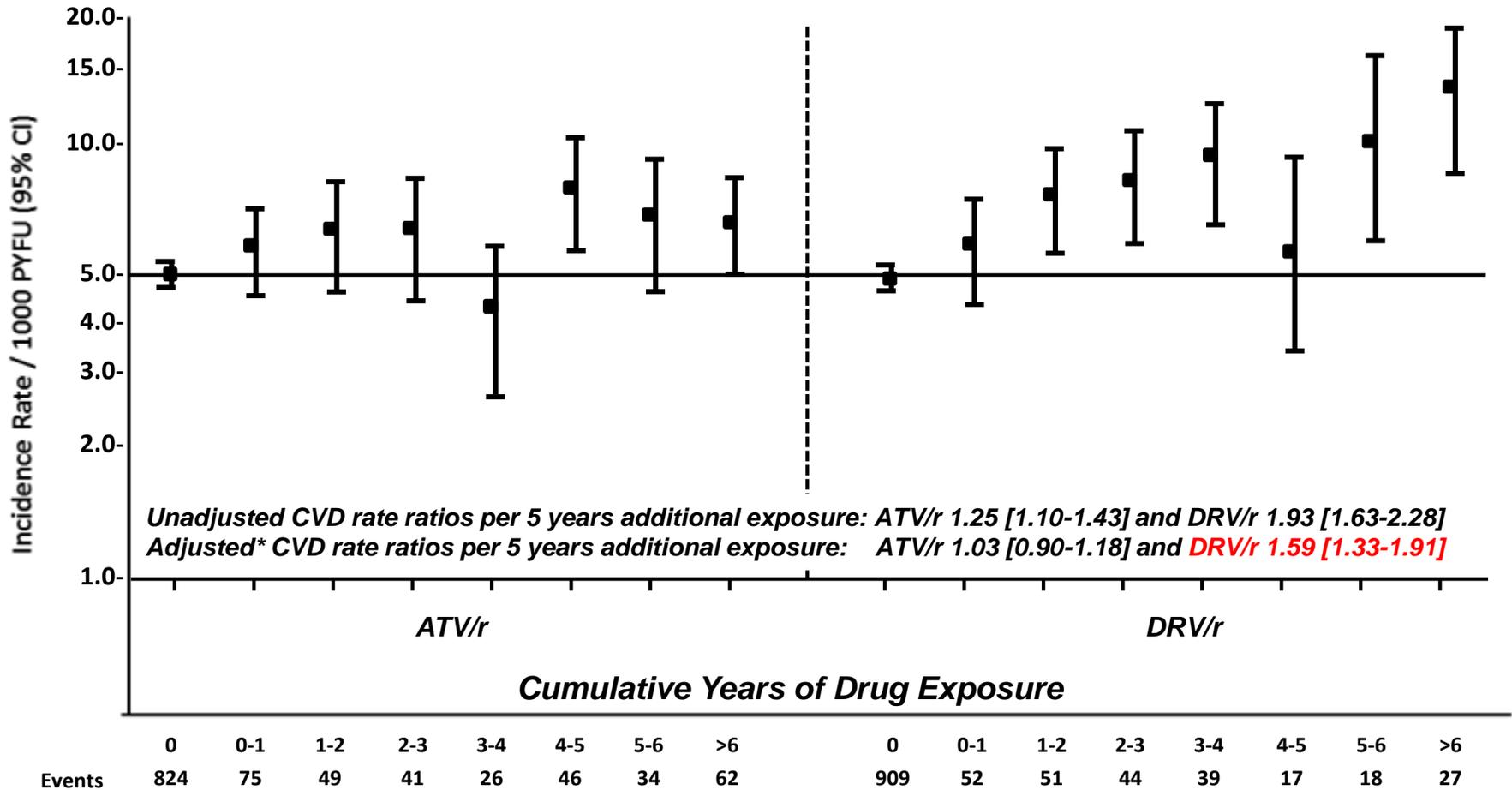


D:A:D: Cumulative Exposure to DRV/r Increase MI Risk



Adjusted for gender, race, HIV exposure group, enrolment cohort, baseline date, prior CVD, nadir CD4 count, current CD4 count, dyslipidaemia**, BMI**, diabetes**, eGFR**, age (all as fixed variates at baseline), HBV, HCV, smoking, family history of CVD, VL., hypertension, AIDS, cumulative exposure to darunavir/r, atazanavir/r, lopinavir/r & indinavir & recent exposure to abacavir (≤6 months) (all as time-updated variables).*

***Factors considered to potentially lie on the causal pathway between PI/r exposure and CVD and values hence fixed at baseline.*

Is this Important?

- Further analyses found **significant associations** between **cumulative darunavir use** and **myocardial infarction** alone (IRR 1.51 per 5 years, 95% CI 1.13 to 2.02) or **stroke** alone (IRR 1.49 per 5 years, 95% CI 1.08 to 2.07).

CVD outcomes with ATV vs non-ATV ART in Veterans Health Administration

- Historical cohort study of patients initiating first-line ART in VHA with PI, INSTI, or NNRTI and who showed pattern of regular care
- Final cohort of incident-treated pts: N = 10,404
 - ATV ART: n = 1532
 - Non-ATV ART: n = 8827
- MI and stroke events assessed by ICD-9 and ICD-10 codes

- **ATV-containing ART associated with decreased MI risk vs non-ATV-containing ART**

CVD Event	Adjusted HR for CVD Events With ATV vs Non-ATV ART (95% CI)
MI	0.65 (0.46-0.91)*
Stroke	1.01 (0.84-1.22)
Ischemic stroke	1.04 (0.86-1.26)
All-cause death	0.93 (0.77-1.14)
MI or stroke	0.93 (0.79-1.09)
MI, stroke, or death	0.98 (0.86-1.11)

* $P = .016$.

Why Not Atazanavir? -VA Cohort Study

Raised Bilirubin is Associated w/Less AMIs & Heart Failure

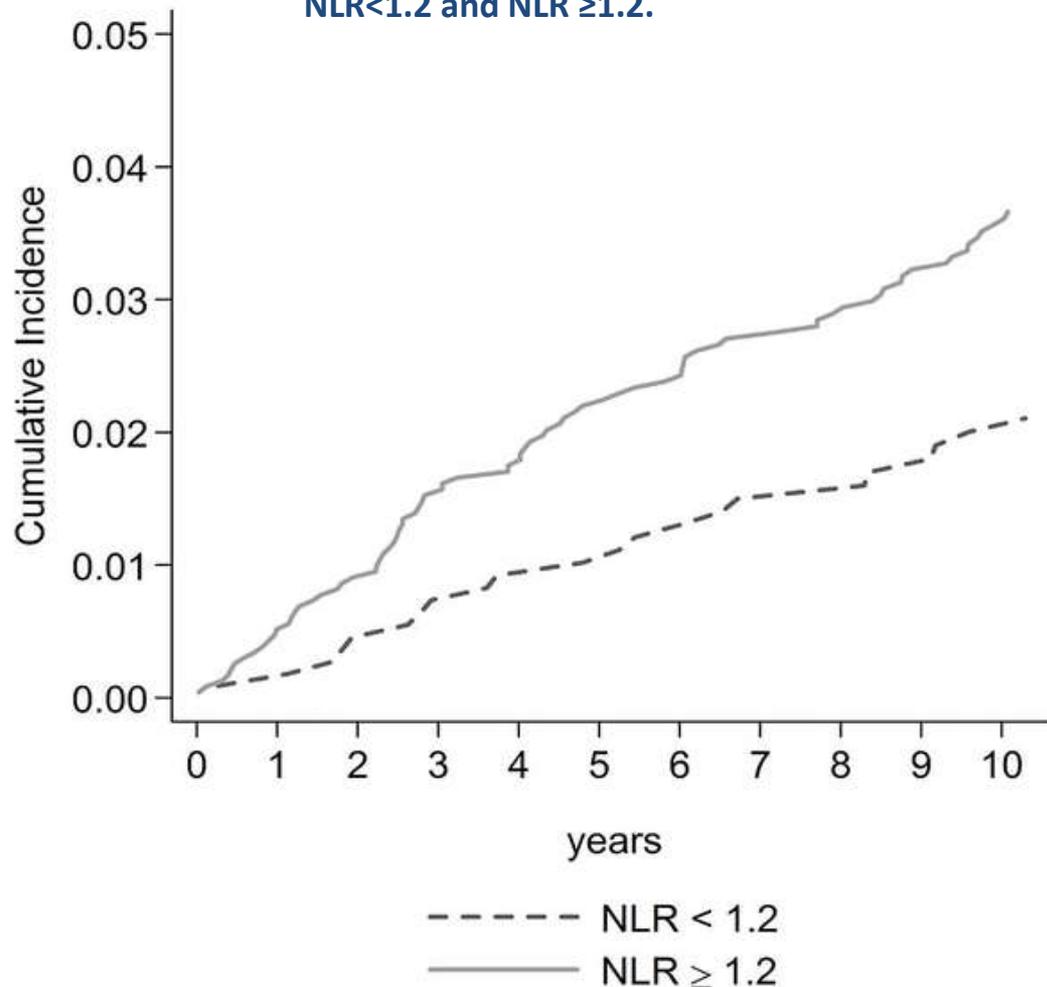
96373 Participants, 30425 HIV+ 7.4 Years Median Follow Up

Total bilirubin (mg/dL)	N	HF			AMI		
		Rate (95% CI)	HR (95% CI)	P	Rate (95% CI)	HR (95% CI)	P
<0.4	24229	7.95 (7.50-8.42)	1 (ref)		3.81 (3.51-4.13)	1 (ref)	
0.5-0.6	23638	7.39 (6.95-7.85)	0.88 (0.81-0.96)		3.36 (3.08-3.68)	0.85 (0.75-0.96)	
0.7-0.8	17462	6.60 (6.12-7.12)	0.79 (0.72-0.87)	<0.01	3.45 (3.11-3.81)	0.89 (0.78-1.02)	0.02
≥0.9	18523	6.41 (5.94-6.92)	0.75 (0.68-0.83)		3.07 (2.76-3.41)	0.80 (0.70-0.92)	
Missing	12521	4.89 (4.40-5.43)	0.72 (0.61-0.84)		2.01 (1.73-2.34)	0.85 (0.68-1.08)	

Models adjusted for age, race-ethnicity, systolic blood pressure, smoking, diabetes, total cholesterol, high density lipoprotein cholesterol, HIV, hepatitis C, liver fibrosis measured by FIB-4, alcohol abuse/dependence, cocaine and obesity; HF-heart failure; AMI-acute myocardial infarction; HR-Hazard Ratio; P-p-value test for overall significance of total bilirubin categories.

The role of NLR on CVD risk in HIV infected patients

Cumulative incidence of CVD in HIV-infected subjects with NLR < 1.2 and NLR ≥ 1.2.



NLR is a predictor of CVD risk in HIV-infected patients, independently from the classic risk factors of the disease (Framingham risk score)

Dolutegravir discontinuation and neuropsychiatric AEs in German Pts

- Retrospective study of therapy discontinuation data extracted from 2 German HIV treatment clinics
 - All HIV-positive pts (N = 1704) initiating INSTI-based treatment (N = 1950 exposures) January 2007 - April 2016
 - Excluded clinical trial participants

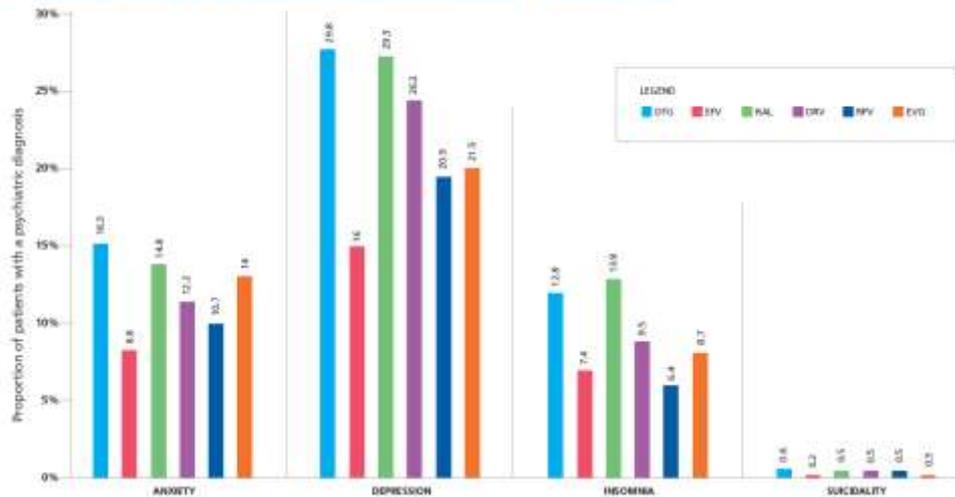
Discontinuation Reason	Drug (Exposures)		
	Dolutegravir (n = 985)	Elvitegravir (n = 287)	Raltegravir (n = 678)
Any AE, n (%)	67 (6.8)	27 (9.4)	28 (4.1)
Neuropsychiatric AE,* n (%)	49 (5.0)	3 (1.0)	14 (2.1)
▪ Insomnia/sleep disturbances	36 (3.7)	2 (0.7)	4 (0.6)
▪ Poor concentration/slow thinking	8 (0.8)	0 (0)	0 (0)
▪ Dizziness	13 (1.3)	1 (0.3)	3 (0.4)
▪ Headache/paresthesia	16 (1.6)	1 (0.3)	6 (0.9)
▪ Depression	7 (0.7)	0 (0)	1 (0.1)

*Can include ≥ 1 symptom.

Psychiatric Disorders Observed in HIV+ Patients Using 6 Common 3rd Agents in OPERA

Ricky Hsu^{1,2}, Jennifer Fusco³, Cassidy Henegar³, Felix Carpio⁴, Karam Mounzer⁵, Michael Wohlfeiler⁶, Vani Vannappagari⁷, Michael Aboud⁸, Lloyd Curtis⁹, Gregory Fusco³

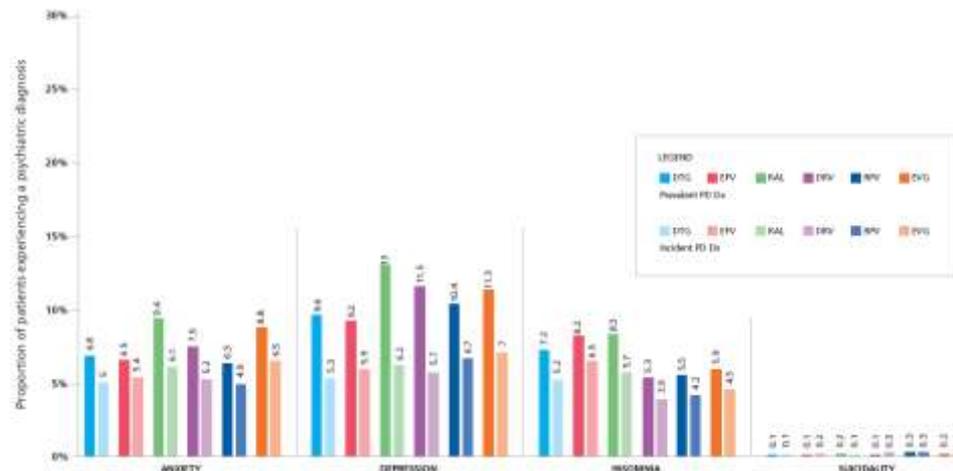
Figure 2. History of psychiatric diagnoses at baseline by anchor agent



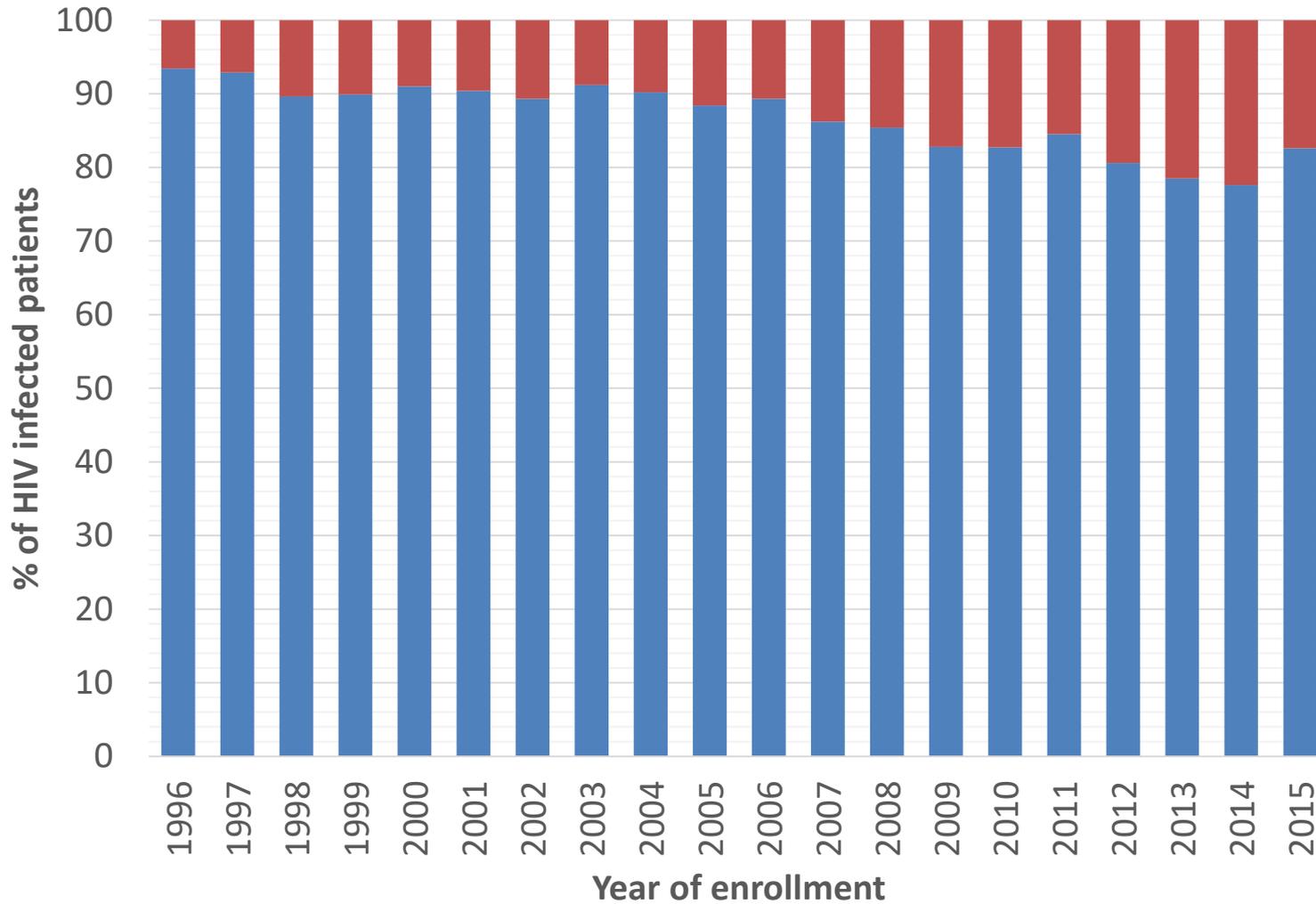
Observational cohort study (*OPERA Database*)
 11,539 HIV+ patients prescribed DTG, EFV, RAL, DRV, RPV or EVG –based cART

KEY FINDING:
 DTG use was not associated with an increased risk of psychiatric events or drug discontinuation due to psychiatric events, despite more patients with a history of psychiatric disorders being prescribed DTG treatment

Figure 3. Prevalent and Incident psychiatric diagnoses during follow-up by anchor agent



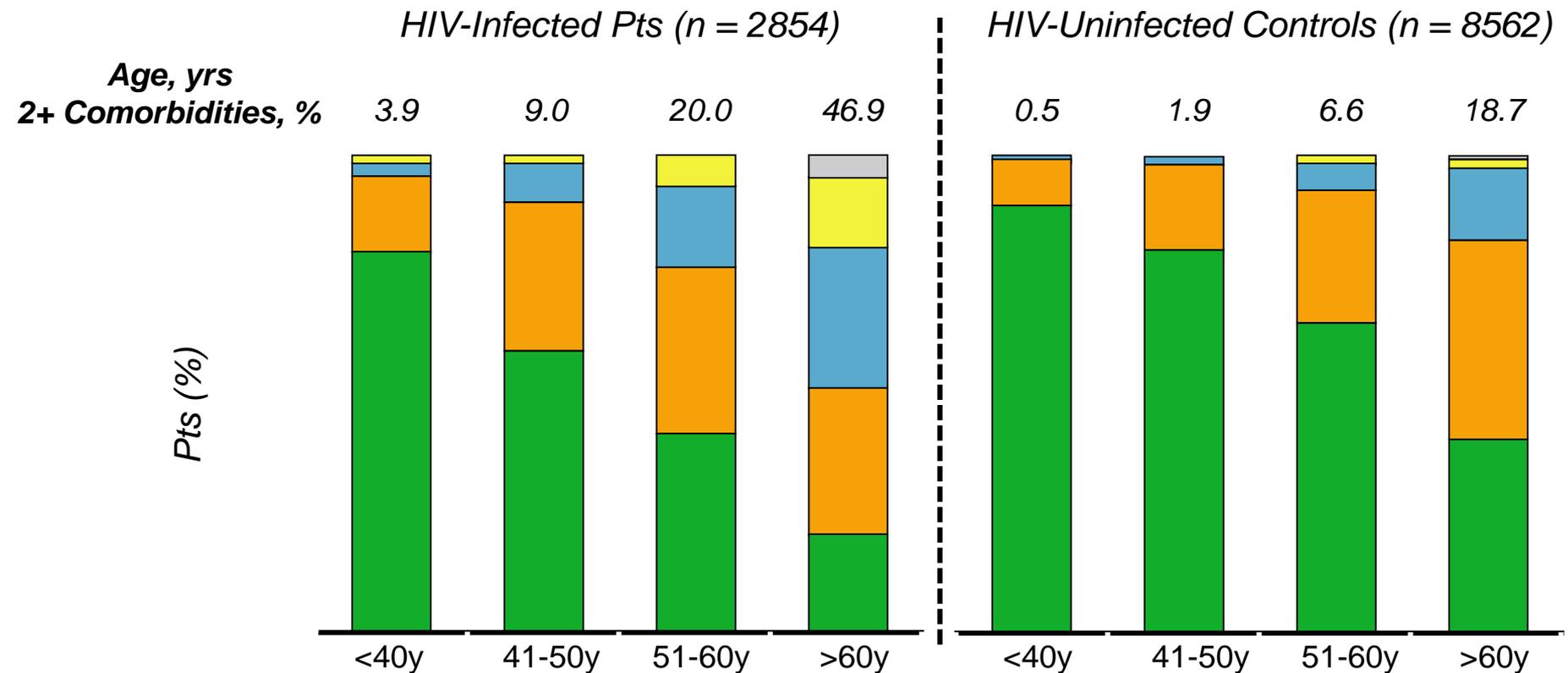
INVECCHIAMENTO DEI PAZIENTI HIV+



- ≥ 50 years...
- <50 years...

Comorbidities Increase With Age and With HIV Infection

- Single-center, case-control study



*Comorbidityes: bone fractures, CVD, diabetes, hypertension, hypothyroidism.
 Guaraldi G, et al. *Clin Infect Dis.* 2011;53:1120-1126.

ART Considerations in Older Pts

- Comorbidities
- Polypharmacy
 - Drug–drug interaction, dosing, adherence challenges
- Renal or hepatic impairment
 - Alterations in pharmacokinetics, potential for drug toxicity
- Challenges with single-tablet regimens
 - Inability to alter single component dosing
 - Difficulty swallowing large tablets

Drugs for Common Conditions in the Aging That May Interact With ART

Comorbidity	Comorbidity Drugs	Interacting ARVs
T2DM	Metformin	DTG/3TC/ABC, ^[1] DTG + FTC/TDF or FTC/TAF, ^[2-4] EVG/COBI/FTC/TDF, ^[5] EVG/COBI/FTC/TAF ^[6]
GERD	Antacid PPI	All ^[1-8] ATV/RTV + FTC/TDF or FTC/TAF, ^[3,4,9] DRV/RTV + FTC/TDF or FTC/TAF ^[3,4,10] RPV + FTC/TDF or FTC/TAF ^[11,12]
CVD	Statin, Antiarrhythmic	EVG/COBI/FTC/TDF, ^[5] EVG/COBI/FTC/TAF ^[6] ATV/RTV + FTC/TDF or FTC/TAF, ^[9,3,4] DTG/3TC/ABC ^[1]
COPD	Beta-agonist Glucocorticoid	EVG/COBI/FTC/TDF, ^[5] EVG/COBI/FTC/TAF ^[6] ATV/RTV + FTC/TDF or FTC/TAF, ^[2,3,9] DRV/RTV + FTC/TDF or FTC/TAF ^[3,4,10]



World Health
Organization

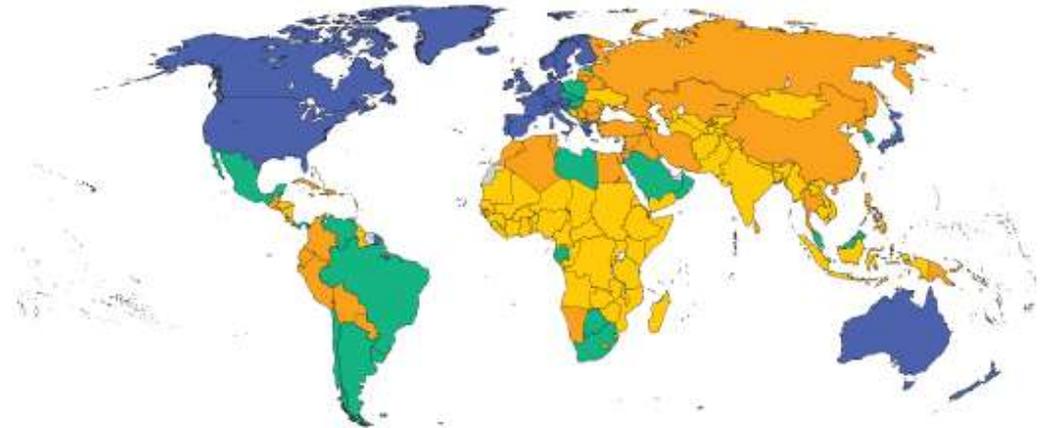
GUIDELINES



CONSOLIDATED GUIDELINES ON
**THE USE OF
ANTIRETROVIRAL DRUGS
FOR TREATING AND
PREVENTING HIV INFECTION**

RECOMMENDATIONS FOR A
PUBLIC HEALTH APPROACH

SECOND EDITION
2016



High-income countries Upper-middle-income countries Lower-middle-income countries Low-income countries No data

- *Low/Middle/High income countries*
- *“Generic/Branded drugs”*

Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents



Developed by the DHHS Panel on Antiretroviral Guidelines for Adults and Adolescents – A Working Group of the Office of AIDS Research Advisory Council (OARAC)

February 2017

- *High income countries*

- *Big Pharma*

- *Medicare/Medicaid*

Private Health insurance





EACS
European
AIDS
Clinical
Society

GUIDELINES

Version 8.2
January 2017



- *High/middle income countries*
- *Branded drugs/some generic drugs*
- *National health systems are different*

Linee Guida Italiane sull'utilizzo dei farmaci antiretrovirali
e sulla gestione diagnostico-clinica
delle persone con infezione da HIV-1

17 Dicembre 2015

Dicembre 2016

In collaborazione con:



Ministero della Salute

Sezioni L ed M del Comitato Tecnico Sanitario



SIMIT
Società Italiana
di Malattie Infettive
e Tropicali



- *High income country*
- *Branded drugs/some generic drugs*
- *SSN Universalistico*