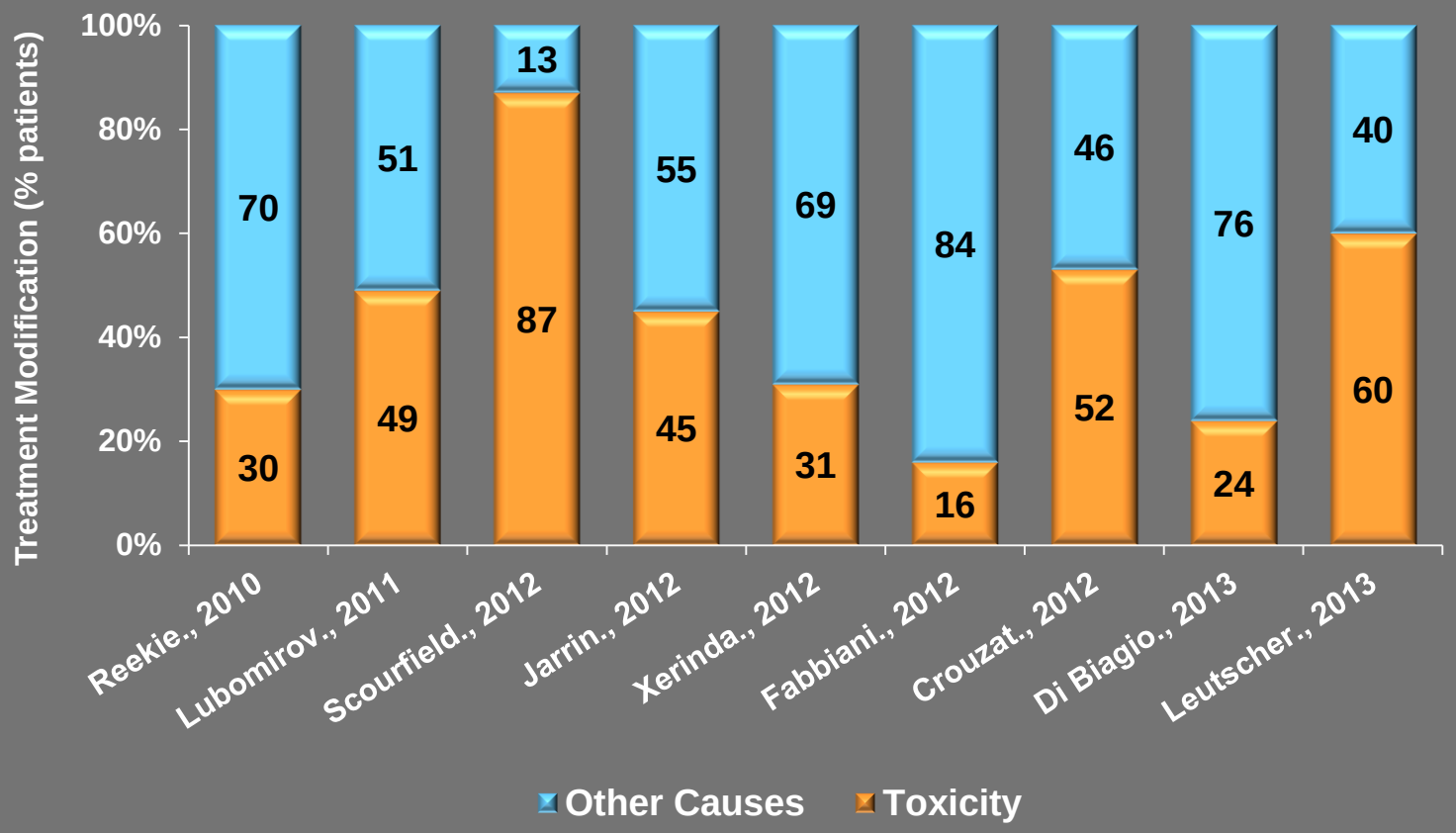


- ***Most EFV-associated neuropsychiatric symptoms are mild and transient, occurring during the first 2-4 weeks***

1. Zolopa A, et al. HIV-11 2012; Glasgow. O424. 2. Gazzard B, et al. AIDS 2011;25:2249-2258

Do these neuropsychiatric effects matter?

Toxicity and efavirenz treatment modification



Switching off contemporary regimens

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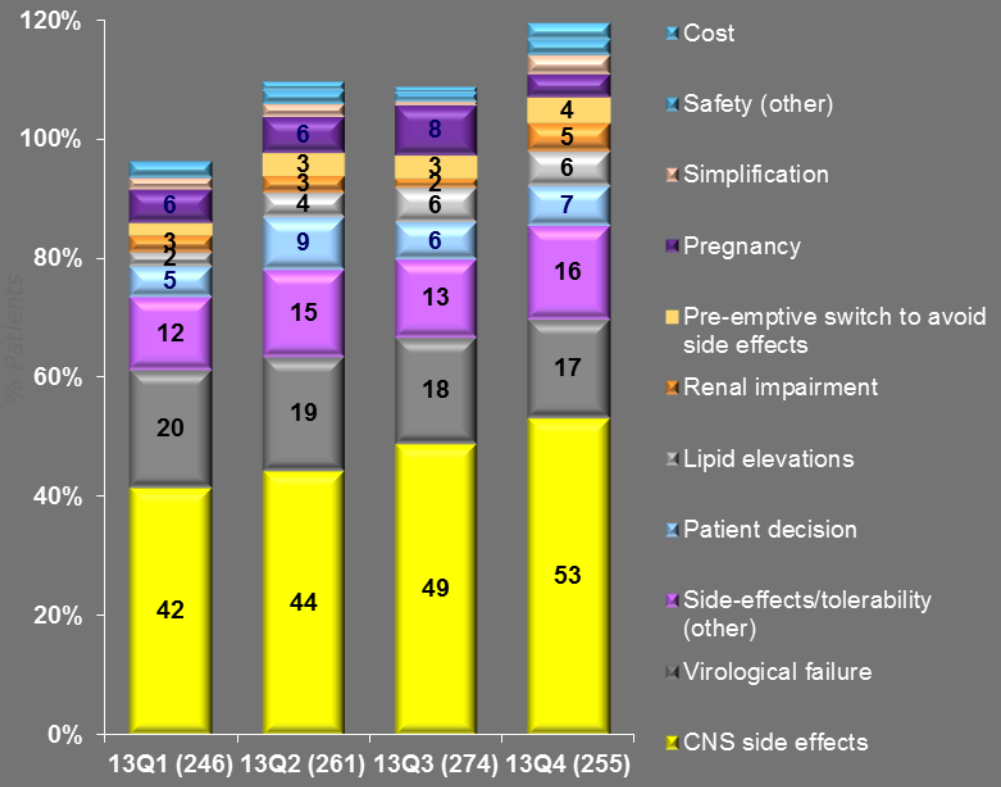
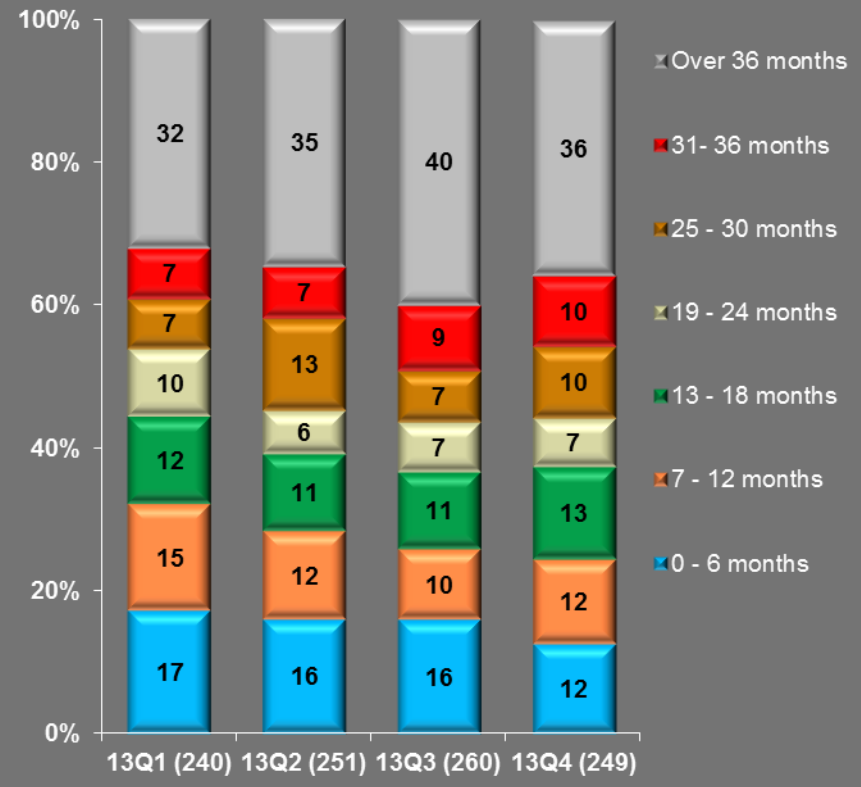
Main Reasons for Switching off Atripla



Duration of Atripla Treatment Prior to Switch



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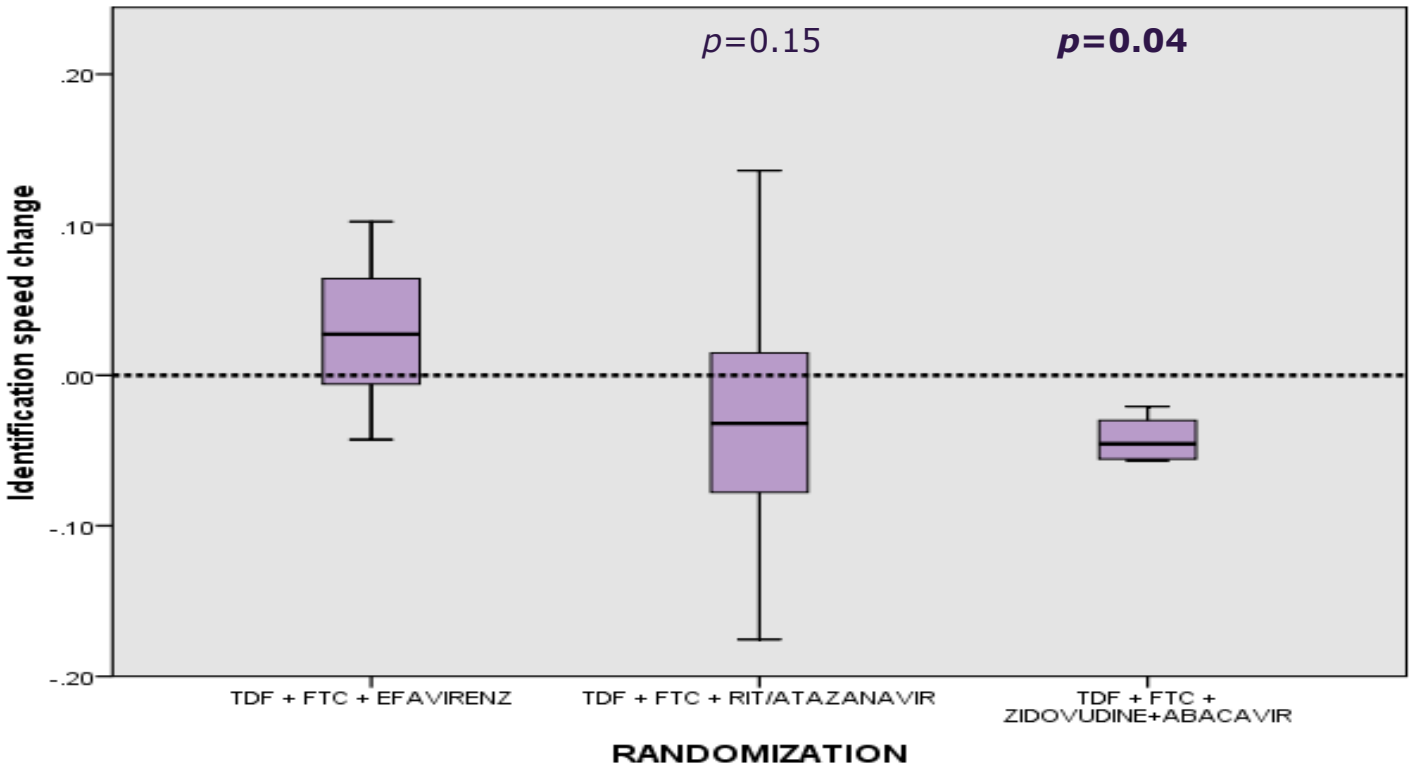
Efavirenz and cognitive function

146 patients
129 (88.4%) were on cART
69 (47%) were classified as cognitively impaired
- 35.6% asymptomatic
- 11.6% mild neurocognitive impairment

Variable		β	OR	95% CI	P-value	β	OR	95% CI	P-value
		Univariate				Multivariate			
Gender	(male versus female)	0.25	0.78	(0.41–1.51)	0.466				
Age	per 10 years	0.26	0.77	(0.58–1.03)	0.078	0.19	0.83	(0.60–1.16)	0.296
Education	per year	0.12	0.89	(0.81–0.97)	**0.012**	0.16	0.85	(0.77–0.94)	**0.002**
Non-Italian born	versus Italian born	1.1	3.01	(1.09–8.35)	**0.034**	1.24	3.46	(1.09–10.99)	**0.035**
IVDU		0.13	1.14	(0.46–2.82)	0.78				
HCV		0.3	0.74	(0.33–1.69)	0.479				
Time since HIV diagnosis	per year	0.02	0.98	(0.93–1.03)	0.355				
AIDS defining illness		0.29	1.34	(0.64–2.81)	0.441				
CD4 nadir	per 100 cells	0.13	0.88	(0.69–1.12)	0.294				
Time on cART	per one year increase	0.02	1.02	(0.94–1.11)	0.639				
Efavirenz use		1.26	3.53	(1.37–9.08)	**0.009**	1.39	4	(1.43–11.20)	**0.008**
CPE rank	>7	0.45	1.43	(0.68–3.00)	0.346				
HIV RNA	per log increase	0.19	0.83	(0.58–1.19)	0.312				
HIV RNA < 50 copies/mL		0.64	1.9	(0.86–4.21)	0.114				
CD4 cell count	per 100 cell increase	0.05	0.96	(0.86–1.07)	0.42				

Neurology. 2011 Apr 19;76(16):1403-9

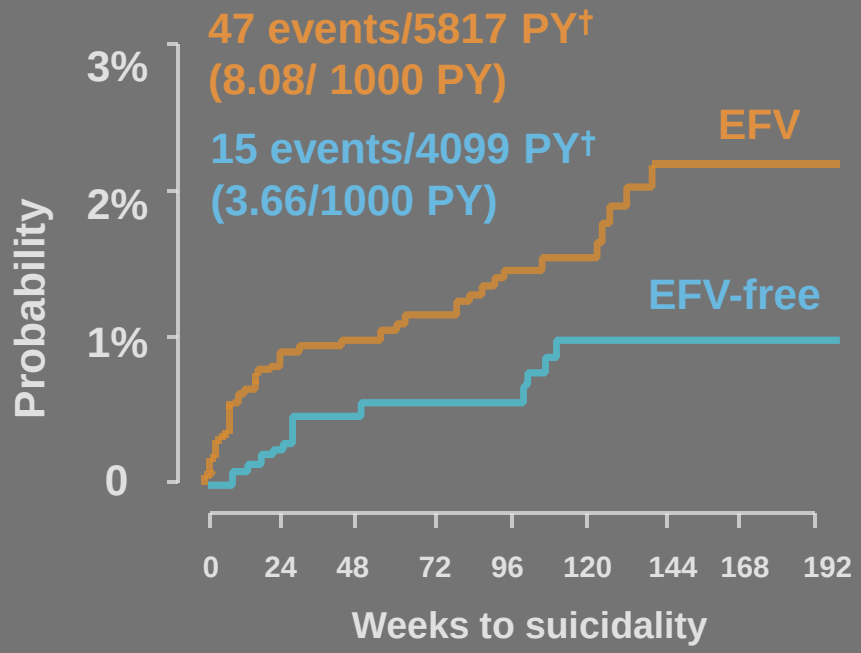
Efavirenz and cognitive function

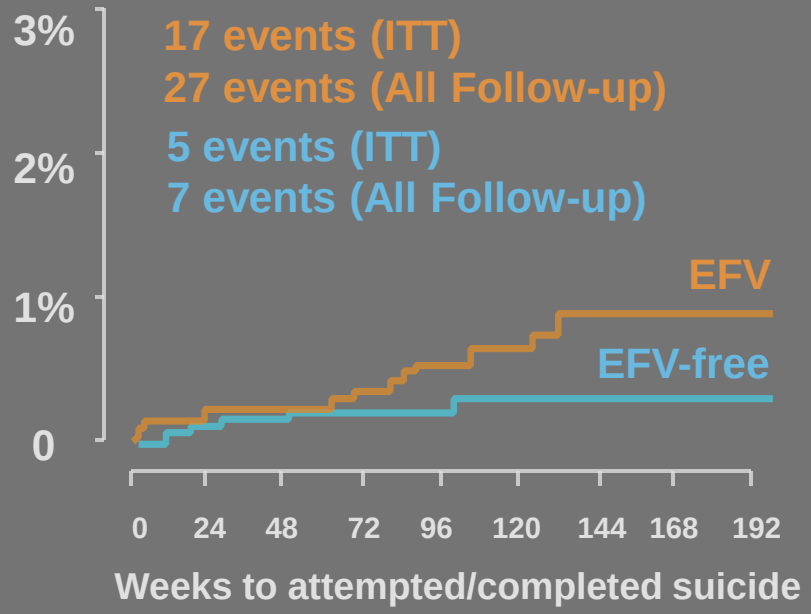


Clin Infect Dis. 2010 Mar 15;50(6):920-9

Efavirenz and suicidal ideation

	HR (95%CI)	P-value
Suicidality – ITT	2.28 (1.27 – 4.10)	0.006
Attempted/Completed Suicide **– ITT** **– All Follow-up***	 2.58 (0.94 – 7.06) 2.6 (1.1 – 5.9)	 0.06 0.03





† Person-years, sum of at-risk follow-up

Mollan K, et al. ID Week 2013. San Francisco, CA. Oral #670

* Includes follow-up beyond DSMB decisions for A5095 and A5175

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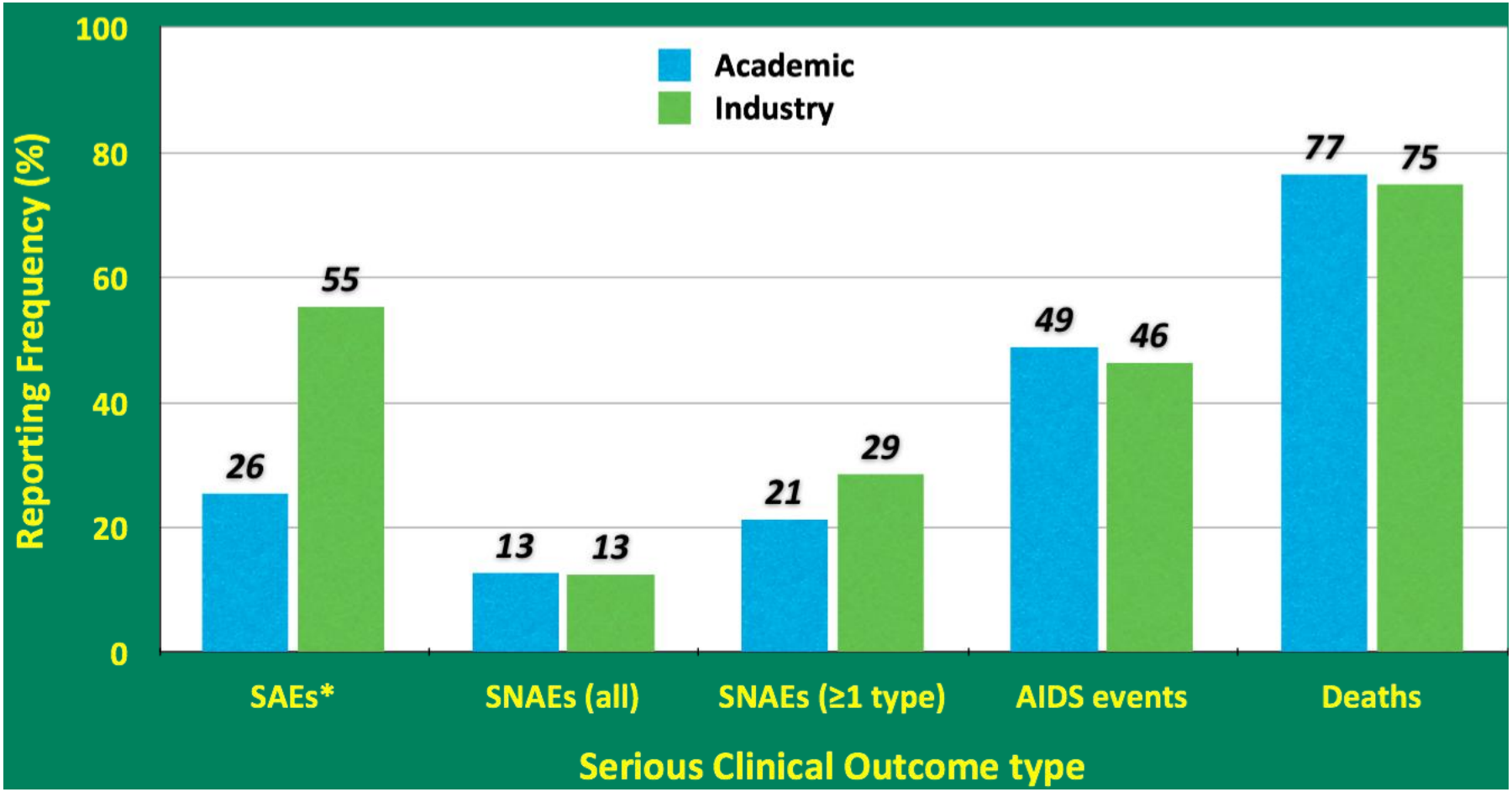
How quick are we at recognising problems?

Toxicities: under-reported



Lee et al, Comorbidity workshop 2013

How quick are we at recognising problems?

Drug / class	FDA approval	Toxicity	Strong signal	Delay (years)
zidovudine	1987	lipoatrophy	1999	12
stavudine	1994	lipoatrophy	1999	5
nevirapine	1996	toxicity at high CD4	2005	9
PIs	1996-	heart attack	2003	7
efavirenz	1998	suicidality	2013	15
abacavir	1998	heart attack	2008	10
tenofovir	2001	fracture	2012	11
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

Drug metabolites

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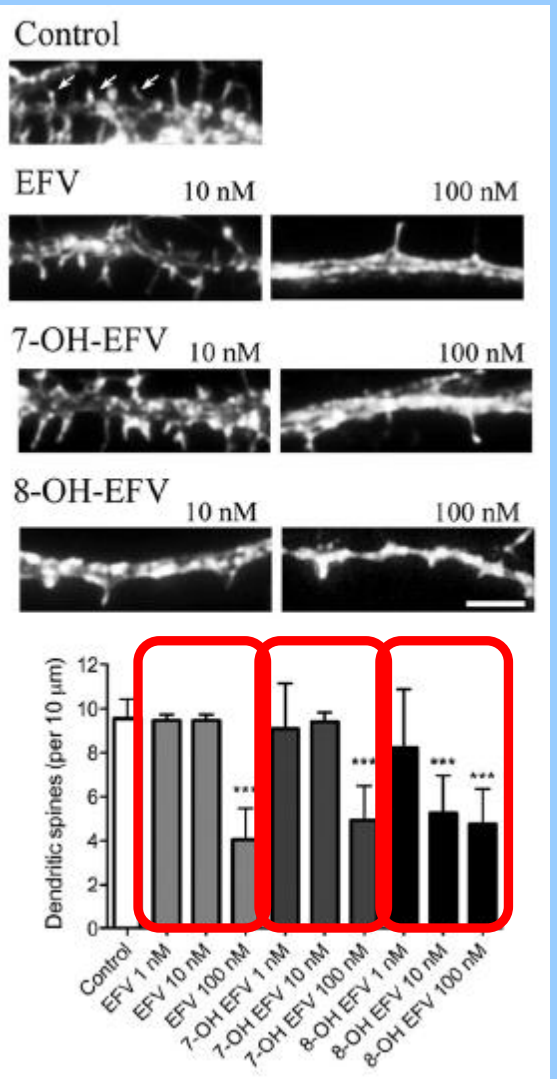
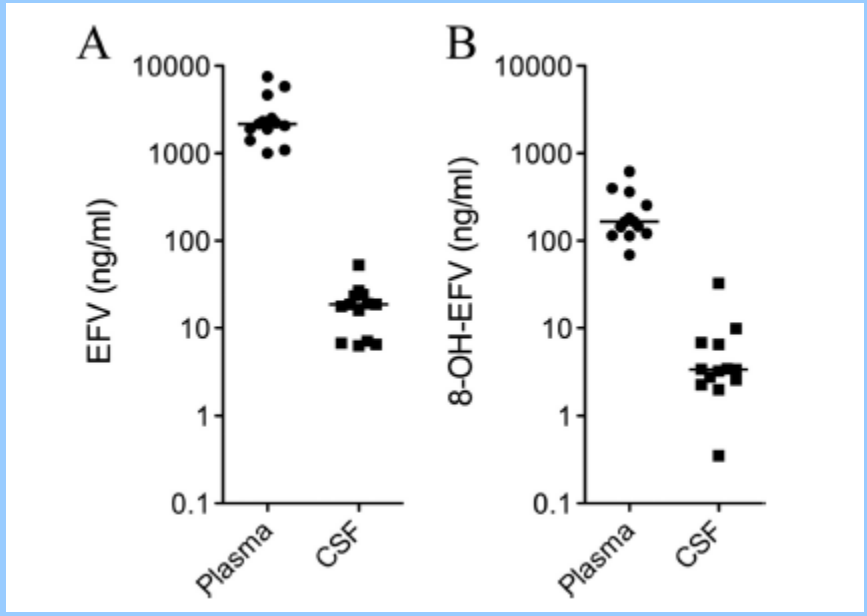
In the lab



In the clinic



Pharmacogenomics. 2013 Jul;14(10):1167-78.

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Management


FIRST STEP IN SOLVING
ANY PROBLEM
IS
RECOGNIZING
THERE IS ONE

Switching NNRTI

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UK multicentre study:

- Subjects with efavirenz associated toxicity
- Randomised immediate versus deferred switch etravirine
- **Double blind study**

	Etravirine* (n = 20)	Efavirenz* (n = 18)
Grades 2–4 CNS adverse events		
All Grades 2–4 CNS adverse events	60%	81%
Median number of CNS adverse events	1	3
Dizziness	15%	19%
Depression	20%	19%
Insomnia	37%	60%
Anxiety	25%	44%
Impaired concentration	30%	31%
Headache	5%	25%
Somnolence	30%	31%
Fatigue	35%	44%
Abnormal dreams	20%	63%
Nervousness	9%	29%
Hallucinations	0%	7%

AIDS. 2011 Jan 2;25(1):65-71

Fixed dose combinations

efavirenz NNRTI
3rd agent Atripla ®

rilprivirine NNRTI 3rd agent Eviplera ®

elvitegravir INI 3rd agent Stribild ®

Switching NNRTI

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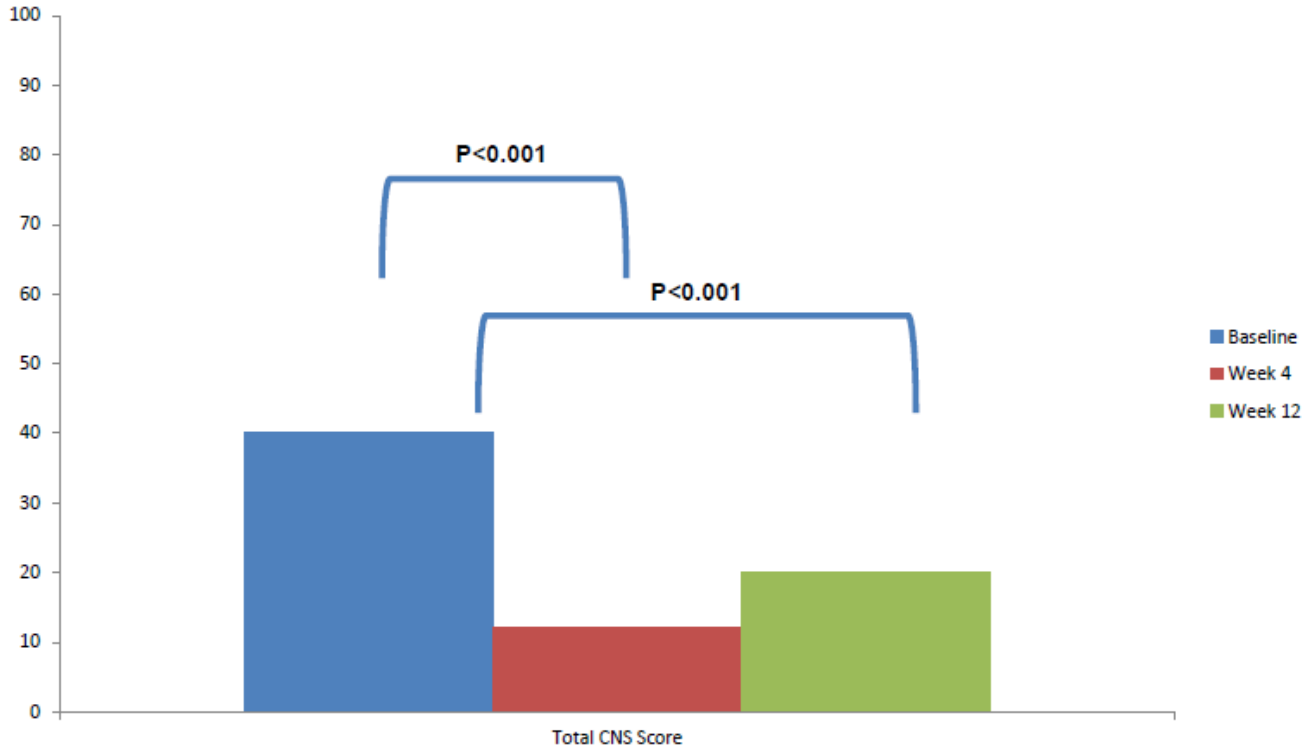
UK multicentre study:

- Subjects with efavirenz associated toxicity
- Switched rilpivirine in fixed dose combination
- **Open label study**
- N=40



Rowlands et al O4. HIV Medicine 2014; 15 (3): 1-16

Switching NNRTI

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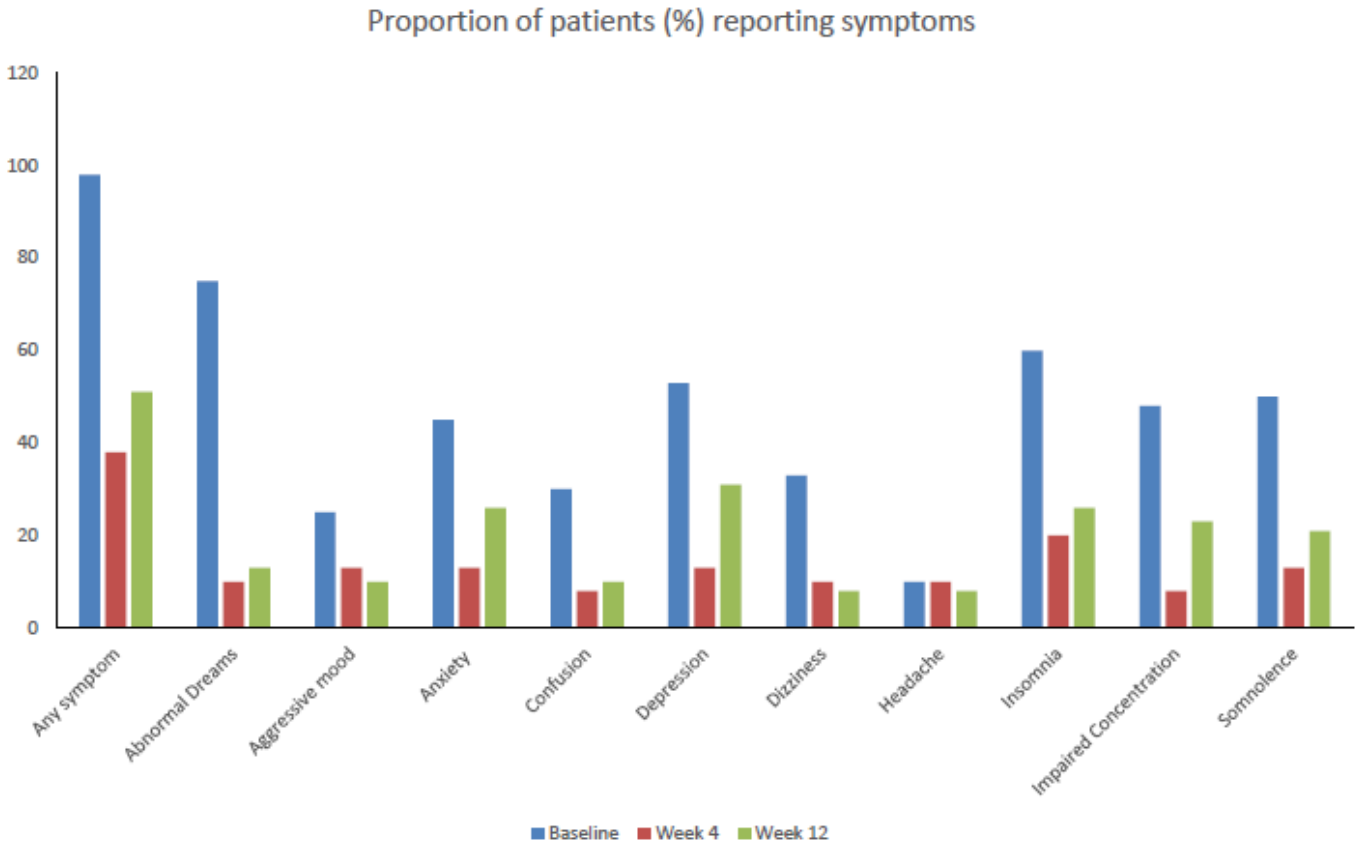
UK multicentre study

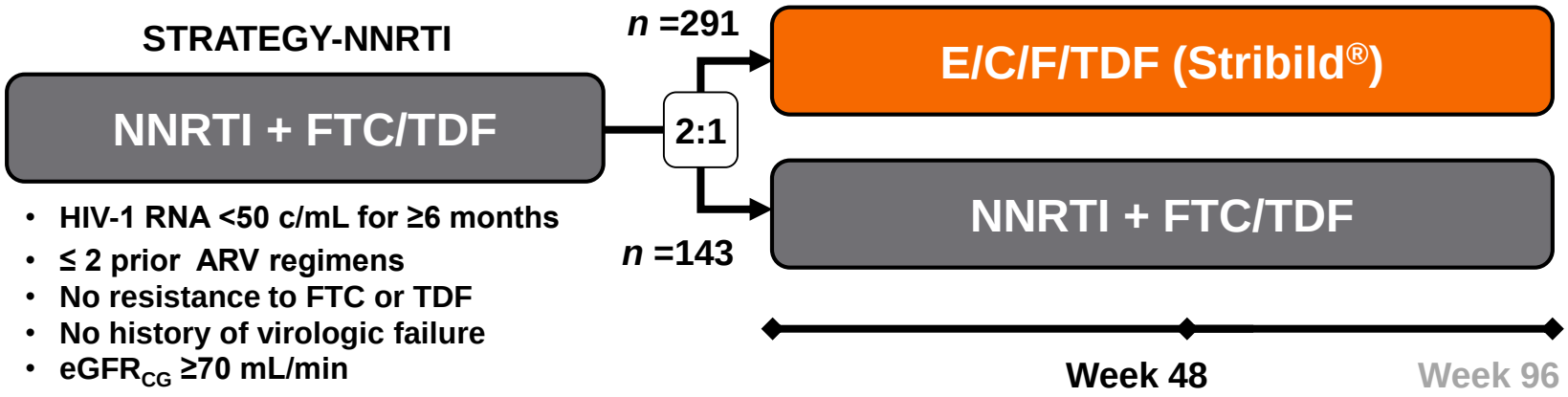


Rowlands et al O4. HIV Medicine 2014; 15 (3): 1-16

Switch to Integrase-I

Study Design

Multicenter, randomized, open-label, 96-week study



- HIV-1 RNA <50 c/mL for ≥6 months
- ≤ 2 prior ARV regimens
- No resistance to FTC or TDF
- No history of virologic failure
- $eGFR_{CG}$ ≥70 mL/min

Primary endpoint: HIV-1 RNA <50 c/mL at Week 48 by Snapshot (noninferiority margin of 12%). If noninferiority established, test for superiority

Secondary endpoint: Safety and tolerability at Weeks 48 & 96

Other endpoints: Patient-reported outcomes*

Pozniak A, et al. CROI 2014; Boston. #553LB

Switch to Integrase-I

Reasons for enrollment and ART history	At screening (*n*=434), %
Reasons subject choose to enroll in study†	
Desire to simplify current regimen‡	48
Concerned about long-term side effects of current regimen	20
Have trouble tolerating current regimen well due to side effects	14
Have trouble taking current regimen on a regular basis	5
NNRTI use¥	
Efavirenz*	78
Nevirapine	17
Rilpivirine**	4
On 1st antiretroviral regimen	91
On 2nd antiretroviral regimen	9
On > 2nd antiretroviral regimen	<1

Pozniak A, et al. CROI 2014; Boston. #553LB

ART simplification

OPEN ACCESS Freely available online

PLoS MEDICINE

Essay

The Ethics of Switch/Simplify in Antiretroviral Trials: Non-Inferior or Just Inferior?

Andrew Carr[1,2*], Jennifer Hoy[3,4], Anton Pozniak[5]

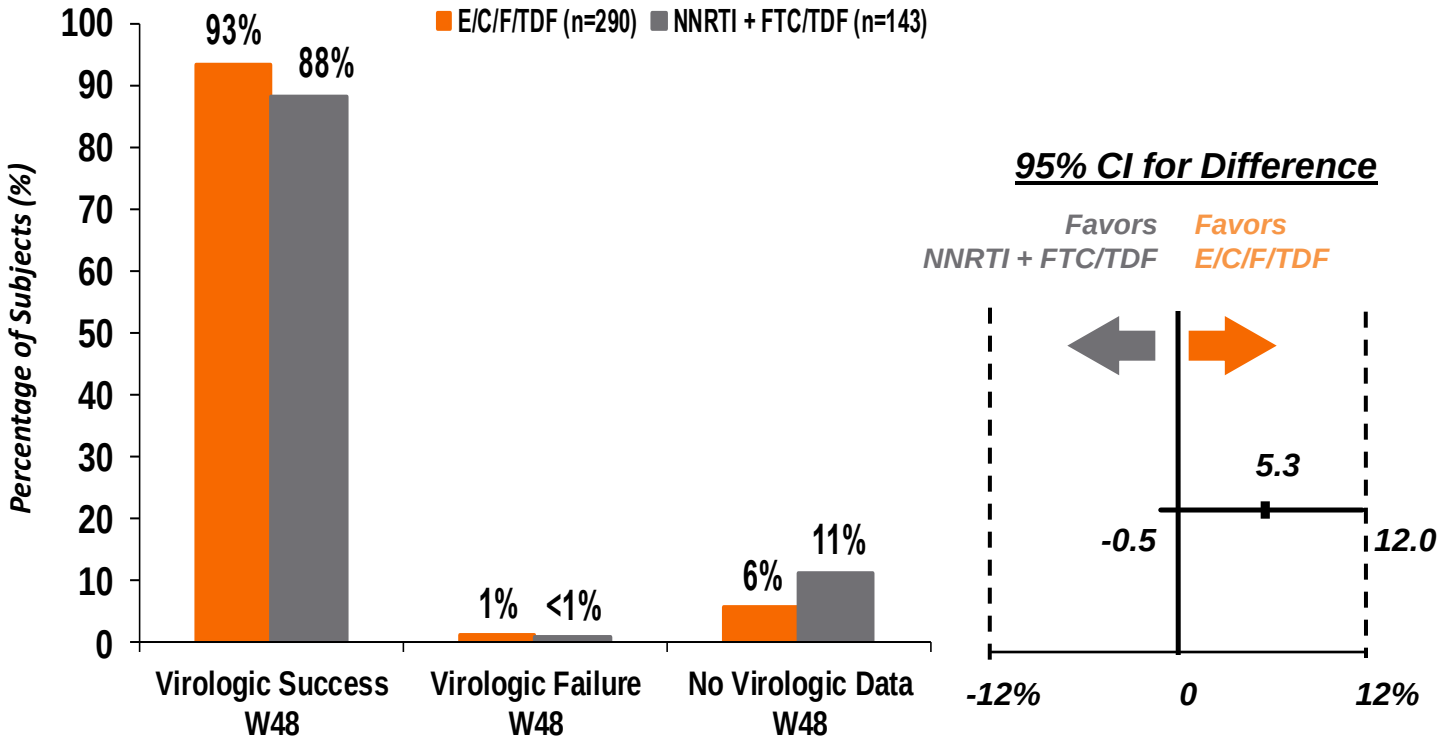
1 Clinical Research Program, Centre for Applied Medical Research, St Vincent's Hospital, Sydney, Australia, **2** HIV/Immunology/Infectious Diseases Unit, St Vincent's Hospital, Sydney, Australia, **3** Infectious Diseases Unit, Alfred Hospital, Melbourne, Australia, **4** Department of Infectious Diseases, Faculty of Medicine, Nursing and Health Sciences, Monash University, Melbourne, Australia, **5** Chelsea and Westminster Hospital, London, United Kingdom

PLoS Med 2012; **9**(7): e1001240

Summary Points

- The high efficacy of antiretroviral therapy has resulted in more trials that switch or simplify existing therapy in patients whose HIV is fully controlled.
- The primary outcome of about half of these trials is virological non-inferiority. As participants already have fully controlled HIV on existing therapy, these trials offer no virological benefit.
- Many trials (i) enrol patients who cannot benefit with the switch, (ii) do not capture (or report) all potential risks, and (iii) are designed with a view to a pharmaceutical company's profits rather than participant benefit.
- A switch/simplification trial is only ethical if participants can meaningfully benefit from the treatment change and are more likely to benefit than suffer harm, and if the study is powered to assess the key expected benefit and reports all end points.

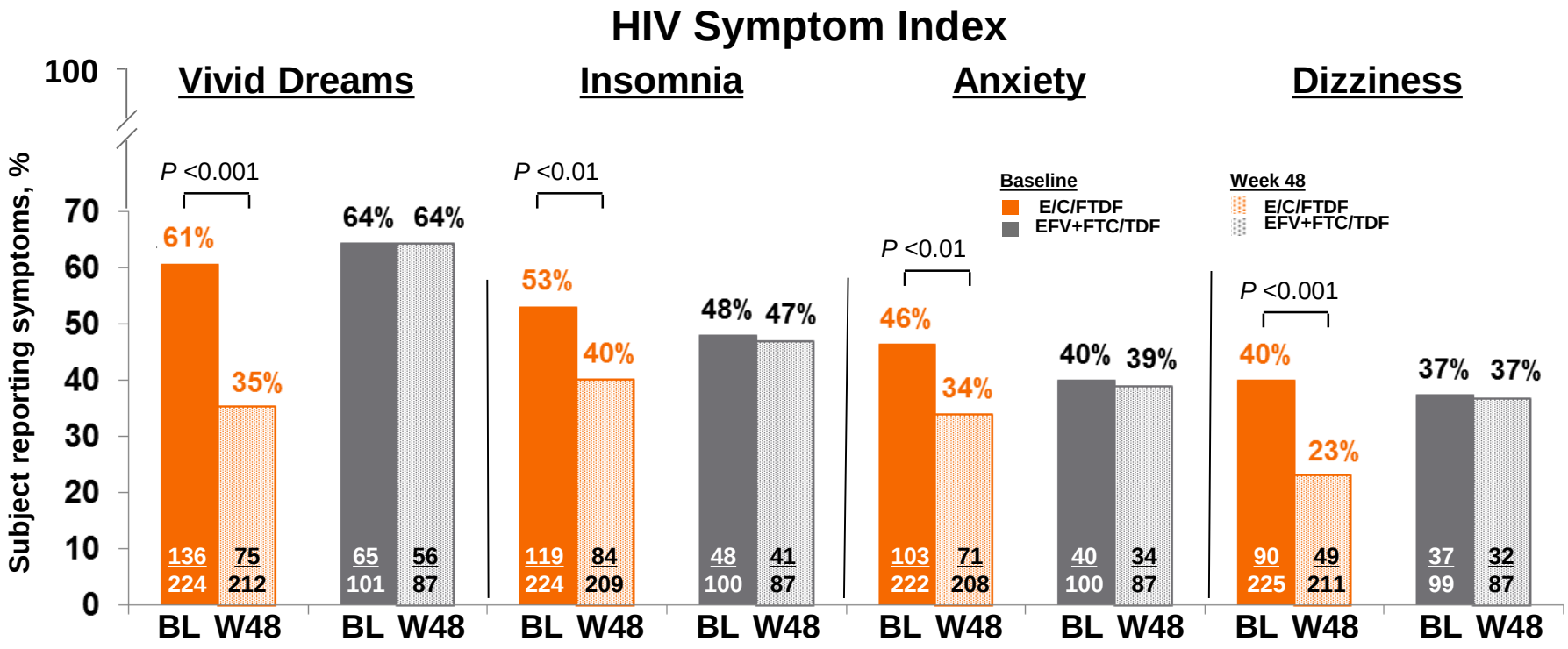
Switch to Integrase-I



CD4 Cell Count (cells/mm³)	Baseline (mean)	ΔWeek 48 (mean)	P-value (Δ W48 - BL)
E/C/F/TDF	586	+56	<0.001
NNRTI + FTC/TDF	593	+58	<0.001

Pozniak A, et al. CROI 2014; Boston. #553LB

Switch to Integrase-I



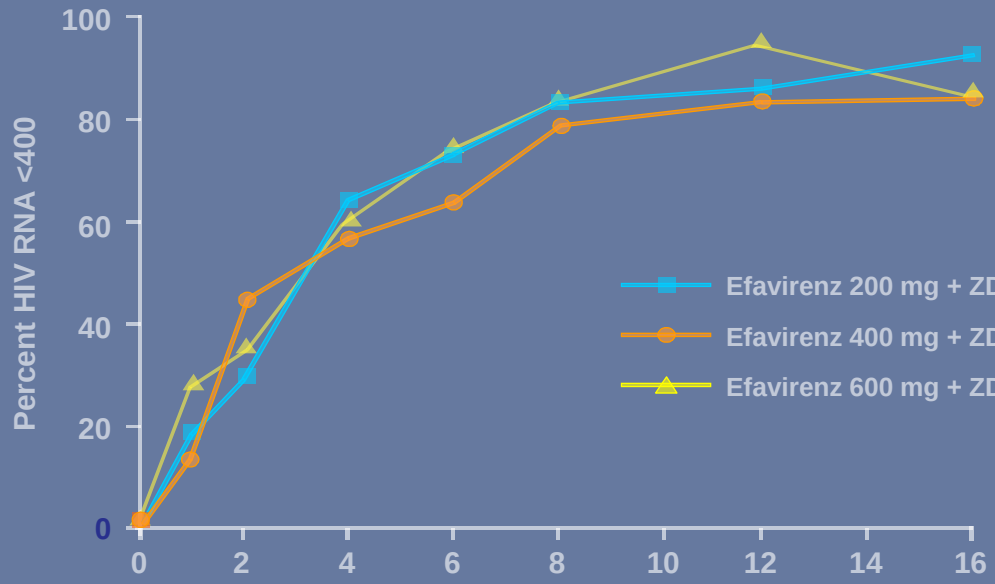
- Rates of all 4 changes occurred at Week 4 and continued at all visits through Week 48
- Subjects who switched to E/C/F/TDF from EFV + FTC/TDF had
  - Lower rates of neuropsychiatric symptoms at Week 48 compared to baseline
  - Higher treatment satisfaction scores at Week 24 (mean: 21 vs. 14, *P* <0.001)^

Pozniak A, et al. CROI 2014; Boston. #553LB

Dose reduction strategies

DMP-005 trial

ZDV/3TC + EFV 200, 400, 600 mg OD
HIV RNA < 400 copies/ml after 16 weeks

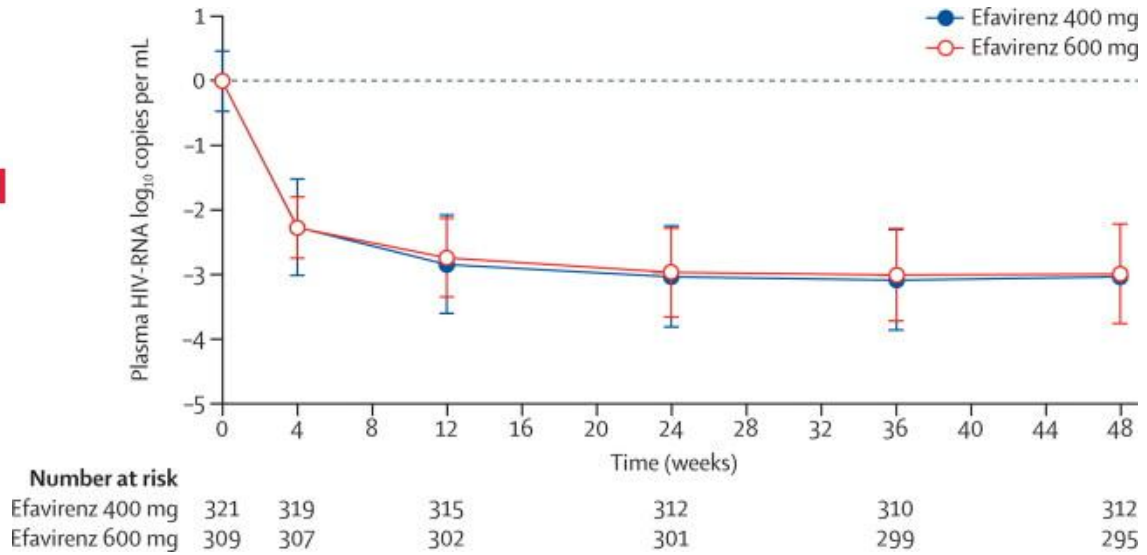


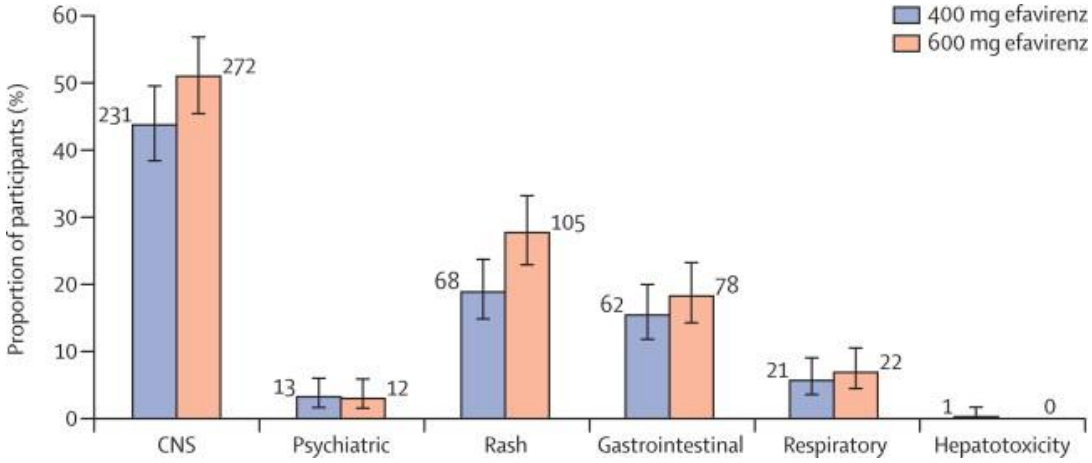
EFV 200 mg N =	32	34	34	30	29	32	31
EFV 400 mg N =	31	31	33	28	30	28	28
EFV 600 mg N =	32	29	32	28	30	27	28

Haas *et al. 5th CROI* 1998. Abstract 698

Dose reduction strategies

encore[1]





Lancet. 2014 Apr 26;383(9927):1474-82

Overview

- Where are we in 2014?
- How have we got here?
- Neuropsychiatric AEs
- Management strategies
- The future

The future and summary

Imperial College London

Summary

- neuropsychiatric events are frequently reported with modern ART
- more frequent and are persistent on efavirenz containing regimens

Management

- recognition of these side effects is key
- switching antiretroviral therapy appears effective management option

Future

- can we predict those at higher risk ?
- can we improve on the time it takes us to recognise serious side effects of antiretroviral agents ?
- how will these data impact on antiretroviral guidelines ?

Thank you