Predicting antiretroviral resistance

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Predicting ARV resistance

Overview

- Incidence of resistance
  - common, current regimens (including ART-naive)
- Risk factors (non-drug) for resistance
- No discussion of
  - genotypic resistance vs. clinical resistance
  - DNA genotyping (unavailable)
  - paediatric data

Predicting ARV resistance

Limited contemporary data

PubMed

"antiretroviral, resistance"	20,269
and predictors	610
and 2021-2025	113
and adults	42

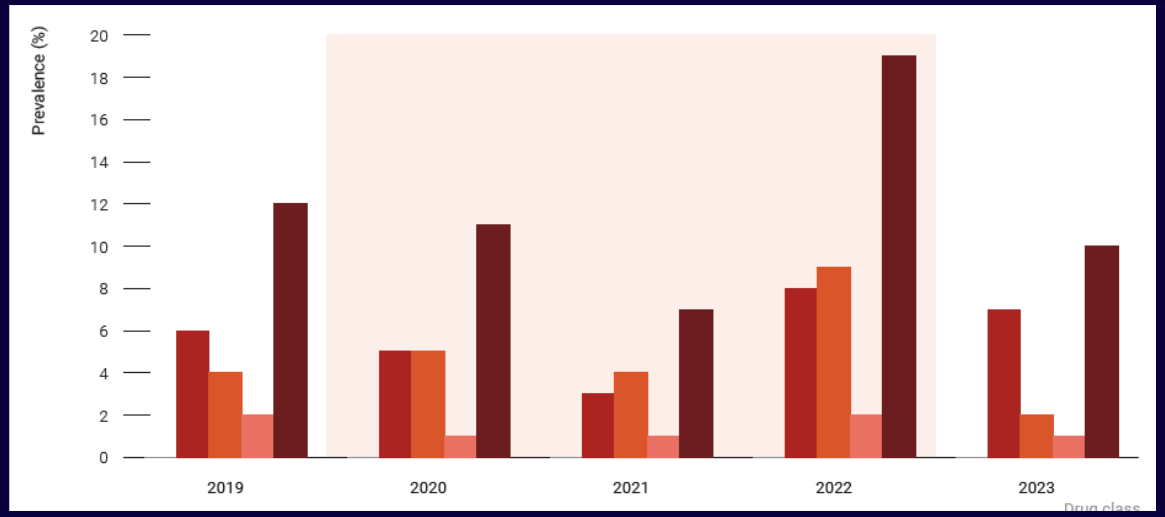
- Mostly from resource-limited settings
- Very few randomised trials, none looking at the value of genotyping
- Supplemented with conference data from 2024-25

PubMed search 22/07/2025

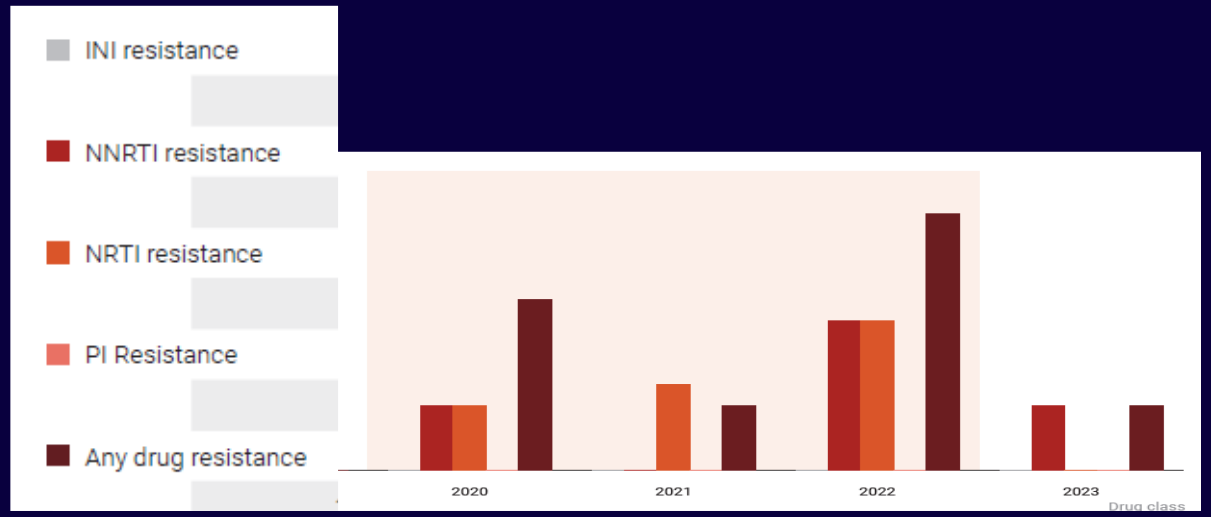
Predicting ARV resistance

ART-naïve: HIV infected last 3 months (Australia 2019-2023)

Male-to-male sexual transmission



Heterosexual transmission



- Resistance more common with male-to-male tranmission
- No INSTI resistance detected
- Resistance to at least one drug, but not necessarily to all drugs, in a class

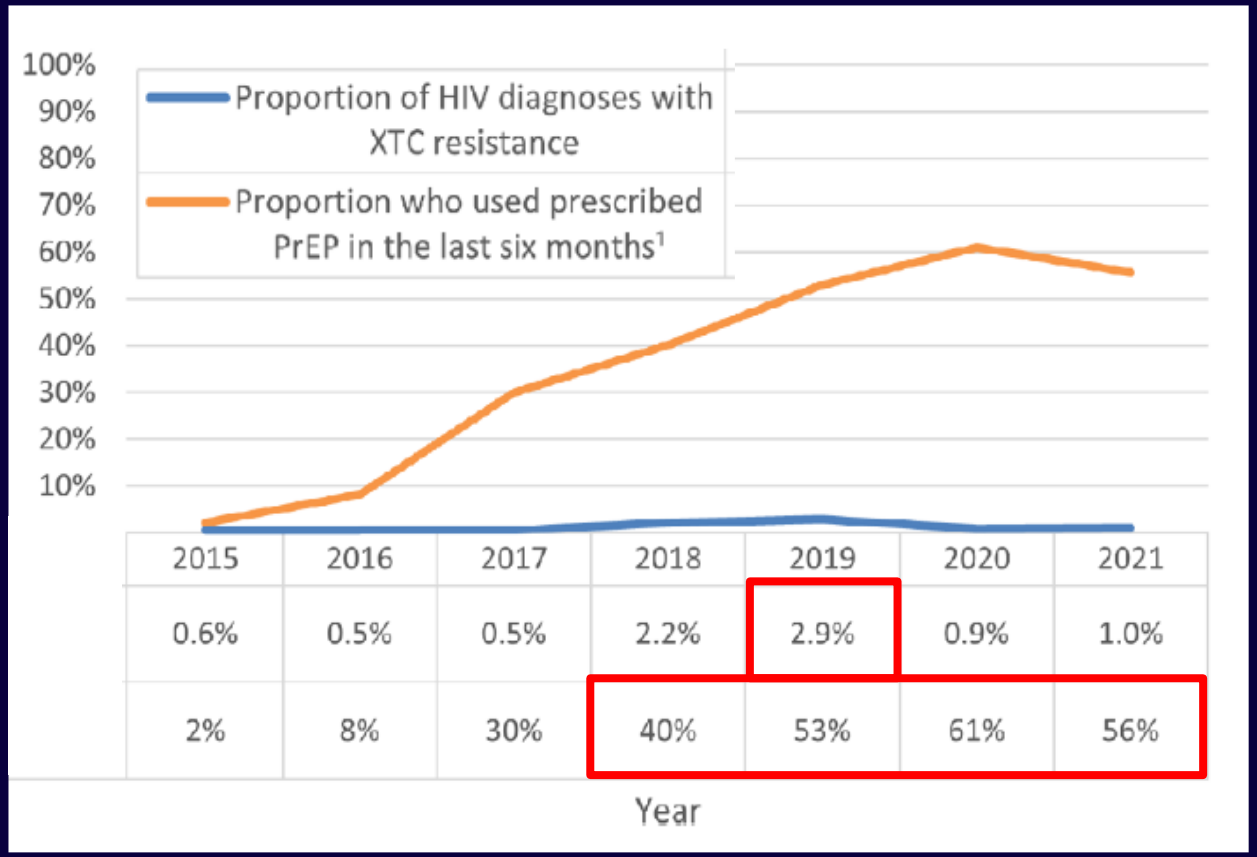
King et al, HIV, viral hepatitis and sexually transmissible infections in Australia – annual surveillance report 2024

Predicting ARV resistance

ART-naïve: previous PrEP (Australia 2015-2021)

- TDF/3TC PrEP
  - 3TC/FTC resistance increased transiently following greater TDF-3TC PrEP use in NSW
    - recent HIV+ 2.9%
    - later HIV+ 0.3%
- No TDF resistance

- Cabotegravir PrEP
  - HIV+: 20 / 4,097 pts 0.5%
  - CAB resistance: 4 / 20 20%

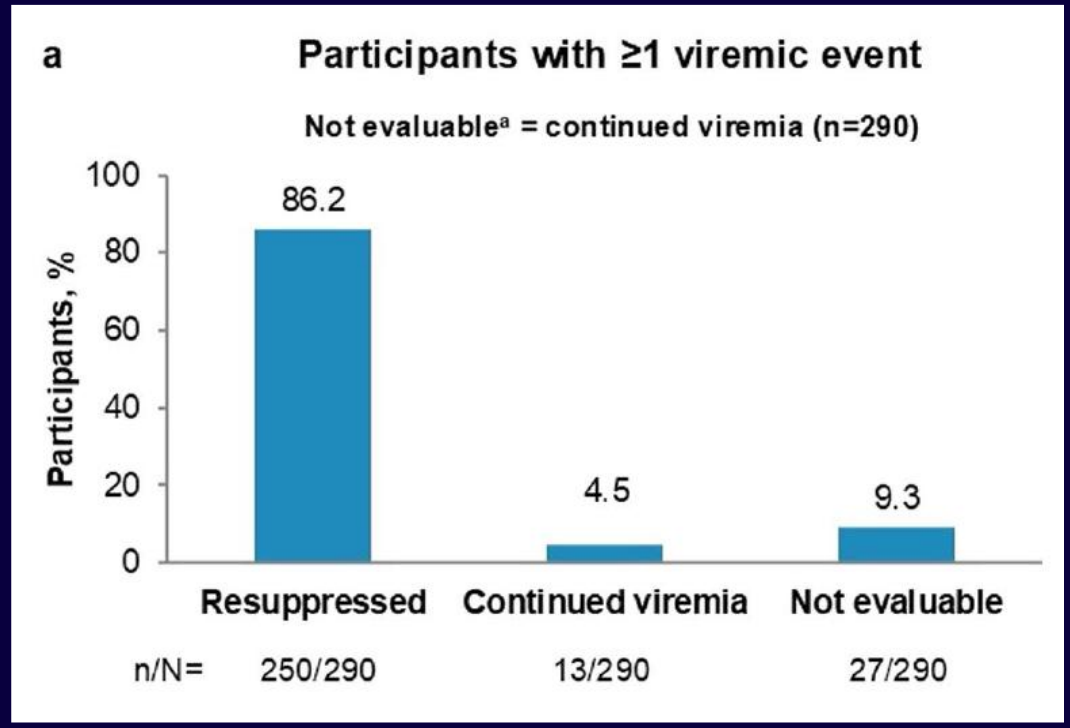


King et al, JIAS 2024; Ahluwalia, AIDS 2022

Predicting ARV resistance

B/F/TAF: randomised trials

- 8 randomised trials (naïve = 2)
- n = 2,801 adults starting B/F/TAF
- Prior resistance not permitted in some trials
- Viraemia (>50 cp/mL) 10.4%
  - Associated with <85% adherence (>5 doses / month)
- Emergent resistance 0



Re-suppression about (only) 81% within 12 weeks of viraemia

Pozniak et al, Infect Dis Ther 2025

Predicting ARV resistance

B/F/TAF: cohorts

Cohort		Rome n = 283	Aquitaine n = 1,430
Previous mutations	M184V	14%	36%
	tNRTI	14%	
	Tenofovir		12%
	K65R	0.7%	
Virological failure		12 (4.2%)	66 (4.6%)
New resistance		0	6 (0.4%)
New resistance in VF		0	6/66 (9%)
Failed to resuppress on B/F/TAF		2 (0.7%)	16/56 (29%)

Armenia et al, J Glob Antimicrob Resist 2022; Bellecave et al, CROI 2025

Predicting ARV resistance

DTG-3TC: randomised trials (GEMINIs 1 and 2)

	DTG-3TC	DTG-TDF/FTC
N	714	711
Virological failure*	23 (3.2%)	21 (3.0%)
New resistance	2 (0.3%)	0
New resistance in VF	2/23 (8.7%)	0

- Virological failure more likely (17% vs 3%) in those with <90% adherence

Cahn et al, HIV Glasgow 2020; Cahn et al, AIDS 2022

Predicting ARV resistance

DTG-3TC: cohort (Italy)

- N = 785 (71% men, mean 52 yrs)
- Virological failure — 18 / 785 = 2.3% (more likely if prior VF)
- New resistance — 0
- Resuppressed on DTG/3TC — 9 of 9

Ciccullo et al, J Glob Antimicrob Resist 2022

Predicting ARV resistance

DTG-3TC: cohorts of patients with prior M184V

Study	N	Timepoint (weeks)	VF, n (%)	INI RAM
DAT'AIDS	105	NR	2 (1.9)	0
SOLAR 3D	50	48	0	0
Baldin 2019	45	(median 22.1 months)	2 (4.4)	0
LAMRES	37	104	3 (8.1)	0
ART-PRO	21	9	0	0
ARCA	21	(median 1.3 years)	0	0
DOLULAM	17	104	0	0
DOLAMA	4	48	1 (25.0)	0
TANGO	4	144	0 (0)	0
Total	304		8 (2.6%)	0

Armenia et al, J Glob Antimicrob Resist 2022

Predicting ARV resistance

CAB/RPV: phase 3/3b trials

ATLAS 2M	CARISEL Protocol 213199	SOLAR Protocol 213500	CARES
N=522[1,2]	N=430[3]	N=454*[4]	N=255[5]
1.7% (n=9) CVF by Week 48†‡	**0.5%** (n=2) CVF by Month 12†§	**0.7%** (n=3) CVF by Month 12†‖	**0.8%** (n=2) CVF by Week 48†¶
1.1% (n=6) CVF with treatment-emergent resistance#	**0.5%** (n=2) CVF with treatment-emergent resistance	**0.7%** (n=3) CVF with treatment-emergent resistance‖	**0.8%** (n=2) CVF with treatment-emergent resistance

- **Virological failure** 16/1661 = 1.0%
- **Resistance at virological failure** 13/16 = 81%

Overton ET, et al. Lancet 2021; Overton ET, et al. Clin Infect Dis 2023
Jonsson-Oldenbüttel C, et al. JAIDS 2024; Ramgopal MN, et al. Lancet HIV 2023; Kityo C, et al. Lancet Infect Dis 2024

Predicting ARV resistance

CAB/RPV: cohorts

Real-world cohorts	n	Follow-up (months)	VF, % (n)	RAMs at VF, % (n)		Resistance if VF+ (%)
				INSTI	INSTI + NNRTI	
Deschanvres, 2023 (Dat'AIDS)	134	6.5	1.2 (14)	0.3 (3)	0.2 (2)	5/14
Borch, 2022 (CARLOS)	200	6	1 (2)	0.5 (1)	0.5 (1)	1/1
Pozniak, 2023 (COMBINE-2 C2C)	89	5.2	1.1 (1)	0 (0)	0 (0)	0/1
Sinclair, 2023 (BEYOND)	150	6	1.3 (2)	0.7 (1)	0.7 (1)	1/2
Maguire, 2024	374	8.5	1.1 (4)	0.5 (2)	0.5 (2)	2/4
Shankaran, 2024	75	NR	4 (3)	4 (3)	1.3 (1)	3/3
Rubenstein, 2023	72	15	1.4 (1)	0 (0)	0 (0)	0/1
Jongen, 2023 (ATHENA)	588	9.6	0.9 (5)	0.3 (2)	0.3 (2)	2/5
Collins, 2022	15	3	6.7 (1)	0 (0)	0 (0)	0/1
Liegeon, 2024	78	8	1.3 (1)	1.3 (1)	1.3 (1)	1/1
Nguyen, 2024	73	9	4.1 (3)	1.4 (1)	1.4 (1)	1/3
Pérez, 2023	62	6	1.6 (1)	0 (0)	0 (0)	0/1
Masich, 2023	24	12	4.2 (1)	0 (0)	0 (0)	0/1
Totals	**1934**		**2.0% (39)**	**14**	**11**	**41% (16)**

Predicting ARV resistance

CAB/RPV: RCT and cohort meta-analysis

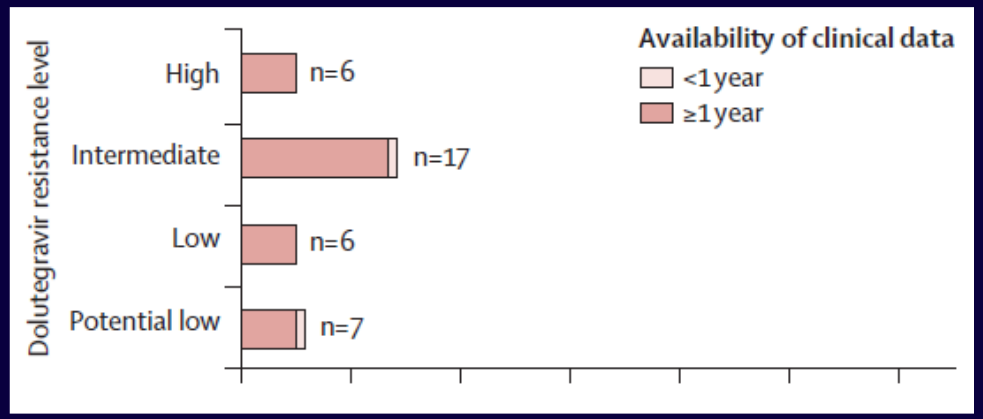
n	n	VF	Resistance (with genotype)	Resistance (%)	INSTI resistance in VF
Induction-switch	513	6	4/5	0.8%	71%
Switch suppressed	7,801	92	22/37	0.3%	61%
Switch viraemic	910	37	7/17	0.8%	41%

Perez Navarro et al, Clin Infect Dis 2025

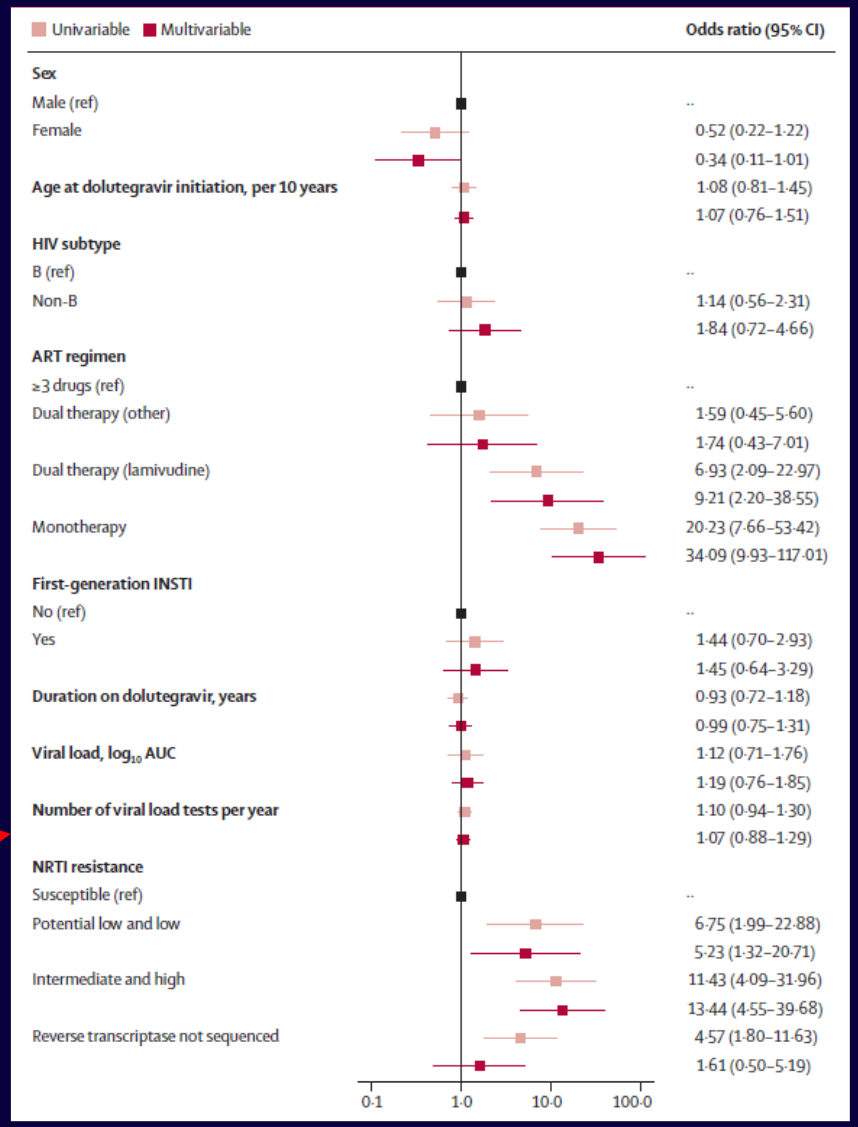
Predicting ARV resistance

Dolutegravir: cohorts

- **Europe / South Africa**
  n=599 adults treated for 12+ months
- **Prevalence = 14%**



- **Risk factors**
  - Dual / monotherapy
  - Associated NRTI resistance

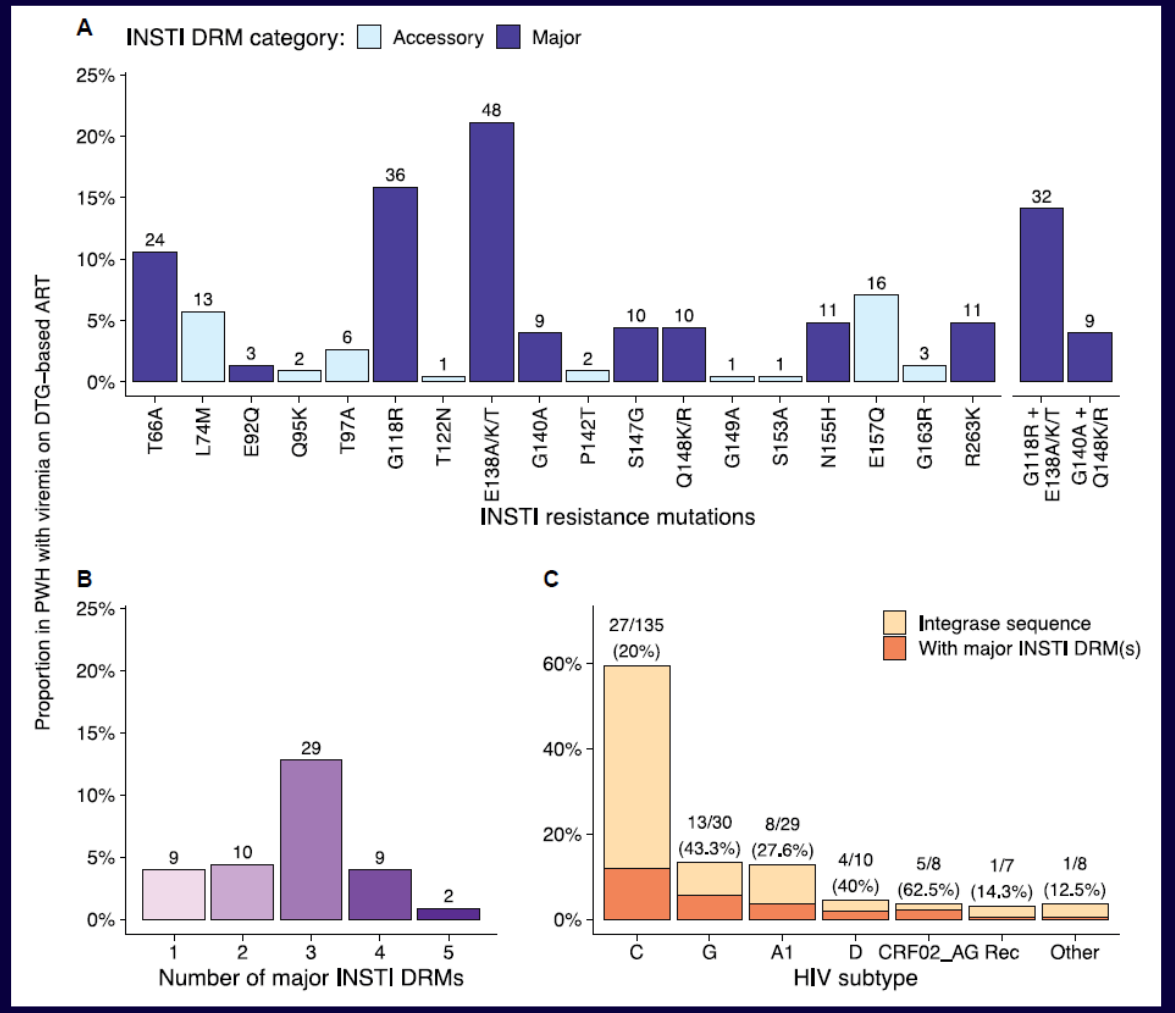


Loosli et al, Lancet HIV 2023

Predicting ARV resistance

Dolutegravir (South Africa)

- N = 488
- TDF/3TC/DTG (TLD) 75%
- 227 genotypes
- INSTI resistance 26%



Loosli et al, Clin Infect Dis 2025

Predicting ARV resistance

Current common ART regimens

		Virological failure (VF)	Resistance overall	Resistance with VF
B-F-TAF	RCTs	10.4%	0	0
	Cohorts	4.5%	0-0.4%	0-9.0%
DTG-3TC	RCTs	2.3-3.2%	0-0.3%	8.7%
DTG-TDF-3TC (TLD)	RCTs	3.0%	0	0
	Cohorts			4-26%
CAB-RPV	RCTs	1.0%	0.8%	81%
	Cohorts	2.0%	0.8%	41-71%

Predicting ARV resistance

Long-acting ARVs

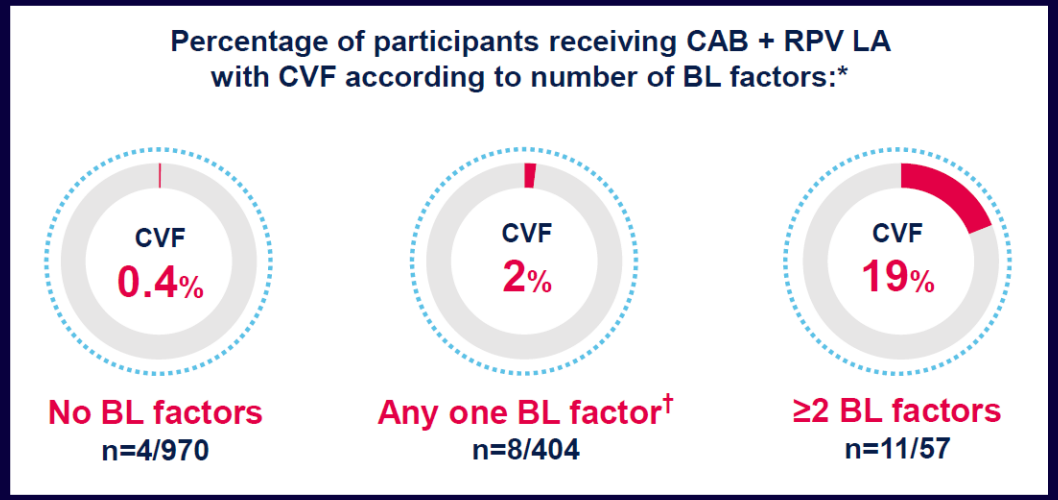
- **Prolonged ARV exposure after cessation of**
  - newer injectables — cabotegravir q 4/12, lenacapavir q6/12 or q12/12
  - weekly tablets — islatravir, lenacapavir, ulonivirine
- **Conceivable that resistance incidence with LA-ARVs will be rare, but relatively frequent in those with**
  - virological failure or
  - who are lost to follow-up

Predicting ARV resistance

Non-ART / non-viral risk factors: CAB-RPV

Covariate	Adjusted risk ratio	P
Archived RPV RAM(s)	21.7	<0.0001
HIV subtype A6/A1	12.9	<0.0001
BMI (per 1 kg/m^2)	1.09	0.045

- Additional univariate predictors
  - q4W
  - L74I
  - sex
  - other NNRTI RAMs
  - CAB RAM
  - other INSTI RAM

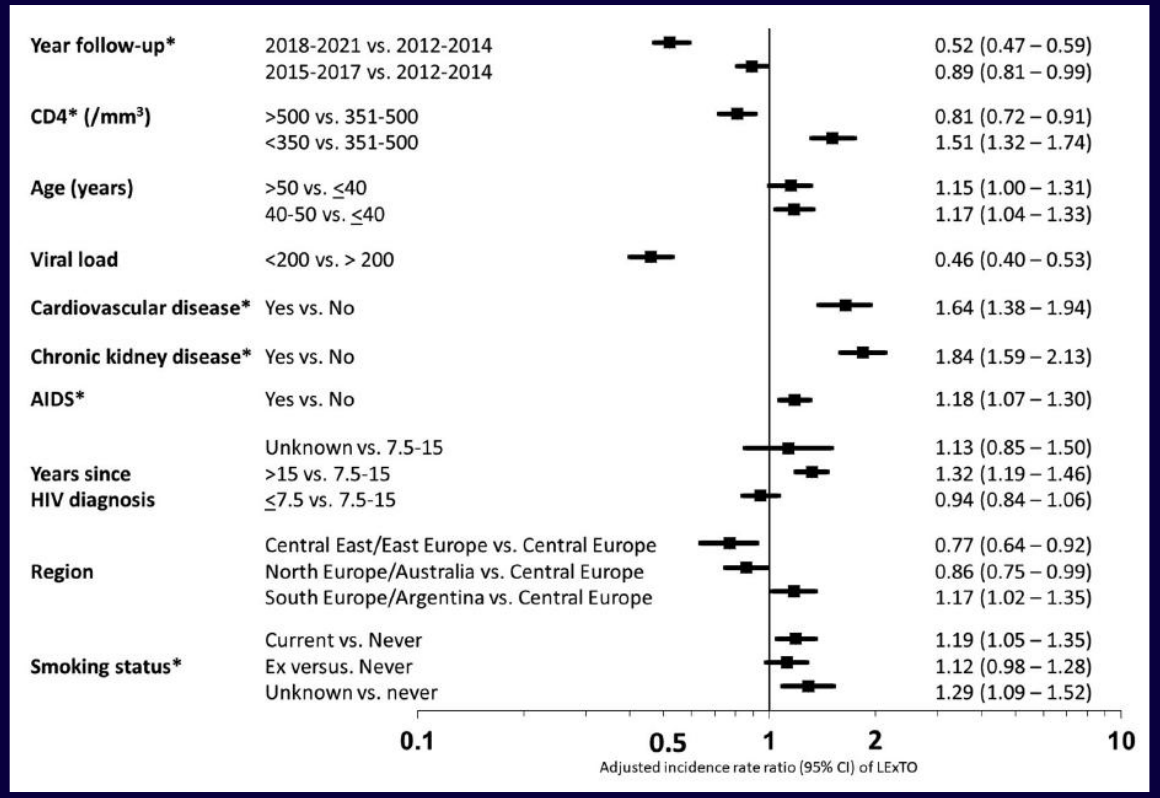


Orkin et al, Clin Infect Dis 2023

Predicting ARV resistance

Non-ART / non-viral risk factors (RESPOND cohort - Limited/exhausted treatment options (LExTO)

Associations



Mocroft et al, AIDS 2024

Predicting ARV resistance

Non-ART / non-viral risk factors (ARCA cohort, Italy)

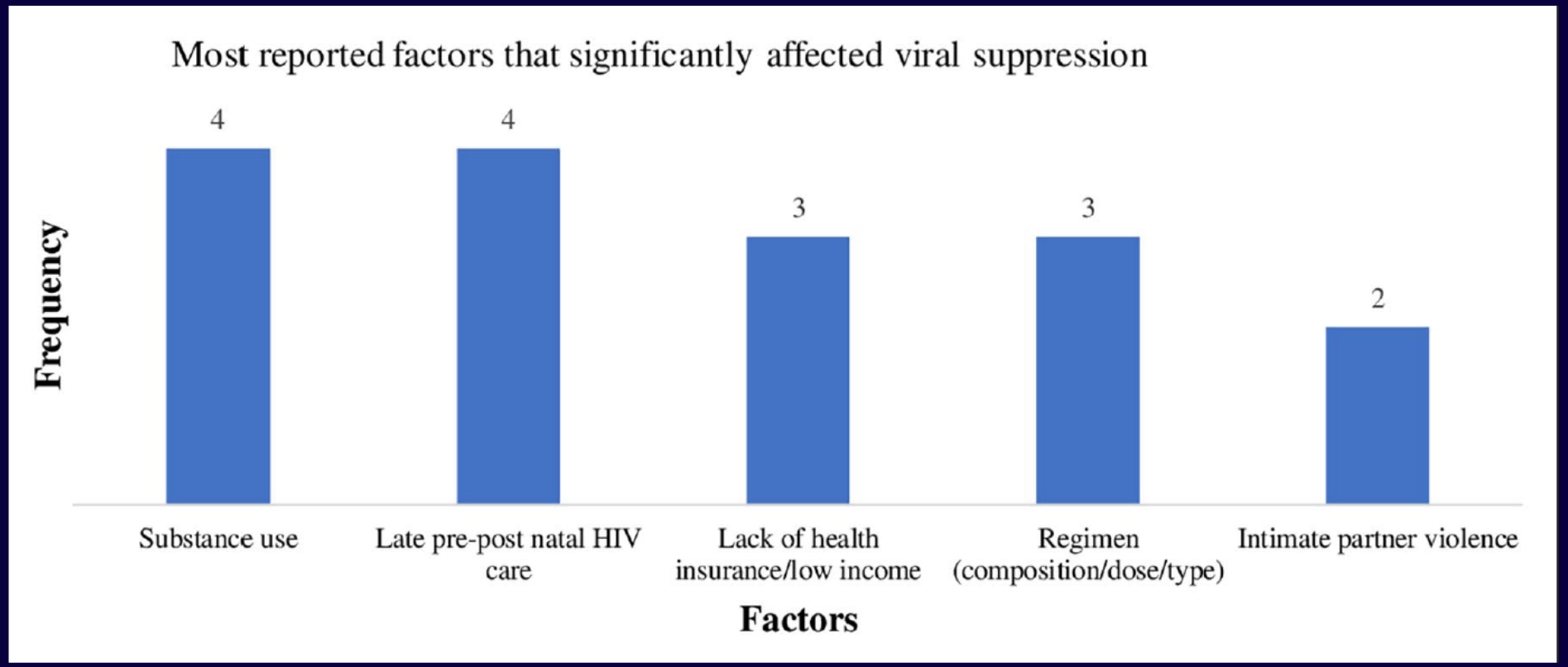
Variable		AOR (all P≤ 0.001)
Male sex		1.28
Vertical transmission		10.60
HCV-negative		1.18
HBV+		1.19
CD4 nadir <200		1.37
AIDS event		1.43
ART started before 2008		2.27
Prior ART number (/1 drug)	PI	1.64
	NRTIs	1.11
	NNRTIs	1.86
	INSTI	1.58

Lombardi et al, Int J Antimicrob Agent 2021

Predicting ARV resistance

Non-ART / non-viral risk factors (USA)

- Women in 8 US cohorts



Labisi et al, Womens Hlth 2022

Predicting ARV resistance

Persistence and reversion

ARV class	Mutation	Reversion
NRTIs	M184V	33% at 4 months
NNRTIs	K103N	30% at 3.5 yrs
	E138K	No data
INSTIs		No data

- Most patients with VF and resistance usually change ART promptly (i.e. do not continue the same ART or cease ART), so persistence of resistance with current ARVs is unknown

Paquet et al, PLoS ONE 2011; De La Cruz et al, Open Forum Infect Dis 2019

Predicting ARV resistance

Conclusions

- **Incidence of resistance**
  - New resistance is uncommon at virological failure (VF) with current daily STRs
  - More likely at VF with long-acting ART than with STRs
  - Rate with loss to follow-up is unknown
  - True extent requires previous genotypes on treatment (looking for subsequent reversion) and complete ART / PrEP history
- **Risk factors are poorly understood**
  - Likely revolves around reasons for non-adherence, including socioeconomic factors

Predicting ARV resistance

Thank you