Primary resistance to integrase strand transfer inhibitors in patients infected with diverse HIV-1 subtypes in sub-Saharan Africa

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Introduction

- WHO since 2016 recommends the use of dolutegravir INSTI as an alternative first-line regimen for use in LMIC's (WHO 2016 consolidated HIV treatment guidelines)

- Due to a rise in pre-treatment drug resistance (PDR), WHO provisional guidelines recommends use of dolutegravir as preferred first-line in countries with PDR ≥10% (WHO 2017 guidelines on response to pre-treatment HIV drug resistance)

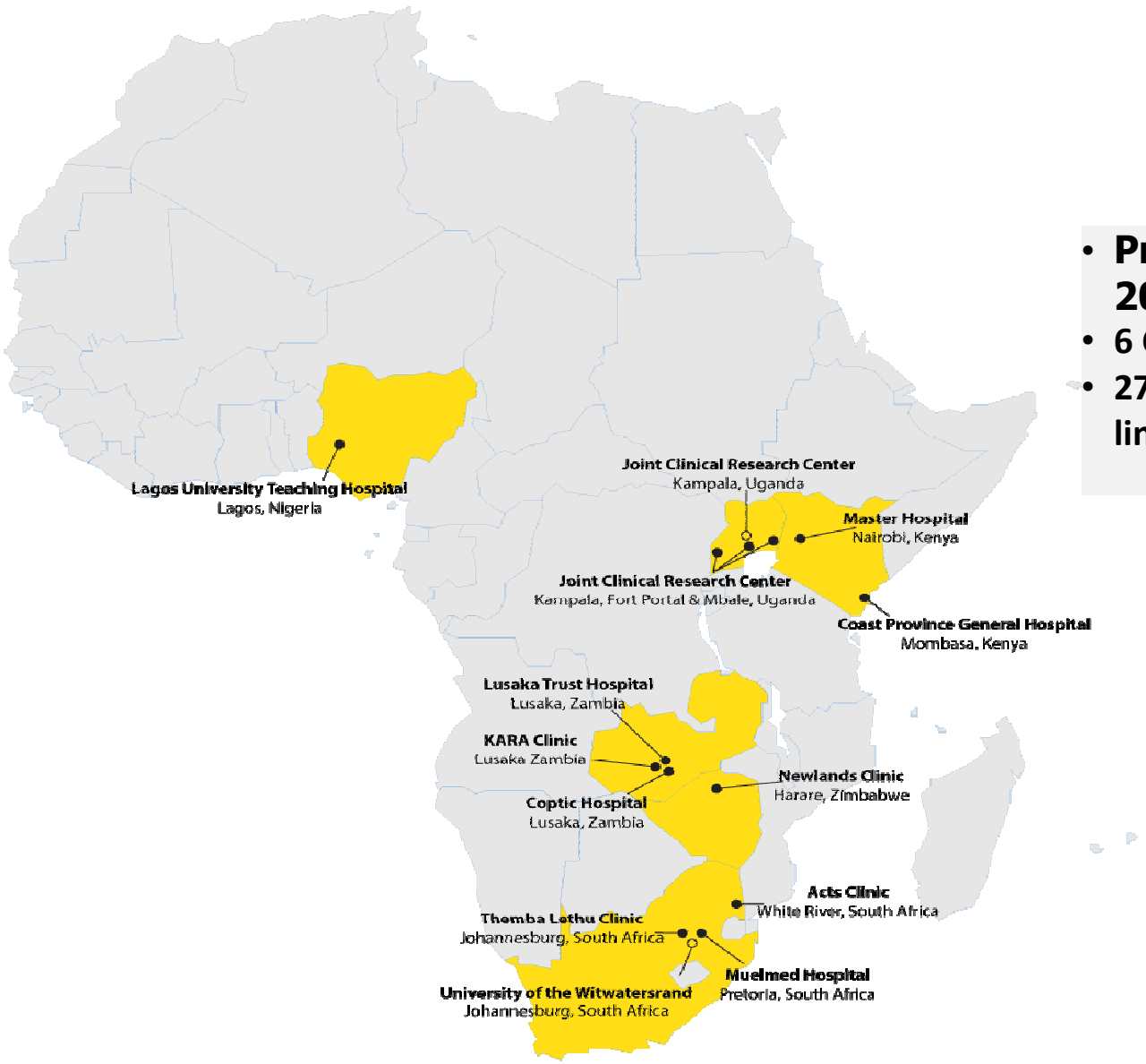
- There is however limited information on primary INSTI resistance for non-B subtypes

- Studies also suggest subtype influence in the pattern of DTG resistance (Quashie PK et al, *JVI* 2012)
  - R263K mainly observed in subtype B
  - G118R observed in non-B subtypes and influenced by codon usage

Methods

Aim: To assess the prevalence of major and accessory INSTI resistance mutations, across diverse HIV-1 subtypes in sub-Saharan Africa

- Secondary aim: To assess codon usage at position G118 influencing occurrence of DTG resistance in non-B subtypes



PASER
PAN-AFRICAN STUDIES TO EVALUATE RESISTANCE

- **Prospective cohort study 2007-2016**
- **6 Countries, 13 clinic sites**
- **2733 patients initiating on first-line**

6 countries, **13** clinical sites

Methods

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- Study design: Baseline analysis of samples from 489 patients selected in a case-control, PASER sub-study to assess impact of minority variants
  - Cases -viral-load (VL) >400 cps/ml @ 12 months
  - 2 Controls matched on baseline Viral-load, CD4 counts, age and country

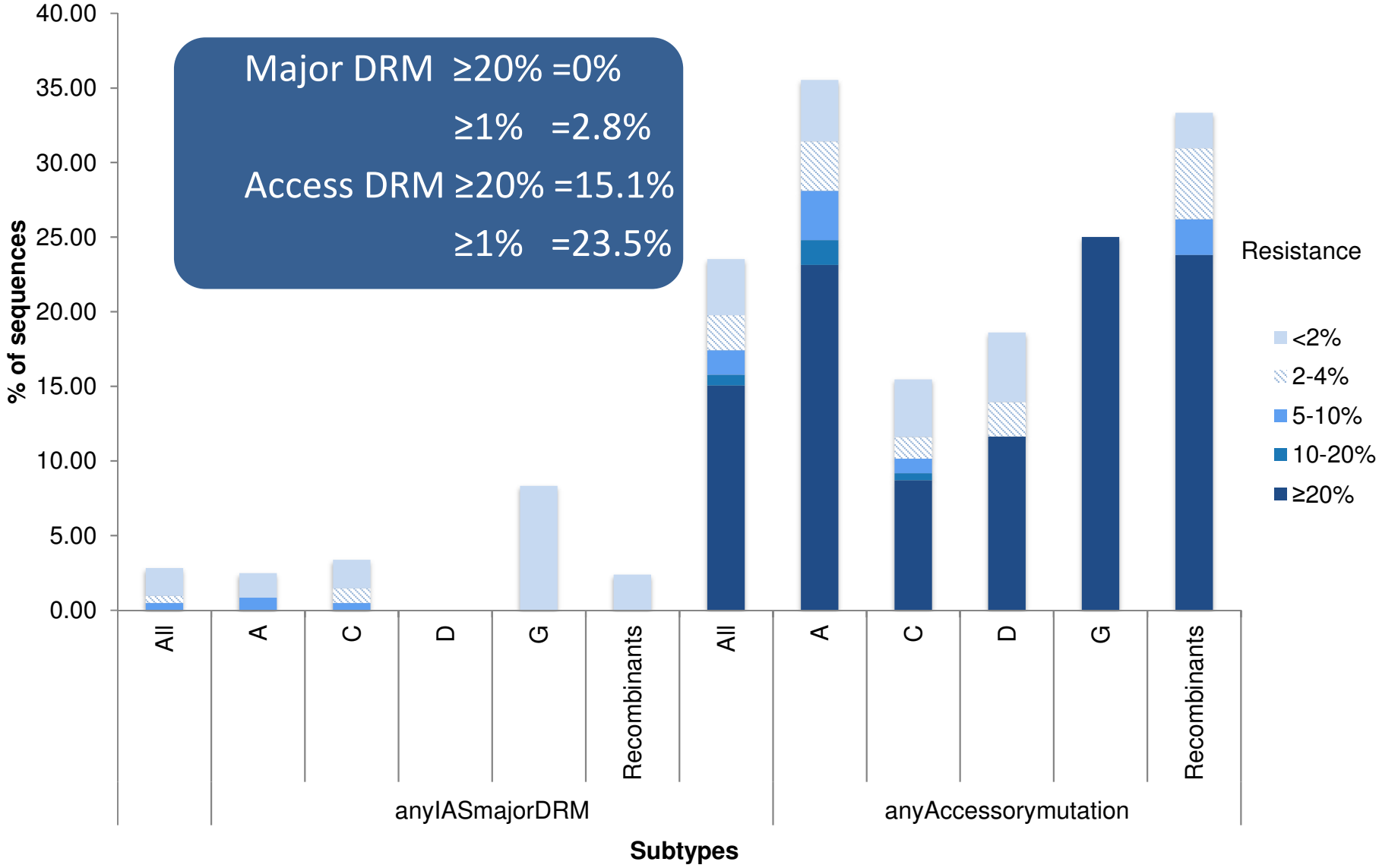
Methods

- Sequencing by Illumina Miseq NGS
- Sequence analysis: PASeq- automated HIVDR pipeline (IRSICaixa, Barcelona https://paseq.org
- Resistance classified by
  - Major DRM-IAS 2017 mutation list
  - Accessory DRM-IAS 2017 mutation list and with Stanford HIVdb ≥10 resistance penalty score
  - Resistance detection thresholds (≥20%, ≥10%, ≥5%, ≥2%, ≥1%)
- HIV subtyping by REGA v3.0

Results

- 425 (87%) of 489 samples successfully genotyped
- Uganda (25.2%), Zambia (23.5%), South Africa (22.8%), Kenya (21.2) and Nigeria (7.3%)
- Subtype C (48.7%), A (28.5%), D (10.1%), recombinants forms (9.9%) and G (2.8%)
  - AD (3.3%) CRF_02AG (2.1%), AC (1.4%) AG (0.9%), AG complex recombinants (1.4%) CD (0.5%), DG (0.2%)

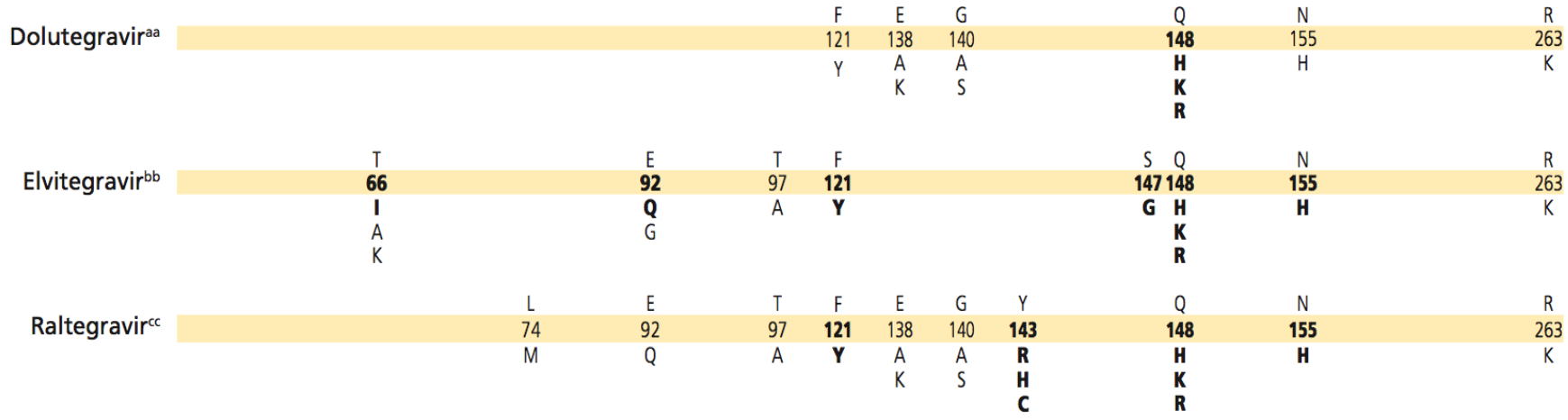
Prevalence of primary INSTI resistance across major subtypes in sub-Saharan Africa



Patterns of major DRM to INSTI regimens

Resistance Threshold[a]	Raltegravir/Eviltegravir							Dolutegravir		
	66	**92**	**121**	**143**	**147**	**148**	**155**	**148**	155	263
≥1%	0.7	0.5	-	0.7	0.2	0.7	0.2	0.7	0.2	0.2
≥2%	0.2	-	-	0.2	-	0.2	0.2	0.2	0.2	0.2
≥5%	0.2	-	-	-	-	0.2	-	0.2	-	-
≥10%	-	-	-	-	-	-	-	-	-	-
≥20%	-	-	-	-	-	-	-	-	-	-

[a]Cumulative resistance thresholds



Variations of primary INSTI DRMs by subtype

			All (n=425)	A (n=121)	C (n=207)	D (n=43)	G (n=12)	Recombinants (n=42)
[a]Any major mut			2.8	2.5	3.4	-	8.3	2.4
[a]Any access mut			23.5	35.5	15.5	18.6	25.0	33.3
L	74	I/M	10.4	14.0	7.7	7.0	16.7	14.3
Q	95	K	0.5	-	-	-	-	4.8
T	97	A	4.0	9.1	1.0	2.3	8.3	4.8
E	157	Q	0.7	-	0.5	2.3	-	2.4
G	163	R/K	0.7	1.7	-	2.3	-	-

[a]≥1%

Codon usage for G118 polymorphisms by subtype

	Glycine codon % (n)			
Subtype (n)	GGA	GGG	GGC	GGT
All (425)	4 (17)	2.1 (9)	83.1 (353)	10.8 (46)
A (121)	6.6 (8)	1.7 (2)	85.1 (103)	6.6 (8)
C (207)	3.4 (7)	1.4 (3)	79.2 (164)	15.9 (33)
D (43)	2.3 (1)	-	97.7 (42)	-
G	-	-	91.7 (11)	8.3 (1)
Recombinants (42)	2.4 (1)	9.5 (4)	78.6 (33)	9.5 (4)
[b]Subtype B (5128)	1.4 (69)	0.2 (10)	91.8 (4707)	6.0 (307)

GGA and GGG have low genetic barrier, single nucleotide transition from glycine to Arginine

GGA→AGA , GGG→AGG

Compared to transversion or two step transition for GGC and GGT

GGC→AGA , GGT→AGA or GGC→CGC, GGT→CGT

[b]*Data source:*Brenner BG et al JAC 2016

Conclusion and recommendation

- Low prevalence of major INSTI resistance present only at <20% threshold, gives some assurance for DTG efficacy
  - Real-life data is still required due to limited knowledge on DRM patterns in non-subtype B viruses
  - Need to determine the role and frequency threshold at which the pre-existing minority INSTI variants are likely to be clinically relevant
- High frequency of G118 polymorphisms with low genetic barrier to resistance
  - Suggest need for resistance monitoring with DTG rollout due to risk of novel resistance patterns previously unobserved in subtype B strains

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