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Mapping patterns of resistance to 2nd-gen INSTI in clinical practice: results from the ROSETTA-registry

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Disclosures

Potential conflict of interests	
Relations that could be relevant for the meeting	Investigator initiated grant Gilead Sciences paid to the UMCU
Sponsorship Payment or other remuneration Shareholder Other relation	No No No No

Rosetta Registry

Aim

Registration of cases with virological failure to 2nd –generation INSTI from clinical practices globally

Improve insight into the associated clinical features and resistance-mutation patterns

Study design

Case registry – Started in September 2023

Rosetta Registry

Inclusion criteria

- On ART for at least 6 months without evidence of current interruption
- Virological failure on 2nd-gen INSTI based ART in Europe, Africa or America´s *
- Associated clinical data of current ART and historical records of previous INSTI exposure
- Integrase (IN) sequences/samples drawn at time of failure to perform resistance testing

*Virological failure: 2 consecutive pVL> 50 copies/mL or a single pVL > 200 copies/mL

2nd Interim Analysis

1 Data selection

220 cases met the **inclusion criteria for the 2nd interim analysis**

1 sample could not be amplified

3 sequences excluded because of APOBEC hypermutation

2 Methodology

Subtype classification: COMET version 2.4

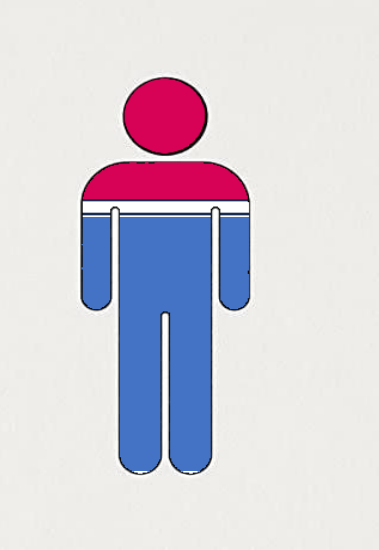
Definition of resistance:

- predicted low/intermediate/high level resistance to any 2nd-gen INSTI (Scores ≥ 15 from Stanford HIVDB Scores vs 9.6)

Statistical analysis: RStudio vs 2023.09.1+494

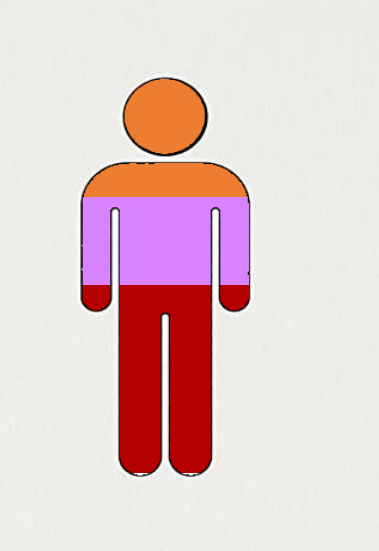
Socio-demographic Characteristics

Gender
(n=220)



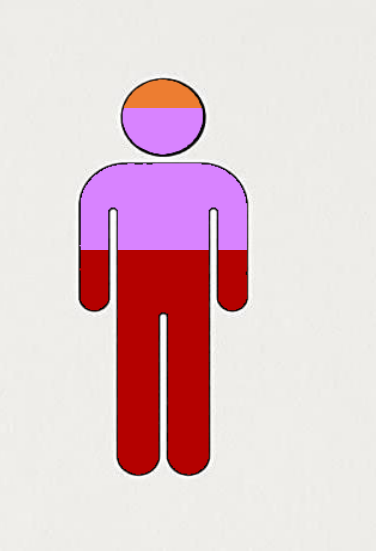
- Female (31.4%)
- Transgender (0.5%)
- Male (68.2%)

Region of Origin
(n=192)



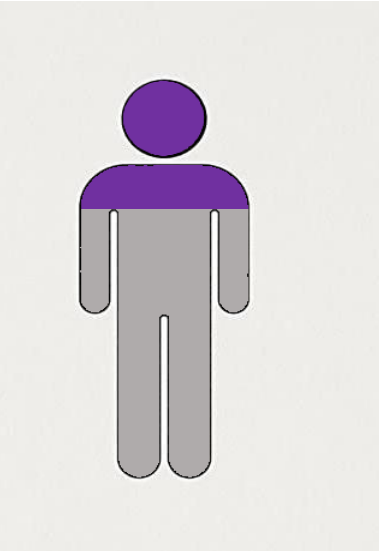
- Africa (21.4%)
- America (24.5%)
- Europe (40.9%)

Region of follow-up
(n=220)



- Africa (12.7%)
- America (23.2%)
- Europe (64.1%)

Disease Stage
(n=123)

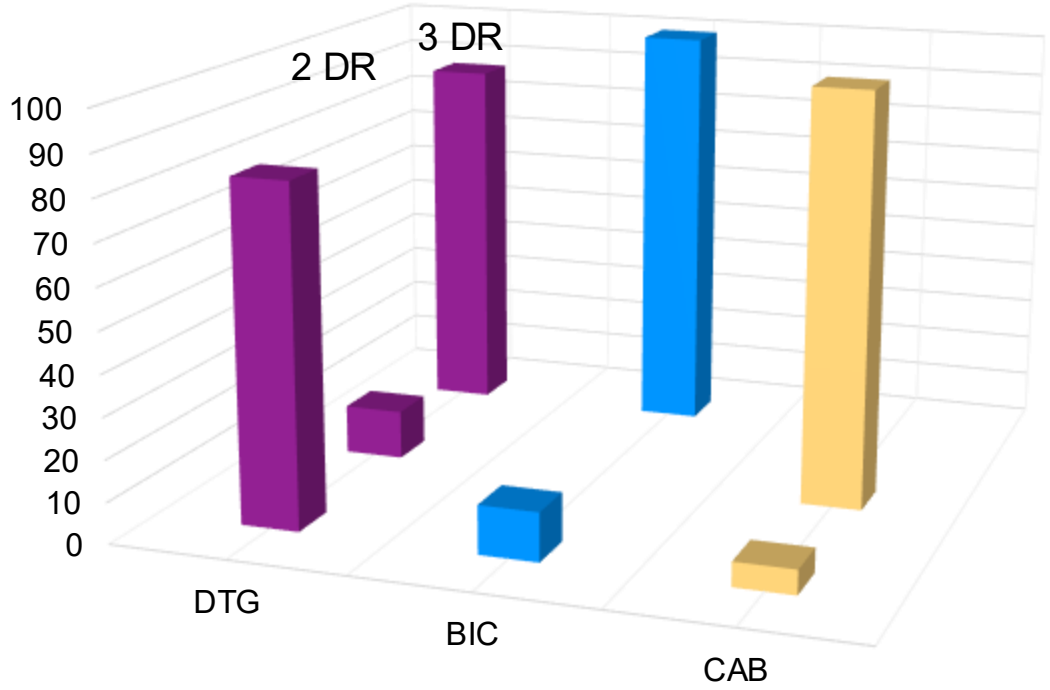


- AIDS (29.3%)
- No AIDS (71.7%)

Median age at failure: 42 years (IQR:34-51)

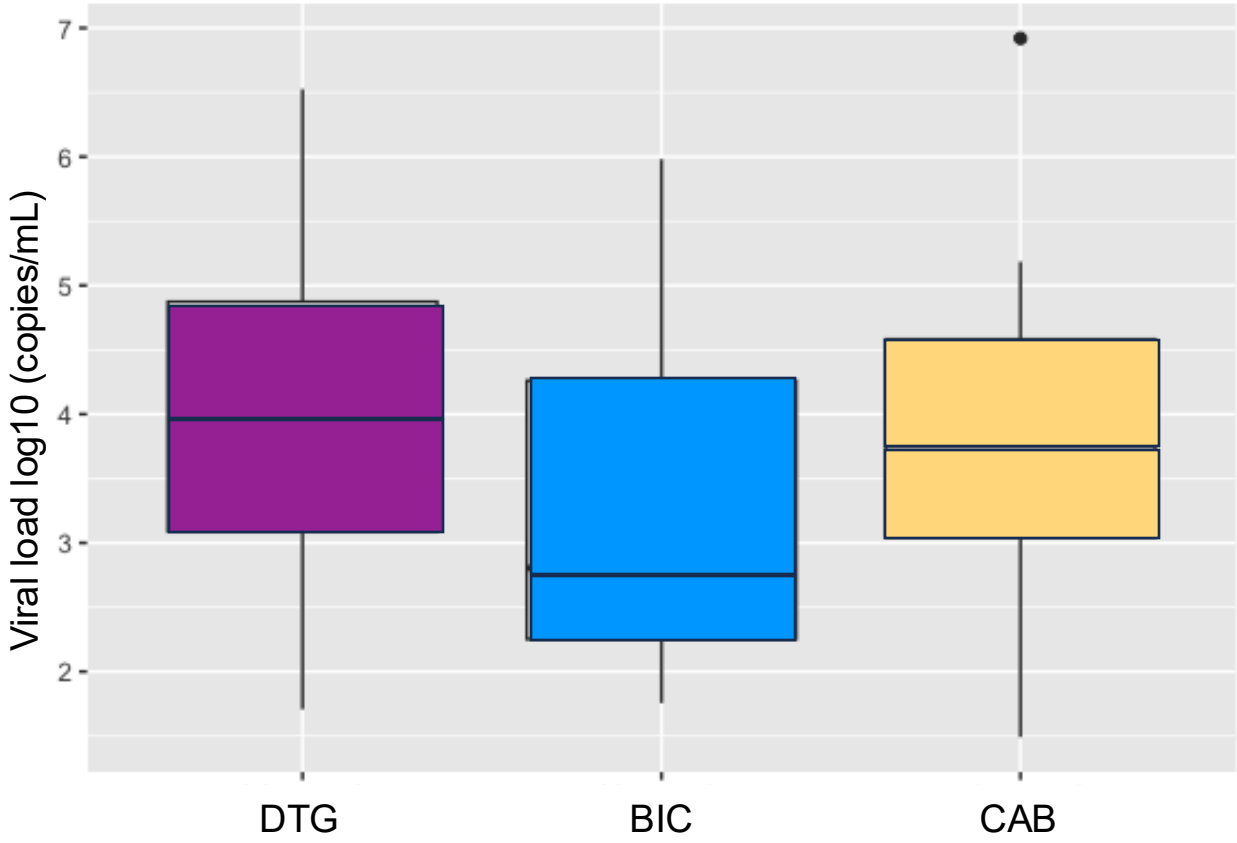
Characteristics of the study population

2nd-gen INSTI regimen at time of failure



	DTG (n=181)	BIC (n=26)	CAB (n=13)
All DR	82.3	11.8	5.9
with 2 DR	11.9	0	100
with 3 DR	88.1	100	0

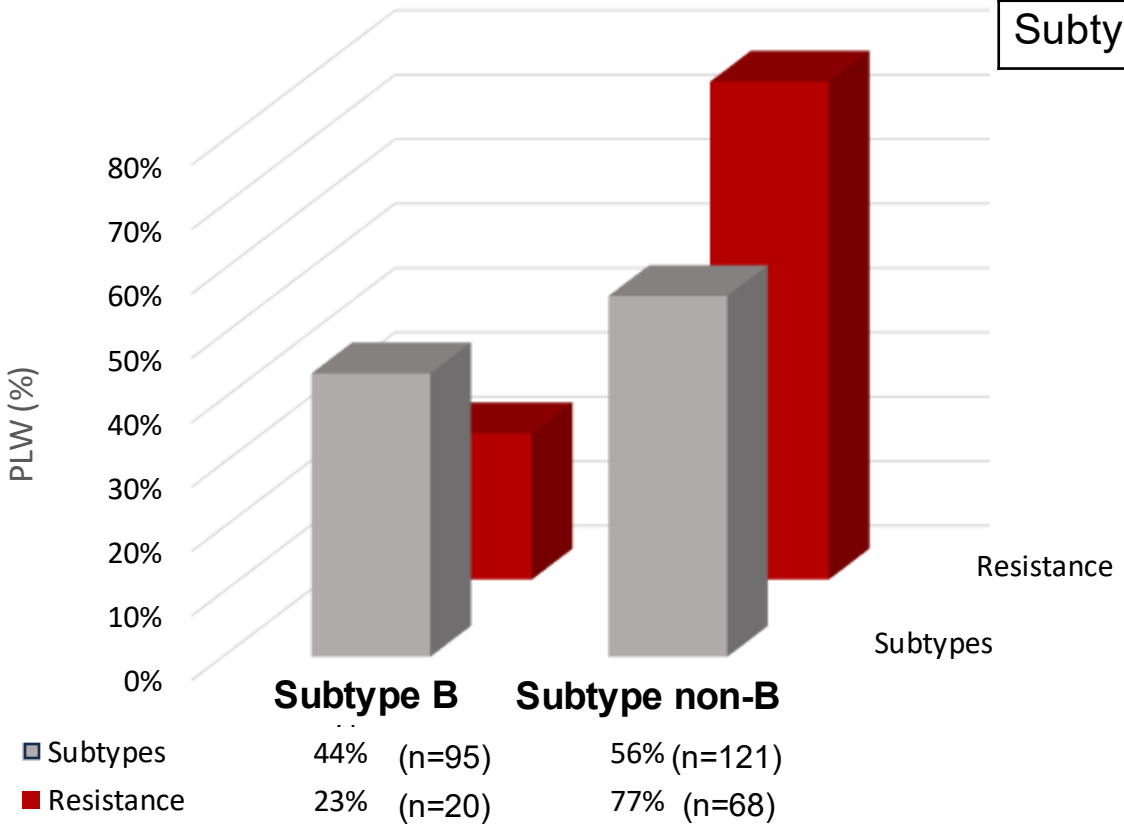
Viral load at failure per drug

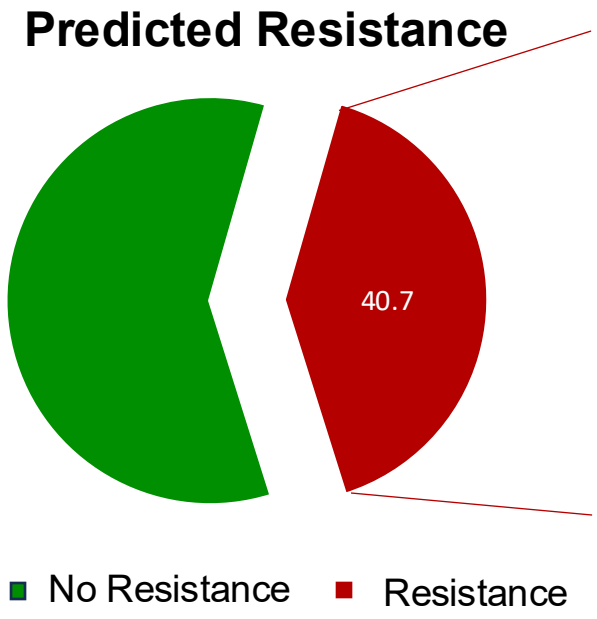


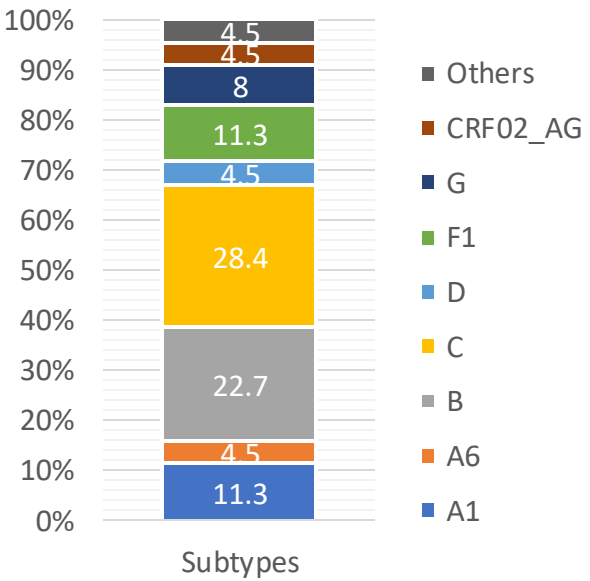
Resistance to 2nd-gen INSTI

Resistance detected in 88 individuals (40.7%)

Median time to failure on 2nd gen INSTI therapy (months) – median (IQR)		
With resistance mutations	13 months (6-28.5)	
No resistance	8 months (5-13)	**p=0.001**
Subtype B- resistance cases	17 months (7-34)	
Subtype non-B resistance cases	12 months (6-29)	p=0.654







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Resistance to 2nd-gen INSTI

Clinical Features	Prevalence of 2nd-gen INSTI Resistance	p-value
Clinical Stage, N = 121		
No AIDS vs AIDS	25.9% (22/85) vs (36.1% 13/36)	=0.258
Exposure before 2nd-gen INSTI, N = 216*		
Naïve vs experienced (BIC and DTG only, n=204)	15.4% (10/65) vs 51.1% (71/139)	**<0.001**
No 1st-gen exposure vs 1st-gen exposure	35.1% (60/171) vs 62.2% (28/45)	**=0.002**
DTG Regimen, N = 181		
Two drugs vs three drugs, N = 159	47.4% (9/19) vs 34.3% (48/140)	=0.264
Two drugs vs three drugs in naïve, N = 56	50% (1/2) vs 9.3% (5/54)	=0.068
VL at time of failure, N = 216		
≤1000 cp/mL vs >1000 cp/mL	38.6% (22/57) vs 41.5% (66/159)	=0.701
Time to failure on 2nd-gen INSTI, N =216*		
≤1 year vs > 1 year	31.1% (42/135) vs 59% (46/78)	**<0.001**

*confirmed in multivariate

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Specific mutational patterns to 2nd-gen INSTI

M184V

For xTC-containing regimens (n=148)
more common **with INSTI resistance** 77% (46/60) than **without** 9% (8/88) (**p<0.001**)

INSTI-mutations

R263K (n=21)

Less common following previous 1st-gen INSTI exposure (2/28 vs 19/60 **p=0.012**)
This observation was confirmed after correction for subtype B vs non-B (**p=0.043**)

G118R (n=14)

Less common following previous 1st-gen INSTI exposure (1/28 vs 13/60 **p=0.031**)
Likely a function of subtype as it was **not observed** in B at 1st time of failure (**p=0.027**)

G140S (n=10)

The genetic pathway towards this mutation **is easier for** subtype B*
Predominantly detected in PWH with subtype B (40%) vs non-B (2.9%) **p=0.019**

* Geretti and Leah…

Summary/Conclusions

- Three continent wide collection of virological failure and resistance cases to all 2nd-gen INSTIs
- We observe differences in resistance patterns based on previous ART exposure and subtypes
- As we enlarge our dataset we expect to gain more insights on these intertangled relationships

Implications:

This data has implications for both individual follow-up regimens and for the development of new INSTI regimens

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Thank you for your attention

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