

HIV-1 integrase strand transfer inhibitor resistance-associated mutations and the implications for cabotegravir use in sub-Saharan Africa: a systematic review and meta-analysis

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Background

- There is evidence to suggest increasing prevalence of resistance to integrase inhibitors in the dolutegravir (DTG) era, at a rate higher than anticipated from clinical trials^{1,2}
- Cabotegravir (CAB) is believed to have a lower barrier to resistance than DTG, so data on DTG resistance cannot necessarily be extrapolated to CAB³
- This raises concerns about the impact on CAB use both as PrEP and as part of treatment, especially in sub-Saharan Africa which bears the highest burden of HIV worldwide
- There is a need to understand the overall prevalence of INSTI and specifically CAB resistance, evaluate if it is increasing and ascertain if certain groups have higher levels of resistance

Aim

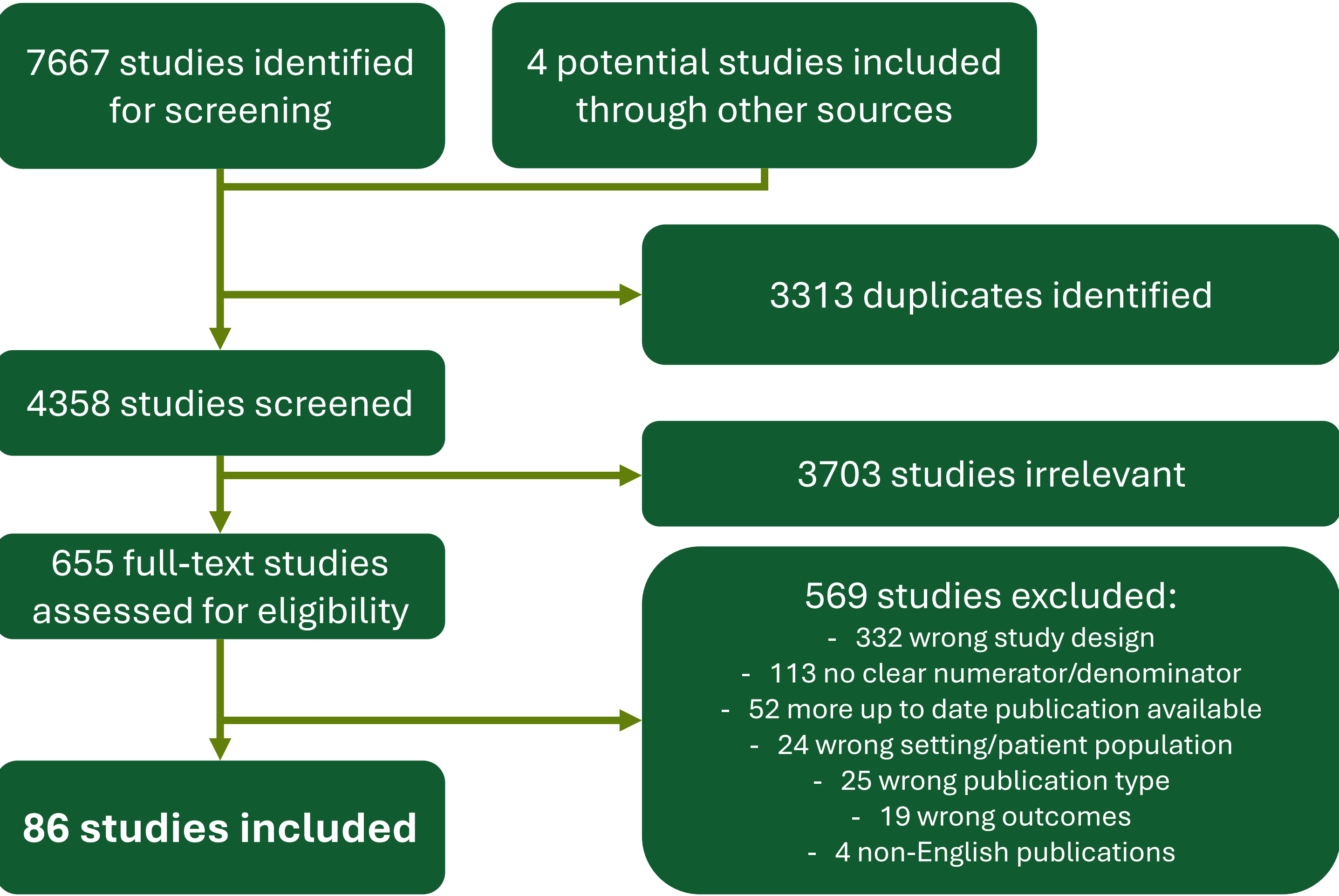
To synthesise all available data on the prevalence of integrase resistance in the WHO African region, focusing on resistance to cabotegravir and the implications for its use in the region.

Methods

- Systematic review & meta-analysis according to PRISMA**
- COVIDENCE Software**
- Databases:** Global Health, Psycinfo, Medline, Embase, African Journals Online
- Key search terms:** HIV, drug resistance mutations, integrase, Africa and adjacent terms
- Registered on PROSPERO:** CRD42024568499
- Inclusion**
 - Epidemiological, clinical, laboratory studies
 - Reporting on prevalence/proportion of INSTI resistance from genotypic sequencing
 - People living with HIV-1
 - WHO African region
- Exclusion**
 - INSTI RAMs not separately described
 - No clear numerator/denominator
- Resistance determined according to Stanford v**
- Data synthesis:**
 - Random effects meta-analysis
 - Measures of effect : prevalence and 95% C.I.
 - Assessment for heterogeneity: I² statistic
 - Subgroup differences by meta-regression



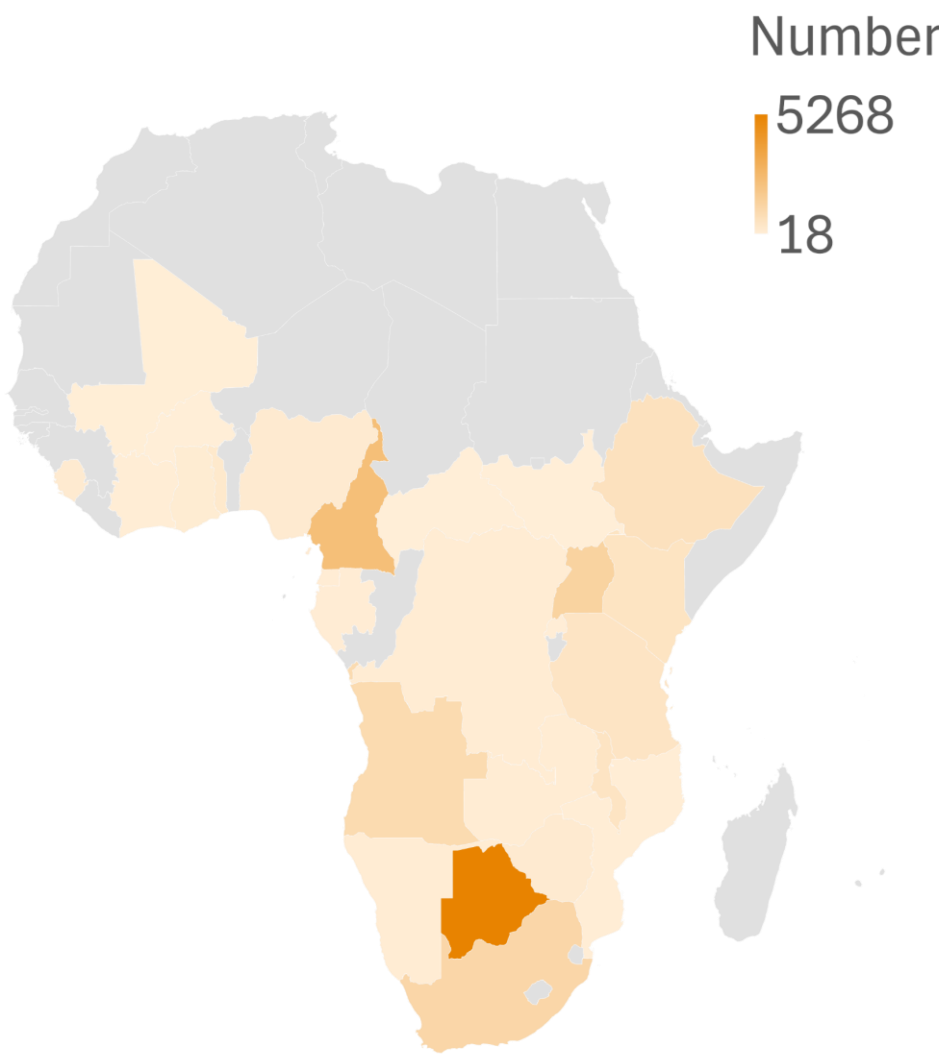
Results – PRISMA Diagram



Results – Demographics

Category		N (23,137)	%
Age Group	Adults	12,621	54.55%
	Children & adolescents	988	4.27%
	Infants	118	0.51%
	Not specified/ disaggregated	9,410	40.67%
INSTI Treatment status	INSTI naïve (confirmed/presumed)	21,231	91.76%
	1st generation INSTI experienced/failure	135	0.58%
	2nd generation INSTI experienced/failure	1,747	7.55%
	Not specified/ disaggregated	24	0.10%
Cabotegravir experienced	Yes	10	0.04%
	No	23,127	99.96%

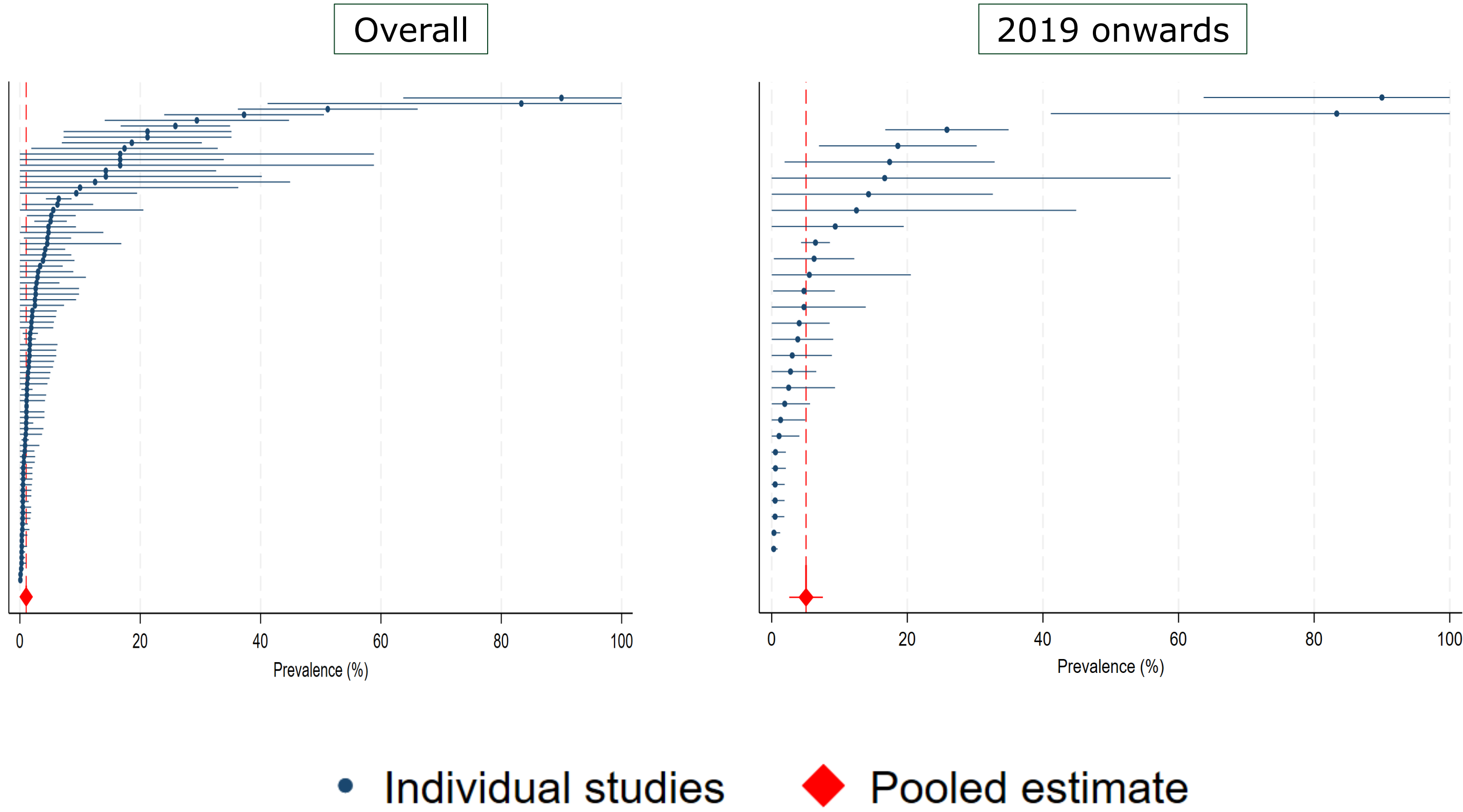
1st generation INSTIs – raltegravir; elvitegravir. 2nd generation INSTIs: dolutegravir, cabotegravir. Studies classified treatment failure in different ways, as such those exposed and reported as having treatment failure were grouped together



Results – Major integrase resistance

Category	No. of studies	Pooled prevalence estimate	95% C.I.	I ²	P-value
Overall	86	1.0%	0.8-1.3%	68.09	P = 0.07
Pre-2019	45	0.7%	0.5-1.0%	50.28	
2019-onwards	29	5.1%	2.6-7.5%	96.22	
INSTI-naïve	60	0.7%	0.5-0.9%	43.19	P <0.001
1 st gen INSTI experienced/failure	5	33.4%	18.0-48.9%	72.52	
2 nd gen INSTI experienced/failure	27	11.0%	5.7-16.3%	97.38	

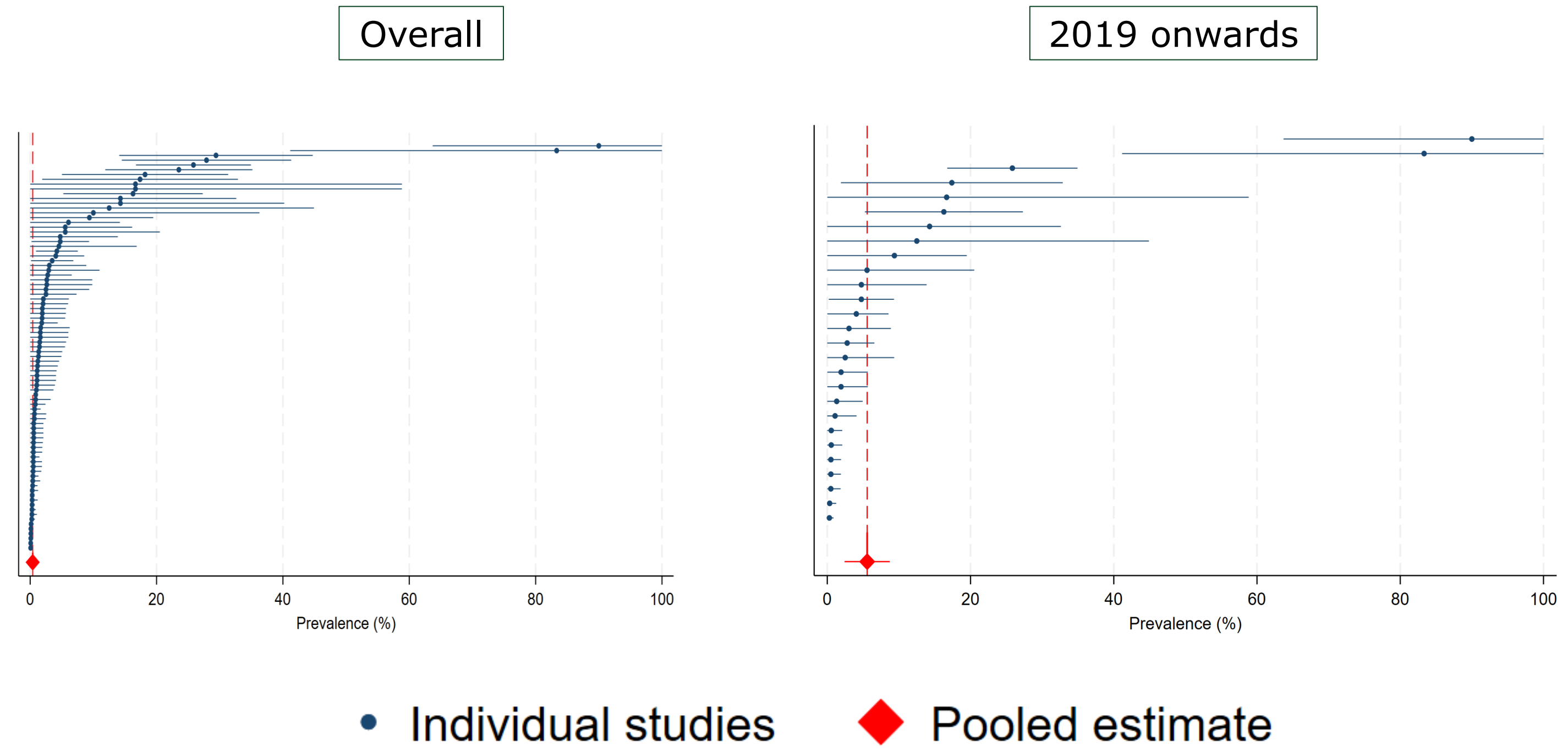
N.B. no evidence of prevalence differing according to geographical region or age group



Results – Intermediate/high-level cabotegravir resistance

Category	No. of studies	Pooled prevalence estimate	95% C.I.	I ²	P-value
Overall	85	0.4%	0.3-0.5%	29.88	P = 0.06
Pre-2019	45	0.3%	0.2-0.5%	39.16	
2019-onwards	27	5.6%	2.4-8.7%	97.68	
INSTI-naïve	60	0.3%	0.2-0.5%	33.47	P <0.001
1 st gen INSTI experienced/failure	5	23.5%	16.4-30.6%	0.00	
2 nd gen INSTI experienced/failure	26	11.0%	5.5-16.6%	97.06	

N.B. no evidence of prevalence differing according to geographical region or age group



Conclusions

- Prevalence of major INSTI resistance and intermediate/high-level cabotegravir resistance was low overall
- Trend towards increasing resistance since 2019
- Prevalence linked to prior INSTI exposure

→ Cabotegravir roll-out should be accompanied by sustained resistance surveillance efforts