KEEPING CNS IN MIND:

Neuropsychiatric Considerations in HIV-1 Infection

Instructions for Use

- Specific slides from this presentation can be used to create a customized story that fits the audience needs
- There are three parts to this presentation
  - Epidemiology
  - InSTI
  - NNRTI
- Slides can be combined with other slides within the Doravirine Slide Toolkit to make a full story
  - Slides 11 and 12 should always be presented together
- Ensure content includes the proper fair balance when used (if making changes to order)
- Always present the data as it appears on the slide

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Presentation Overview

- Epidemiology and pathogenesis
- Neuropsychiatric adverse events associated with NNRTIs
- Neuropsychiatric adverse events associated with InSTIs
- Summary

InSTIs, integrase strand transfer inhibitors; NNRTIs, non-nucleoside reverse transcriptase inhibitors.

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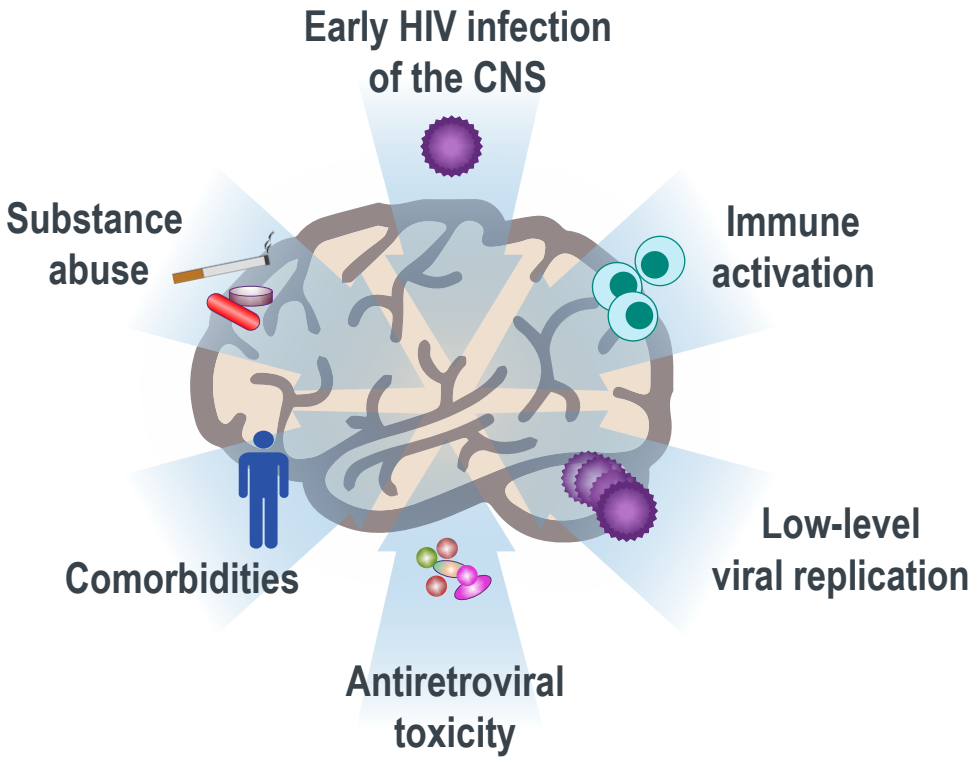
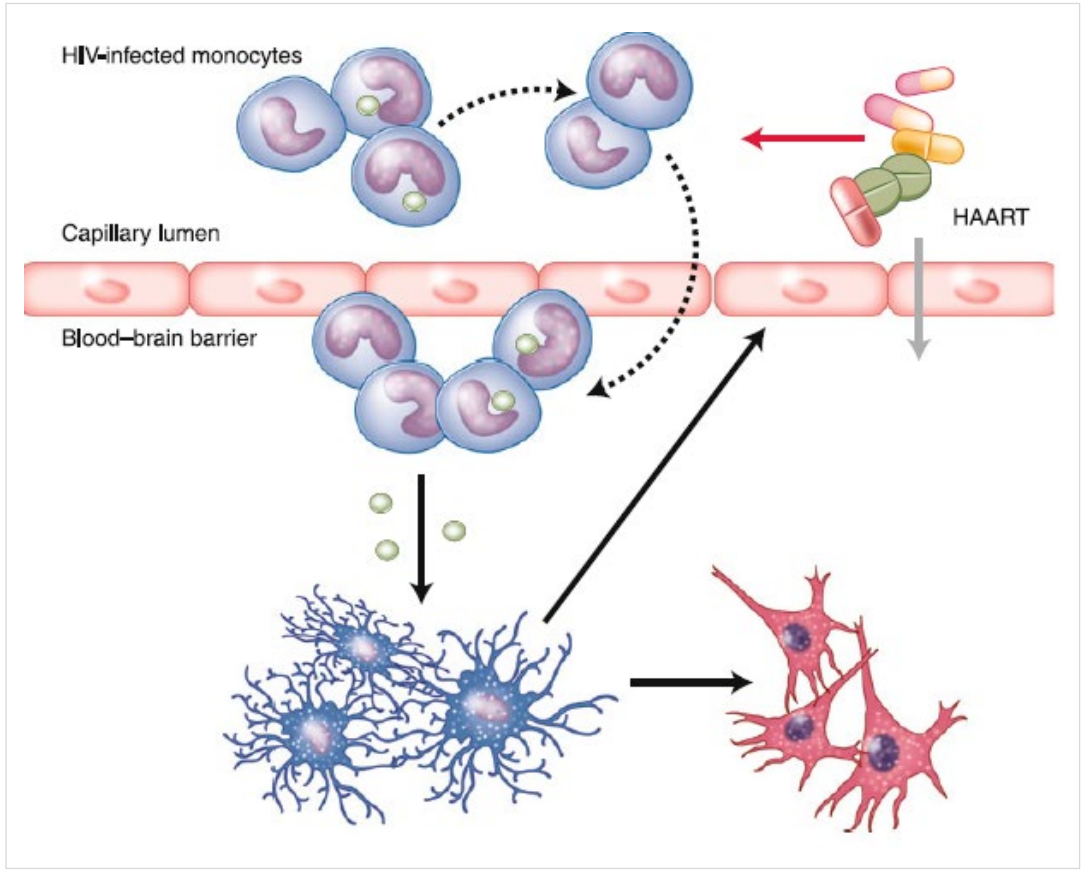
EPIDEMIOLOGY AND PATHOGENESIS

The Relationship Between HIV Infection and Neuropsychiatric Comorbidities is Complex and Has Many Contributing Factors[1,2]

Etiology of Psychiatric Symptoms in PLWH



Pathogenesis of HIV in the CNS



HAART, highly active antiretroviral therapy.

References: **1.** Farhadian S et al. *Curr Infect Dis Rep.* 2017;19(12):50. **2.** Valcour V et al. *Curr HIV/AIDS Rep*. 2011;8(1):54-61.

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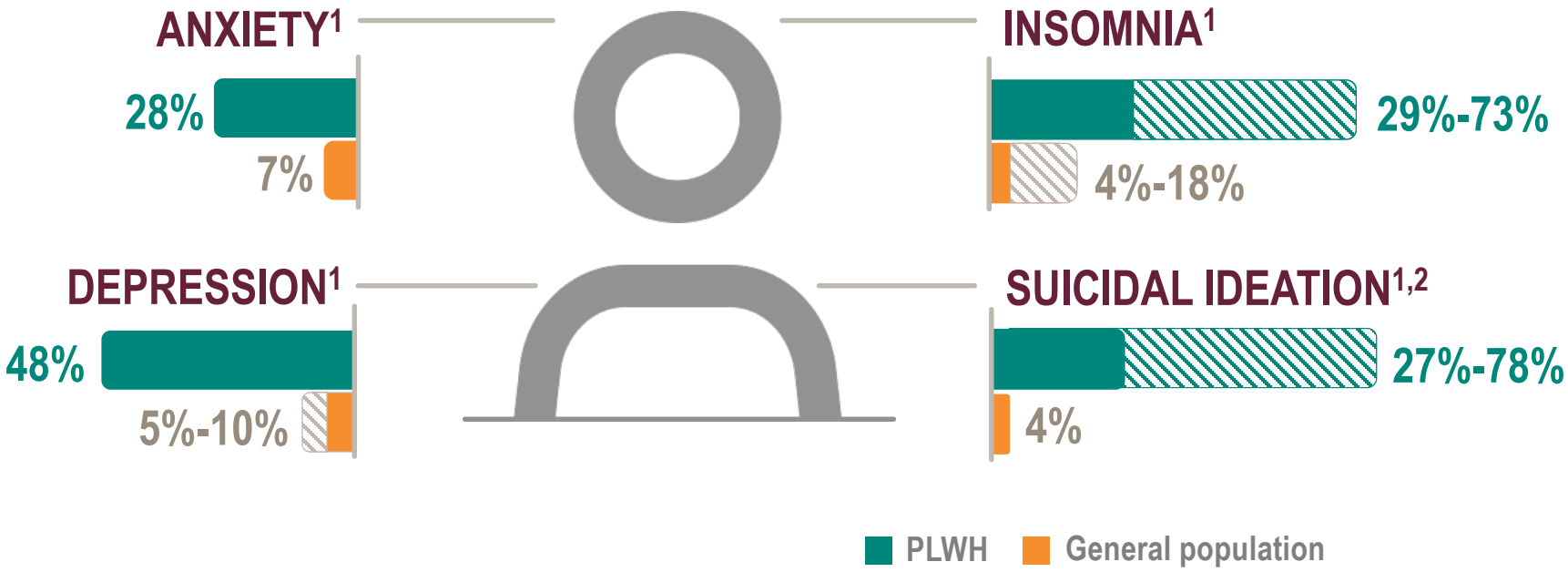
Psychiatric Disorders Are Substantially More Frequent Among PLWH Compared With the General Population[1]



PLWH, persons living with HIV.

References: **1.** Fettiplace A et al. *J Acquir Immune Defic Syndr*. 2017;74(4):423-431. **2.** Piscopo K, Lipari RN. SAMHSA website. https://www.samhsa.gov/data/sites/default/files/NSDUH-DR-FFR3-2015/NSDUH-DR-FFR3-2015.htm. Published September 2016. Accessed April 15, 2019.

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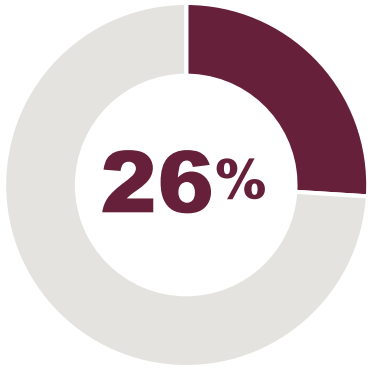
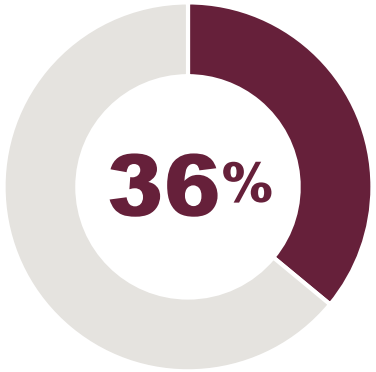
PLWH Experience Substantial Cognitive Deficits

Studies have reported varying rates in the prevalence of baseline cognitive impairment among PLWH



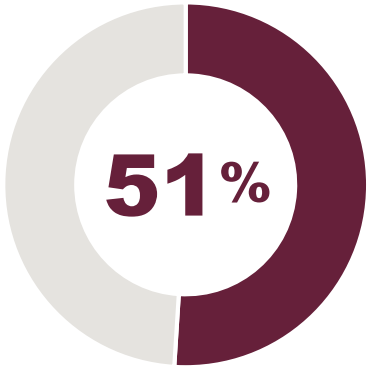
ACTG-ALLRT study[1]

More than 1 out of 4 patients were cognitively impaired at baseline even after starting at least 20 weeks of ART[1]



CHARTER and HNRC studies[2]

36% of patients who were reported to be asymptomatic were cognitively impaired at baseline while on ART[2]



PIVOT study[3]

51% of patients on stable ART were cognitively impaired at baseline while on ART[3]

ACTG, AIDS Clinical Trials Group; ALLRT, ACTG Longitudinal Linked Randomized Trials; ART, antiretroviral therapy; CHARTER , The CNS HIV Antiretroviral Therapy Effects Research; HNRC, HIV Neurobehavioral Research Center; PIVOT, Protease Inhibitor monotherapy Versus Ongoing Triple-therapy.

References: **1.** Robertson KR et al. *AIDS.* 2007;21(14):1915-21. **2.** Heaton RK et al. *J Neurovirol*. 2011;17(1):3-16.
3. Winston A et al. *PLoS One*. Published online April 30, 2013. doi:10.1371/journal.pone.0061949.

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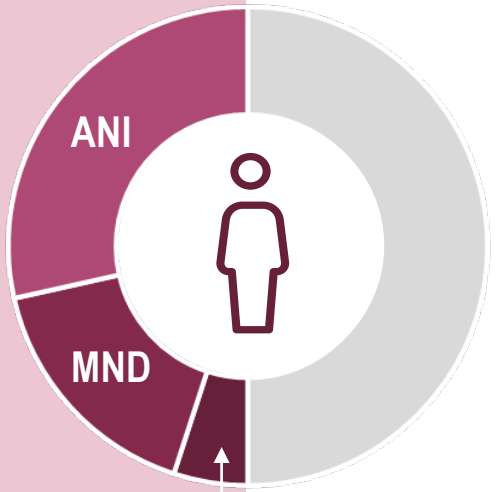
Despite Advances With cART, the Prevalence of All Neurocognitive Disorders in HIV Remains Unchanged

Pre-cART era[1,2]

Greater impairments in motor skills, cognitive speed, and verbal fluency[2]

Post-cART era[1,2]

Impairments associated with memory (learning) and executive function[2]



Potential factors contributing to the unchanged prevalence of neurocognitive decline in cART era include[3]:

- Irreversible brain injury prior to cART initiation
- Poor CNS penetration of cART, leading to incomplete viral suppression
- Presence of drug-resistant viral strains in CNS
- Increased beta-amyloid deposition in the brain
- Possible neurotoxicity of cART drugs

ANI, asymptomatic neurocognitive impairment; cART, combination antiretroviral treatment; HAD, HIV-associated dementia; MND, mild neurocognitive disorder.

References: **1.** Saylor D et al. *Nat Rev Neurol*. 2016;12(4):234-248. **2.** Clifford DB, Ances BM. *Lancet Infect Dis*. 2013;13(11):976-986. **3.** Heaton RK et al. *J Neurovirol*. 2011;17(1):3-16.

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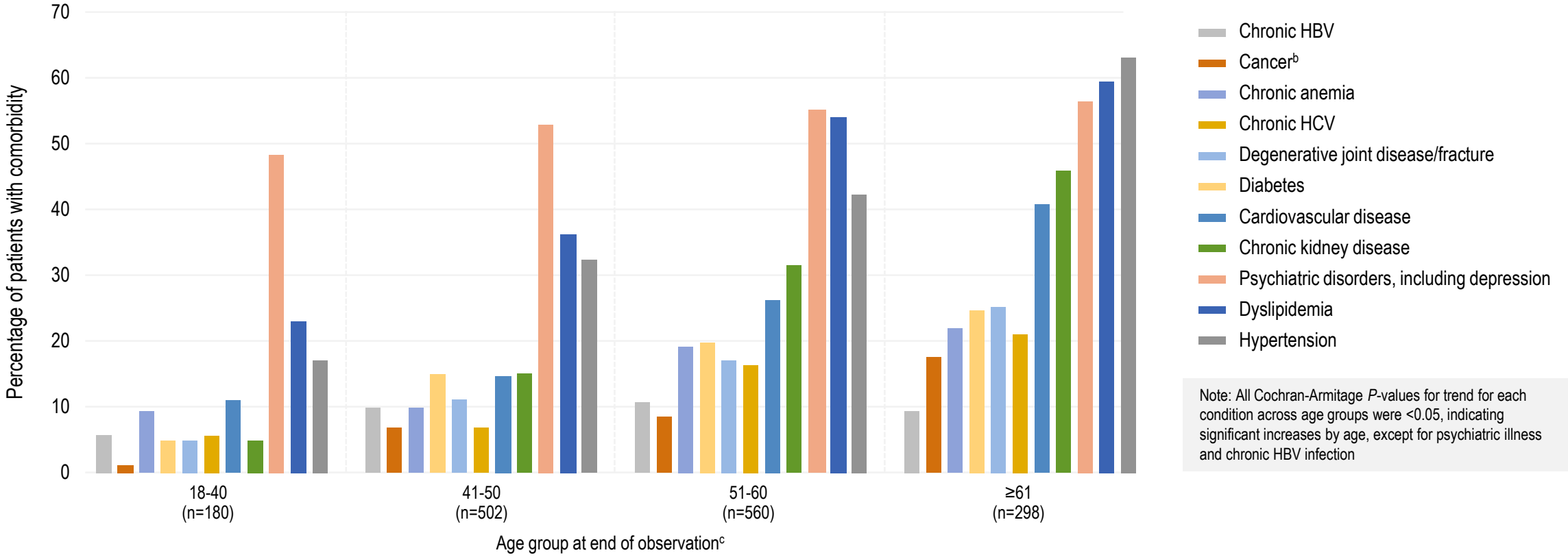
Psychiatric Disorders Continue to be One of the Highest Non-AIDS Comorbidities in PLWH, and Continue to Increase With Age[1]

Percentage of HOPS Cohort[a] Patients with Non-AIDS Comorbidities (N=1,540)



Note: All Cochran-Armitage *P*-values for trend for each condition across age groups were <0.05, indicating significant increases by age, except for psychiatric illness and chronic HBV infection

[a]HOPS cohort: patients at 8 US HIV clinics seen from 1/1/1997 to 6/3/2015, who were followed for at least 5 years with ≥75% of observation time on ART and had ≥75% of time on ART with HIV RNA levels <200 copies/mL.
[b]Excluding skin cancers but including malignant melanoma.
[c]Earliest of death, last HIV healthcare provider contact, or 6-30-2015.

Reference: 1. Palella FJ et al. Poster presented at: the 24th Conference on Retroviruses and Opportunistic Infections; February 13-16, 2017; Seattle, WA.

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NEUROPSYCHIATRIC ADVERSE EVENTS ASSOCIATED WITH NNRTIs

Historically, EFV Has Been Associated With Higher Rates Of NPAEs Than Its Comparators, As Evidenced In Clinical Trials[1]

	DMP006 (1999)		BMS 034 (2004)		ECHO and THRIVE (2011)[a]	
Duration (weeks)	48		48		96	
	EFV (n=154)	IDV (n=148)	EFV (n=405)	ATV (n=405)	EFV (n=255)	RPV (n=288)
Neurological AEs[b]	58[c]	26			38.4[c]	19.1
Dizziness	9	8	6[c]	2	27.8[c]	10.4
Somnolence					6.3	2.9
Attention disturbances	9	8			2.4	0.7
Headache			6 (6)			
Psychiatric AEs[b]					24.7[c]	16.3
Abnormal dreams					13.7[c]	7.6
Insomnia						
Sleep disorders					3.9	1.4
Nightmares						
Depressive disorders					2.7	4.5
Anxiety					3.1	1
Discontinuation due to AEs[b]	27[c]	43	8	6	4.3	2.8

[a]Viral load <100,000 copies/mL; [b]Percentage of patients on EFV (percentage of patients on comparator drug); [c]Significant *P* value.
AE, adverse event; ATV, atazanavir; EFV, efavirenz; IDV, indinavir; RPV, rilpivirine.
Reference: **1.** Apostolova N et al. *J Antimicrob Chemother*. 2015;70(10):2693-2708.

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Historically, EFV Has Been Associated With Higher Rates Of NPAEs Than Its Comparators, As Evidenced In Clinical Trials[1] (cont'd)

	STaR (2012)		GS-US-236-0102 (2013)		STARTMRK (2009-2013)		SINGLE (2013)	
Duration (weeks)	48		96		240		96 (48)	
	EFV (n=392)	RPV (n=394)	EFV (n=352)	ELV/c (n=348)	EFV (n=282)	RAL (n=281)	EFV (n=419)	DTG (n=414)
Neurological AEs[a]	51[b]	30			49.6	18.5	47	22
Dizziness	26	8	26	7	35.1	7.8	5	<1
Somnolence	7	3			7.4	1.1		
Attention disturbances								
Headache	14	12	11	16	14.2	9.3	3	3
Psychiatric AEs[a]	38[b]	16			30.9	18.5	38	29
Abnormal dreams	25	6	28	15	13.1	6.8	17	7
Insomnia			16	11	8.2	7.5	4	4
Sleep disorders								
Nightmares					5.3	2.8		
Depressive disorders	9	7	14	12			3	2
Anxiety	9	5					3	2
Discontinuation due to AEs[a]	8.7[b]	2.5	7	5	10[b]	5	10[b,c]	2

[a]Percentage of patients on EFV (percentage of patients on comparator drug); [b]Significant *P* value; [c]Data at 48 weeks.
DTG, dolutegravir; ELV/c, elvitegravir/cobicistat; RAL, raltegravir.

Reference: **1.** Apostolova N et al. *J Antimicrob Chemother*. 2015;70(10):2693-2708.

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ETR Showed Less Frequent and Severe NPAEs Compared With EFV[1]

The SENSE trial compared NPAEs in treatment-naïve patients during 12 weeks with patients randomized to receive ETR or EFV

Grade 1-4 treatment-emergent NPAEs		
	All events (*P*<0.001)	Drug-related events[a] (*P*<0.001)
ETR arm (n=79)	27.8%	16.5%
EFV arm (n=78)	55.1%	46.2%

[a]Primary end point.
ETR, etravirine.
Reference: **1.** Nelson M et al. *AIDS*. 2011;25(3):335-340.

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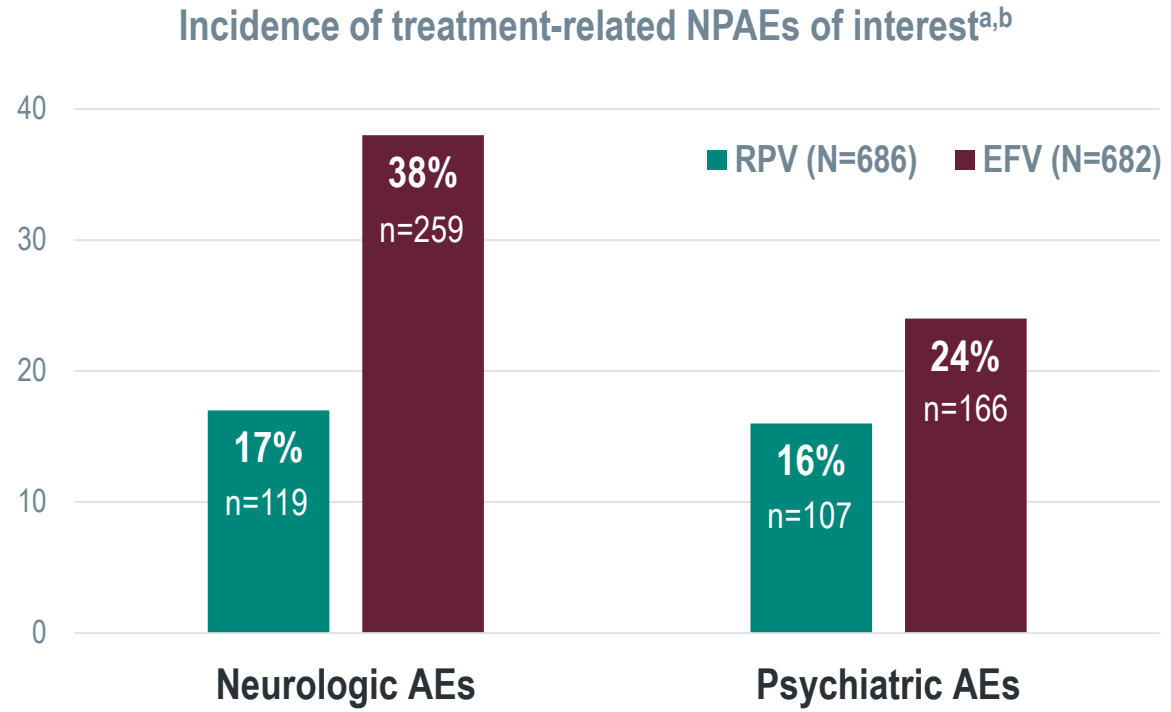
RPV Demonstrated Lower CNS AEs vs EFV[1]

In a 96-week study of treatment-naïve patients, RPV patients had fewer overall treatment-related neurologic and psychiatric AEs than EFV patients



There was a significantly lower incidence of both dizziness and abnormal dreams/nightmares in the RPV group than in the EFV group

- Dizziness: 8% in RPV group vs 27% in EFV group (*P*<0.0001)
- Abnormal dreams/nightmares: 8% in RPV group vs 13% in the EFV group (*P*=0.004)

[a]Reported in ≥2% of patients in either group; [b]Judged by the investigator to be at least possibly related to treatment (RPV or EFV).

Reference: 1. Sension M et al. Poster presented at the 49th Annual Meeting of the Infectious Diseases Society of America and the HIV Medicine Association. Boston, MA. October 20–23, 2011.

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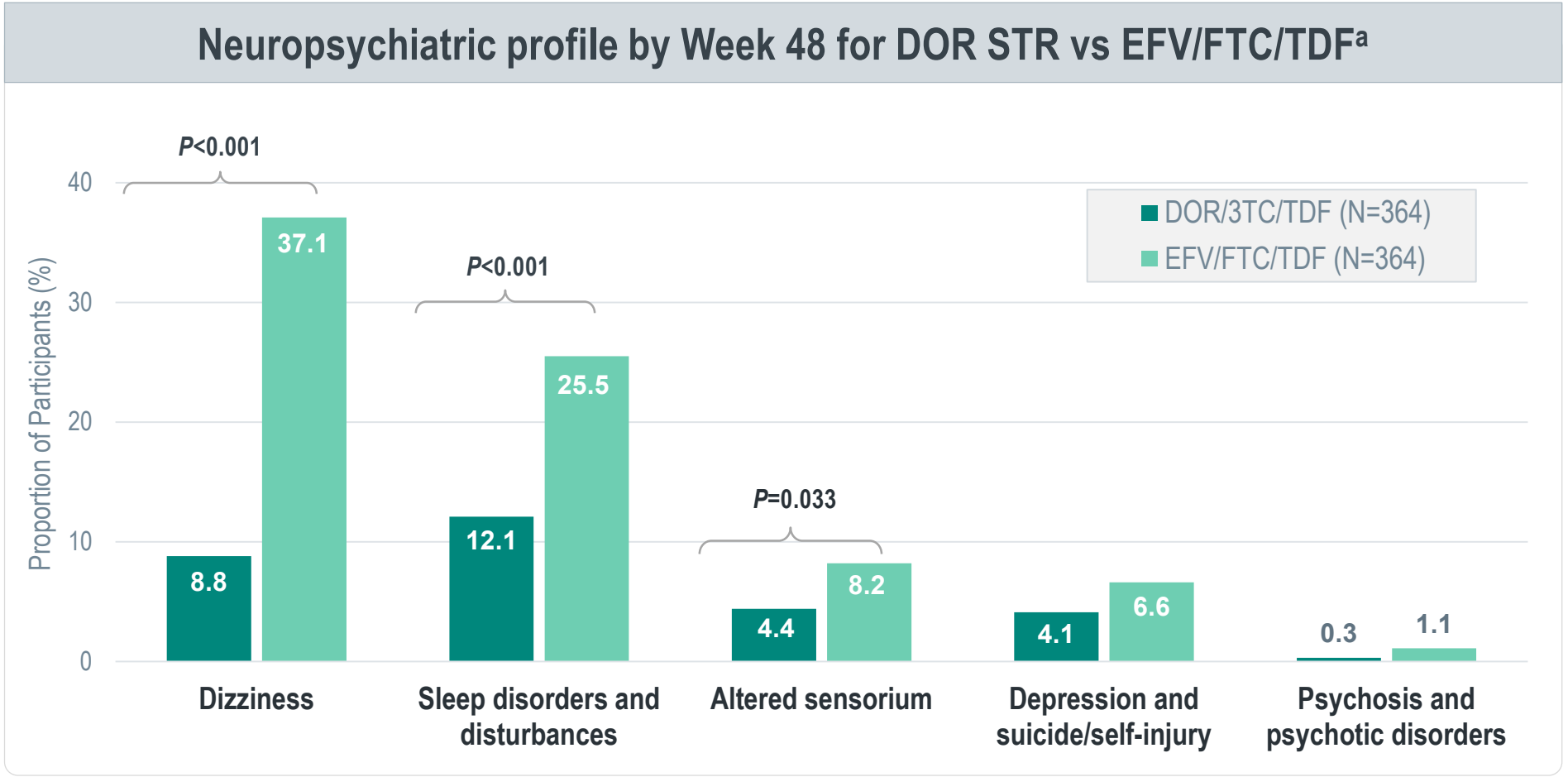
DOR Showed Favorable CNS AE Profile vs EFV in Phase 3 Studies[1]



DOR, doravirine; EFV/FTC/TDF, efavirenz/emtricitabine/tenofovir disoproxil fumarate; STR, single tablet regimen.
[a]Statistical testing was not prespecified for the secondary categories (depression and suicide/self-injury; psychosis and psychotic disorders).
Reference: **1.** Orkin C et al. *Clin Infect Dis*. 2019;68(4):535-544.

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Guideline Recommendations For NNRTI Use in the Presence of Neuropsychiatric Illness or Adverse Effects Associated With ART[1]

Considerations for initial therapy and common and/or severe AEs associated with ART

Psychiatric illness	HIV-associated neurocognitive disorders
Consider avoiding EFV- and RPV-based regimens	Avoid EFV-based regimens if possible
Psychiatric symptoms, including suicidality, can be exacerbated with EFV and RPV use	Assessment of ART's beneficial effects on improvement of HAD-related symptoms may be confounded by EFV-related neuropsychiatric effects

Neuropsychiatric events: EFV > RPV, DOR > ETR. Consider switching from EFV, RPV to ETR, PI/c, or PI/r

EFV: Somnolence, insomnia, abnormal dreams, dizziness, impaired concentration, depression, psychosis, and suicidal ideation
RPV: Depression, suicidality, and sleep disturbances
DOR: Sleep disorders and disturbances, dizziness, altered sensorium, depression, and suicidality/self-harm

PI/c, protease inhibitor/cobicistat; PI/r, protease inhibitor/ritonavir.

Reference: 1. Guidelines for the use of antiretroviral agents in adults and adolescents living with HIV. AIDSinfo website. https://aidsinfo.nih.gov/contentfiles/lvguidelines/adultandadolescentgl.pdf. Updated July 10, 2019. Accessed August 23, 2019.

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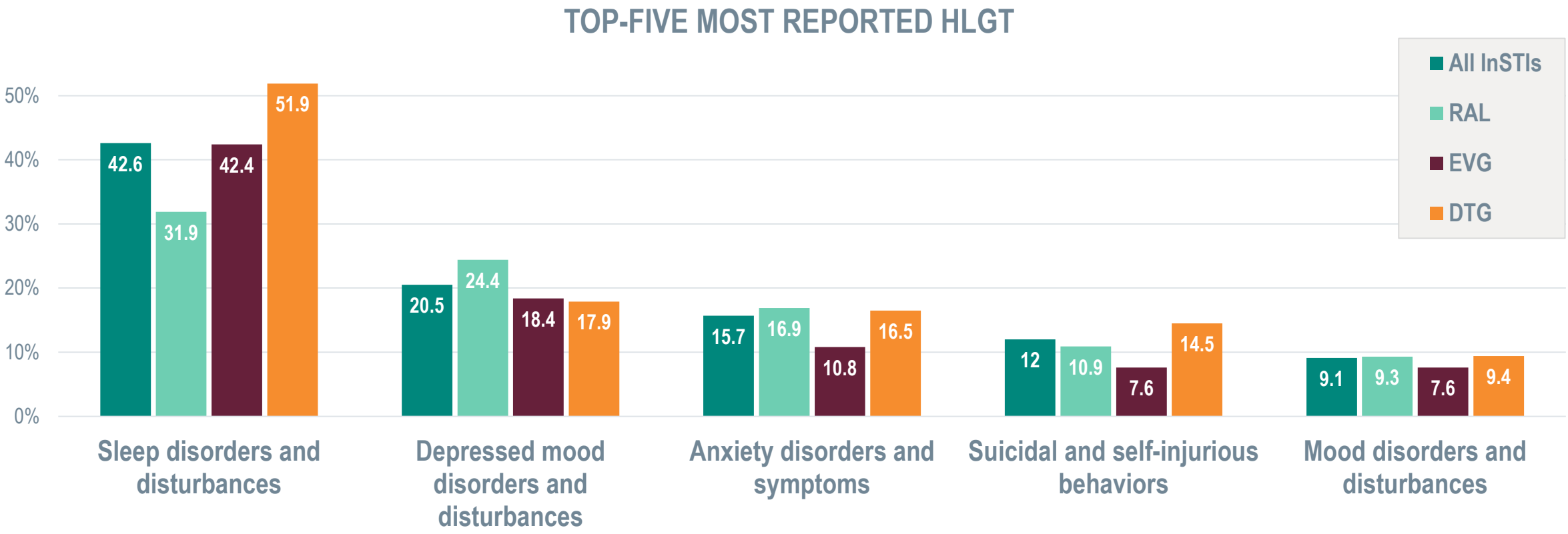
NEUROPSYCHIATRIC ADVERSE EVENTS ASSOCIATED WITH InSTIs

Multiple Classes Of Neuropsychiatric Adverse Events Are Associated With the InSTI class[1]

Top psychiatric disorders involving InSTIs reported in the WHO international pharmacovigilance database include disorders related to sleep, mood, anxiety, and suicidal behavior



EVG, elvitegravir; HLGT, high level group term; WHO, World Health Organization.

Reference: 1. Kheloufi F et al. *AIDS*. 2017;31(12):1775-1777.

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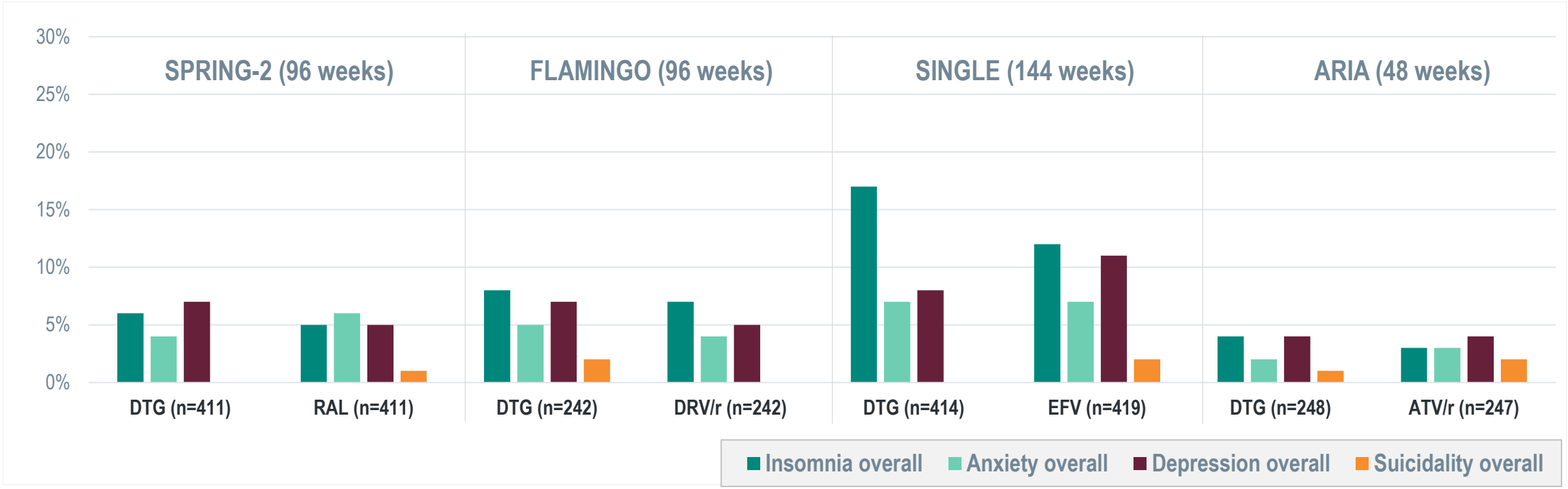
DTG Demonstrated Low Rates Of Neuropsychiatric AEs Across Phase 3 Treatment-Naïve Clinical Trials[1]



- Higher incidence of NPAEs was observed in the SINGLE study, but rates of drug-related anxiety, depression, and suicidality were lower than patients taking the comparator (EFV)

ATV/r, atazanavir/ritonavir; DRV/r, ritonavir-boosted darunavir.

Reference: 1. Yombi JC. *AIDS Rev*. 2018;20(1):14-26.

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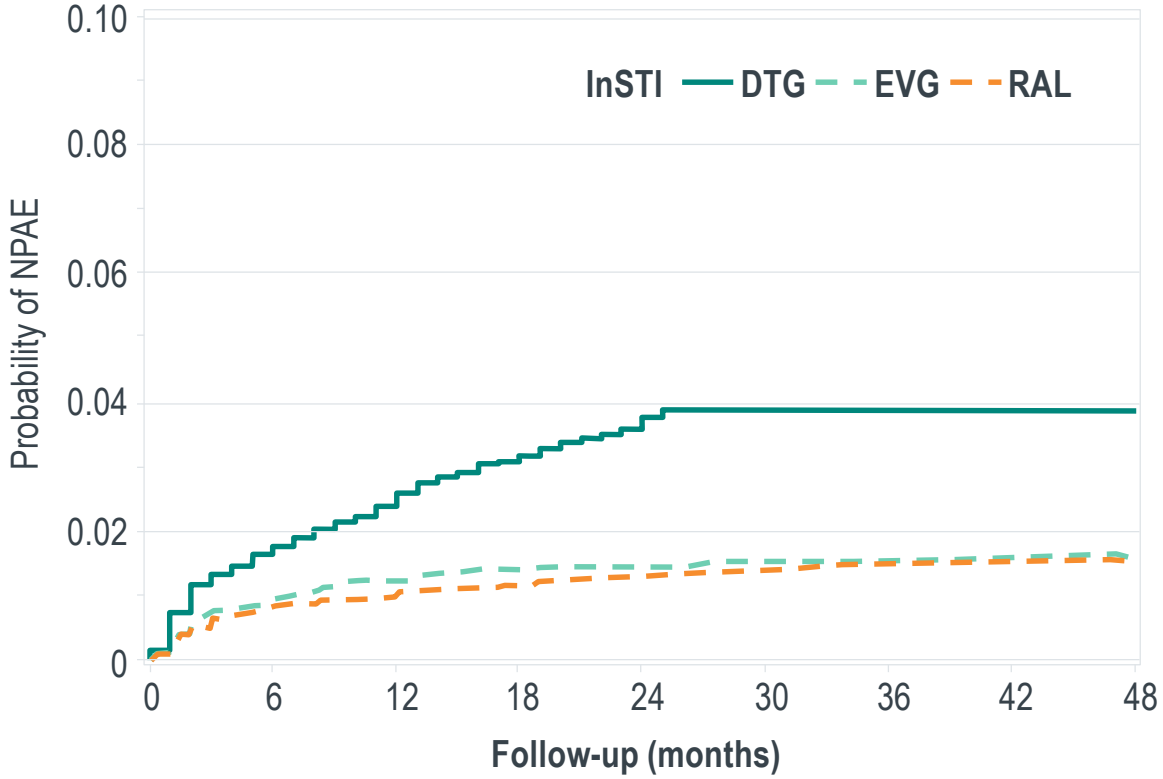
However, DTG Demonstrated Significant Neuropsychiatric AEs in Real-World Studies

Time to discontinuation owing to NPAEs for each InSTI during follow-up (based on French cohort study)[1]



- In a French cohort study analyzing InSTI discontinuation among 21,315 patients, neuropsychiatric side effects were significantly more frequent with DTG (*P*<0.001)[1]
- In a German cohort study, neuropsychiatric AEs were most common with DTG and resulted in greater discontinuations compared to EVG or RAL[2]
  - The neuropsychiatric AEs leading to discontinuation between January 2007 and April 2016 were 5.0% (49/985) for DTG, 1.0% (3/287) for EVG, and 2.1% (14/678) for RAL[2]

References: 1. Cuzin L et al. *J Antimicrob Chemother*. 2019;74(3):754-760. **2.** Hoffman C et al. *HIV Med*. 2017;18(1):56-63.

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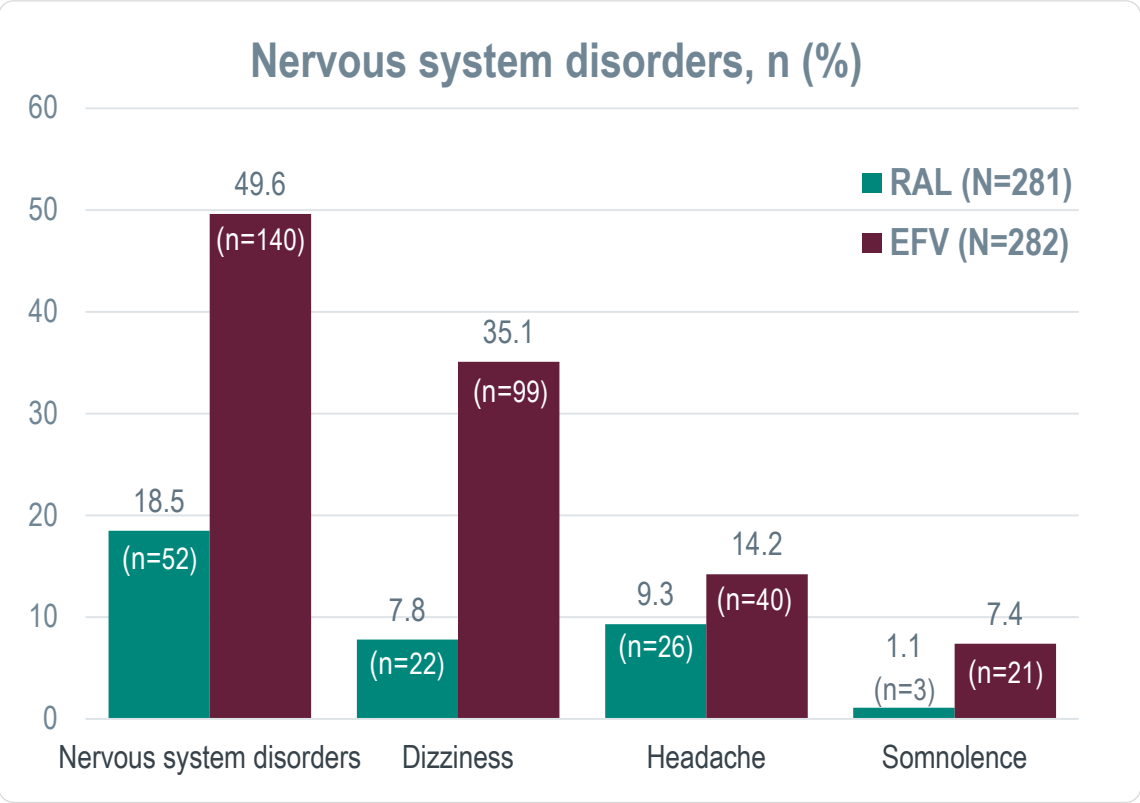
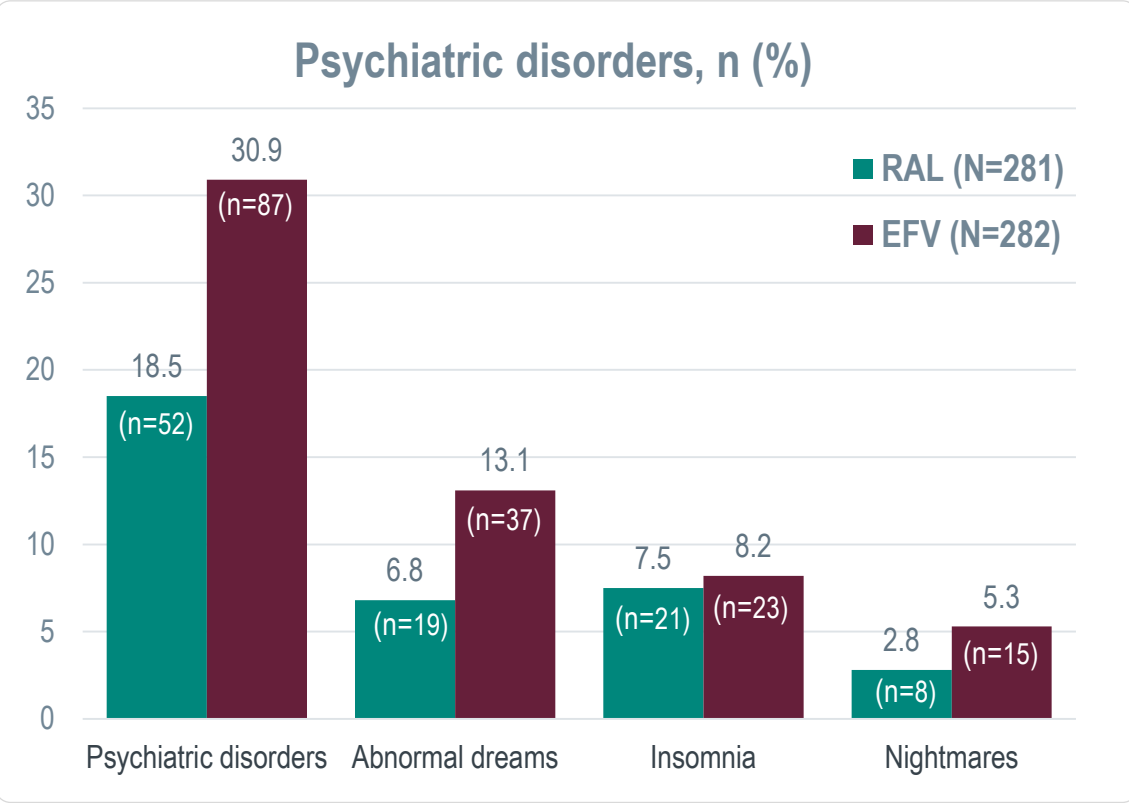
RAL Has Demonstrated Less Neuropsychiatric AEs vs EFV[1]

- In STARTMRK trial, significantly fewer RAL patients than EFV patients experienced neuropsychiatric side effects (39.1% vs 64.2%, *P*<0.001)

Percentage of patients with specific drug-related clinical adverse experiences reported in ≥5% of either treatment group





Reference: 1. Rockstroh JK et al. *J Acquir Immune Defic Syndr*. 2013;63(1):77-85.

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SUMMARY

Neuropsychiatric AEs Are Pervasive in the PLWH Population Across Multiple Treatment Classes

- High prevalence of neuropsychiatric complications in HIV setting leads to reduced cognition and nonadherence
- NNRTI and InSTI classes demonstrate neuropsychiatric AEs in clinical trials and real-world studies
- EFV stands out in the NNRTI class with its higher prevalence of treatment-associated CNS toxicities
- The InSTI class has variable neuropsychiatric symptom presentation with results also presenting differently in real-world settings