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**Co-morbidities and Adverse
Drug Reactions in HIV**



POPPY

Pharmacokinetic and
clinical observations in
people over 50

RESTLESS LEGS SYNDROME AND HEALTH-RELATED QUALITY OF LIFE IN HIV: RESULTS FROM THE POPPY SLEEP SUBSTUDY

Ken M. Kunisaki, D. De Francesco, C.A. Sabin, A. Winston, P.W.G. Mallon, J. Vera, F. Post, Ian Williams, Emmanouil Bagkeris, Nicki Doyle, W. Khalil, S. Redline for the Pharmacokinetics and Clinical Observations in People Over Fifty (POPPY) Study

Restless Legs Syndrome (RLS)



"If it only happens when you rub your tummy, it's not Restless Leg Syndrome."

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'I'M AFRAID THIS GOES BEYOND RESTLESS LEG SYNDROME. THIS LEG HAS AMBITION.'

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RLS—Background

- RLS (aka Willis-Ekbom Disease)
- Sensory symptoms of the legs, when resting quietly/trying to fall asleep in the evening, relieved by movement
- Interferes with sleep onset
- Commonly occurs in patients with:
 - Iron deficiency
 - Advanced chronic kidney disease
 - Diabetes
 - Idiopathic
- Felt to represent a neurological disorder
 - Familial clustering (Genes: MEIS1, PTPRD, CRBN)



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RLS—Pathophysiology

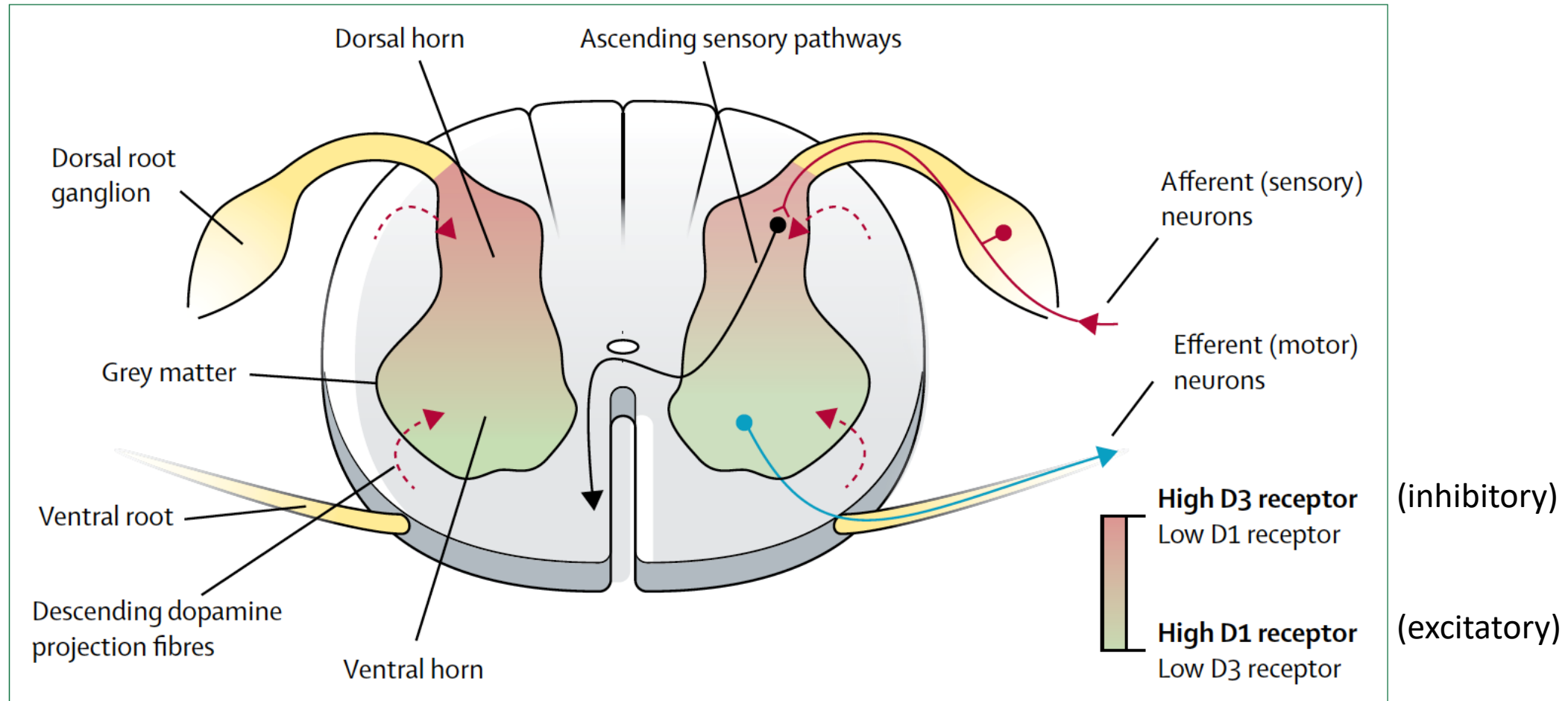


Figure 1: Proposed modulation of dopamine D1 receptors and D3 receptors in the spinal cord

Trenkwalder C. *Lancet Neurol* 2018;17:994-1005

Hypotheses

- Persons with HIV (PWH) will be more likely to report RLS symptoms than those without HIV
- PWH with RLS symptoms will report worse quality of life (QoL) than those without RLS.



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Methods

- POPPY cohort (ClinicalTrials.gov: NCT 01737047)
 - 6 sites in London/UK, 1 site in Brighton/UK, 1 site in Dublin/IRL
 - n=1377
 - HIV+ (≥ 50 y/o) / HIV+ (<50 y/o) / HIV- (≥ 50 y/o)
- Sleep **Substudy** Questionnaires
 - NIH RLS Questionnaire
 - Health-related QoL surveys: SF-36 Physical/Mental Health, PROMIS Sleep Disturbance and Sleep-Related Impairment



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NIH RLS Questionnaire

- Do you have unpleasant sensations in your legs (such as unpleasant crawling or creeping sensations in the feet, calves or thighs) combined with an urge or need to move your legs?
- Do they occur mainly or only at rest and do they improve with movement?
- Are they worse in the evening or night than in the morning?
- How often do they occur? (<1/yr, <1/mo, 2-4/mo, 2-3/wk, 4-5/wk, 6-7/wk)



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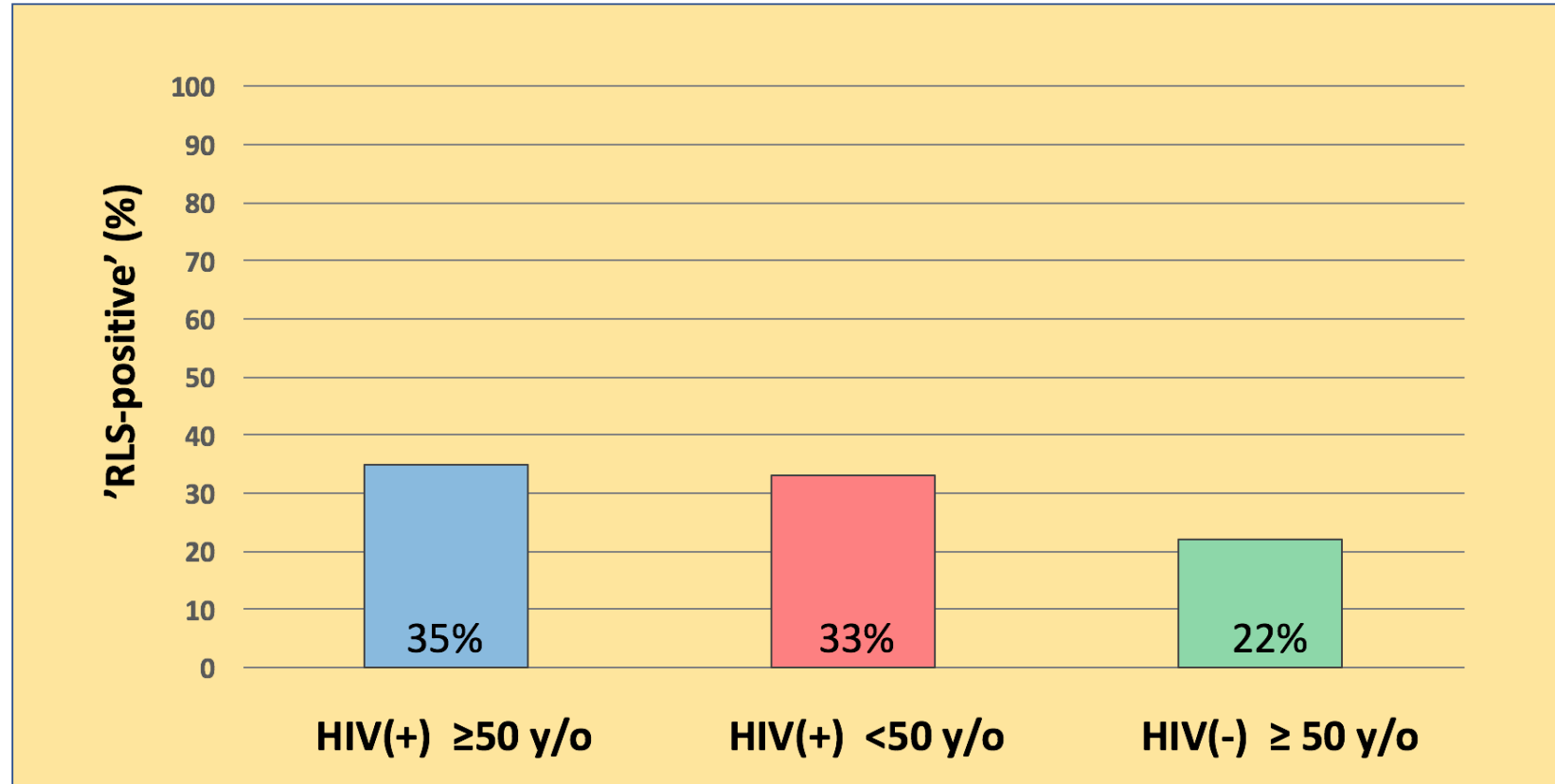
Statistical Methods

- *Hypothesis 1*: Persons with HIV (PWH) will be more likely to report RLS symptoms than those without HIV
 - **Logistic regression, adjusting for age, sex and ethnicity**
- *Hypothesis 2*: PWH with RLS symptoms will report worse quality of life (QoL) than those without RLS.
 - **Wilcoxon tests comparing QoL in those with and without RLS, separately in PWH and controls**

Results

Characteristics	HIV+, ≥50 y/o n=220	HIV+, <50 y/o n=99	HIV-, >50 y/o n=116
Age, years	60 (56, 65)	45 (40, 50)	60 (57, 66)
Female	12%	18%	33%
White ethnicity	91%	82%	90%
MSM	82%	72%	52%
Current EtOH	79%	86%	91%
Current Smoker	26%	29%	15%
Recreational drugs	25%	31%	15%
Current CD4, cells/mm ³	597 (470, 780)	620 (470, 785)	-
Nadir CD4, cells/mm ³	177 (80, 270)	264 (126, 416)	-
HIV-RNA <40 copies/mL	92%	90%	-

RLS symptom (main item) is common and more frequent in HIV



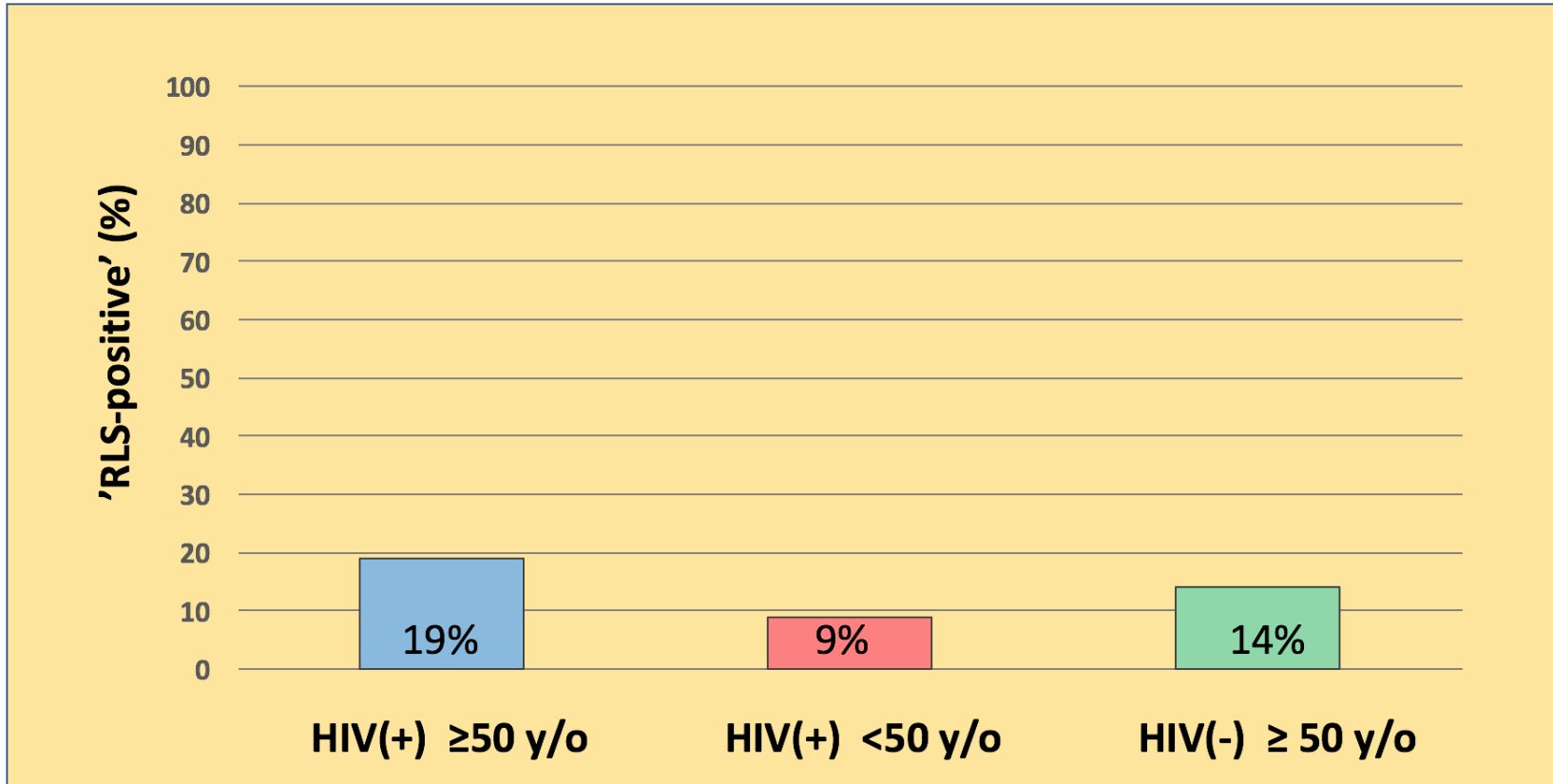
After adjusting for age, sex, and race, PWH were more likely to report main RLS symptoms [aOR 2.4 (1.4 to 4.1), p=0.002]

RLS main symptom is associated with worse HR-QoL in PWH

	PWH			HIV-negative		
Questionnaire	RLS (n=110)	No RLS (n=209)	p-value	RLS (n=25)	No RLS (n=91)	p-value
PROMIS Sleep Related Impairment	55 (50-60)	49 (44-55)	<0.001	46 (44-50)	46 (39-50)	0.27
PROMIS Sleep Disturbance	54 (49-61)	49 (44-55)	<0.001	50 (46-55)	47 (43-51)	0.06
SF-36 physical health	45 (33-54)	53 (46-57)	<0.001	55 (51-57)	56 (53-58)	0.57
SF-36 mental health	44 (35-54)	54 (44-58)	<0.001	53 (47-59)	55 (50-58)	0.54

Values reported as median (interquartile range)

RLS full symptoms (all 3 of 3 items) similar in frequency amongst PWH and controls



After adjusting for age, sex, and race, PWH were not more likely to report all RLS symptoms
aOR 1.5 (0.8 to 2.9), $p=0.21$ (1-item: [aOR 2.4 (1.4 to 4.1), $p=0.002$])

RLS full symptoms presence is associated with worse HR-QoL in PWH

Questionnaire	PWH			HIV-negative		
	RLS (n=51)	No RLS (n=268)	p-value	RLS (n=16)	No RLS (n=100)	p-value
PROMIS Sleep Related Impairment	53 (47-62)	50 (44-57)	0.004	46 (41-49)	46 (40-50)	0.99
PROMIS Sleep Disturbance	55 (50-62)	51 (46-57)	0.002	50 (45-54)	47 (43-52)	0.22
SF-36 physical health	48 (38-55)	52 (43-56)	0.011	56 (53-58)	55 (52-58)	0.46
SF-36 mental health	44 (38-55)	51 (42-58)	0.05	54 (47-60)	55 (50-58)	0.77

Values reported as median (interquartile range)

Conclusions

- **RLS symptoms are commonly reported in PWH**
- **RLS symptoms are associated with health-related QoL impairments in PWH**
- **Next steps are to determine risk factors (e.g. iron deficiency, CNS inflammation) and effects of RLS treatment (e.g. iron replacement, gabapentin [alpha-2-delta voltage-dependent Ca⁺⁺ channel inhibitors], dopaminergic drugs [second line]).**



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Note: The views expressed are those of the authors, and not necessarily those of the US Government, NIH, VA, UK NHS, NIHR, Department of Health, or the authors' institutions