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Emerging Neurological Toxicities in HIV disease

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St. Mary's Hospital London

27 May 2016

001/IHQ/16-05//1320 May 2016

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Disclaimer:

Gilead Sciences Europe Ltd has provided the funding for this session

The presentation express the views and opinion of the presenter which are based on information and data available at the time

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Overview

1	Historical CNS toxicities
2	Changing demographics of PLWH
3	Changes to treatment
4	Emerging toxicities
5	Management and the future

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The history

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%

The most significant and frequently observed adverse reactions with EFV are neuropsychiatric symptoms

EFV, efavirenz; AZT, zidovudine; 3TC, lamivudine; IDV, indinavir

Sustiva PI, Bristol-Myers Squibb Pharma EEIG, March 2016

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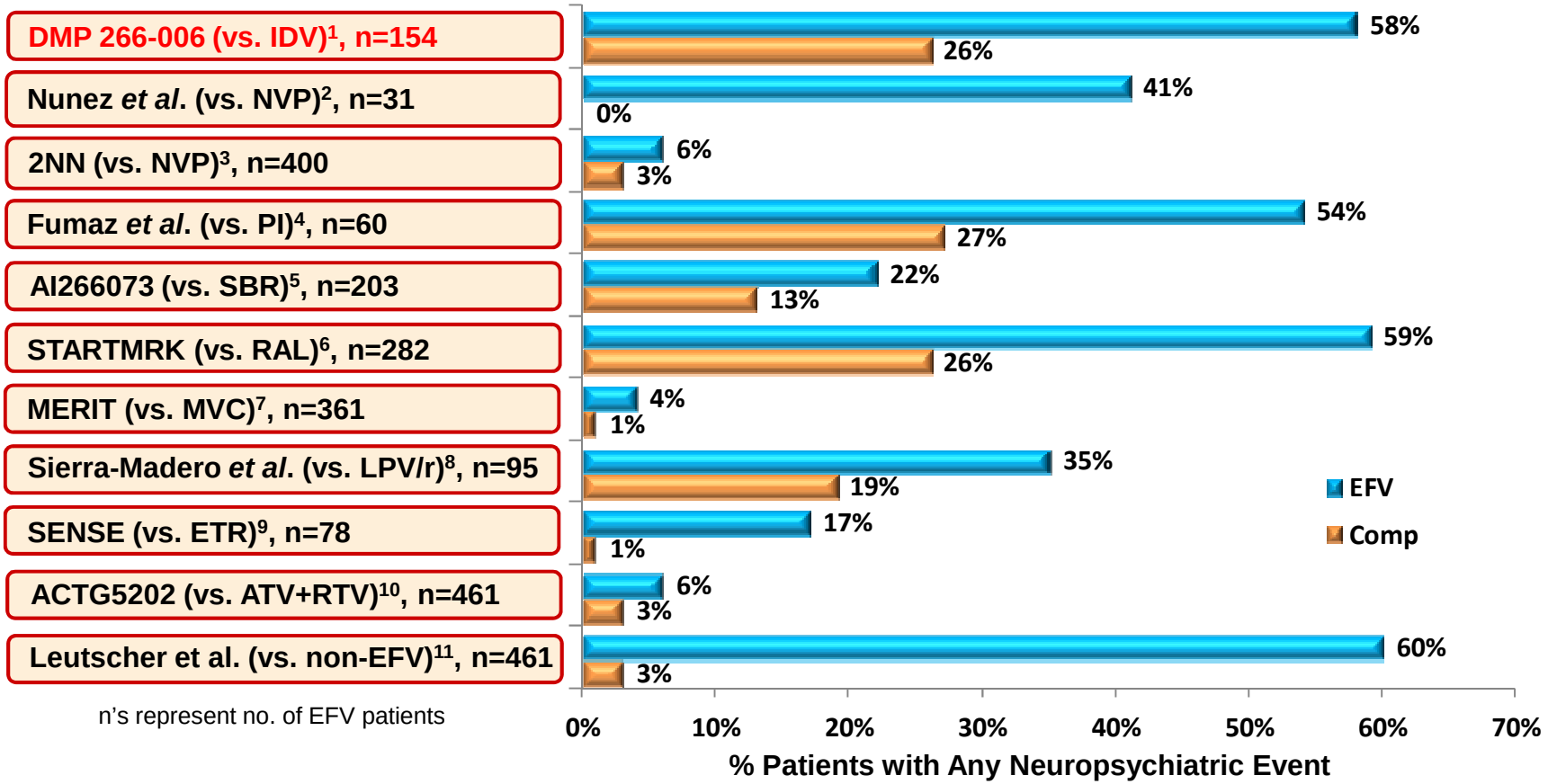
The history



IDV, indinavir; NVP, Nevirapine, PI, protease inhibitor; SBR, stable baseline regimen; RAL, raltegravir; MVC, maraviroc; LPV, lopinavir; ATV, atazanavir; ETR, etravirine; RTV, ritonavir; EFV, efavirenz; Comp, comparator

1. Staszewski S, et al. NEJM 1999;341:1865–1873; 2. Nunez M, et al. HIV Clin Trials 2002;3:186–194; 3. Van Leth, F et al. Lancet 2004;363:1253–1263; 4. Fumaz C, et al. JAIDS 2005;38:560–565; 5. DeJesus E, et al. JAIDS 2009;51:163–174; 6. Lennox J, et al. Lancet 2009;374:796–806; 7. Cooper D, et al. JID 2010;201:803–813; 8. Sierra-Madero, et al. JAIDS 2010;53:582–588; 9. Gazzard B, et al. AIDS 2011;25:2249–2258; 10.Daar E, et al. Ann Intern Med 2011;154:445–456; 11. Leutscher PDC, et al. Scan J Inf Dis 2013; Early Online.

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Efavirenz and cognitive function

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

	Univariate analysis			Multivariate analysis		
Variable	β	OR (95% CI)	p	β	OR (95% CI)	p
Sex (male vs female)	−0.25	0.78 (0.41-1.51)	0.466			
Age (per 10 years more)	−0.26	0.77 (0.58-1.03)	0.078	−0.19	0.83 (0.60-1.16)	0.296
Education (per 1 year more)	−0.12	0.89 (0.81-0.97)	0.012[a]	−0.16	0.85 (0.77-0.94)	0.002[a]
Non-Italian born (vs Italian born)	1.10	3.01 (1.09-8.35)	0.034[a]	1.24	3.46 (1.09-10.99)	0.035[a]
Injecting drug users	0.13	1.14 (0.46-2.82)	0.780			
HCV coinfection	−0.30	0.74 (0.33-1.69)	0.479			
Time from HIV diagnosis (per 1 year more)	−0.02	0.98 (0.93-1.03)	0.355			
Past AIDS-defining events	0.29	1.34 (0.64-2.81)	0.441			
CD4 cell count nadir (per 100 cells more)	−0.13	0.88 (0.69-1.12)	0.294			
Time from first cART regimen (per 1 year more)	0.02	1.02 (0.94-1.11)	0.639			
Patients on cART at test	0.56	1.75 (0.61-5.02)	0.298			
Time on current cART >12 months	0.07	1.08 (0.51-2.25)	0.848			
Efavirenz use	1.26	3.53 (1.37-9.08)	0.009[a]	1.39	4.00 (1.43-11.20)	0.008[a]
CPE rank ≥7	0.45	1.43 (0.68-3.00)	0.346			
HIV RNA (per 1 log more)	−0.19	0.83 (0.58-1.19)	0.312			
HIV RNA <50 copies/mL	0.64	1.90 (0.86-4.21)	0.114			
CDA cell count (per 100 cells more)	−0.05	0.96 (0.86-1.07)	0.420			

cART, combination antiretroviral therapy; CI, confidence interval; CPE, CNS penetration effectiveness; HCV, hepatitis C virus; OR, odds ratio.
[a]Significant.

Ciccarelli N et al. Neurology 2011; 76(16):1403–1409

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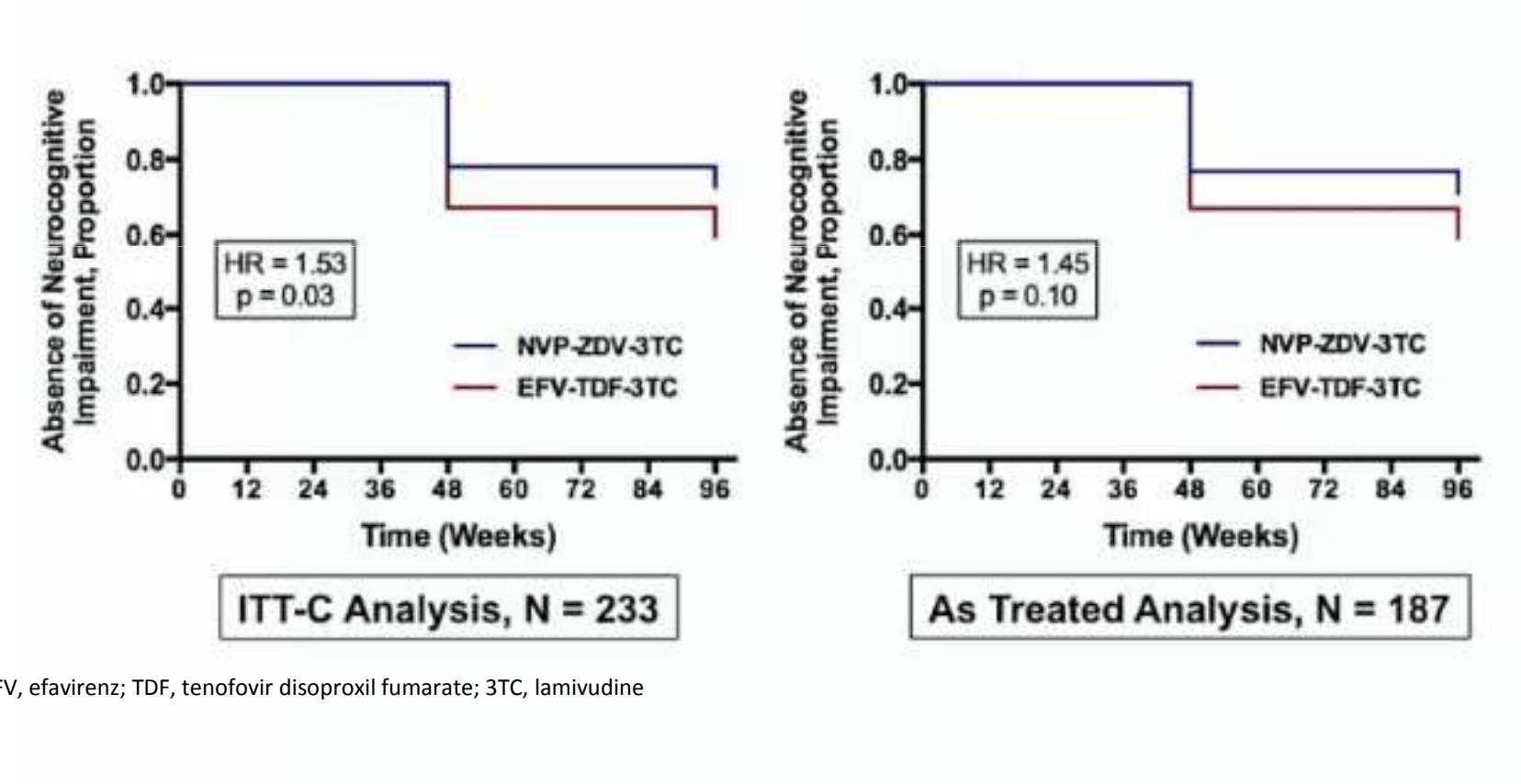
Efavirenz and cognitive function

- EFV-TDF-3TC was associated with shorter time-to-impairment



EFV, efavirenz; TDF, tenofovir disoproxil fumarate; 3TC, lamivudine

Zhang et al, CROI 2015, Abstract 56

Suicide and ART - DAD

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	Number/person-years	Rate per 1000 person-years (95% CI)	Adjusted RR (95% CI)	p
Suicide or psychiatric disease as underlying cause of death				
Total	193/371,333	0.52 (0.45–0.59)		
EFV-containing	24/78,580	0.31 (0.81–0.43)	0.59 (0.33–1.06)	<0.0001
Other NNRTI-containing	31/64,288	0.48 (0.31–0.65)	0.93 (0.53–1.62)	
Other ART	66/157,664	0.42 (0.32–0.52)	0.81 (0.49–1.32)	
No ART–naïve	21/40,454	0.52 (0.30–0.74)	1.00	
No ART–experienced	51/30,348	1.68 (1.22–2.14)	3.24 (1.95–5.38)	

Smith C et al. J Int AIDS Soc. 2014; 17(4 Suppl 3): 19512

Overview

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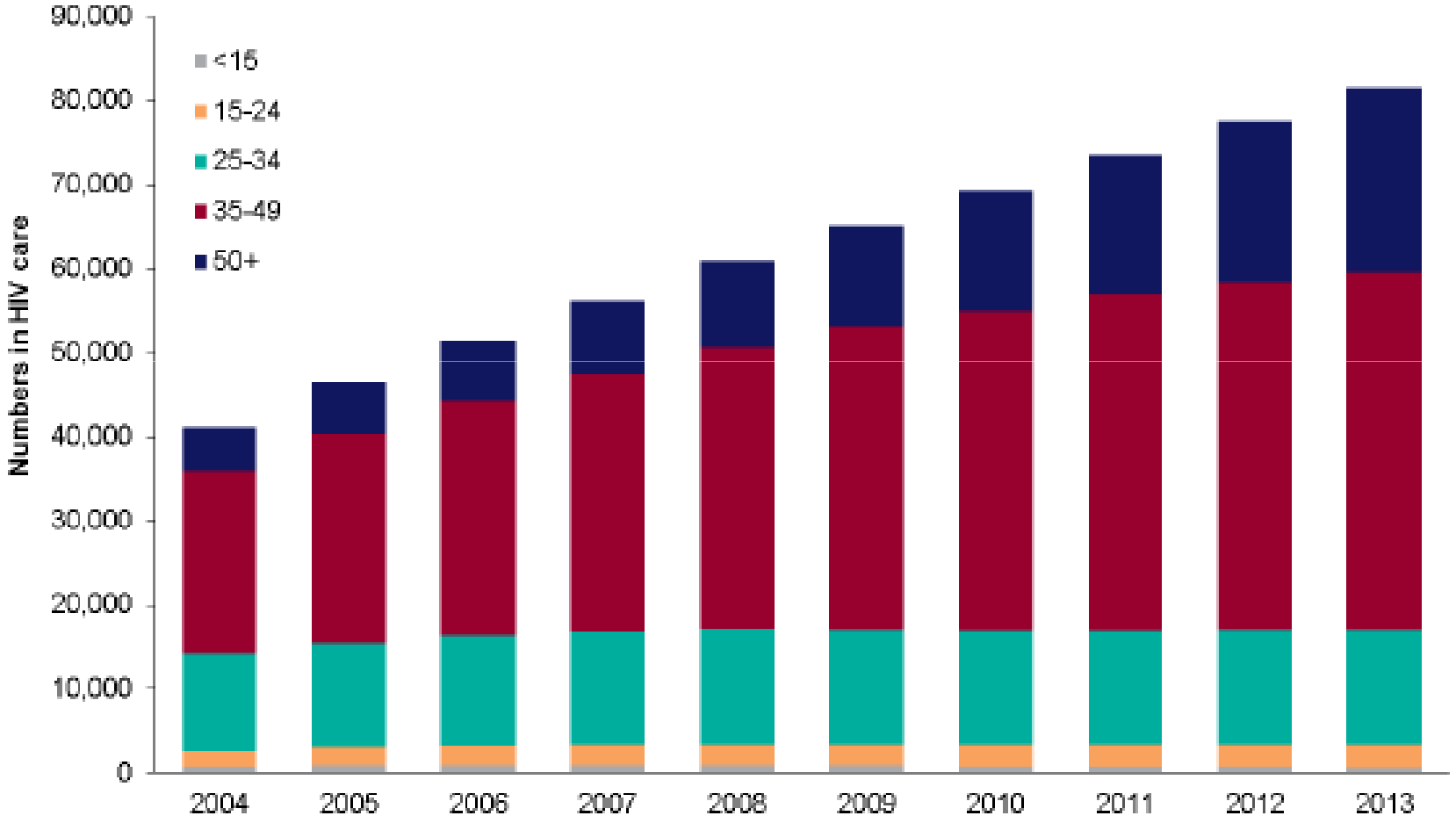
Age of our cohorts



Yin Z, Brown AE, Hughes G, Nardone A, Gill ON, Delpech VC & contributors. HIV in the United Kingdom 2014 Report: data to end 2013. November 2014. Public Health England, London.

What we hear about ageing and HIV

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Non infectious comorbidities are more prevalent and occur at younger ages in HIV-infected cohorts

HIV causes premature ageing

The presence of non infectious comorbidities is due to 'inflammageing'

Ageing changes the spectrum of HIV disease

Antiretroviral toxicities differ in older PLWH versus younger subjects

HIV causes accelerated ageing

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European HIV and ageing cohorts:

POPPY

Pharmacokinetic and clinical observations in people over 50

Status[1]:

- Fully recruited and now in follow up phase
- 1400 subjects
  - 700 HIV +ve over 50
  - 350 HIV –ve over 50
  - 350 HIV +ve under 50

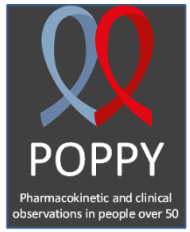
agehiV cohort study

Status[2]:

- Fully recruited and follow up phase well established
- 1200 subjects
  - 600 +ve over 45
  - 550 controls over 45

1. POPPY: NCT01737047; 2. agehiV: NCT01466582

Lifestyle factors



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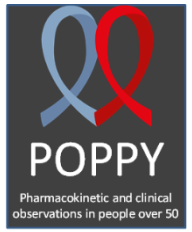
		PLWH>50	PLWH<50	HIV-ve >50
Smoking status	Current (%)	23.9	26.5	21.4
	Ex-smoker (%)	36.9	27.2	37.8
	Never (%)	38.6	42.7	39.8
Alcohol	Current consumption (%)	77.8	73.5	84.7
	Previous consumption only (%)	13.1	11.0	7.1
	Units per week (if current or previous; median (range))	7 (0, 75)	3 (0, 45)	10 (0, 63)
Recreational drugs in past 6 months	Any (%)	27.5	26.5	13.3
	Marijuana (%) *	14.7	12.5	1.0
	Methadone (%) *	2.6	10.3	1.0
	Mephedrone (%) *	9.2	13.2	5.1
	Amphetamine (%) *	5.2	7.4	0
	Crystal Meth (%) *	3.3	8.1	5.1

*** Recreational drugs with >5% use in a study group**

Winston A, BHIVA 2015, Abstract O6

Healthcare utilisation



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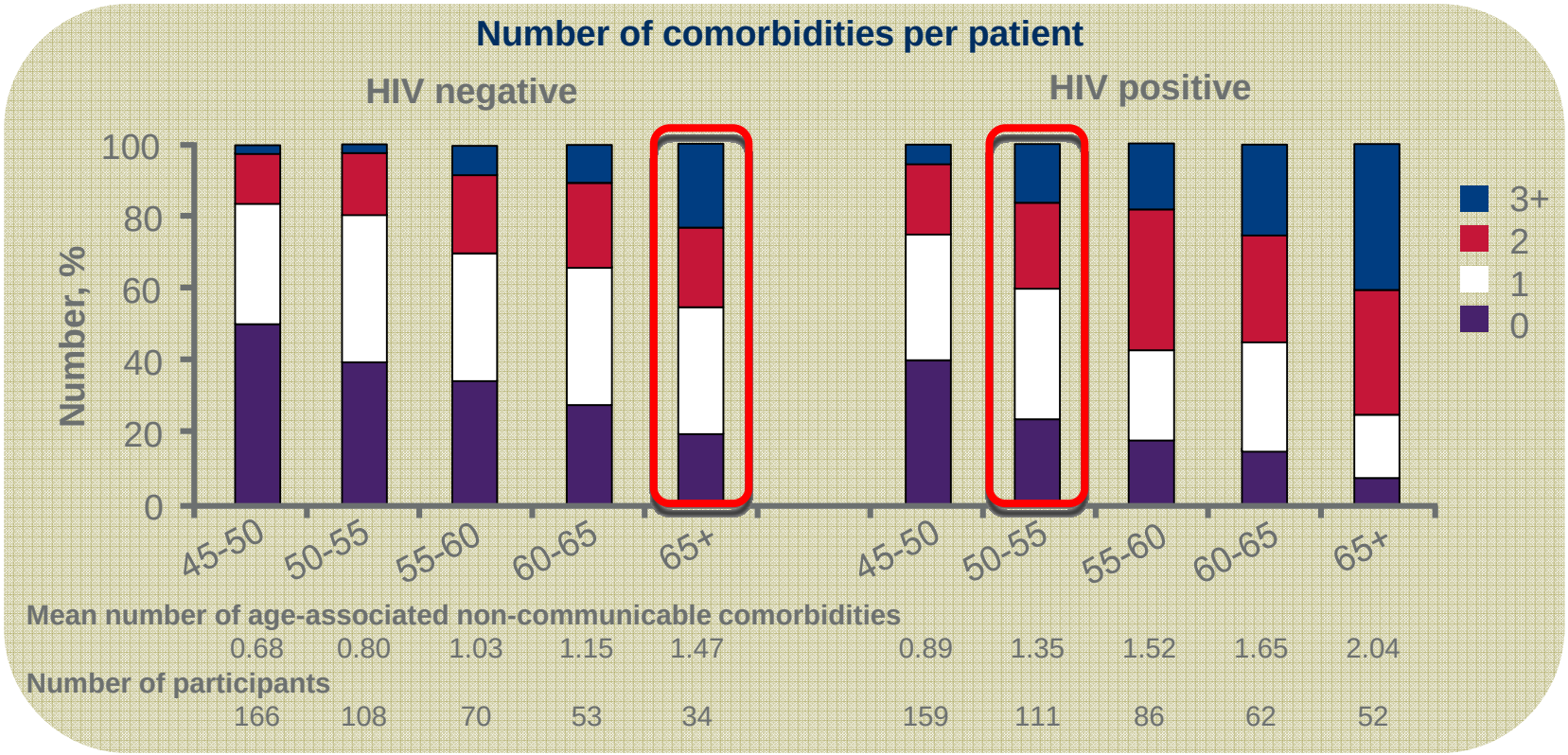
Over the past 12 months:

	PLWH>50	PLWH<50	HIV-ve >50	P-value
Attended GP	**74%** (227)	**70%** (94)	**78%** (78)	0.32
Attended A&E	**18%** (56)	**19%** (26)	**14%** (14)	0.59
Hospital specialist	**44%** (135)	**36%** (49)	**33%** (32)	0.07
Psychiatrist	**28%** (85)	**13%** (18)	**12%** (12)	0.03
Undergone a hospital procedure	**28%** (85)	**13%** (18)	**12%** (12)	0.0001

Winston A, BHIVA 2015, Abstract O6

AGEhiV outputs

- Significantly more hypertension, angina, MI, liver disease, renal failure and cancer in HIV-infected subjects



Schouten J et al. Clin Infect Dis. 2014 Dec 15;59(12):1787–1797

Immunological markers

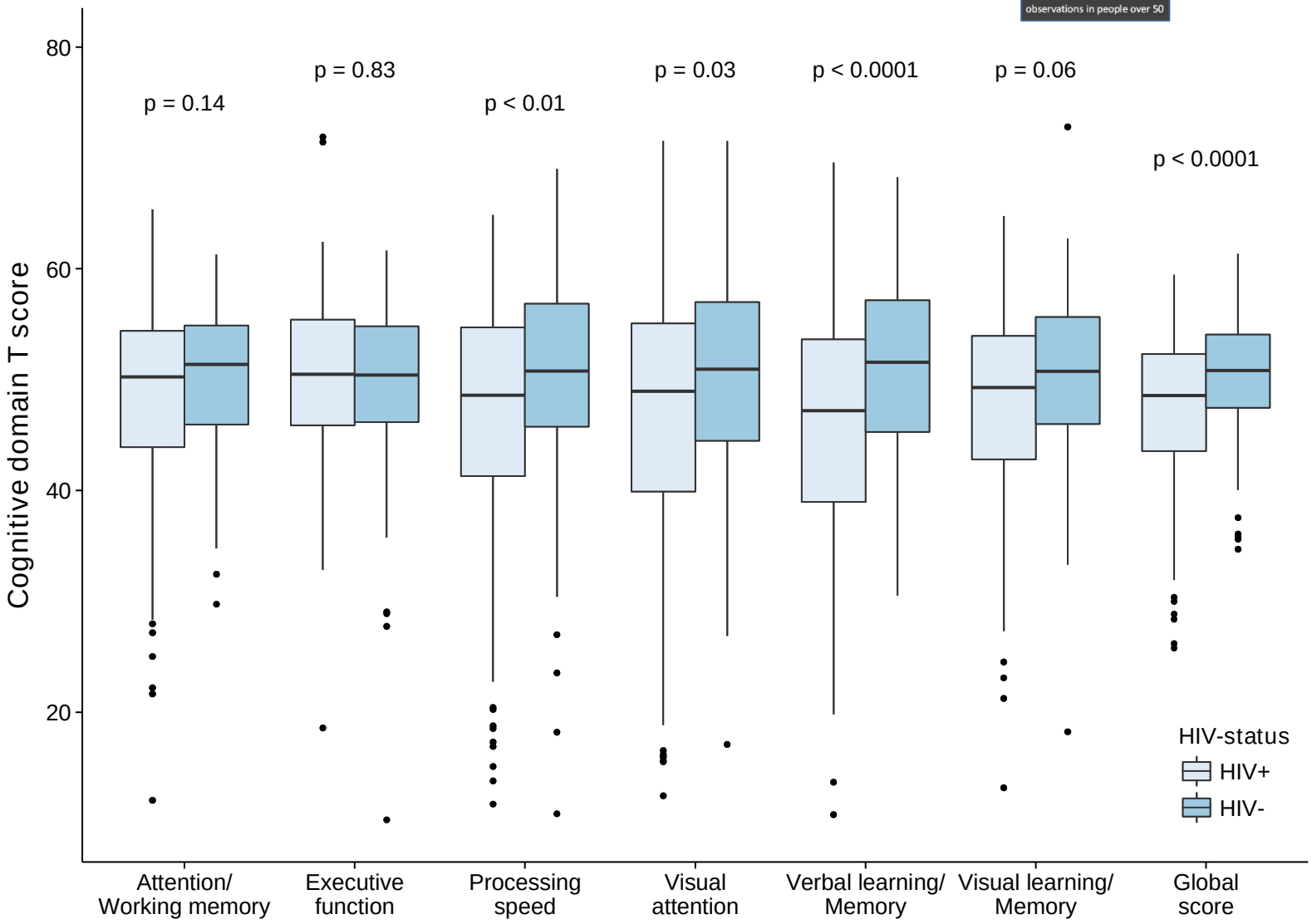
	HIV+ median (IQR)	HIV- median (IQR)	*P* HIV+/HIV-	BBD median (IQR)	*P* HIV+/BBD	*P* HIV-/BBD
T cell activation						
$CD4^+CD38^+HLA^-DR^+$	2.6 (1.7-4.0)	1.6 (1.0-2.6)	.001	0.8 (0.6-0.8)	<.001	.001
$CD8^+CD38^+HLA\text{-}DR^+$	7.5 (4.5-10.8)	5.6 (3.3-9.7)	.100	0.4 (0.3-0.9)	<.001	<.001
T cell senescence						
$CD4^+57^+$	12.1 (6.3-18.4)	12.2 (7.0-19.3)	.736	4.1 (3.7-4.5)	.002	<.001
$CD4^+CD27^-CD28^-$	4.8 (1.1-8.5)	6.0 (1.5-12.3)	.485	0.1 (0.1-1.3)	<.001	<.001
$CD8^+57^+$	50.6 (36.8-57.2)	45.1 (35.6-57.4)	.773	30.2 (19.0-31.9)	<.001	<.001
$CD8^+CD27^-CD28^-$	38.1 (24.8-46.4)	36.4 (22.6-50.1)	.802	16.8 (7.3-28.5)	.002	.014
T cell exhaustion						
$CD4^+PD\text{-}1^+$	6.8 (5.2-10.7)	6.2 (3.4-8.4)	.106	3.3 (2.9-3.9)	<.001	.010
$CD8^+PD\text{-}1^+$	19.6 (14.1-23.9)	16.1 (11.6-24.0)	.138	3.4 (2.8-7.5)	<.001	<.001

Conclusions: No evidence for increased immunological ageing is found in the HIV+ compared to matched uninfected controls. Immunological ageing is increased in the HIV+ group as well as the uninfected controls when compared to blood bank donors

This illustrates the crucial importance of using appropriate controls for these studies.

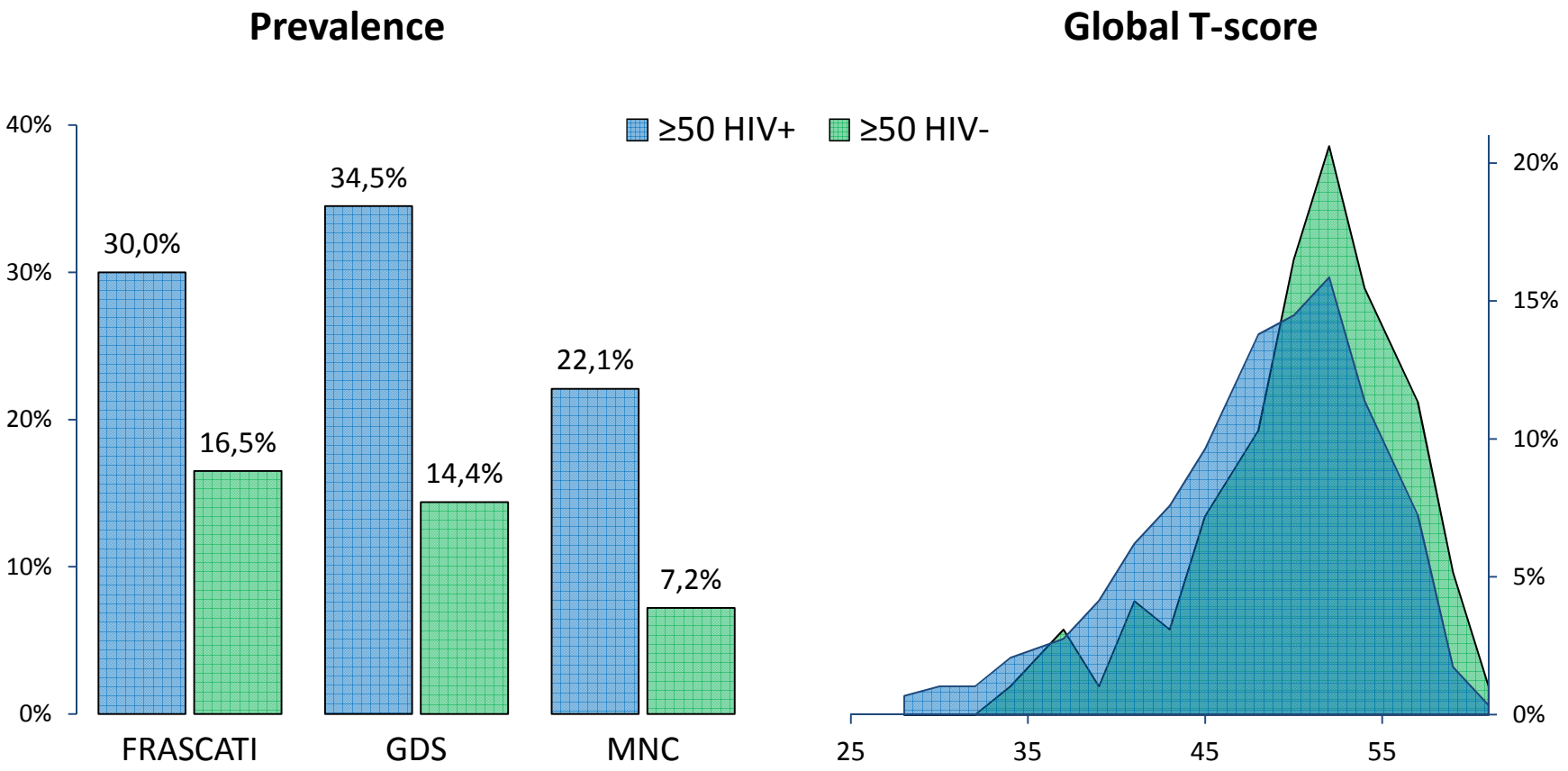
Adapted from Kootstra NA, EACS 2015, BPD3/3

Cognitive function



Underwood J et al. EACS 2015, Barcelona. Poster #PE15/9

Prevalence of CI



OR (95% CI):	2.17 (1.20, 3.92)	3.12 (1.69, 5.78)	3.64 (1.61, 8.24)
p-value:	0.011	<0.001	0.001

	≥50 HIV-	≥50 HIV+	*p*-value
Median (IQR):	50.8 (47.5, 54.1)	48.6 (43.5, 52.3)	<0.001

Adapted from De Francesco D. EACS 2015, Barcelona. Abstract #PS11/4

Global cognitive function and EACS questions

POPPY
Pharmacokinetic and clinical observations in people over 50

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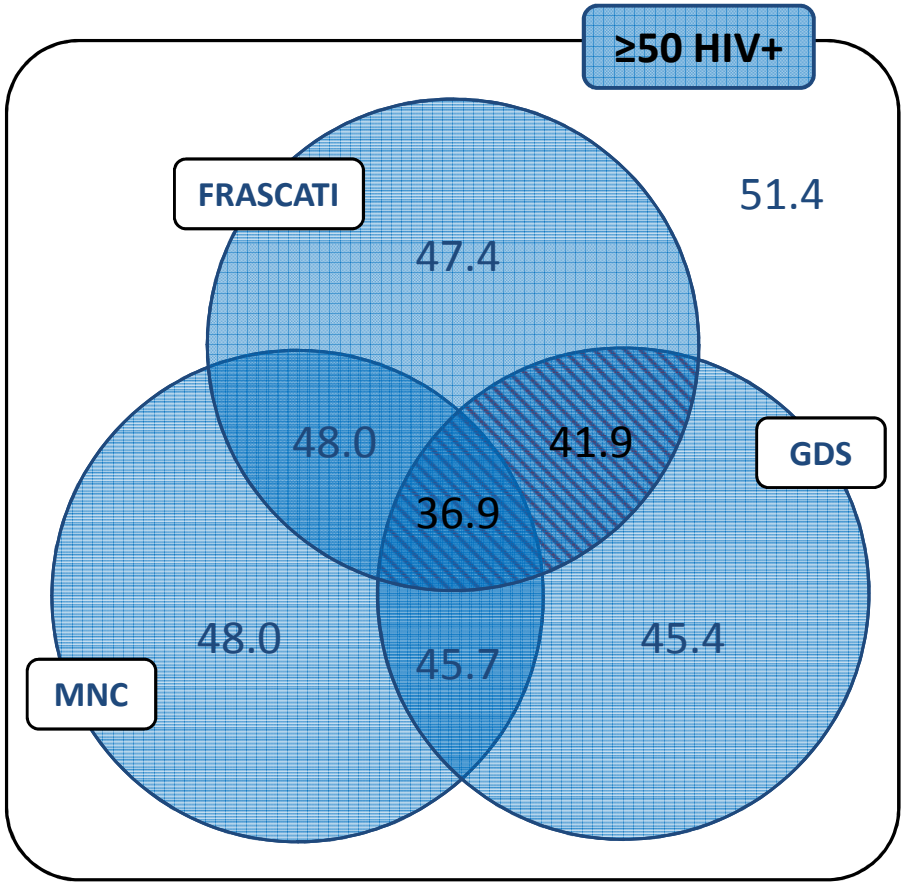
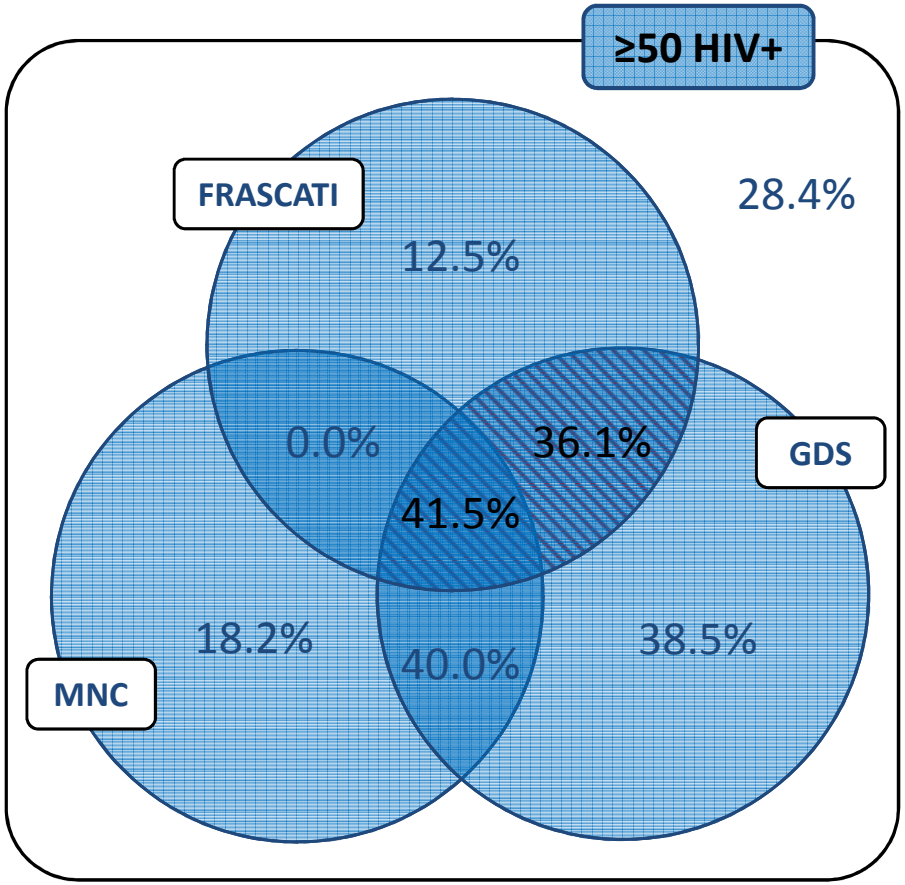
Median global T-score



% with ≥2 cognitive complaints



Adapted from De Francesco D. EACS 2015, Barcelona. Abstract #PS11/4

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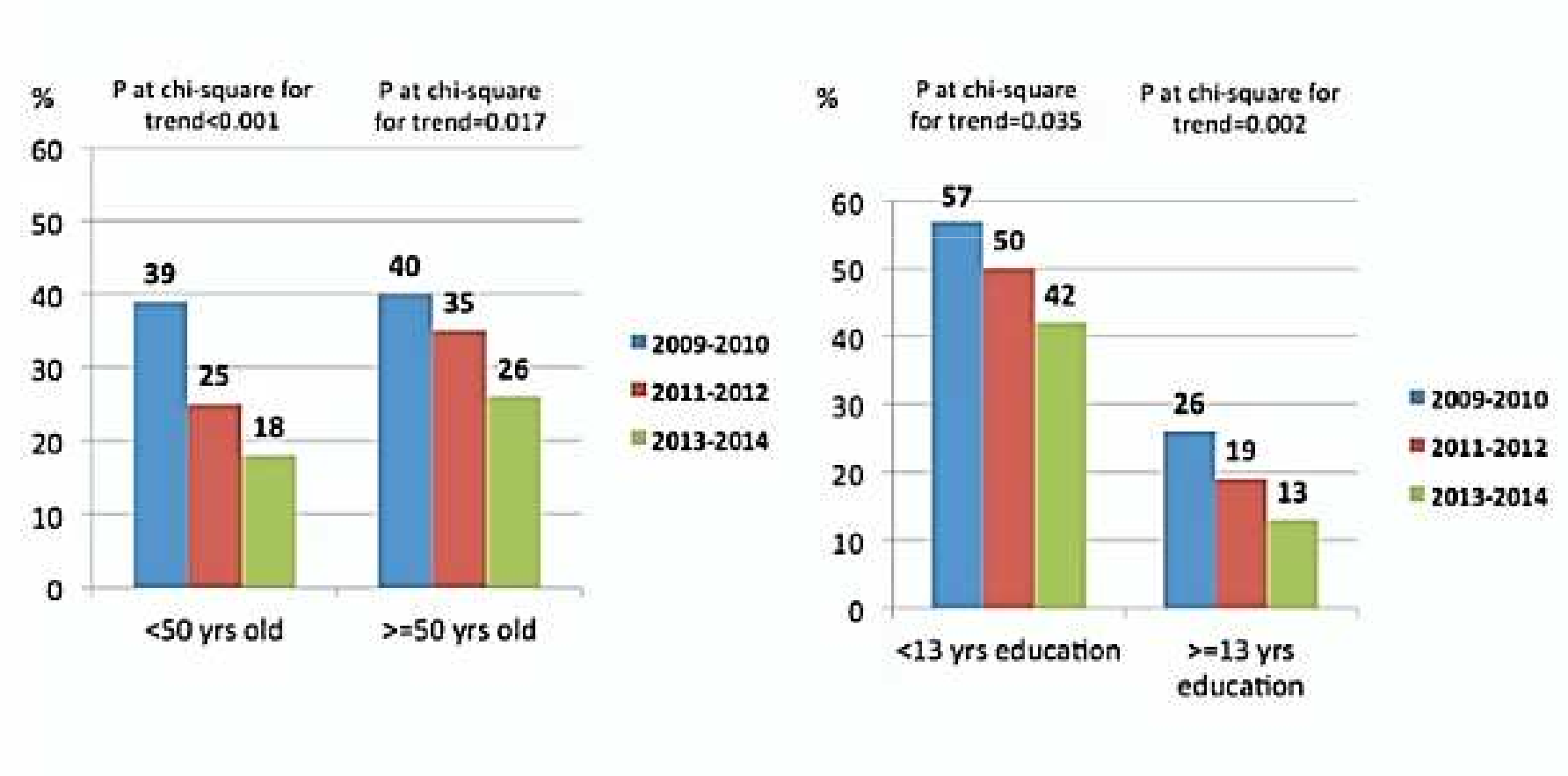
Italian cohort

- HAND prevalence by calendar year, age and level of education



Pinnetti C et al. CROI 2015, Abstract 63

Antiretroviral pharmacology and ageing

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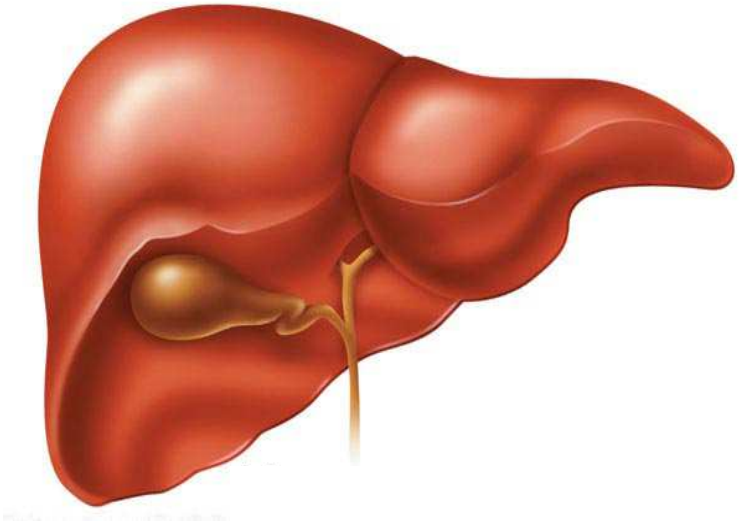
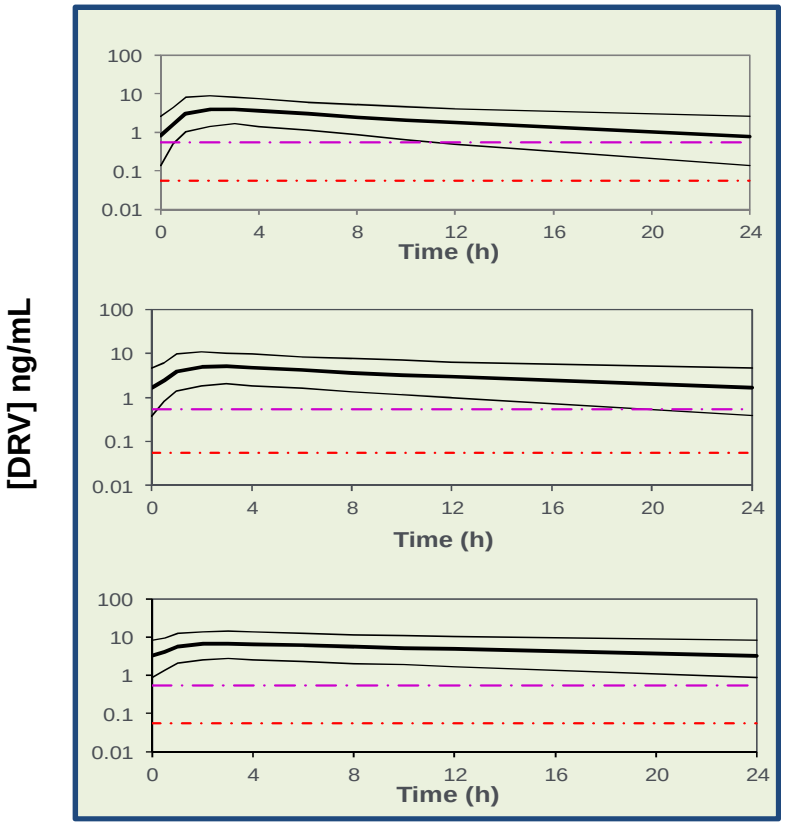


- Simulations at fixed age points illustrated the change in PK profiles with increasing age
- RTV AUC and patient age were significantly associated with DRV clearance

Darunavir 95% prediction intervals determined from simulations of 1000 patients aged:



Dickinson L et al. 10th International Congress on Drug Therapy in HIV Infection, Glasgow 2010. Poster 184

Antiretroviral pharmacology and ageing

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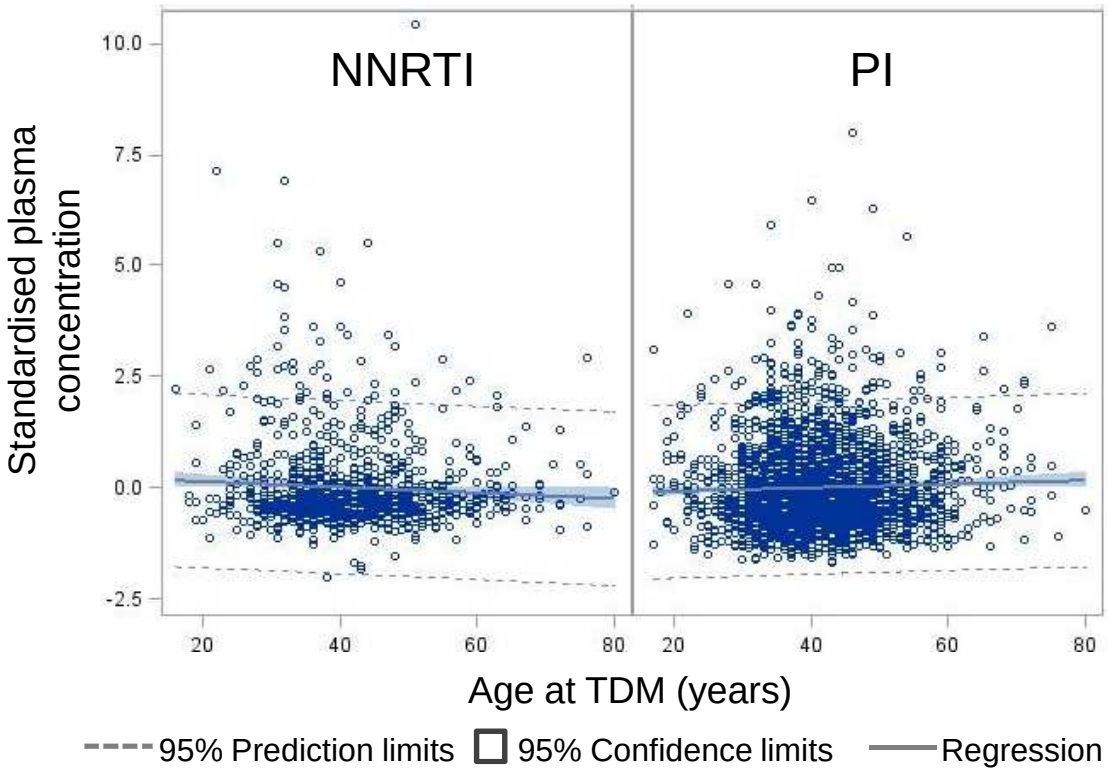
- Data from 3,589 TDM samples were available for 2,447 subjects
- As age increased, NNRTI concentrations remained constant, but PI concentrations increased



Winston A et al. J Antimicrob Chemother 2013; 68: 13542–1359

Antiretroviral pharmacology and ageing

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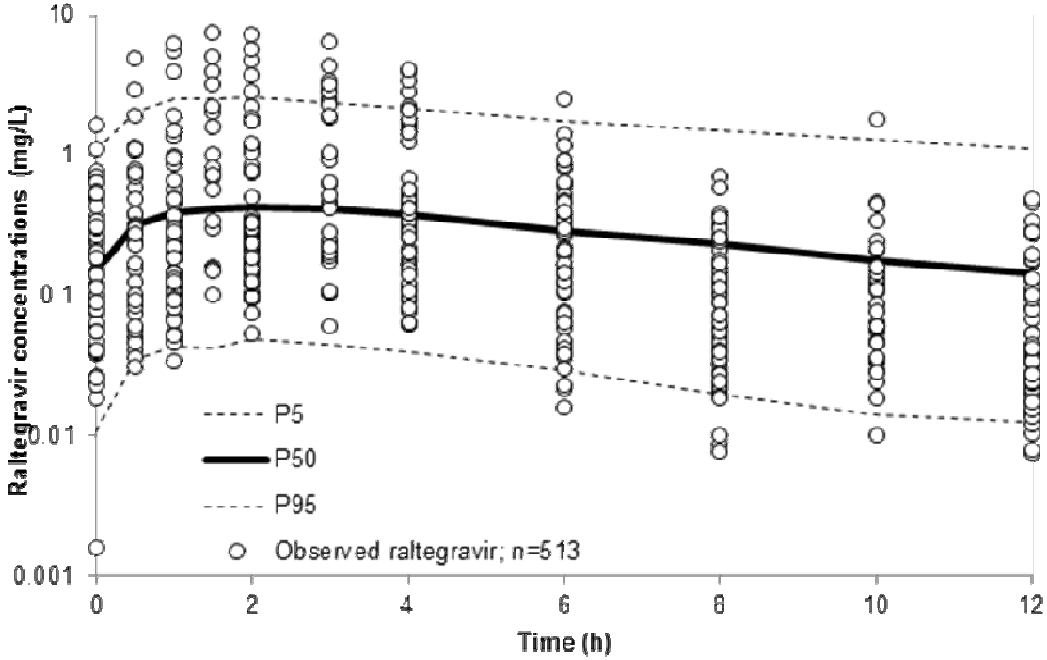
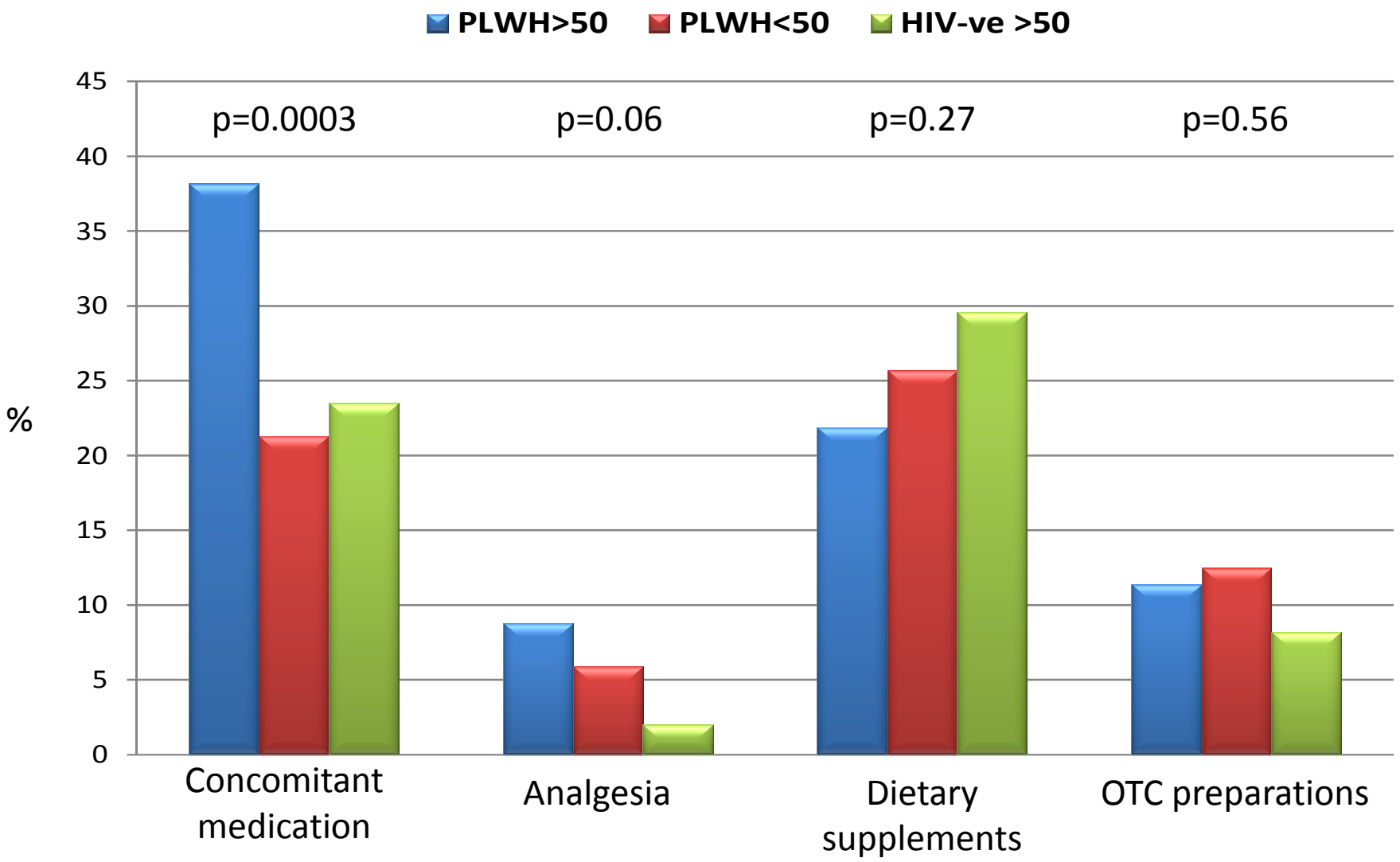


Factors associated with raltegravir exposure in PK model

- Low fat meal associated reduced raltegravir exposure
- Neither age nor darunavir/r administration associated with raltegravir exposure

Vera JH et al. HIV Clin Trials. 2015; 16(1):39–42

Non ARV medication use



Winston A, BHIVA 2015, Abstract O6

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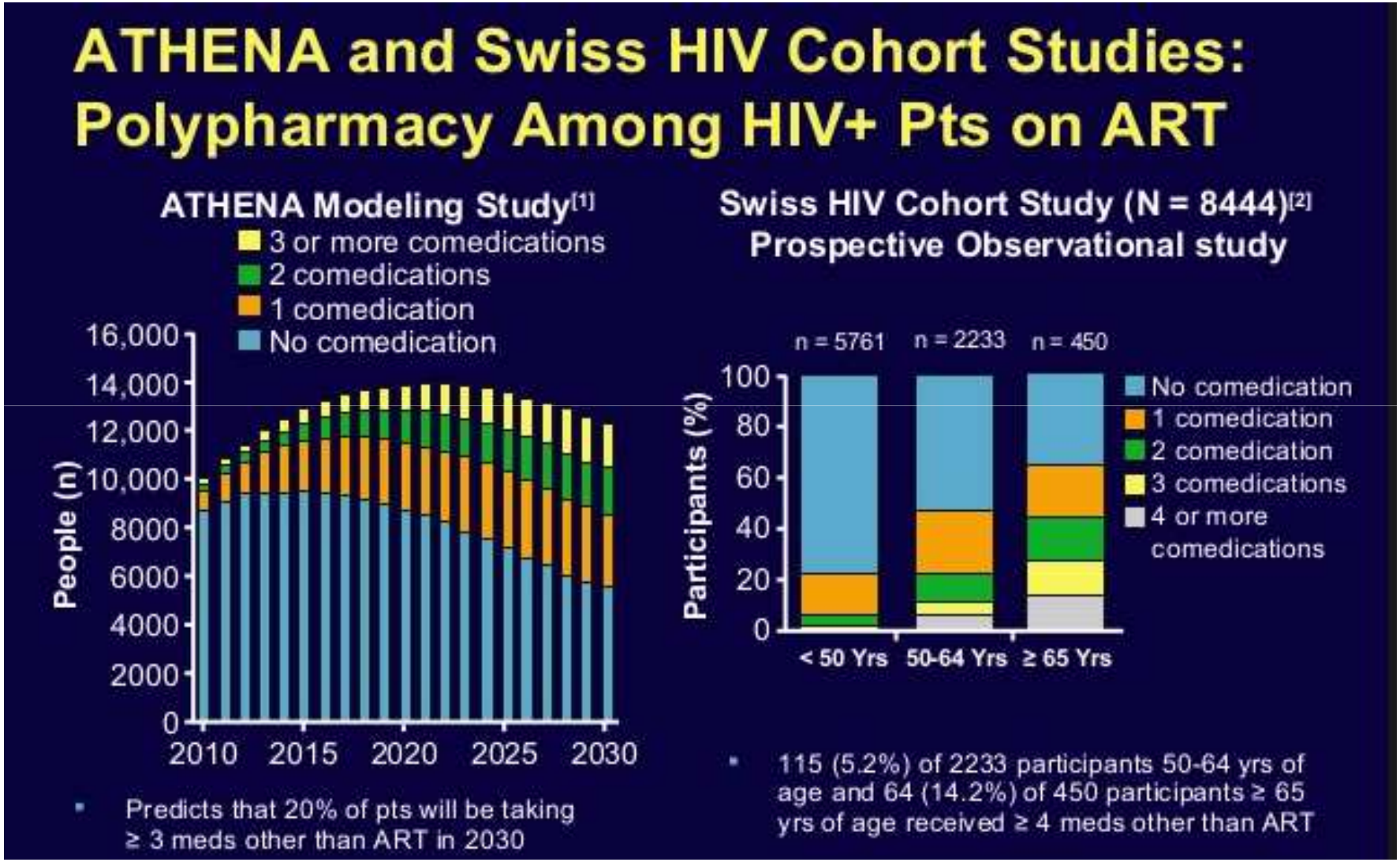
Polypharmacy



1. Smit M et al. Lancet Infect Dis. 2015 Jul;15(7):810–818; 2. Hasse B et al. Clin Infect Dis. 2011 Dec;53(11):1130–1139

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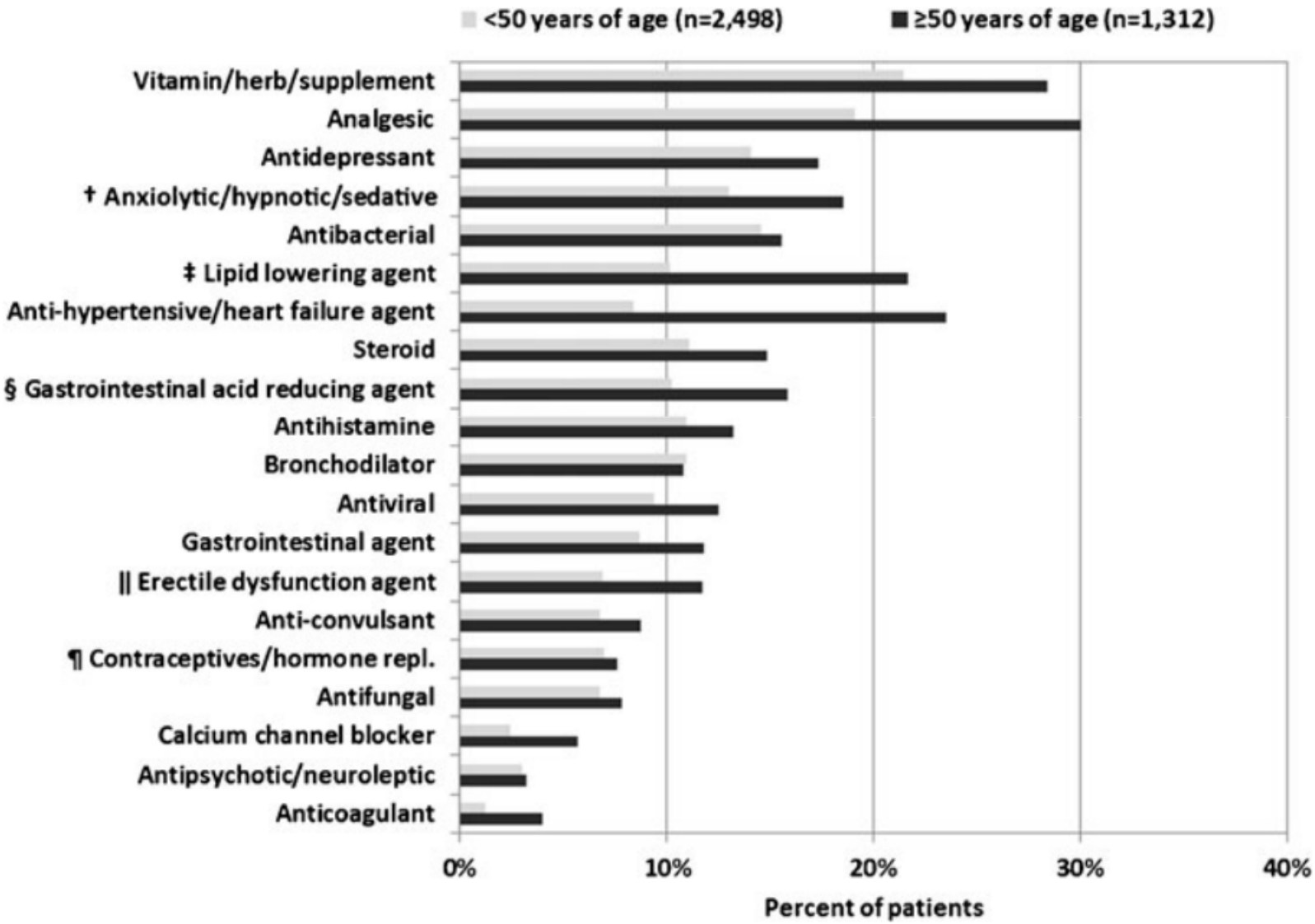
Polypharmacy



Holtzman C et al. J Gen Intern Med. 2013 Oct;28(10):1302–1310

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What do the guidelines say?

Guideline	AIDS or HIV-related symptoms	CD4+ cell count (cells/mm³) <200	200–350	350–500	>500
EACS guidelines 2015 [1]	Highly recommended	Highly recommended	Highly recommended	Recommended	Recommended
WHO guidelines 2015 [2]	Highly recommended	Highly recommended	Highly recommended	Highly recommended	Highly recommended
IAS-USA 2014 [3]	Highly recommended	Highly recommended	Highly recommended	Highly recommended	Highly recommended
DHHS 2015 [4]	Highly recommended	Highly recommended	Highly recommended	Highly recommended	Highly recommended
British HIV association 2015 [5]	Highly recommended	Highly recommended	Highly recommended	Highly recommended	Highly recommended
GeSIDA/Plan Nacional 2016 [6]	Highly recommended	Highly recommended	Highly recommended	Highly recommended	Highly recommended
French HIV expert group 2014 [7]	Highly recommended	Highly recommended	Highly recommended	Highly recommended	Highly recommended
Italian HIV guidelines working group [8]	Highly recommended	Highly recommended	Highly recommended	Highly recommended	Recommended
Russian guidelines 2014 [9]	Highly recommended	Highly recommended	Highly recommended	Highly recommended	Recommended
DAIG/ÖAG guidelines 2014 [10]	Highly recommended	Highly recommended	Highly recommended	Highly recommended	Recommended

1. EACS Guidelines 2015, available at http://www.eacsociety.org/guidelines/eacs-guidelines/eacs-guidelines.html ; 2. WHO guidelines 2015, available at http://apps.who.int/iris/bitstream/10665/186275/1/9789241509565_eng.pdf ; 3. IAS-USA recommendations 2014, available at https://www.iasusa.org/content/antiretroviral-treatment-adult-hiv-infection-2014-recommendations-international-antiviral-society-usa-panel ; 4. DHHS 2015 guidelines, available at https://aidsinfo.nih.gov/contentfiles/lvguidelines/adultandadolescentgl.pdf ; 5. BHIVA guidelines 2015, available at http://www.bhiva.org/documents/Guidelines/Treatment/consultation/150621-BHIVA-Treatment-GL-Final-draft-for-consultation.pdf; 6. GeSIDA Plan Nacional 2016, available at http://www.gesida-seimc.org/contenidos/guiasclinicas/2016/gesida-guiasclinicas-2016-tar.pdf; 7. French 2013 guidelines, available at http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4062879/ ; 8. Italian HIV Guidelines 2015, available at http://www.newmicrobiologica.org/PUB/allegati_pdf/2015/3/299.pdf ; 9. Russian guidelines, available at: http://www.hivrussia.org/files/Protokol_corr.pdf ; 10. German and Austrian AIDS societies guidelines 2014, available at http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3776256/

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Guidelines (international):

Guideline	Initial options
WHO guidelines 2013 [1]	NNRTI: EFV + TDF/FTC; EFV + TDF/3TC
EACS (Oct 2015) [2]	INSTIs: DTG + TDF/FTC; DTG + ABC/3TC RAL + TDF/FTC; EVG/c/TDF/FTC Boosted PIs: DRV/r + TDF/FTC NNRTIs: RPV + TDF/FTC
IAS-USA 2014 [3]	INSTIs: DTG + TDF/FTC; DTG + ABC/3TC RAL + TDF/FTC; EVG/c/TDF/FTC NNRTIs: EFV + TDF/FTC; EFV + ABC/3TC RPV + TDF/FTC Boosted PIs: ATV/r + TDF/FTC; ATV/r + ABC/3TC DRV/r + TDF/FTC
DHHS 2015 [4]	INSTIs: DTG/ABC/3TC; DTG + TDF/FTC; EVG/c/TAF/FTC; EVG/c/TDF/FTC; RAL + TDF/FTC Boosted PI: DRV/r + TDF/FTC

1. WHO guidelines 2015, available at http://apps.who.int/iris/bitstream/10665/186275/1/9789241509565_eng.pdf ; 2. EACS Guidelines 2015, available at http://www.eacsociety.org/guidelines/eacs-guidelines/eacs-guidelines.html ; 3. IAS-USA recommendations 2014, available at https://www.iasusa.org/content/antiretroviral-treatment-adult-hiv-infection-2014-recommendations-international-antiviral-society-usa-panel ; 4. DHHS 2015 guidelines, available at https://aidsinfo.nih.gov/contentfiles/lvguidelines/adultandadolescentgl.pdf

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Guidelines (national):

Guideline	Initial options
Italian HIV guidelines working group [1]	INSTIs: DTG + TDF/FTC; DTG + ABC/3TC; RAL + TDF/FTC; RAL + ABC/3TC; EVG/c/TDF/FTC NNRTIs: EFV + TDF/FTC; EFV + ABC/3TC; RPV + TDF/FTC Boosted PIs: ATV/r + TDF/FTC; ATV/r + ABC/3TC; DRV/r + TDF/FTC; DRV/r + ABC/3TC
DAIG/ÖAG guidelines 2015 [2]	TDF/FTC or ABC/3TC plus one of the following options: DTG or RGV or RPV or DRV/r or ATVr OR TAF/FTC/EVG/c. Alternatives are (NRTI) TDF + 3TC, (3rd drug) EFV or LPV/r or TDF/FTC/EVG/c
GeSIDA/Plan Nacional 2016 [3]	INSTIs: DTG + TDF/FTC; DTG + ABC/3TC; RAL + TDF/FTC; EVG/c/TDF/FTC
French HIV expert group 2014 [4]	TDF/FTC plus one of the following four options: EFV; RPV; ATV/r; DRV/r ABC/3TC plus one of the following two options: EFV; ATV/r
British HIV Association 2015 [5]	TDF/FTC plus one of the following six options: ATV/r; DRV/r; DTG; EVG/c; RAL; RPV
Russian guidelines 2014 [6]	NNRTI: EFV + 2 NRTIs: AZT-F; ABC; TDF; ZDV; 3TC; TDF/FTC

1. Italian HIV Guidelines 2015, available at http://www.newmicrobiologica.org/PUB/allegati_pdf/2015/3/299.pdf ; 2. German and Austrian AIDS societies guidelines 2014, available at http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3776256/ ; 3. GeSIDA Plan Nacional 2016, available at http://www.gesida-seimc.org/contenidos/guiasclinicas/2016/gesida-guiasclinicas-2016-tar.pdf; 4. . French 2013 guidelines, available at http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4062879/; 5. BHIVA guidelines 2015, available at http://www.bhiva.org/documents/Guidelines/Treatment/consultation/150621-BHIVA-Treatment-GL-Final-draft-for-consultation.pdf; 6. Russian guidelines, available at: http://www.hivrussia.org/files/Protokol_corr.pdf

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Guidelines (Alan's summary):

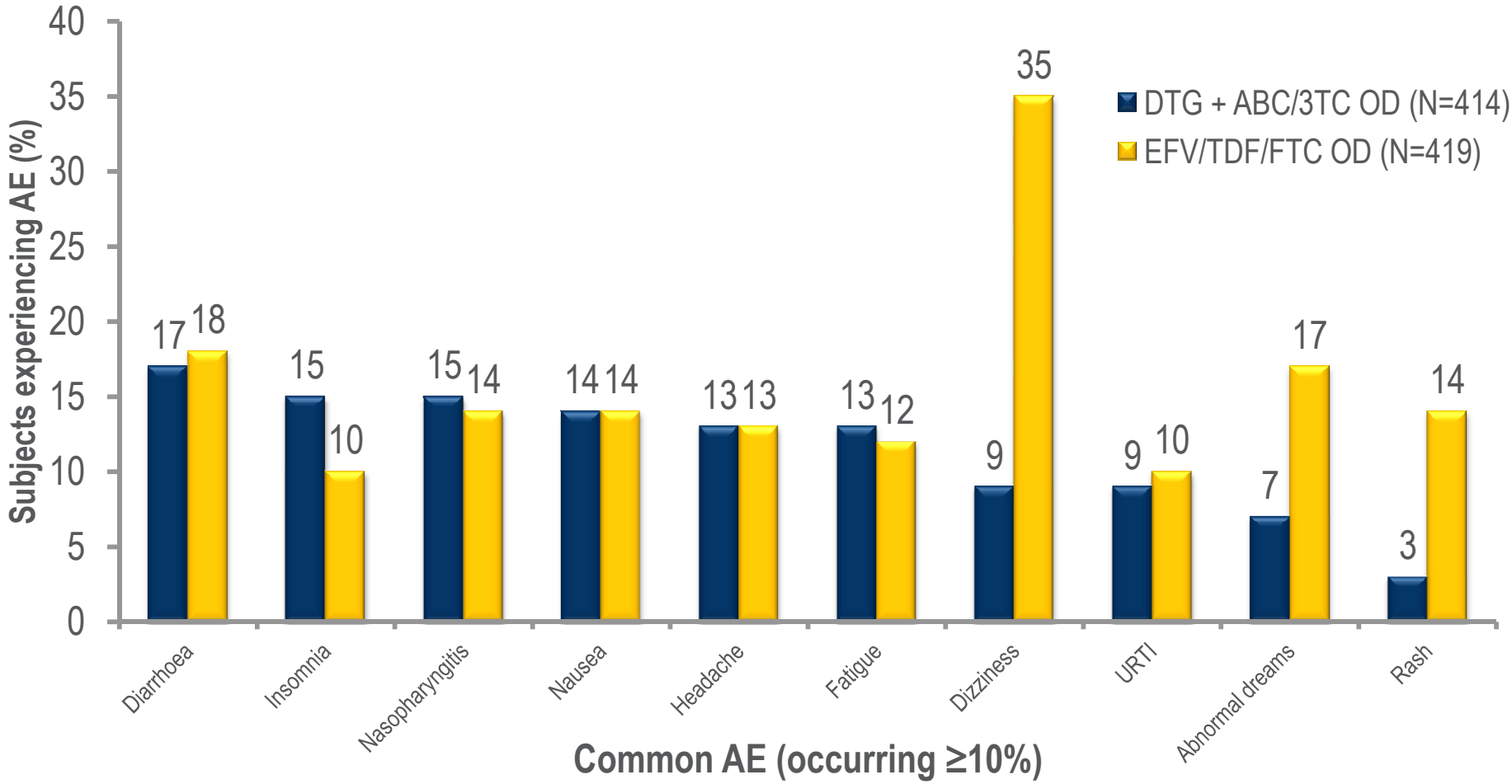
NRTI backbone	3rd agent
	INI: • DTG • RTG • ELV/c
	NNRTI: • RPV
	PI: • DRV/r • ATV/r

001/IHQ/16-05//1320 May 2016

Overview

1	Historical CNS toxicities
2	Changing demographics of PLWH
3	Changes to treatment
4	Emerging toxicities
5	Management and the future

Emerging toxicities INI



Walmsley S et al. N Engl J Med 2013; 369: 1807–1818.

abstract
948

Unexpectedly High Rate of Intolerance for Dolutegravir in Real Life Setting

Guido van den Berk, Josephine Oryszczyn, Willem Blok, Narda van der Meche, Rosa Regez, Daoud Ait Moha, **Kees Brinkman**

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background

- Integrase inhibitors (INSTI)are now preferred antiretrovirals in first line cART.
- Dolutegravir (DGV) is possibly considered as one of the most efficacious, convenient and tolerated INSTI, with hardly any chance for drug-drug interactions.
- Since we encountered many patients who stopped DGV because of intolerance, we analyzed the experience with DGV in our whole patient population since licensing in the Netherlands (aug 2014)

methods

- OLVG cohort: ±3000 patients, (97,4% on cART)
- retrospective analysis of all patients who started DGV, either as initial therapy or after switching from other antiretrovirals for any reason.
- Baseline characteristics at the moment of DGV start were recorded.
- We calculated the proportion of patients who stopped DGV, analyzed the reason for interruption and evaluated potential risk factors.
- Chi-squared test and Z-score to check for significant differences between groups and proportions.

results

	total (N=387)		naives(N=65)		non-naives (N=322)		
median age (IQR)	48		46	(22)	48	(13)	ns
female	44	11,4%	8	12,3%	36	11,2%	ns
dutch origin	136	35,1%	28	43,1%	108	33,5%	ns
median CD4/mm3 (IQR)	650		530	(395)	655	(345)	ns
median DGV days (IQR)	220		196	(147)	221	(148)	ns
DGV separate..	156		15		141		
DGV in STR..	231		50		181		
DGV stopped	62	16,0%	13	20,0%	49	15,2%	ns
median DGV days (IQR)	78		81	(71)	75	(99)	ns
female	5	11,4%	3	37,5%	2	5,6%	p=0.01
DGV separate	24	15,4%	1	6,7%	23	16,3%	ns
DGV in STR	38	16,6%	12	24,0%	26	14,4%	ns

reason for interruption

other than toxicity*	6	9,7%	1	7,7%	5	10,2%	
toxicity	56	90,3%	12	92,3%	44	89,8%	ns
sleeping..	19	31,3%	5	38,5%	14	28,6%	ns
gastro-intestinal..	18	29,5%	4	30,8%	14	28,6%	ns
neuro-psychiatric..	12	19,7%	3	23,1%	9	18,4%	ns
paresthesia..	6	9,7%	0	0,0%	6	12,2%	ns
headache..	8	12,9%	0	0,0%	8	16,3%	ns
fatigue..	9	14,6%	1	7,7%	8	16,3%	ns
allergy..	1	1,7%	1	7,7%	0	0,0%	ns
other..	5	8,2%	1	7,7%	4	8,2%	ns

*LTFU, HBV protection, insurance, induction, patient request, interaction

results

DGV treatment was stopped in 62/387 (16,0%) patients. There were no virological failures. Main reason for DGV interruption was intolerance in 56/62 (90,3%) patients: 19/56 (31,3%) sleeping problems, 18/56 (29,5%) gastrointestinal problems, 12/56 (19,7%) psychiatric problems, 8/56(12,9%) headache, 9/56 (14,6%) fatigue and 6/55 (10,9%). Some patients reported more than one toxicity.

Psychiatric reason to stop (n=12) varied from anxiety, depression and agitation to psychosis (n=2)

conclusion

In a real life setting a substantial proportion of patients unexpectedly interrupted DGV treatment for reasons of intolerance, in particular sleeping, gastrointestinal and psychiatric problems.

This was much higher than reported in clinical trials.

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Emerging toxicities INI

EFV to DTG switch (BHIVA 2016)

	BASELINE		WEEK 4		
	IS N 19	DS N 21	IS N 19	DS N 21	p-value
Overall CNS score(0 – 100) median(IQR)	33(20-53)	40(27-53)	10(7-20)	33(20-43)	<0.001
Proportion of patients with:					
Overall grade 3/4 CNS AE(%)	19(100)	20 (95.2)	5 (26.3)	20 (95.2)	<0.001
Insomnia(%)	9(47.4)	13 (61.9)	4 (21.1)	9 (42.9)	
Dizziness(%)	4(21.1)	6 (28.6)	0 (0)	6 (28.6)	
Depression(%)	8(42.1)	8 (38.1)	1 (5.3)	8 (38.1)	
Anxiety(%)	7(36.8)	11 (52.4)	2 (10.5)	4 (19.1)	
Confusion(%)	3(15.8)	0 (0)	0 (0)	0 (0)	
Impaired concentration(%)	5(26.3)	6 (28.6)	2 (10.5)	4 (19.1)	
Headache(%)	0 (0)	4 (19.1)	0 (0)	4 (19.1)	
Somnolence(%)	4 (21.1)	8 (38.1)	1 (5.3)	6 (28.6)	
Aggressive behaviour(%)	2 (10.5)	5(23.8)	1 (5.3)	4 (19.1)	

Bracchi M et al, BHIVA 2016, Poster 18

Overview

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Bracchi M et al, BHIVA 2016, Poster 18

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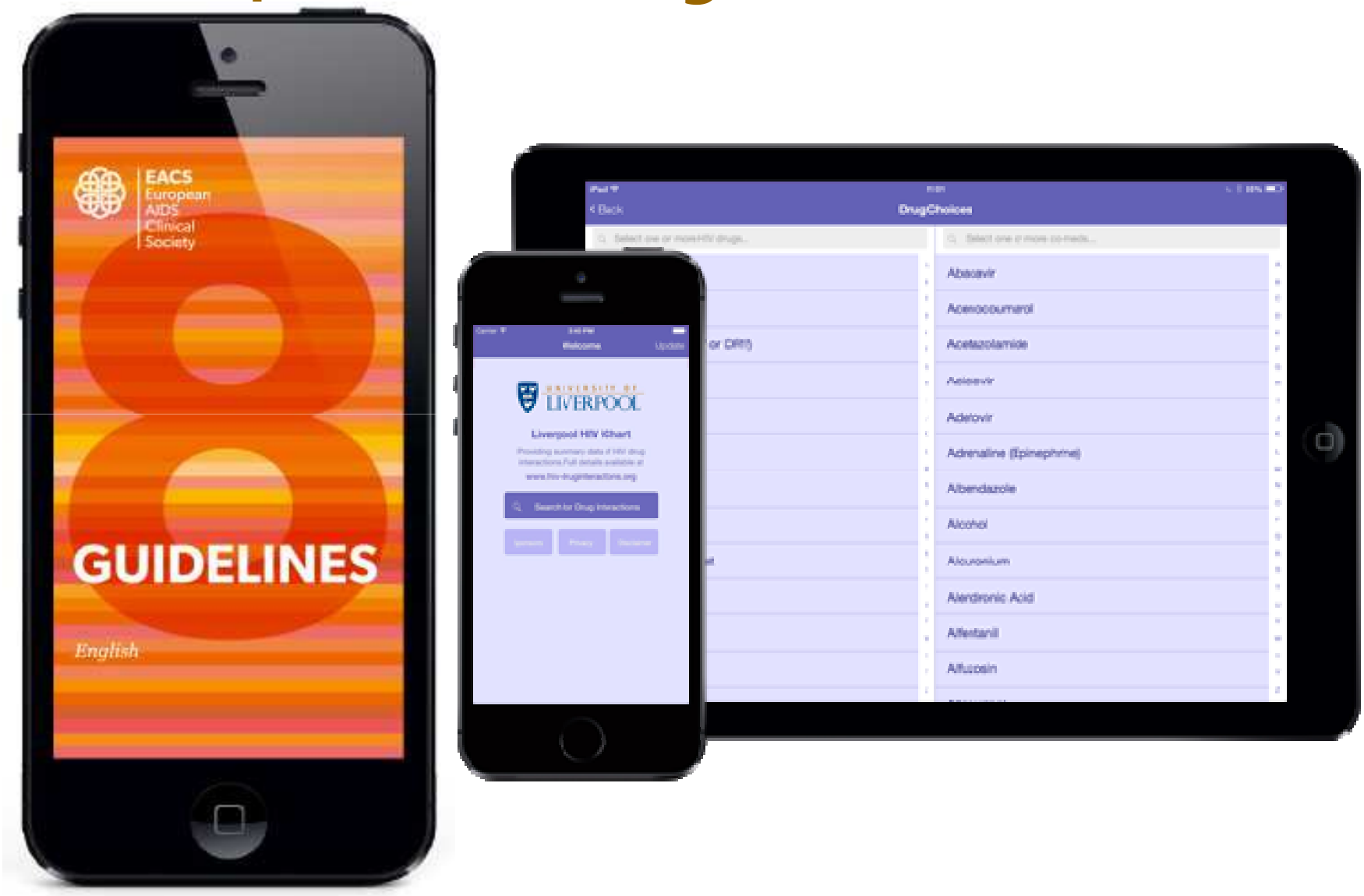
General patient management



EACS Guidelines 8.0, available at http://www.eacsociety.org/files/2015_eacsguidelines_8_0-english_rev-20160124.pdf ;
HIV iChart app, available at http://www.hiv-druginteractions.org/checker

The future

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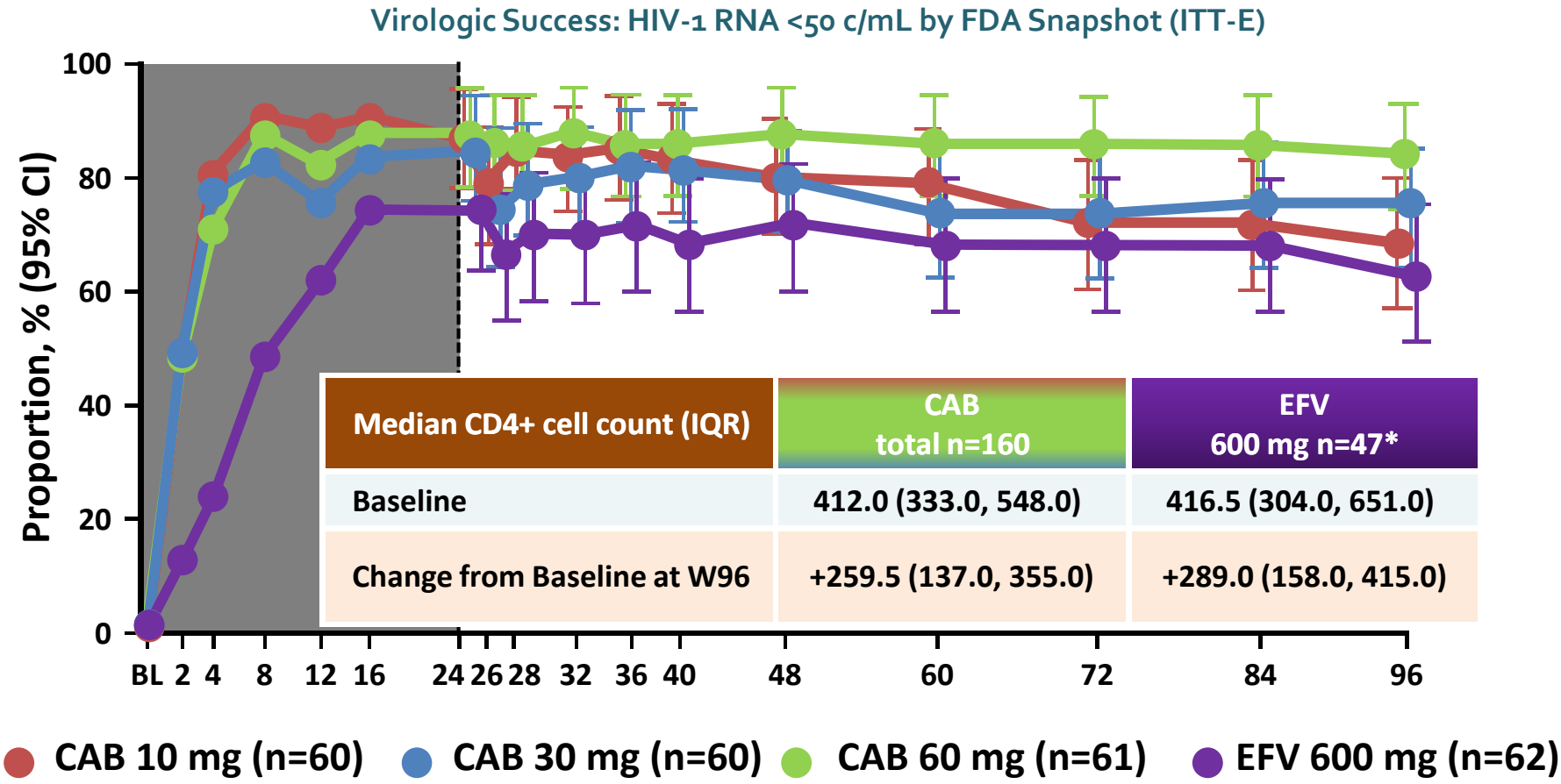
- Cabotegravir and rilpivirine as Two-Drug Oral Maintenance Therapy: LATTE Week 96 results



Margolis D, CROI 2015, Abstract 554LB

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The future

Are we likely to see changes in prevalence of neurological toxicities in PLWH?

Factor	Reduction in risk factor	Ongoing or increasing in risk factor
Treatment of HIV infection	Duration untreated HIV-infection Reduced AIDS	Longer duration antiretroviral therapy
Type of ART	Historical infective and clearly neurotoxic antiretroviral therapy	Novel strategies with unknown long term side effects
Ageing		Increasing age and likely increase in number of co-morbidities
Lifestyle		Recreational drug use

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Summary

1	Historical CNS toxicities • Still describing new toxicities on old drugs!
2	Changing demographics of PLWH • Comorbidities, ageing and polypharmacy may exacerbate ART toxicities
3	Changes to treatment • Guidelines are all in general agreement and moving to INI based regimens
4	Emerging toxicities • Clinical vigilance essential • Important not to overcall toxicities
5	Management and the future • Management involves a holistic and multidisciplinary approach • Future treatment strategies likely to include INI

Thank you !