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Integrase inhibitors and the brain

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St. Mary's Hospital London

May 2017

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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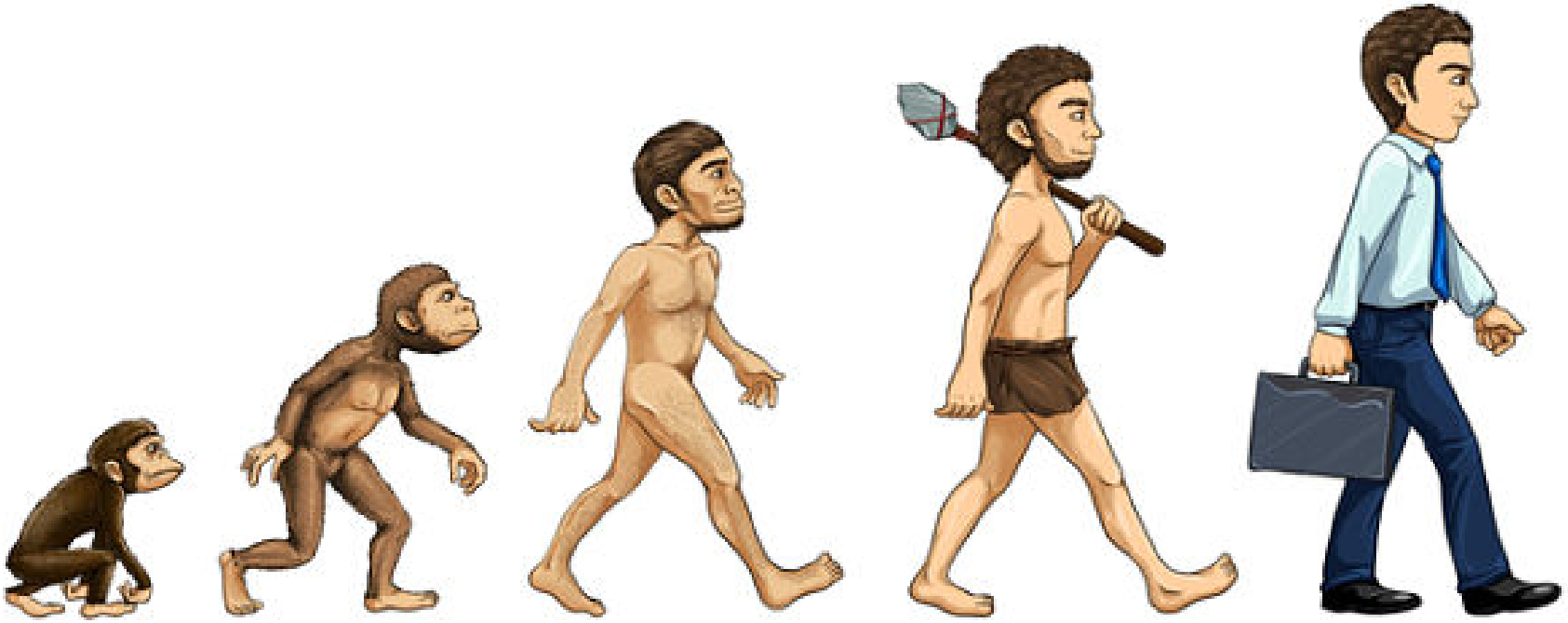
Evolution of HIV therapy



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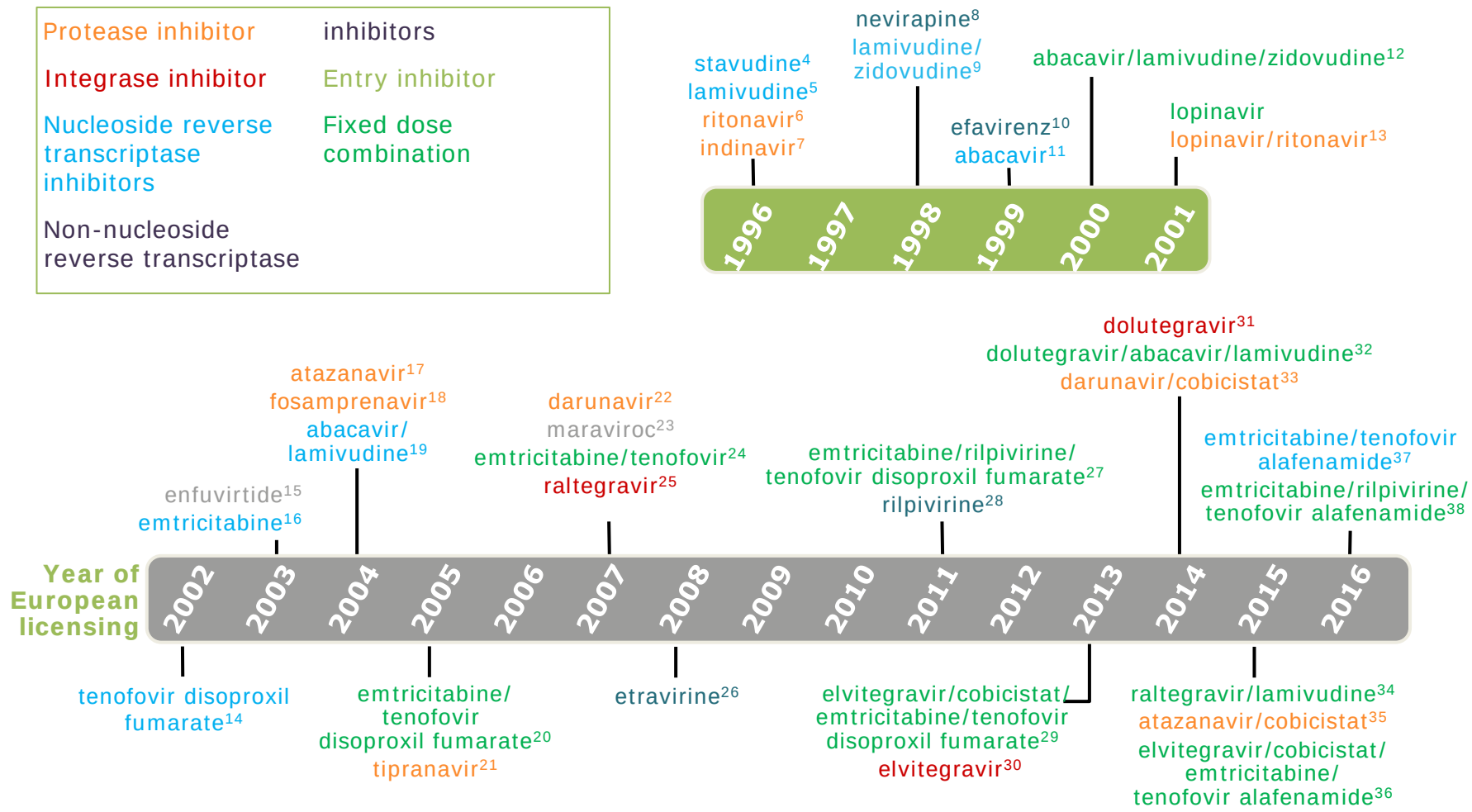
Antiretroviral therapy

Approved medications for HIV infection: 1996–2016[1-3]

Protease inhibitor	inhibitors
Integrase inhibitor	Entry inhibitor
Nucleoside reverse transcriptase inhibitors	Fixed dose combination
Non-nucleoside reverse transcriptase	



1. DHHS. Guidelines for the Use of Antiretroviral agents in HIV-1-Infected adults and adolescents. Available at https://aidsinfo.nih.gov/contentfiles/lvguidelines/glchunk/glchunk_37.pdf [Accessed May 2017]; 2. EACS. Guidelines 8.2 Feb 17. Available at: http://www.eacsociety.org/files/guidelines_8_2-english_web.pdf [Accessed May 2017]; 3. WHO. HIV/AIDS. Available at: http://www.who.int/hiv/en/ [Accessed May 2017]; 4-38. Public assessment reports . European Medicines Agency. Available at: http://www.ema.europa.eu/ema/ [Accessed May 2017].

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ART Guidelines preferred initial regimens

Guideline	Year	NNRTI	INSTI	Boosted PI
WHO	2016	TDF/3TC (or FTC) +EFV as a fixed dose combination		
EACS (8.2)	2017	TAF/FTC/RPV* TDF/FTC/RPV*	TAF/FTC or TDF/FTC with EVG/c or RAL or DTG ABC + 3TC with DTG	TAF/FTC or TDF/FTC with DRV/r or DRV/c
IAS-USA	2016		TAF/FTC with EVG/c or RAL or DTG ABC + 3TC with DTG	
DHHS	2016		TDF/FTC with EVG/c or RAL or DTG TAF/FTC with EVG/c or RAL or DTG ABC + 3TC with DTG	TDF/FTC + DRV/r TAF/FTC + DRV/r

*VL< 100,000 copies/ml and CD4 > 200

NNRTI, Non-nucleoside Reverse Transcriptase Inhibitor; INSTI, Integrase Inhibitor; PI, Protease Inhibitor; TDF, Tenofovir Disoproxil Fumarate; 3TC, Lamivudine; EFV, Efavirenz; DTG, Dolutegravir; TAF, Tenofovir Alafenamide; FTC, Emtricitabine; RPV, Rilpivirine; EVG, Elvitegravir; c, cobicistat; RAL, Raltegravir; ABC, Abacavir; r, Ritonavir

WHO 2016, EACS 2017, IAS-USA 2016, DHHS 2016

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Alan's guidelines summary

NRTI backbone	3rd agent
TDF/FTC ABC/3TC TAF/FTC	INI: • DTG • RTG • EVG/c
	NNRTI: • RPV*
	PI: • DRV/r

*TAF/FTC/RPV is not approved in Spain

NRTI, Non-reverse Transcriptase Inhibitor; TDF, Tenofovir Disoproxil Fumarate; FTC, emtricitabine; ABC, Abacavir; 3TC, Lamivudine; TAF, Tenofovir Alafenamide; INI, Integrase Inhibitor; DTG, Dolutegravir; RTG, Raletgravir; EVG, Elvitegravir; c, cobicistat; RPV, Rilpivirine; DRV, Darunavir

Author's opinion

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Integrase inhibitors and the brain

1	Our cohorts
2	Historical CNS toxicities
3	CNS signals with INI

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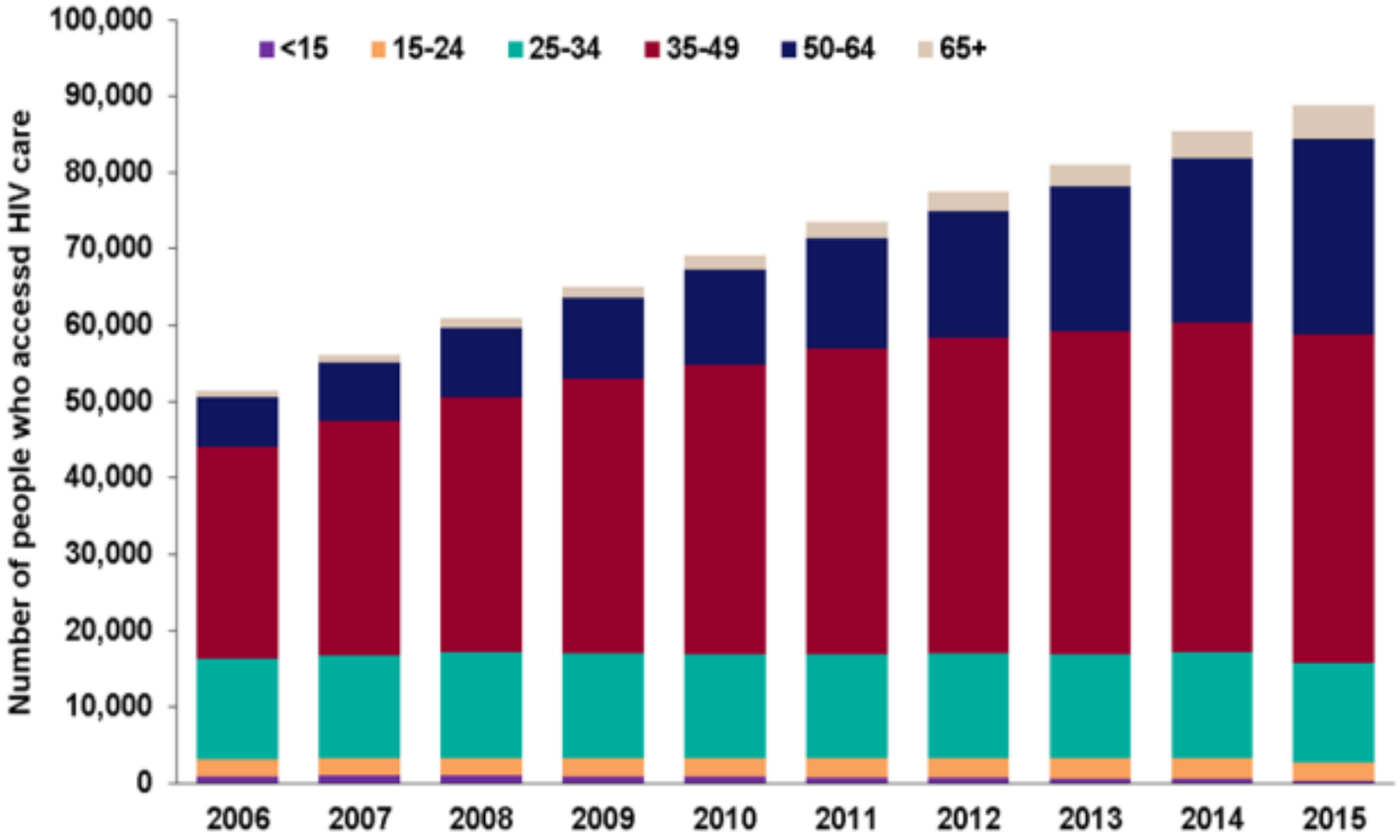
Age of our cohorts



Public Health England October 2016. Available at: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/602945/HIV_diagnoses_late_diagnoses_and_numbers_accessing_treatment_and_care.pdf Last accessed May 2017

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European HIV and ageing cohorts:

POPPY

Pharmacokinetic and clinical observations in people over 50

- 1400 subjects
  - 700 PLWH over 50
  - 350 controls over 50
  - 350 PLWH under 50

ageiv cohort study

- 1148 subjects
  - 598 PLWH over 45
  - 550 controls over 45

PLWH, People Living with HIV

De Francesco et al. BMC Infectious Diseases. 2016 16:167 , Schouten J et al. Clin Infect Dis. 2014 59(12):1787-97

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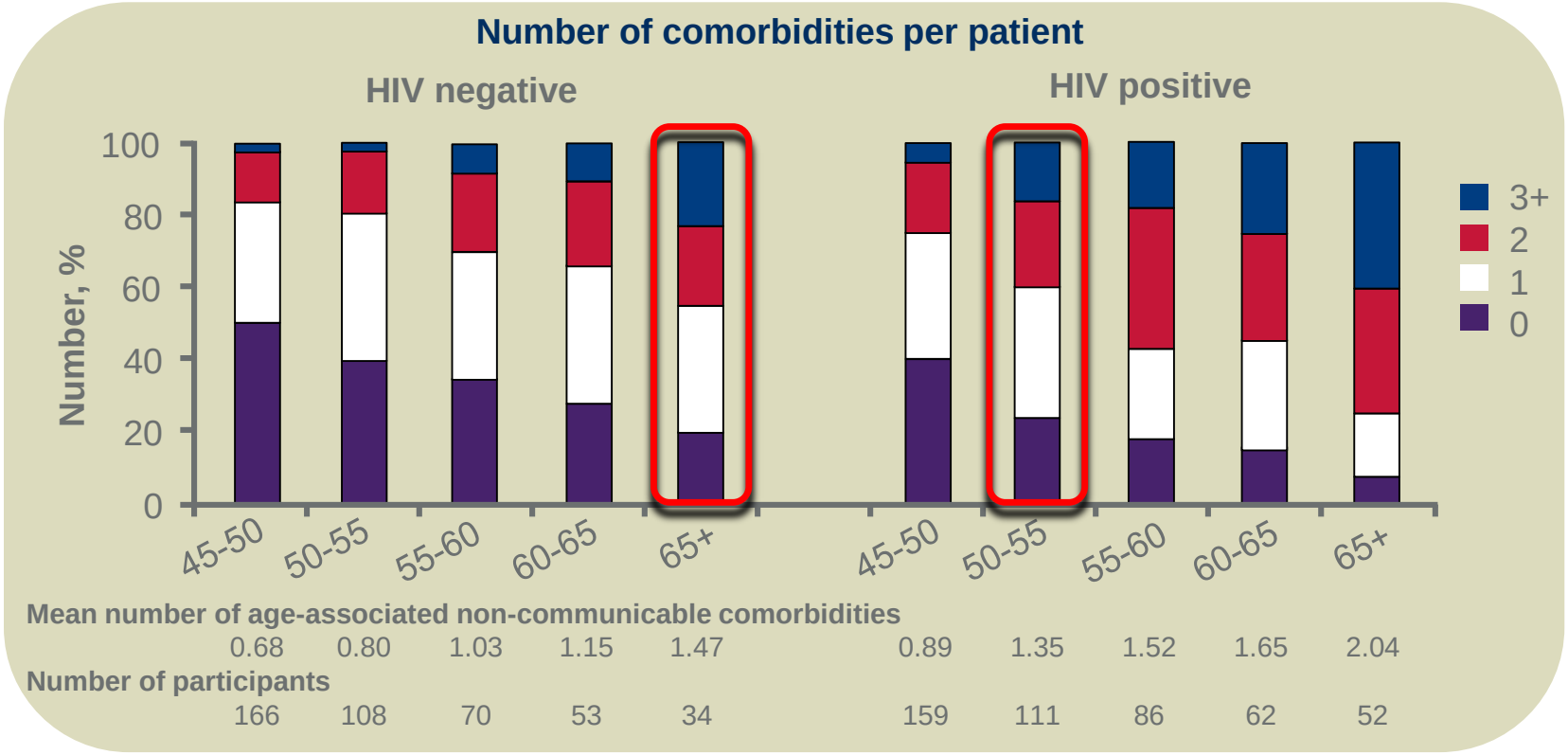
Prevalence of co-morbidities

- Cohort study of HIV and comorbidities in The Netherlands (N=452 HIV-negative and 489 HIV-positive persons)
- 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):1787-97

Lifestyle factors

POPPY
Pharmacokinetic and clinical observations in people over 50

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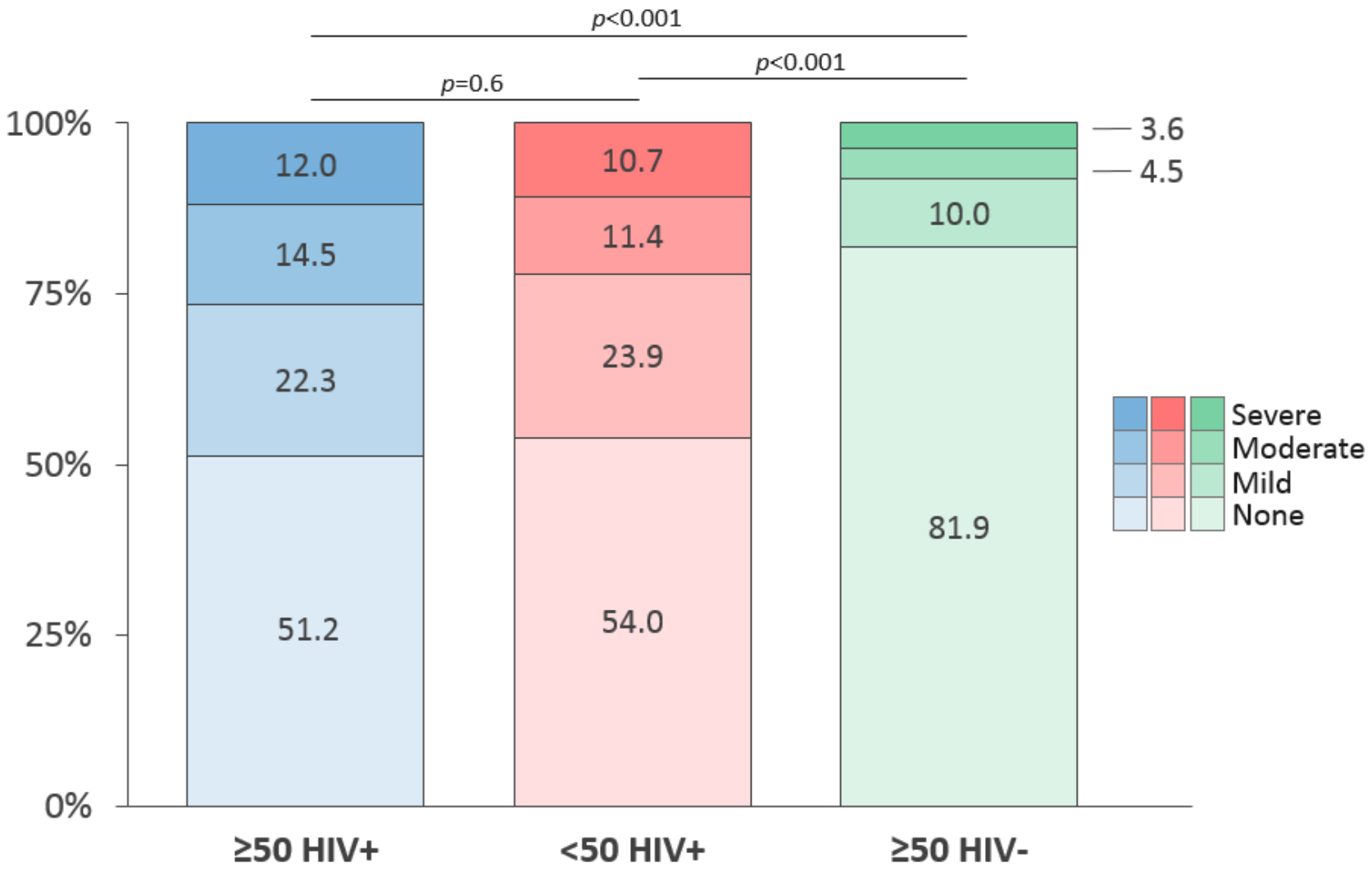
		Age >50, HIV+ (N=637)	Age <50, HIV+ (N=340)	*p*-value	Age >50, HIV- (N=276)	*p*-value
Alcohol, n (%)	**Never drank**	46 (7.2%)	29 (8.5%)	0.35	14 (5.1%)	0.07
	Previous drinker	84 (13.2%)	35 (10.3%)		19 (6.9%)	
	Current drinker	507 (79.6%)	276 (81.2%)		243 (88.0%)	
Years drinking [current/previous drinkers] median (IQR)		39 (35, 45)	25 (19, 30)	<0.001	41 (36, 46)	0.03
Smoking, n (%)	**Never smoked**	256 (40.4%)	152 (45.0%)	0.003	126 (45.8%)	0.03
	Ex-smoker	242 (38.2%)	93 (27.5%)		110 (40.0%)	
	Current smoker	136 (21.5%)	93 (27.5%)		39 (14.2%)	
Years smoking [current/previous smokers] median (IQR)		32 (19, 39)	21 (14, 27)	<0.001	28 (13, 37)	0.006
Current/past ID use, n (%)		59 (9.3%)	46 (13.6%)	0.04	6 (2.2%)	<0.001
Rec. drugs use 6 months before visit n, (%)		164 (25.8%)	116 (34.1%)	0.006	42 (15.2%)	<0.001

IQR, Inter-quartile range; ID, Injectable drugs

De Francesco et al. (2016) J Int AIDS Soc 19(8Suppl 7): 21487, O215

Depression



De Francesco et al. (2016) J Int AIDS Soc 19(8Suppl 7): 21487, O215

Depression and cognitive impairment

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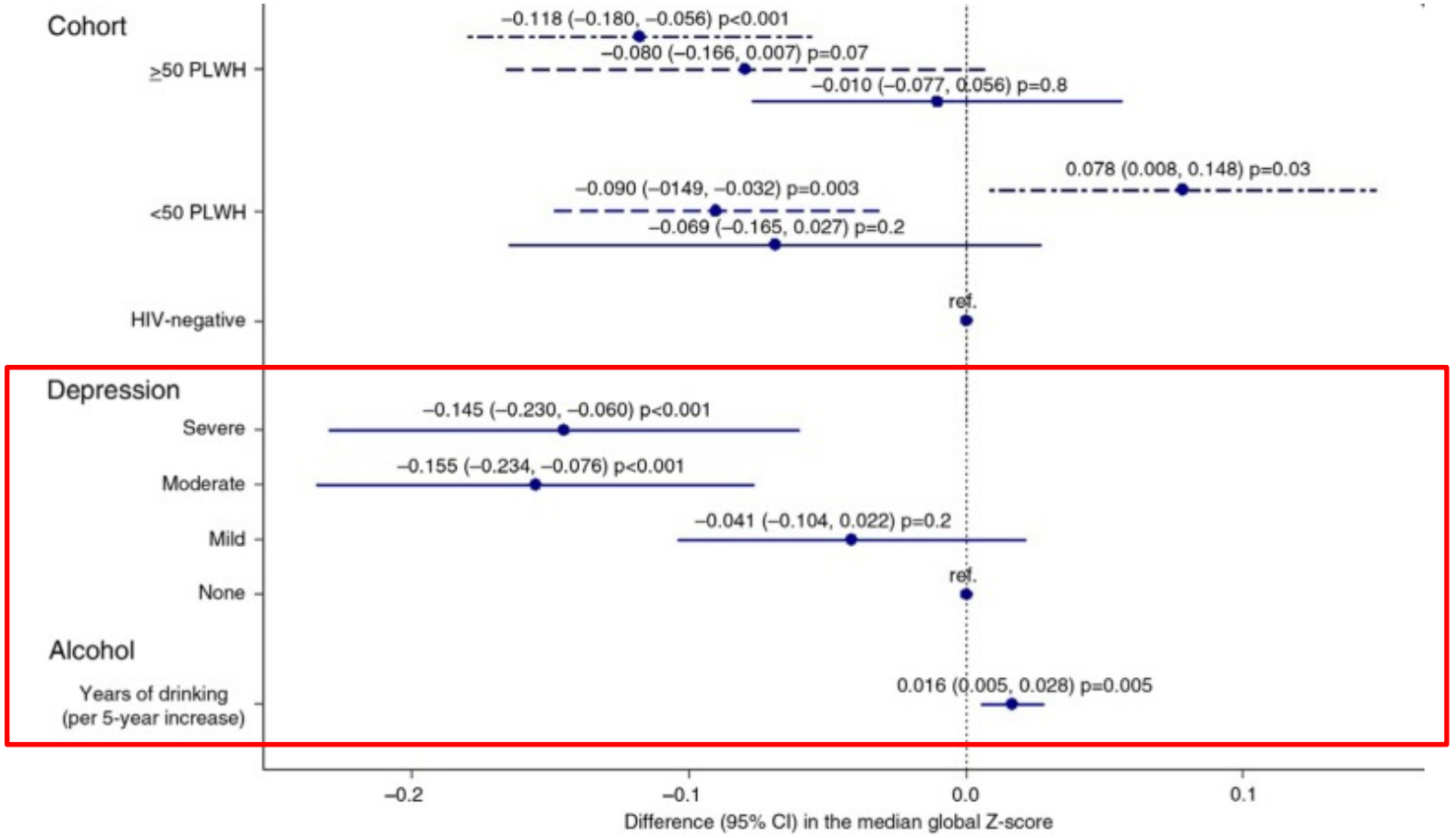
POPPY
Pharmacokinetic and clinical observations in people over 50

Differences (with 95% CI) in the median global Z-score across cohorts (≥50 PLWH, <50 PLWH and HIV-negative controls)



PLWH, People living with HIV; CI, Confidence Interval

De Francesco et al. (2016) J Int AIDS Soc 19(8Suppl 7): 21487, O215

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Integrase inhibitors and the brain

1	Our cohorts
2	Historical CNS toxicities
3	CNS signals with INI

The history of EFV-associated CNS toxicities

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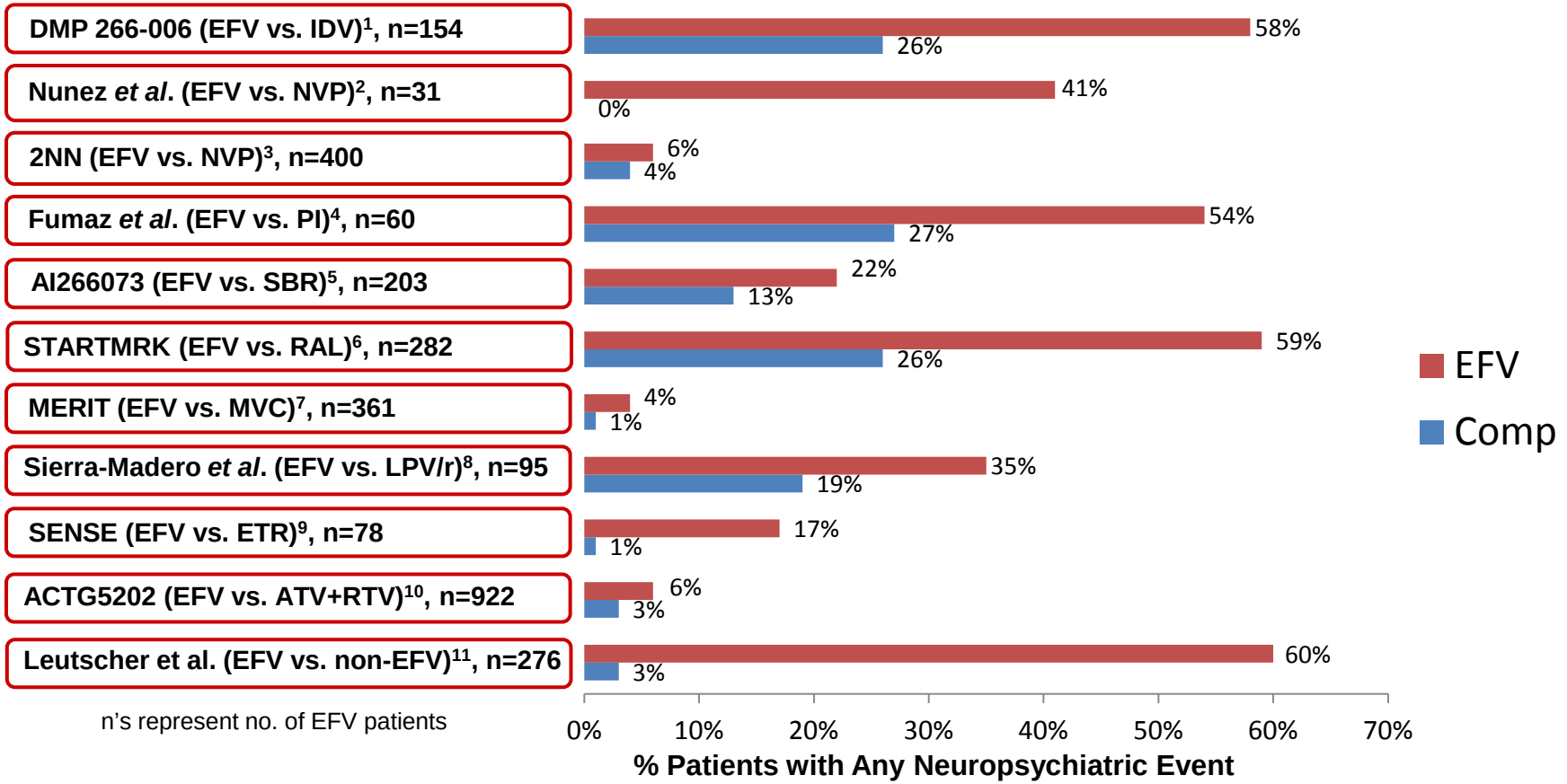

IDV, indinavir; NVP, Nevirapine, PI, protease inhibitor; SBR, stable baseline regimen; RAL, raltegravir; MVC, maraviroc; LPV, lopinavir; ATV, atazanavir; ETR, etravirine; RTV, ritonavir; EFV, efavirenz; Comp, comparator

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

Factors associated with cognitive 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			

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

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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Suicide and ART – D.A.D. cohort

Rates of death from suicide, according to current ART use

	Number/person-years	Rate per 1000 person-years (95% CI)	Adjusted RR (95% CI)
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)
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)

RR, relative risk; EFV, Efavirenz; NNRTI, Non-Nucleotide Reverse Transcription Inhibitor; ART, Antiretroviral Therapy

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

How long does it take to identify a problem?

Drug/class	FDA approval	Toxicity	Signal	Delay (years)	Risk (95%CI)
stavudine[1]	1994[14]	Lipoatrophy	1999[7]	5	RR 1.95 (1.18-3.22)
nevirapine[2]	1996[14]	Toxicity at high CD4	2005[8]	9	Female 12 x higher risk Male 5 x higher risk
PIs	1996[14]	Heart attack	2003[9]	7	RH 2.56 (1.03-6.34)
efavirenz[3]	1998[14]	Suicidality	2013[10]	15	HR 2.28 (1.27,4.10)
abacavir[4]	1998[14]	Heart attack	2008[11]	10	RR 1.14 (1.08–1.21)
tenofovir[5]	2001[14]	Fracture	2012[12]	11	HR 1.080 (1.02,1.15)
Raltegravir[6]	2007[14]	Myopathy	2013[13]	5	OR 2.64 (1.57-4.45)

PIs, Protease Inhibitors; RR , Relative risk; RH , Relative hazard; HR , Hazard ratio; OR, overall risk

1.Stavudine SPC https://www.medicines.org.uk/emc/medicine/21122, 2.Nevirapine SPC https://www.medicines.org.uk/emc/medicine/322, 3. Efavirenz SPC https://www.medicines.org.uk/emc/medicine/11284, 4. Abacavir SPC https://www.medicines.org.uk/emc/medicine/2476, 5.Tenofovir SPC https://www.medicines.org.uk/emc/medicine/9008, 6. Raltegravir SPC https://www.medicines.org.uk/emc/medicine/20484, 7. Sain-Marc et al, AIDS 1999; 8. FDA Public Health Advisory for Nevirapine, 2005, 9. Mary-Krause M et al, AIDS. 2003 Nov 21;17(17):2479-86 10. Mollan et al, IDSA 2013; 11.DAD Study Group, Lancet 2008; 12. Bedimo et al , AIDS 2012; 13. Lee et al, JAIDS 2013; 14. FDA Antiretroviral drugs used in the treatment of HIV infection, https://www.fda.gov/forpatients/illness/hivaids/treatment/ucm118915.htm Last accessed May 2017

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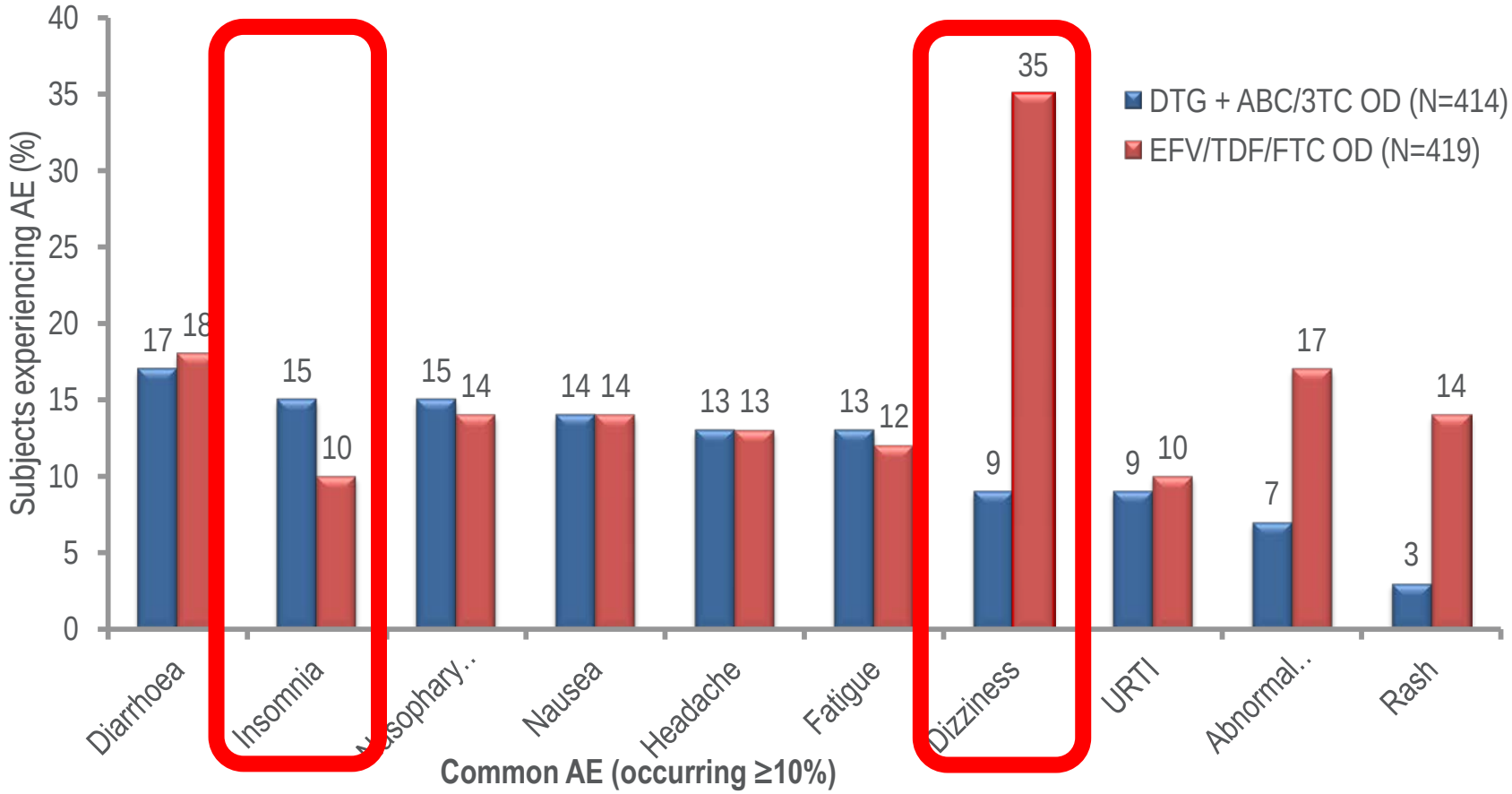
Initial signals – phase III

Safety profile of Dolutegravir and Abacavir-lamivudine compared to Efavirenz-tenofovir-emtricitabine, over 48 Weeks

- A Phase 3 study with 833 adult participants who had not received previous therapy for HIV-1 infection and who had an HIV-1 RNA level of 1000 copies per millilitre or more



DTG+ABC/3TC, Dolutegravir plus Abacavir-lamivudine; EFV/TDF/FTC, Efavirenz-tenofovir disoproxil fumarate- emtricitabine

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

Initial signals – CROI 2016

Retrospective analysis of ~3,000 HIV+ patients (97% on ART), all 387 patients who started DTG, either as treatment naïve or after switching from other ART

n (%)	Total (N=387)	Treatment-naive (n=65)	Treatment-experienced (n=322)
Stopped DTG	62 (16)	13 (20)	49 (15)
Median days (IQR)	78	81 (71)	75 (99)
Reason for interruption (>5% of patients)			
Intolerance	56 (90)	12 (92)	44 (90)
Sleeping	19 (31)	5 (39)	14 (29)
Gastro-intestinal	18 (30)	4 (31)	14 (29)
Neuro-psychiatric	12 (20)	3 (23)	9 (18)
Paresthesia	6 (10)	0	6 (12)
Headache	8 (13)	0	8 (16)
Fatigue	9 (15)	1 (8)	8 (16)
Other	5 (8)	1 (8)	4 (8)
Other than intolerance*	6 (10)	1 (8)	5 (10)

*Other than intolerance: LTFU, HBV protection, insurance, infection, patient request, interaction

- A substantial proportion of patients (16%, 62/387) discontinued DTG treatment and the majority (90%, 56/62) discontinued due to intolerance.
- Higher discontinuation rate due to adverse event rates than reported in clinical trials

Brinkman K, et al. CROI 2016. Boston, MA. #948

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Dolutegravir cohort data

Clinic	No. of patients	d/c due to AEs n (%)	Main reasons for d/c
OLVG[1]	387	62 (16%)	Sleeping, gastro-intestinal, neurological
Brighton[2]	128	16 (13%)	Sleep
Foch[3]	105	11 (10.4%)	Vertigo, headache, insomnia, malaise
Cardiff[4]	63	6 (10%)	Sleep
Manchester[5]	178	15 (8.4%)	CNS, malaise and joint pain
Cologne[11]	985	67 (6.8%)	Neuropsychiatric (5.0%), gastro-intestinal (0.7%), skin (0.3%), renal (0.2%), hepatic (0.1%)
St Thomas [6]	181	9 (5%)	Insomnia, malaise/myalgia
DOL-ART[10]	411	18 (4,4%)	Depression (1.2%), GI symptoms (1%)
Ramòn Y Cajal[9]	827	36 (4,3%)	Headache, dyslipidemia, insomnia, dizziness, mood disorders
Cruser Kobler AIDS centre[8]	73	3 (4.1%)	CNS (2), gastro-intestinal (1) 19% patients had AEs, and 11% CNS AEs
Liverpool[12]	178	8 (4%)	n/a, 33% have AEs of whom 20% CNS, 10% gastrointestinal, 7% neurological, 3% musculoskeletal, 3% lethargy
Llibre[14]	873	25 (3%)	Neuropsychiatric toxicity definition included anxiety, depression, insomnia, dizziness, nightmares, paresthesia, somnolence, tremor and vertigo (adjusted HR of 3.18 DTG vs RAL & 4.93 DTG vs EVG/COBI)
Imperial[7]	138	3 (2%)	Sleep dizziness
Osaka[13]	101	n/a	20.8% reported CNS AEs: headache (7.9%), insomnia (5.9%)

d/c, discontinuation; AE, adverse events; CNS, central nervous system

1. Brinkman K, et al. CROI 2016, Boston, MA. #948; 2. Kirby, et al. BHIVA 2016, Manchester UK. P26; 3. Zucman D, et al. AFRAVIH 2016, Brussels, Belgium. P1405; 4. Cunningham, et al, BHIVA 2016, Manchester, UK. P36; 5. Jewsbury S, et al. BHIVA, Manchester, UK. 2016. P20; 6. Simons R, et al. Guy's and St Thomas' NHS Foundation Trust, P9; 7. Negedu, et al. BHIVA, Manchester UK. April 2016. p 28; 8. Tau L, et al. HIV Drug Therapy, Glasgow, UK. 2016. P108; 9. Vivancos-Gallego M, et al. HIV Drug Therapy, Glasgow, UK, 2016. P116; 10. Postel N, et al. HIV Drug Therapy, Glasgow, UK, 2016. P133; 11. Sabranski M, et al. HIV Drug Therapy, Glasgow, UK, 2016. O214; 12. Fernandez C, et al. HIV Drug Therapy, Glasgow, UK, 2016. P212; 13. Yagura H, et al. HIV Drug Therapy, Glasgow, UK, 2016. P312; 14. Llibre JM et al. CROI 2017. Seattle, WA. P651.

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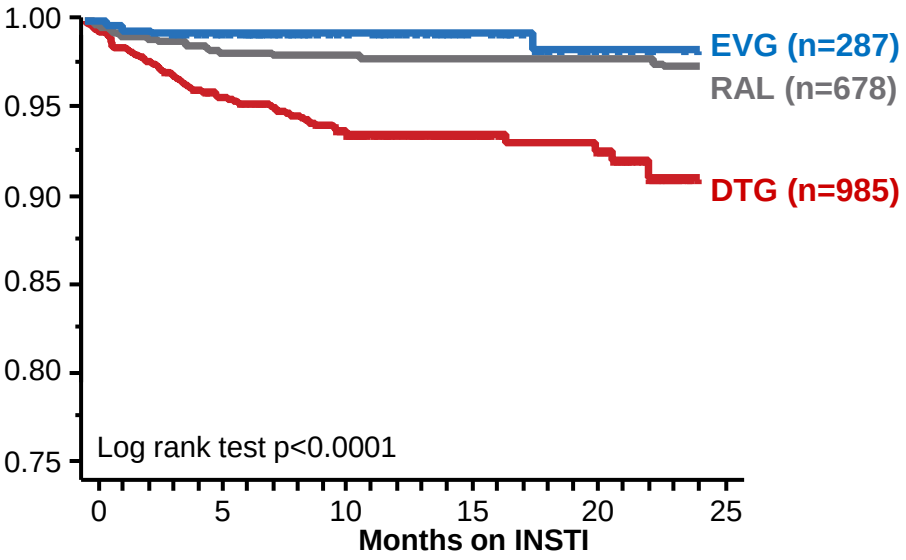
Cohort data

Retrospective analysis of anonymized data for all HIV+ patients (1704 patients, 1950 INSTI therapies) under routine care in two large German HIV centres (Jan 2007 – April 2016)

%	DTG n=985	EVG n=287	RAL n=678
AEs Leading to Discontinuation (>2% with any INSTI)			
Renal	0.2	3.5	0
Gastro-Intestinal	0.7	2.8	0.9
Neuropsychiatric	5.0	1.0	2.1
-sleep disturbance	3.7	0.7	0.6
-headache, dizziness, or paresthesia	2.9	0.7	1.3
-depression	0.7	0	0.1
Estimated AE Discontinuation Rates within 12 Months			
Any AE	7.6	7.6	3.3
Neuropsychiatric AE	5.6	0.7	1.9

Discontinuation due to neuropsychiatric AEs



- Overall discontinuation rates were similar across all 3 INSTIs
- Neuropsychiatric AEs were most common with DTG and resulted in greater discontinuations compared to EVG or RAL
- Neuropsychiatric symptoms reproducible in 6 out of 6 cases with DTG re-exposure[2]
- 86% of patients had no tolerability problems after DTG switched to another ART
- Likelihood of neuropsychiatric discontinuation more than doubled for DTG with ABC vs. without ABC

DTG, Dolutegravir; EVG, Elvitegravir; RAL, Raltegravir; AEs, Adverse Events; INSTI, Integrase Inhibitors; ABC, Abacavir

Sabranski M et al.. HIV Drug Therapy 2016. #O214, Hoffman, C, et al. HIV Medicine 2017

Randomised controlled trial data

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JAIDS
JOURNAL OF ACQUIRED IMMUNE DEFICIENCY SYNDROME

Articles & Issues | Collections | For Authors | Journal Info

< Previous Abstract | Next Abstract >

Psychiatric Symptoms in Patients Receiving Dolutegravir

Fettiplace, Anna PhD, MBChB; Stainsby, Chris BSc Hons; Winston, Alan MD; Givens, Naomi MSc; Puccini, Sarah BSc Hons; Vannappagari, Vani PhD; Hsu, Ricky MD; Fusco, Jennifer BS; Quercia, Romina MD, PhD; Aboud, Michael MBChB, MRCP; Curtis, Lloyd MA, MRCP

JAIDS Journal of Acquired Immune Deficiency Syndromes: 1 April 2017 - Volume 74 - Issue 4 - p 423–431
doi: 10.1097/QAI.0000000000001269
Clinical Science

OPEN SDC

Conclusions: Analysis of 3 different data sources shows that, similar to other frequently prescribed anchor drugs to treat HIV infection, PSs are also reported in DTG-treated patients. These events are reported with low frequency and rarely necessitate DTG discontinuation.

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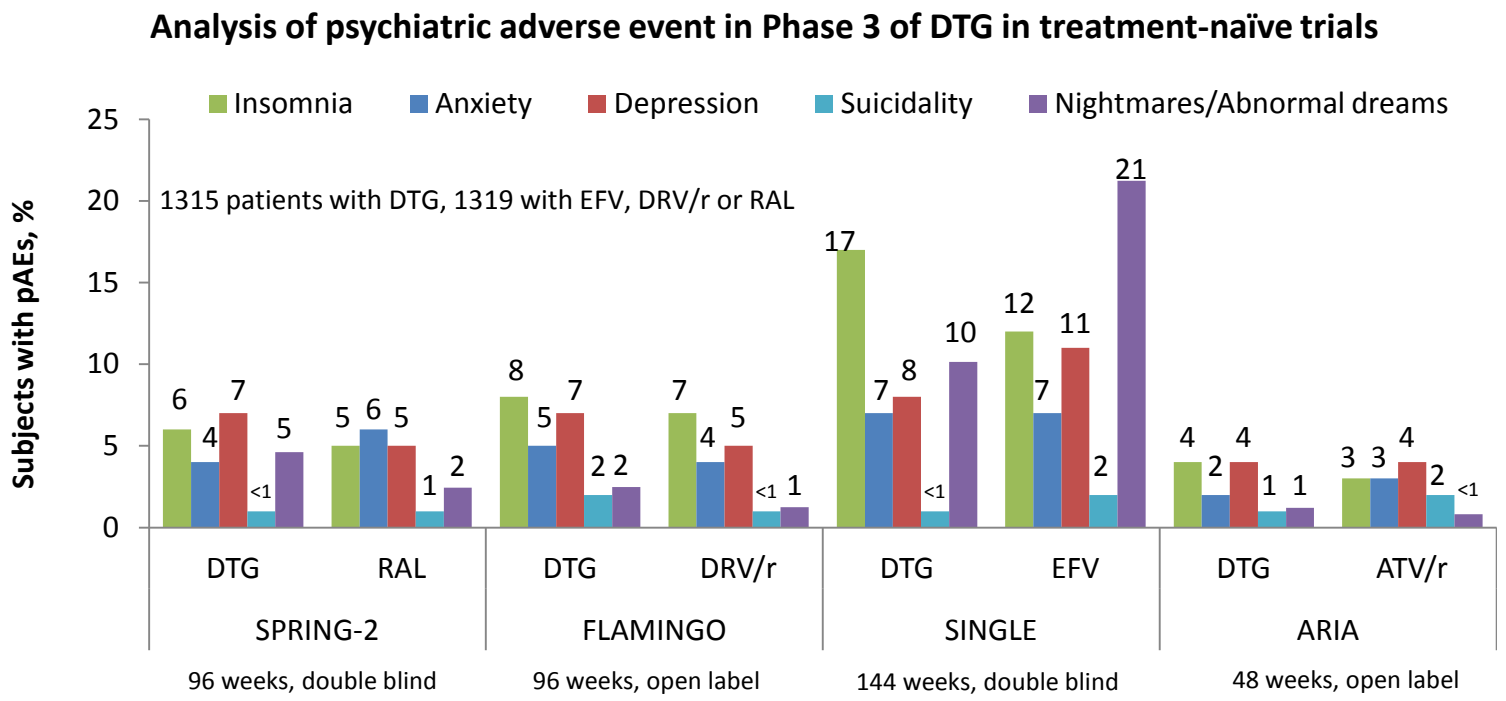
Psychiatric Adverse Events across DTG Treatment-Naïve Phase III Clinical Trials



- In these trials, majority of DTG pAEs were grade 1/2, leading to few discontinuations
- Insomnia was the most frequent pAEs with 2 discontinuations. The rates of insomnia was similar across different trials, except SINGLE
- Insomnia was reported in 126 patients on DTG (9.6%) vs. 96 on comparator arm (7.3%). 46% were attributed to treatment (DTG) vs 38% in comparator arm
- The rate of insomnia reported in the SINGLE study may be partially due to the study design bias related to the comparator arm in the context of a double blind study

pAEs, psychiatric Adverse Events; DTG, Dolutegravir; EFV, Efavirenz; DRV/r, Darunavir/Ritonavir; RAL, Raltegravir; ATV/r, Atazanavir/Ritonavir

Quercia R, et al. HIV Drug Therapy, Glasgow 2016, Oral Poster #P210

Characteristics of psychiatric symptoms in the OPERA Cohort: 2013-2106

	ART REGIMENS			
Total number of patients 6,347	DTG Regimen (n=2029)	EFV Regimen (n=1608)	RAL Regimen (n=963)	DRV Regimen (n=1747)
Prevalence of diagnoses during follow-up, n (%)				
Insomnia	157 (7.7)	139 (8.6)	82(8.5)	96 (5.5)
Discontinued	13 (0.6)	19 (1.2)	7 (0.7)	9 (0.5)
Anxiety	134 6.6)	110 (6.8)	98 (10.2)	132 (7.6)
Discontinued	7 (0.3)	13 (0.8)	14 (1.5)	20 (1.1)
Depression	205 (10.1)	153(9.5)	136 (14.1)	204 (11.7)
Discontinued	13 (0.6)	25 (1.6)	24 (2.5)	19 (1.1)
Suicidality	3 (0.1)	3 (0.2)	2 (0.2)	1(0.1)
Discontinued	0	1 (0.1)	0	0
Incidence of new diagnoses during follow-up, n (%)				
Insomnia	110 (5.4)	110 (6.8)	55 (5.7)	71 (4.1)
Discontinued	6 (0.3)	15 (0.9)	6 (0.6)	8 (0.5)
Anxiety	98 (4.8)	89 (5.5)	64 (6.6)	93 (5.3)
Discontinued	3 (0.1)	10 (0.6)	8 (0.8)	12 (0.7)
Depression	98 (4.8)	104 (6.5)	69 (7.2)	109 (6.2)
Discontinued	5 (0.2)	17 (1.1)	7 (0.7)	12 (0.7)
Suicidality	3 (0.1)	3 (0.2)	2 (0.2)	1(0.1)
Discontinued	0	1 (0.1)	0	0

ART, Antiretroviral Therapy; DTG, Dolutegravir; EFV, Efavirenz; RAL, Raltegravir; DRV, Darunavir

Fettiplace, A et al. JAIDS Journal of Acquired Immune Deficiency Syndromes. 74(4):423-431, April 1, 2017

HIV/IHQ/17-05//1539a Date of Preparation: May 2017

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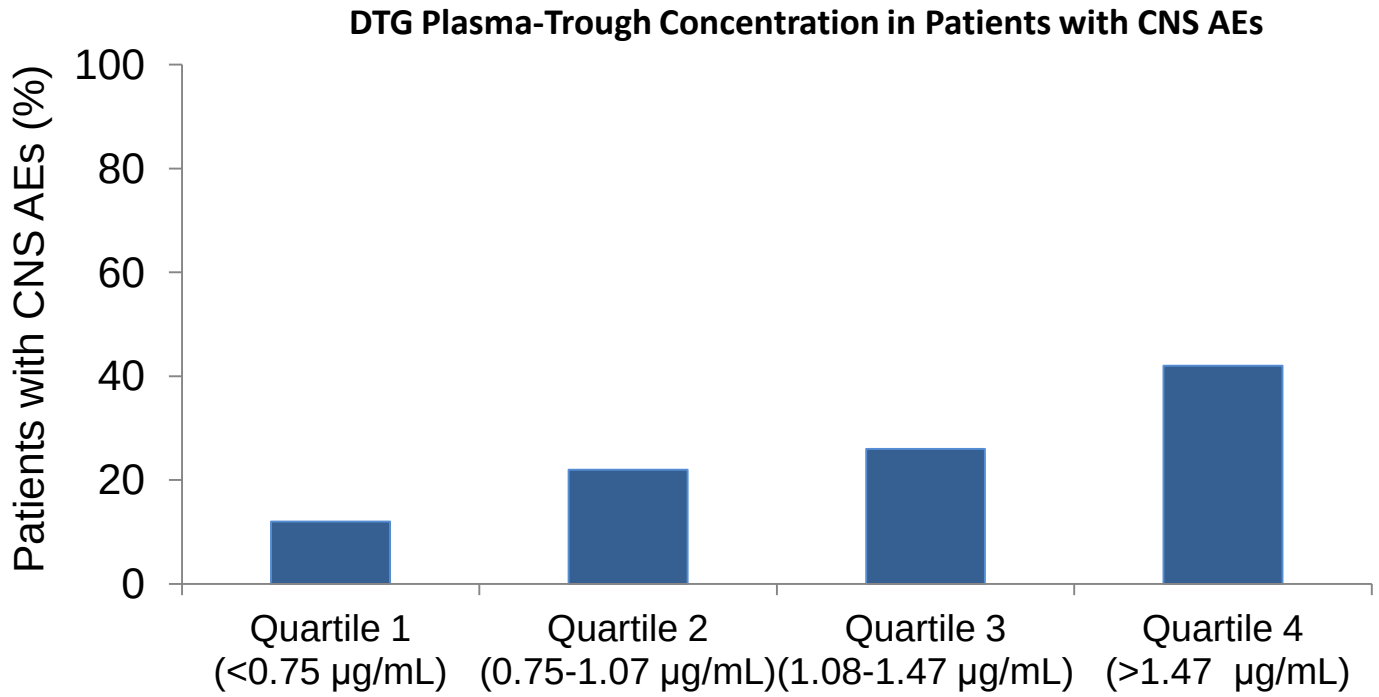
Pharmacokinetic considerations

Evaluation of association of DTG concentration and CNS side effects in 162 HIV-infected patients on DTG in Osaka, Japan, Apr 2014 to Mar 2016



"A positive correlation between DTG plasma trough concentration and CNS side effects was identified in a Japanese population."

AEs, adverse events; DTG, Dolutegravir; CNS, Central Nervous System

Yagura H, et al. CROI 2017. Seattle, WA. Poster #426

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Pharmacokinetic considerations

	Dolutegravir	Raltegravir	Elvitegravir/c
Number	12	41	3
CSF:plasma ratio	0.5%	2%	0.3%
Proposed IC50 (ng/mL)	0.2	3.6	3.9
Median [CSF] (ng/mL)	18	31	6.3
Comment	All above IC50	All above IC50	1 out of 3 below IC50
References	Clin Infect Dis. 2014 Oct;59(7):1032-7	J Antimicrob Chemother (2014) 69 (1): 241-245	AIDS Research and Human Retroviruses (2016) 32 (5)

CSF, Cerebrospinal fluid

The contribution of abacavir

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Intolerance

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de Boer, Mark G.J

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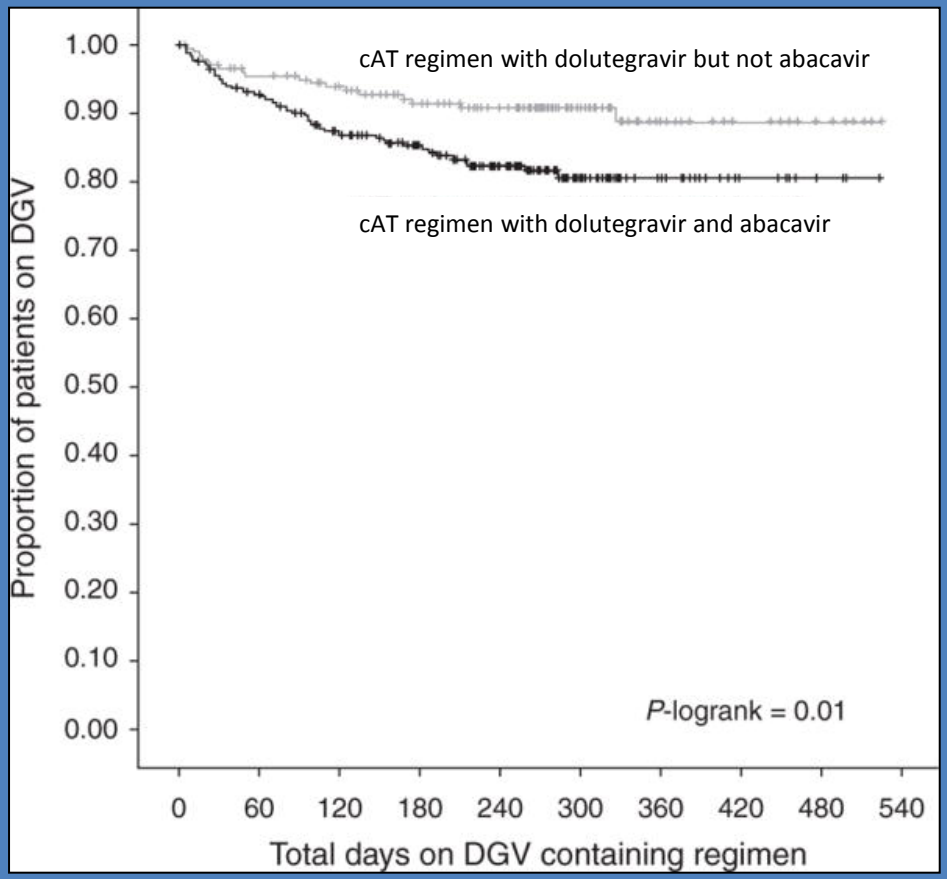

De Boer et al. (2016) AIDS 30(18): 2831-2834

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The contribution of abacavir

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ISSN: 0269-9370
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[Correspondence]

Intolerance of dolutegravir-containing combination antiretroviral therapy: not just a pharmacokinetic drug interaction

Cattaneo, Dario; Rizzardini, Giuliano; Gervasoni, Cristina

Novel regimens – SWORD strategy

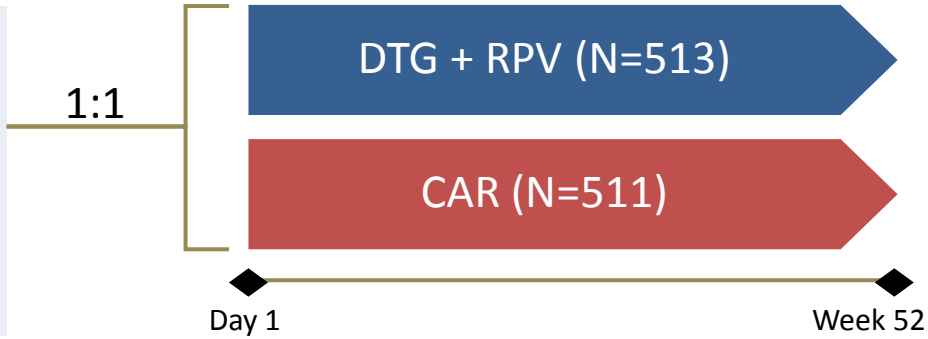
Imperial College London

Screening

VL <50 c/mL on INI, NNRTI or PI + 2 NRTIs

- Inclusion Criteria
  - On stable CAR ≥6 months before screening
  - 1st or 2nd ART with no change in prior regimen due to VF
  - Confirmed HIV-1 RNA <50 c/mL during the 12 months before screening
  - HBV negative

Early Switch Phase



	DTG + RPV (n=513)	CAR (n=511)
Age, mean (SD) ≥50 years	43 (11.1) 29%	43 (10.2) 28%
Female	23%	21%
Race, non-white	18%	22%
CD4+ cell count, cells/mm^3 (median) ≤500; >500	611 32%; 68%	638 29%; 71%
Baseline 3rd-agent class : PI; NNRTI; INI	26%; 54%; 20%	27%; 54%; 19%
Baseline TDF use	73%	70%
Duration of ART prior to Day 1, median, months	51	53

* Data pooled across SWORD-1 and SWORD-2.
DTG, dolutegrevir; RPV, rilpivirine; CAR, combination antiretroviral therapy

Llibre JM, et al. CROI 2017. Seattle, WA. Oral #44LB

Adverse Events with Onset through Week 52

	Early Switch Phase	
	DTG + RPV (n=513) n (%)	CAR (n=511) n (%)
Any AE	395 (77)	364 (71)
AEs occurring in ≥5% of subjects in either group		
Nasopharyngitis	49 (10)	50 (10)
Headache	41 (8)	23 (5)
Upper respiratory tract infection	24 (5)	37 (7)
Diarrhoea	32 (6)	27 (5)
Back pain	15 (3)	31 (6)
Any Serious AEs*	27 (5)	21 (4)
Drug-related AEs		
Grades 1-2	89 (17)	8 (2)
Grades 3-4	8 (2)	1 (<1)
AEs leading to withdrawal from the study	21 (4)	3 (<1)
CNS AEs leading to withdrawal	9 (2)	1 (<1)

- Two deaths in the study, both unrelated to study drug. DTG+RPV Kaposi's Sarcoma (N=1), CAR Lung cancer (N=1)

DTG, Dolutegravir; RPV, Rilpivirine; CAR, Combination Antiretroviral Therapy; AEs, Adverse Events; CNS, Central Nervous System

Llibre JM, et al. CROI 2017. Seattle, WA. Oral #44LB

HIV/IHQ/17-05//1539a Date of Preparation: May 2017

Integrase inhibitors and the brain: Summary

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1	Our cohorts • Are ageing • Have a high prevalence of mental health disorders
2	Historical CNS toxicities • Have taken many years to characterise
3	CNS signals with INI • Are present • Must not be ignored; but should not limit the use of this important class of drugs

HIV/IHQ/17-05//1539a Date of Preparation: May 2017

Thank you

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- St. Mary's Hospital London (Alan Winston, Lucy Garvey, Matthew Scott, Linda McDonald)
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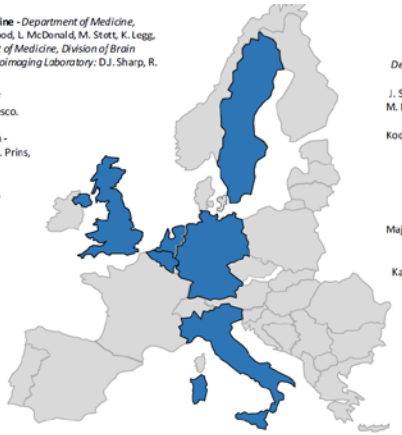
POPPY

Pharmacokinetic and clinical observations in people over 50

ageing hiv cohort study

SEVENTH FRAMEWORK PROGRAMME



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