Antiretroviral resistance to integrase strand transfer inhibitors

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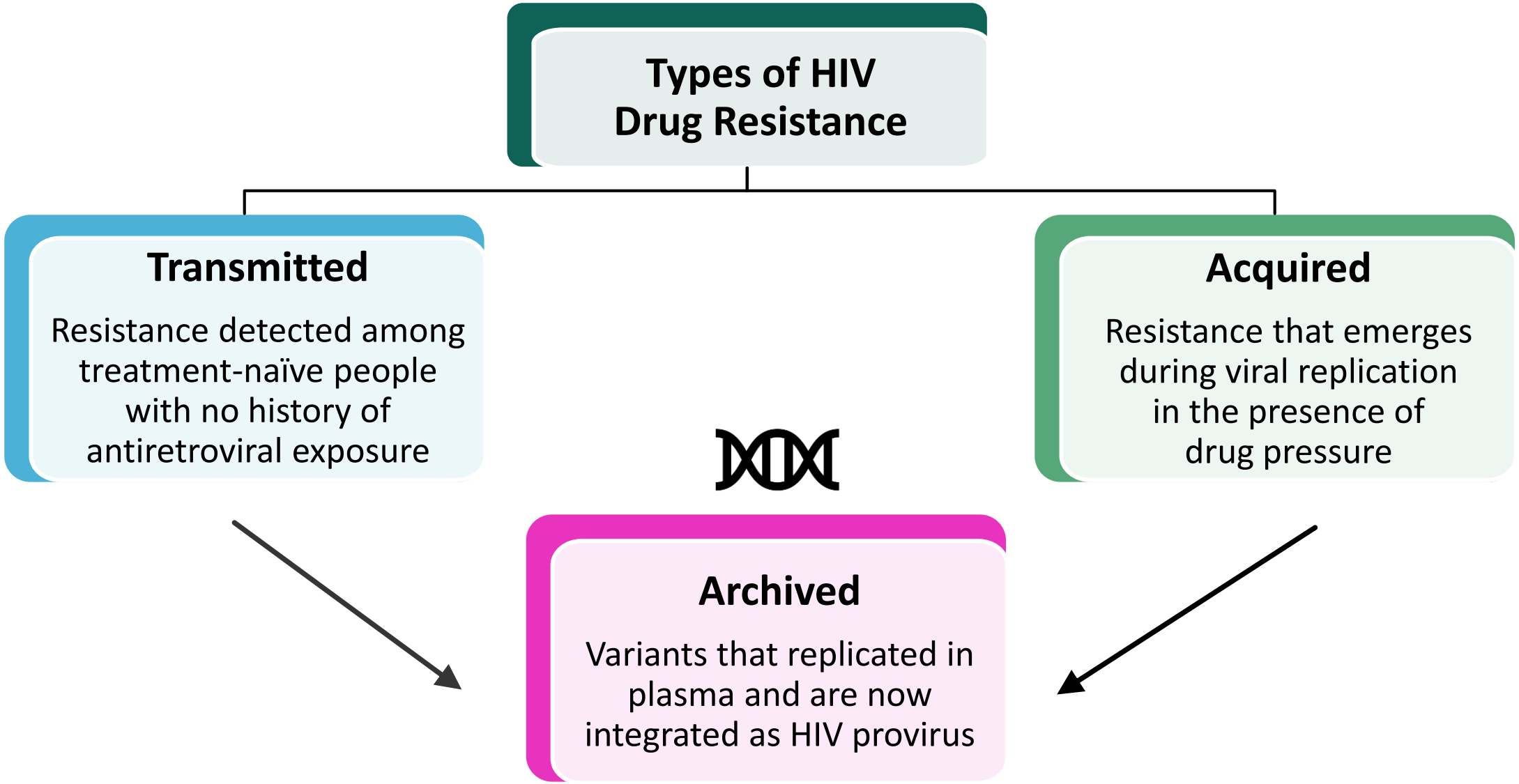
03 Dec 2024

Disclosures

- Personal payments: Abbott, Gilead, GSK, MSD, Roche, ViiV
- Research funding (to institution): Gilead, Roche, ViiV

INSTI Resistance: Themes

- Epidemiology
- Mechanisms
- Implications


Types of HIV Drug Resistance
Transmitted
Resistance detected among treatment-naïve people with no history of antiretroviral exposure
Acquired
Resistance that emerges during viral replication in the presence of drug pressure
Archived
Variants that replicated in plasma and are now integrated as HIV provirus

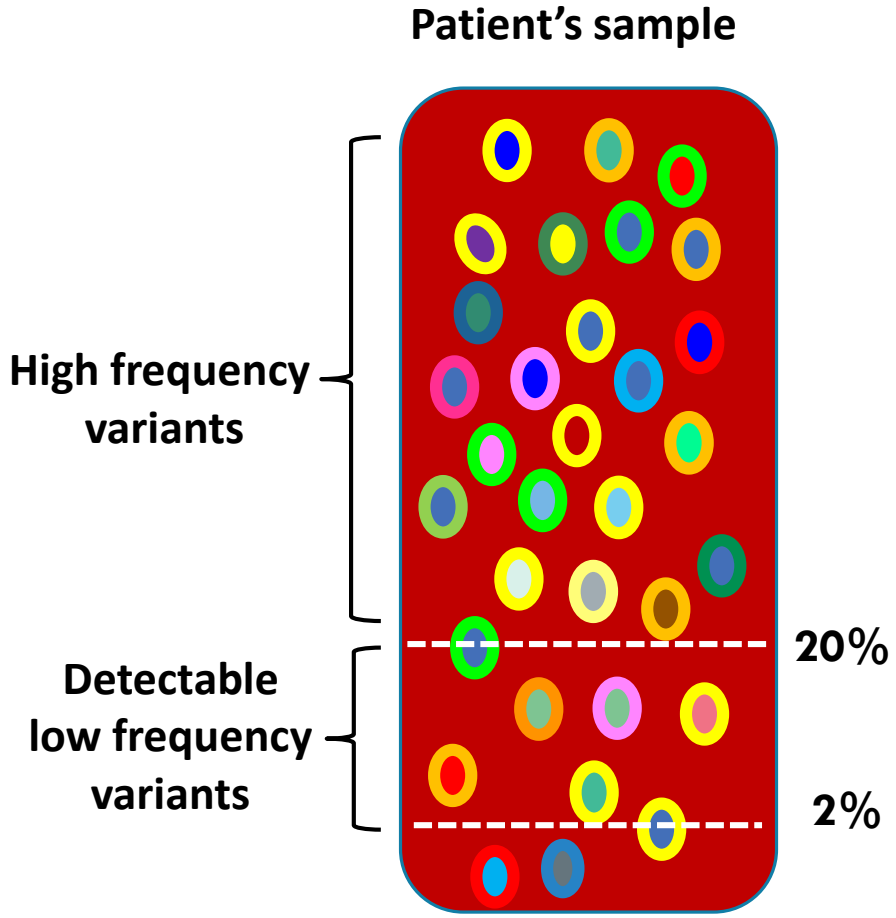
Detecting Drug Resistance by Genotyping

Conventional or Sanger sequencing

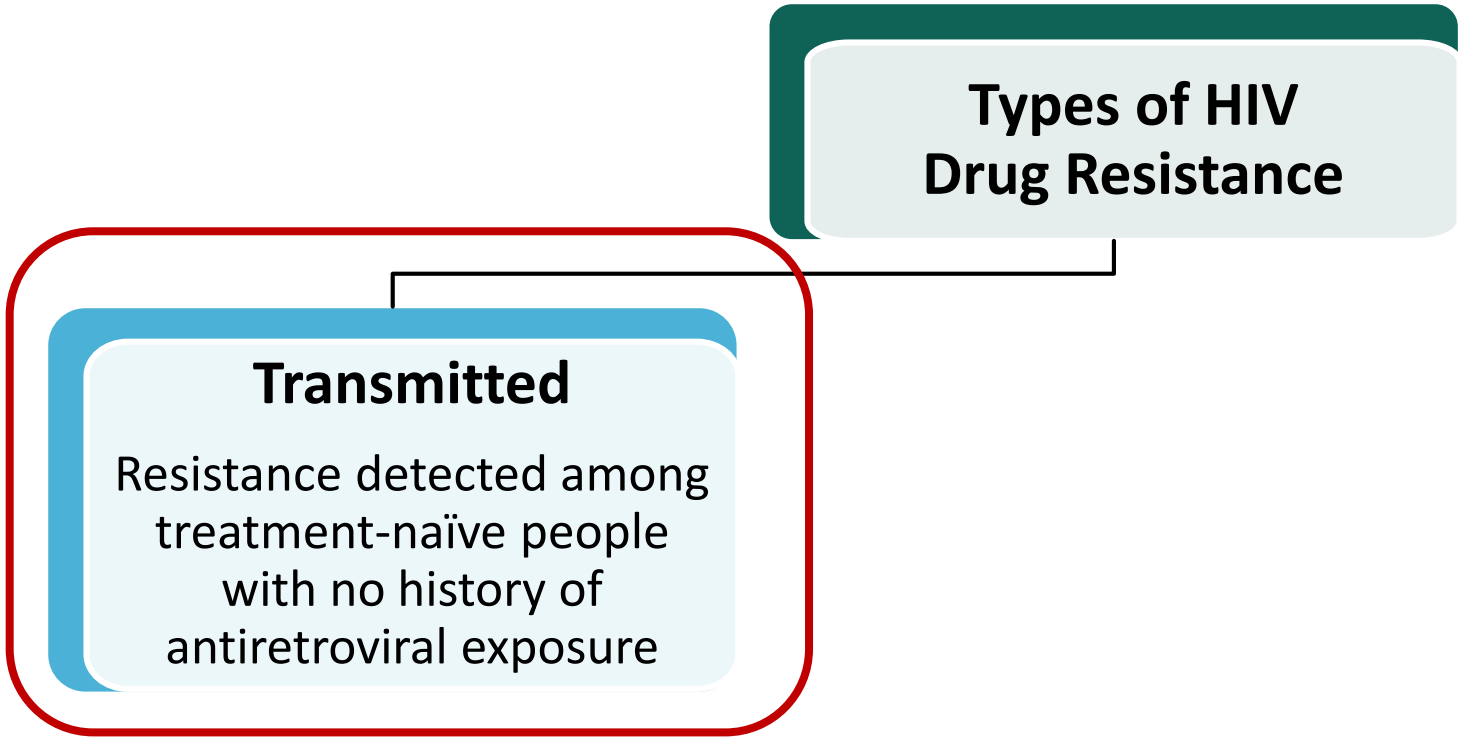
- Detects variants with a ≥20% frequency threshold and reports a single consensus sequence from all the viral variants detected

Deep or next generation sequencing (NGS)

- Detects variants with a ≥2% frequency threshold and reports and quantifies individual variants



Geretti et al. BHIVA Conference 2023


Types of HIV Drug Resistance
Transmitted
Resistance detected among treatment-naïve people with no history of antiretroviral exposure

TDR in Recent HIV Infections, England 2015-2019[1]

- **Samples & data:** From national surveillance
- **Recent (≤4 months) infection:** Based on strength of HIV-specific Ag/Ab binding, testing history, CD4 count & VL
- **RAMs:** Established surveillance lists[2,3]
- **Majority RAMs:** >20% of sample variants
- **Minority RAMs:** 2-20% of sample variants

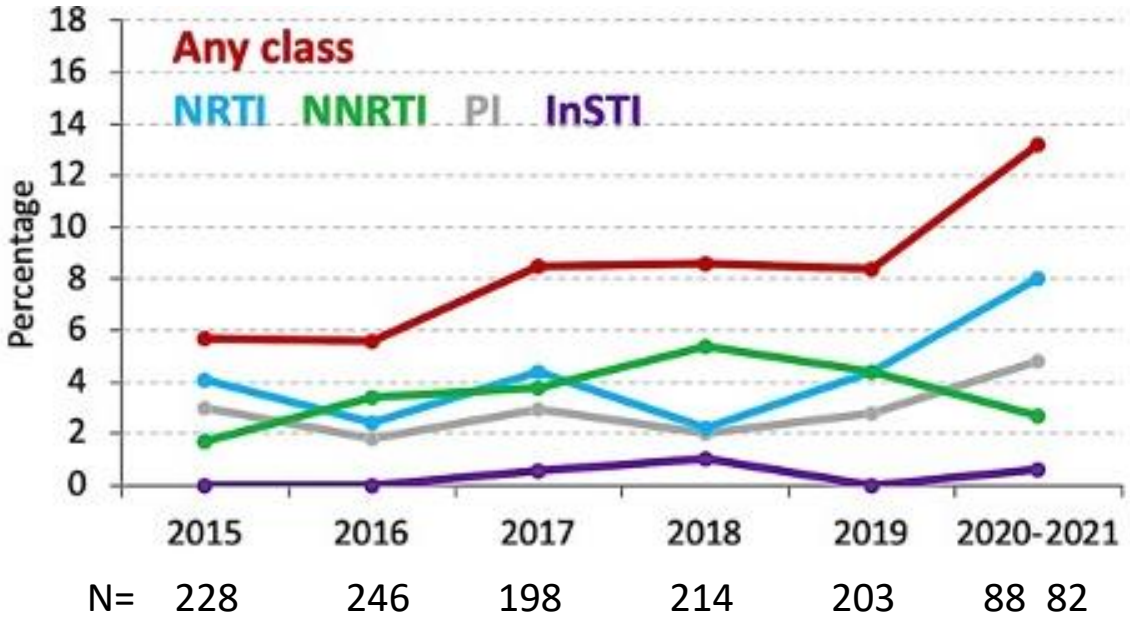
TDR= Transmitted drug resistance; VL= Viral load

1. Geretti et al. EACS 2023
2. https://hivdb.stanford.edu/pages/surveillance.html
3. Tzou et al. J Antimicrob Chemother. 2020

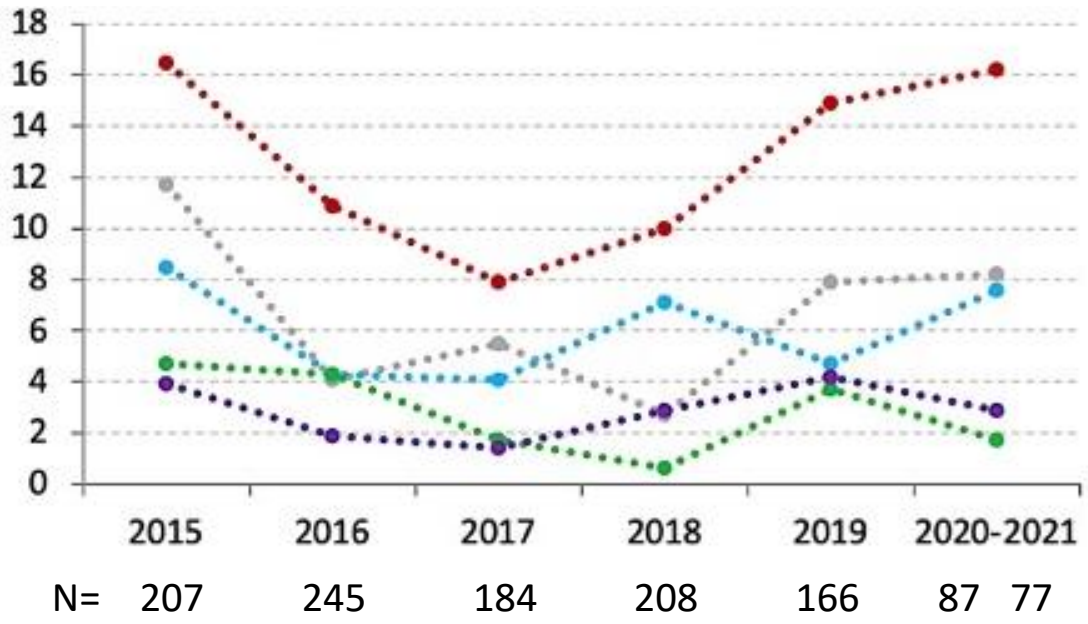
TDR in Recent HIV Infections, England 2015-2019[1]

- **Population:** n=1211; median age 32, 90% male, 71% MSM, 71% White, 46% from London
- **Sequences:** PR n=1136, RT n=1028; INT n=1140

Majority RAMs*



Minority RAMs§



*INSTI RAMs: 2017 n=1 E138K;
2018 n=1 E92G + n=1 E138K; 2020-2021 n=1 R263K

§T66AIK, E92GQ, G118R, E138K, G140AC, Y143CH, S147G, Q148H, N155H

1. Geretti et al. EACS 2023

Class	RAM	2015		2016		2017		2018		2019		2020		2021	
		>20%	2-20%	>20%	2-20%	>20%	2-20%	>20%	2-20%	>20%	2-20%	>20%	2-20%	>20%	2-20%
NRTIs	M41L					2	1	1		2		2	1		
	K65R												1		
	D67EGN		2	1	2	1	1		6	1			1		4
	T69D								1						
	K70R	1													
	K70E								1						
	L74IV										2	2			
	V75A														1
	F77L	1			1									1	
	M184IV		1		1	1		2			3			4	1
	L210W					1	1			1		1			
	T215DEIS	2		3		2	1	1	4	3		2			
	K219NQR	3	2	1		2	1		1	1					
INSTIs	T66AIK				1				1		3				1
	E92GQ							1	1						1
	G118R				1						1				
	E138K		2		1	1	1	1	1		1				
	G140AC		1						1						
	Y143CH		3		1								1		
	S147G										1				
	Q148H								1				1		
	N155H						1								
	R263K											1			

TDR in Recent HIV Infections, England 2015-2019[1]

Other observations

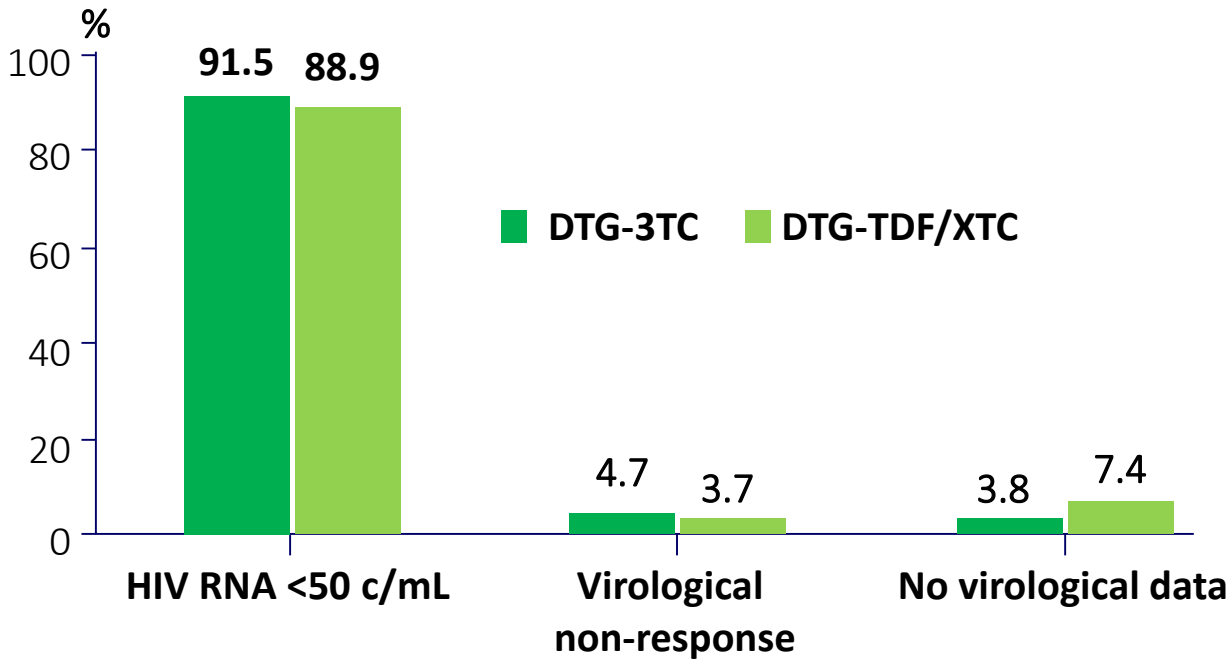
- Most cases of majority TDR were single RAMs
  - 11 samples had >1 RAM: n=10 with 2 RAMs, n=1 with 3 RAMs, n= 1 with 7 RAMs
  - None of the samples with multiple RAMs had INSTI RAMs
- Through the years, subtype B ↓ from 55% to 37%, subtype A6 ↑ from 0% to 3.5%

1. Geretti et al. EACS 2023

D2ARLING: 1st line ART Without Baseline Genotype

- Randomised, open-label, single-centre trial (Argentina)
- n=214 ART-naïve adults without baseline resistance test randomised 1:1 DTG/3TC vs DTG+TDF+XTC

Virological responses (wk 48 ITT-e, snapshot)



HIV RNA <50 c/mL at wk 48 by BL VL and CD4

Baseline	DTG/3TC	DTG+TDF+XTC
HIV RNA >100,000 c/mL	31/33 (94%)	28/33 (85%)
CD4 <200 cells/mm³	17/21 (81%)	22/23 (96%)

Cordova et al. HIV Glasgow 2024, Abs. P044

Key Take Aways for Clinical Practice

INSTI TDR currently rare in high-income countries

INSTI RAMs can occur as minority variants, but significance is uncertain

Common forms of NRTI TDR unlikely to impact the activity of DTG or BIC based ART

Baseline resistance testing continues to have a role when considering a life-time of ART

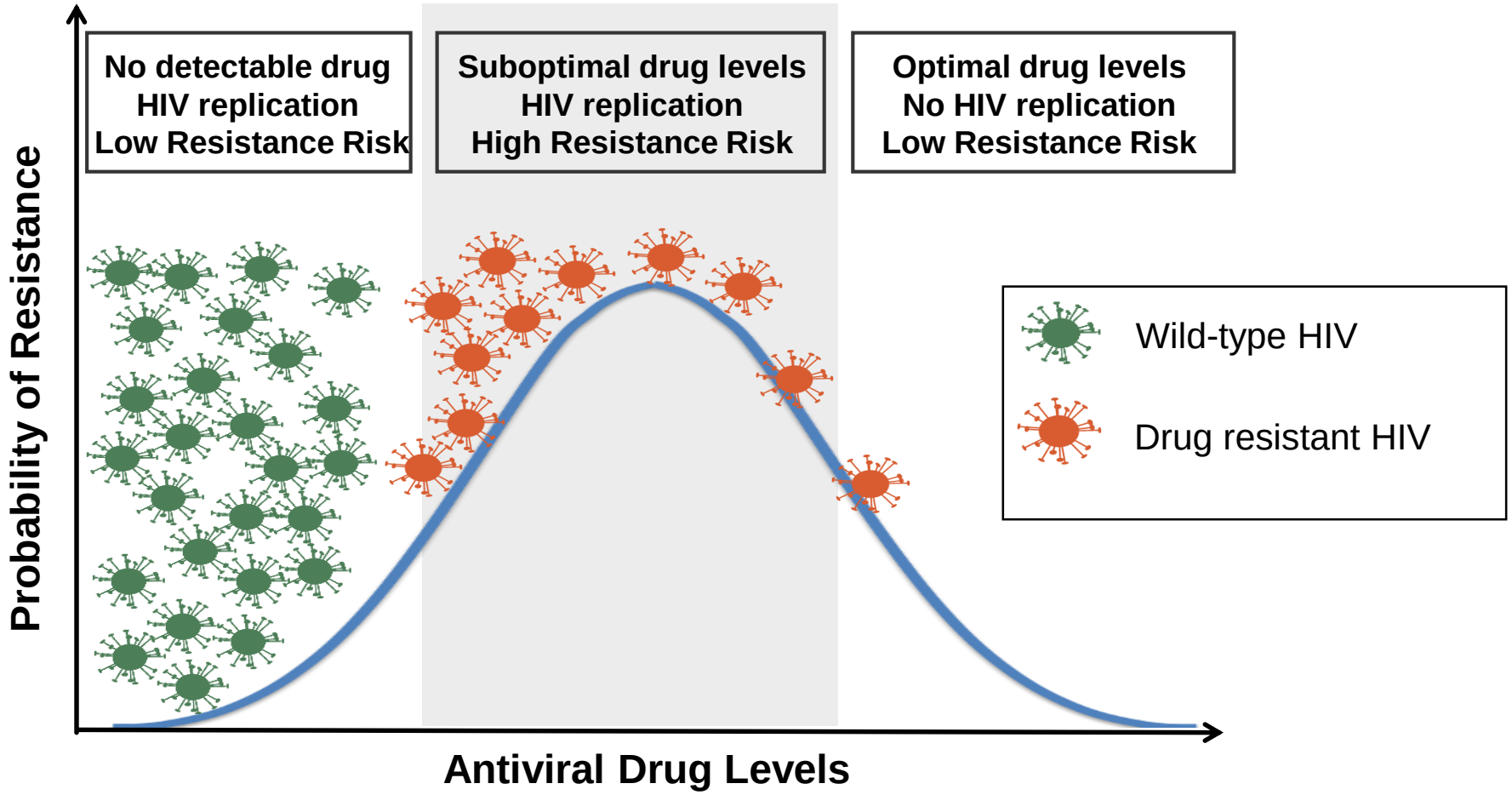
Although prevalence of INSTI RAMs is low, baseline testing should include integrase

Types of HIV Drug Resistance

Acquired

Resistance that emerges during viral replication in the presence of drug pressure

Emergence of drug resistance requires co-existing virus replication and drug pressure



Tang et al. Drugs 2012; Gardner et al. AIDS 2009; DHHS. Drug Resistance 2019

Barrier to Resistance: A Simplified Overview

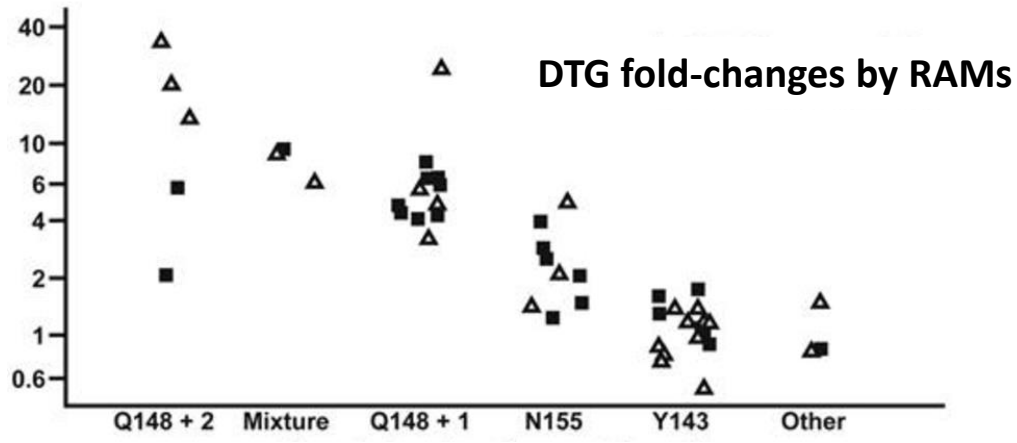
Class	Barrier			Emergence of resistance during viraemia	Activity in viraemic individuals despite resistance
NRTIs	+	→	++	Abacavir + 3TC > Tenofovir + XTC	Demonstrated for Tenofovir + XTC TAF > TDF *(in vitro)*
NNRTIs	+	→	++	Likely	Demonstrated for Etravirine + DRV/r Doravirine: Limited clinical evidence
INSTIs	+	→	+++	Raltegravir Elvitegravir Cabotegravir > Bictegravir Dolutegravir	Demonstrated for DTG BID
Boosted PIs	+++	→	++++	Uncommon	Multiple mutations required to abolish activity
Entry Inhibitors	+	→	++	T20 Ibalizumab > Fostemsavir Maraviroc	Not expected
Lenacapavir		++		Common	To be confirmed

3TC= Lamivudine; XTC= Lamivudine or Emtricitabine; TAF= Tenofovir alafenamide; TDF= Tenofovir disoproxil fumarate; DRV/r= Darunavir/ritonavir; DTG= Dolutegravir; BID= Twice daily; BIC= Bictegravir; T20= Enfuvirtide

1. Ogbuagu et al. CROI 2023 Abs. 523

INSTI Resistance in Clinical Practice

Treated with INSTI	First or subsequent line, pre-existing RAMs, adherence, disease stage
Viraemic	Frequency of monitoring, level and duration of viraemia
Tested for resistance	Viral load cut-off, Sanger vs. NGS
RAMs detected	Key RAMs: G118R, N155H, **Q148HKR**, R263K
Interpretation of resistance	Impact of RAMs



Eron et al. JID 2012

INSTI Resistance in Clinical Trials

Treated with 2NRTIs + DTG or DTG + 3TC – 1st line* N=4146

Tested for resistance N=71

RAMs detected N=0

Treated with 2NRTIs + DTG or DTG + 3TC – Switch§ N=2702

Tested for resistance N=14

RAMs detected N=2

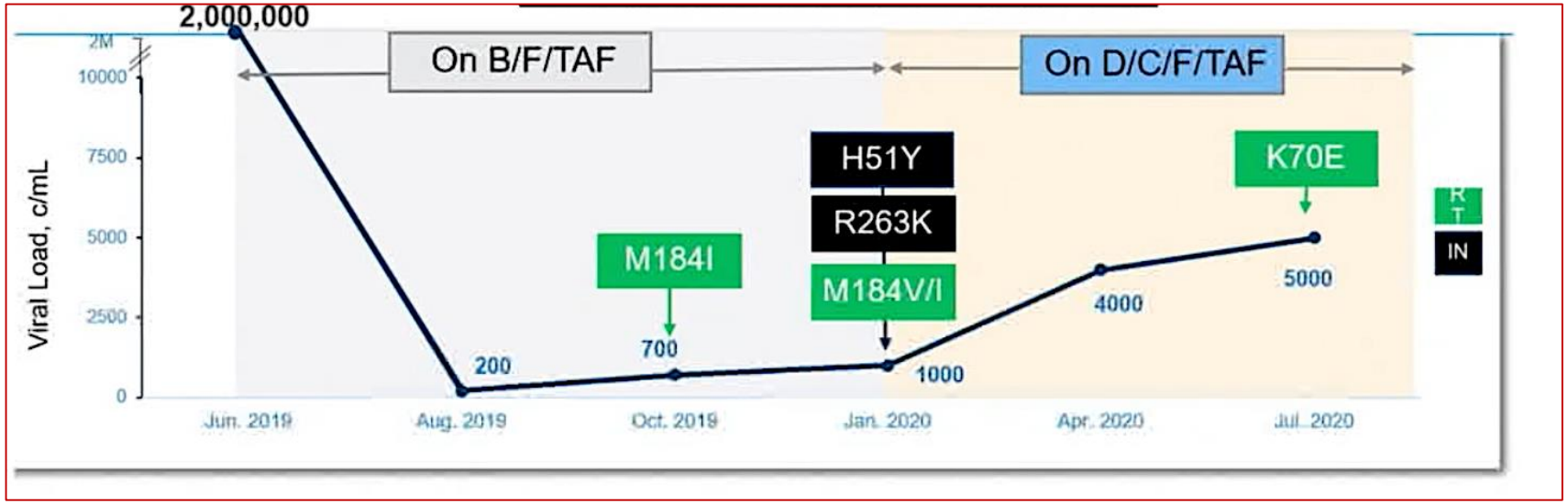
*ADVANCE, NAMSAL, SPIRNG-1&2, SINGLE, GEMINI, FLAMINGO, ARIA, INSPIRING, GS1489315, GS 1490325, ODYSSEY-A

§SWORD, CARES, TANGO, SALSA, GS-1844, ARTIST, ASPIRE, 2SD, NEAT 022, STRIVING

INSTI Resistance in Clinical Trials

No emergence of INSTI RAMs in naïve and switch Phase 3/4 trials of B/F/TAF (n=>3500)

Case report



Late presenter
HIV RNA 2M c/mL
CD4 57 cells/mm^3
PML
Incomplete adherence

Braun et al. HIV Glasgow 2024. Poster 125

INSTI Resistance in a Nutshell

- DTG and BIC: high barrier, extremely low rates of resistance in high-income countries
  - *But resistance can occur*
  - *Predictors of DTG resistance: Previous failure, NRTI RAMs, DTG mono or dual therapy (cross-sectional dataset with heterogeneous treatment histories)*[1]
- Rates may be increasing in some cohorts in LMICs
  - *WHO Report 2024: Rates in viraemic patients 4-20%*[2]
  - *Mainly in the context of second-line ART, switching ART with viraemia, prolonged viraemia, previous failure, NRTI resistance*
  - *Lack of accurate prevalence estimates, variable numerators and denominators*
  - *Potential for transmission?*
- Extensive but not complete cross-resistance within the class

Resistance on DTG-based ART in Africa

Setting	HIV RNA copies/mL triggering test	% with integrase RAMs
North-East Lesotho[3]	Confirmed ≥50 or single ≥500	**10%**
Malawi, Age 2-14 years[4]	Confirmed ≥1000	**16%**
Togo, Children & Adolescents[5]	>200	**9%**

1. Loosli et al. Lancet HIV 2023; 2. https://www.who.int/news/item/05-03-2024-new-report-documents-increase-in-hiv-drug-resistance-to-dolutegravir; 3. Labhardt et al. CROI 2024 Abstract 678; 4. Bello et al. CROI 2024 Abstract 187; 5. Konu et al. CROI 2024 Abstract 987

INSTI Resistance in LESOTHO

Treated with INSTI N=15,349

Viraemic N=157 (infrequent monitoring)

Tested for resistance N=85

RAMs detected N=8

Interpretation of resistance High impact RAMs N=6

Tschumi et al. Clin Infect Dis 2024

INSTI Resistance in Clinical Trials

Treated with DTG-based ART – 2nd line* N=1832

Tested for resistance N=77

RAMs detected N=16 (G118R/S, E138K, G14OR, Q148R, R263K)

*ARTIST, RADIANT-TB, SAILING, DAWNING, NADIA, D2EFT, ODYSSEY-B

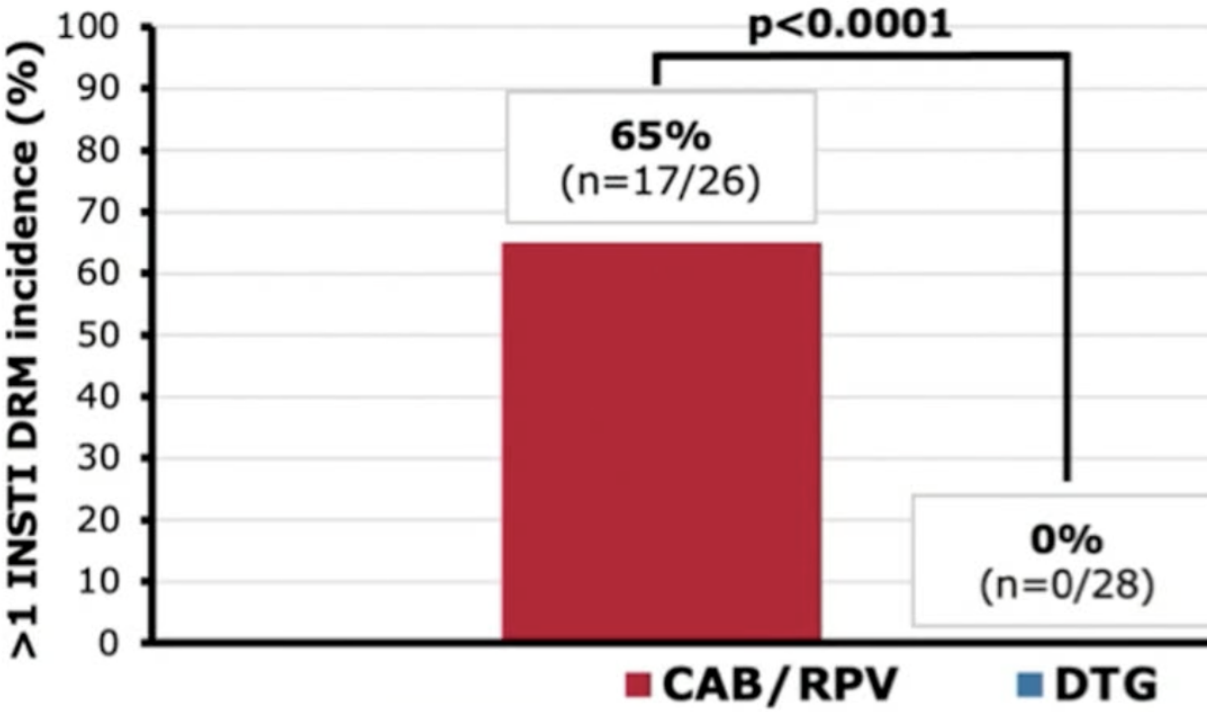
INSTI Resistance in Clinical Trials

Treated with CAB in switch studies — N=5703

Tested for resistance — N=26

RAMs detected — N=17

Risk of INSTI RAMs in switch studies



Perez-Navarro et al. IAS 2024

Key Take Aways for Clinical Practice

INSTI RAMs are rare in 1st line and switch use of DTG or BIC-based ART

Higher rates with CAB

Poor virological monitoring, previous failure, resistance to other regimen components, prolonged viraemia, and advanced disease increase the risk of INSTI RAMs

Higher drug exposure – *through higher adherence, absorption, or dosing* – can overcome some forms of INSTI resistance

No Q148 > Q148 +1 RAM > Q148 +2 RAMs predict the likelihood of a responses

Determinants of Drug Resistance

Virus

- Level of replication
- Fitness
- Genetic properties
- Phenotype
- Interaction between resistance pathways

Drugs

- Structure
- Intrinsic barrier
- Drug exposure vs. drug susceptibility *"Inhibitory quotient"*
- Regimen composition

Patient

- Adherence
- Immune status
- Factors that modulate adherence and drug exposure

HIV drug resistance is never a black or white phenomenon

INSTI Resistance: Themes

- Epidemiology
- Mechanisms
- Implications
- **Q&A**

Thank you