Does Subtype Matter?

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Background

- We know HIV type matters:
  - NNRTIs don't work and some PIs don't work well in HIV-2
- We know HIV group matters:
  - Group O and first-generation NNRTIs
- Do we know if HIV subtype matters?
  - There are currently multiple subtypes and CRFs
  - Majority of information on treatment outcome and resistance is for subtype B limited data on C, D and A1.

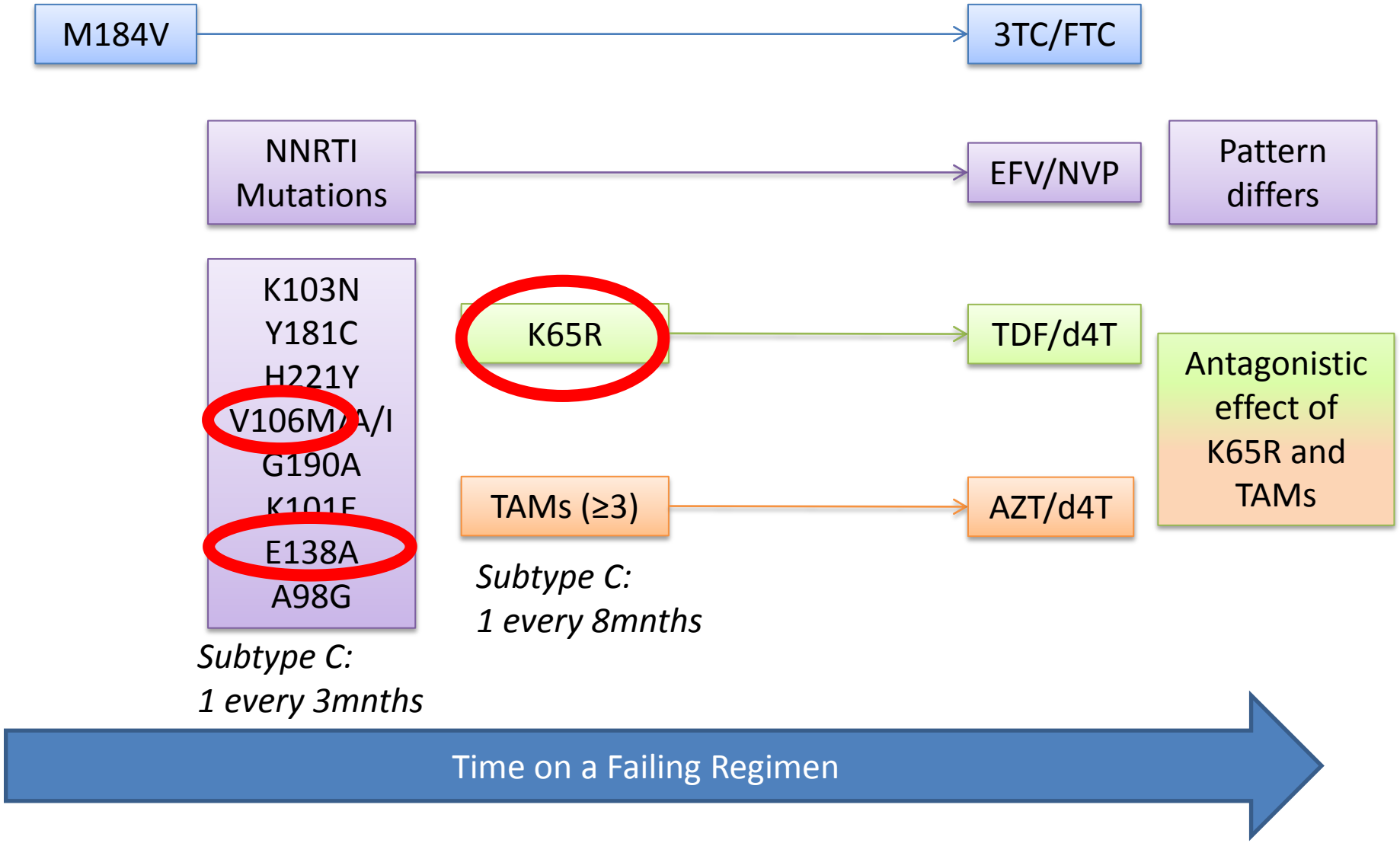
Where does the resistance come from?

- What type of resistance could the patient have:
  - PrEP
  - Transmitted
  - Acquired

- What are the mutation patterns:
  - Treatment history
  - Length of Treatment Failure
  - Region (subtype)

Site	South Africa Cape Town (Orrell et al., 2009)	South Africa Johannesburg (Wallis et al., 2010)	South Africa Durban (Marconi et al., 2008)	South Africa CIPRA-SA (Wallis et al. 2011)
Sample Size Clinical Sites	110 1	226 2	115 2	67 2
Switch Criteria	Viral load >5000 RNA copies/ml	Viral load >5000 or 1000 RNA copies/ml	Viral load >1000 RNA copies/ml	Viral load >1000 RNA copies/ml
Frequency of Monitoring	6 monthly-viral load & CD4+ T-cell	6 monthly-viral load & CD4+ T-cell	6 monthly-viral load & CD4+ T-cell	3 monthly-viral load & CD4+ T-cell
% with failure & resistance	85%	83%	83.5%	82%
M184V	78%	72%	64.3%	67.2%
NNRTI K103N	86% 55%	78% 38%	Unknown 51%	75% 50%
V106M	31%	17%	19%	14%
TAMS >3	23%	11%	32.2%	1.5%
K65R	9%	4.5%	2.6%	3%
Q151M	Unknown	2.5%	0.9%	0%
NRTI+NNRTI	83%	73%	64.3%	63%

Overview of First-line failure Mutations



RT Mutations associated with different subtypes

- Increase frequency of K65R after d4T exposure (Wallis et al., 2010) and TDF exposure (Sunpath et al., 2012);
- Subtype C development of V106M instead of V106A (Brenner, et al., 2003; Morris et al., 2003);
- K103N at greater frequency and higher levels in women with subtypes C and D rather than A (Flys; JAIDS, 2006);
- E138A naturally occurs in a higher level in subtype C compared to subtype B (Sluis-Cremer et al., Antiviral Res 2015).

Is K65R more prevalent in subtype C?

- Observed in 4.5% of patients (d4T)[1]
- Observed in 69% of patients (TDF)[2]
- The more frequent development of the K65R mutation may be a result of subtype C nucleotide sequence difference and/or a delay in treatment switch and or combination of d4T and TDF treatment.
- A5273[3]
  - Occurred in 22% (107) participants:
  - 2% (n=5) treated with ZDV/d4T;
  - 70% (n=63) treated with TDF;
  - 38% (n=39) treated with both TDF and ZDV/d4T.

1: Wallis et al., JAIDs 2010; 2:Sunpath et al., AIDs 2012; 3 Wallis et al., IHIVDRW 2016

K65R and Subtype

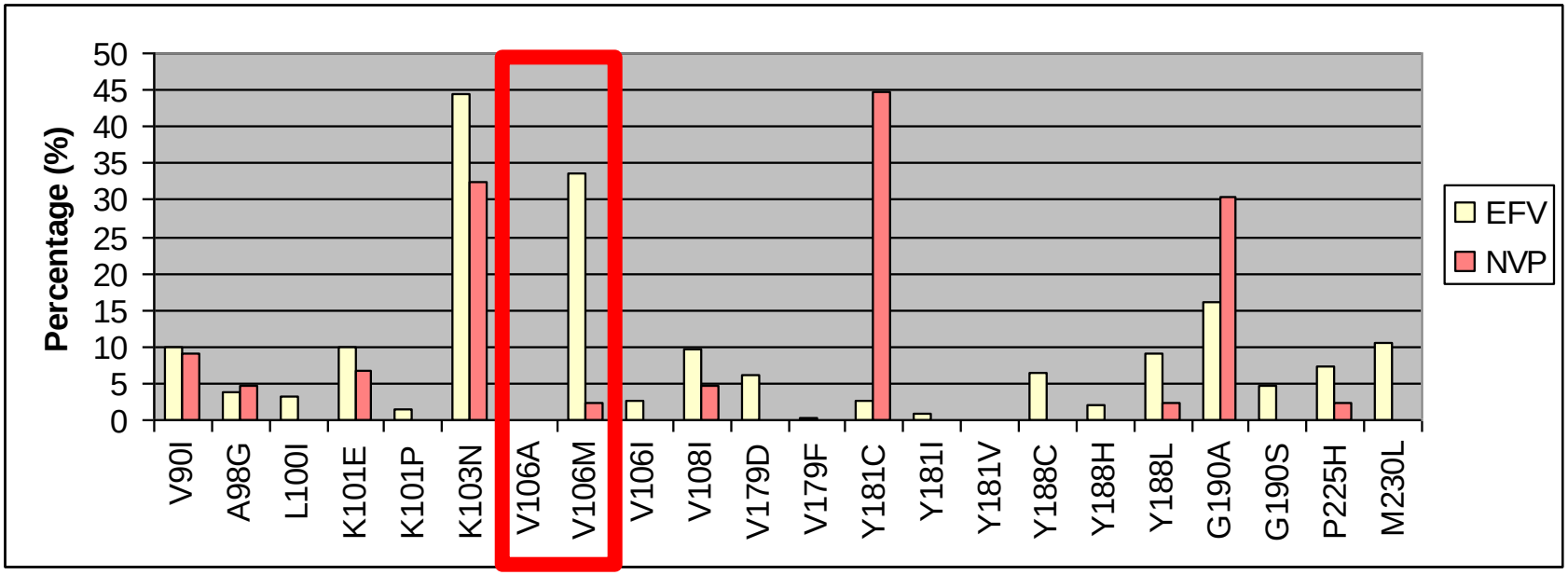
- Culture studies have revealed K65R occurs faster in HIV-1 subtype C (Brenner, AIDS 2006).

- 11% of patients infected with CRF02_AG majority failing a TNF based regimen in Nigeria developed K65R (Hawkins, JAIDS 2009).

	Subtype			
Mutation	A (n = 32), n (%)	C (n = 15), n (%)	D (n = 15), n (%)	*P**
M184V	23 (72)	10 (67)	8 (53)	0.50
K65R	5 (16)	3 (20)	0 (0)	0.20†
No. TAMs				
0	10 (32)	4 (27)	8 (53)	0.19‡
1–2	6 (19)	3 (20)	4 (27)	
3–4	14 (44)	8 (53)	3 (13)	
5–6	2 (6)	0 (0)	1 (7)	
TAM group§				
I	1 (5)	2 (18)	2 (29)	0.47
II	7 (32)	3 (27)	2 (29)	
I+II	14 (64)	6 (55)	3 (43)	

Lyagoba et al., JAIDs 2010

EFV vs. NVP based Regimens: NNRTI mutations



- Y181C is selected by NVP more than EFV
- V106M is selected more by EFV (34%) than NVP (2%)
- Wider range mutations selected for by EFV rather than NVP
- Small % NNRTI (5%) alone

Wallis et al., JAIDs 2010

E138A and Subtype C

- E138A is more common in subtype C than subtype B;
- In one of the databases (Stanford University), E138K and E138Q were also more common in RTI experienced subtype C sequences (1.0% and 1.1%, respectively) than in subtype B sequences (0.3% and 0.6%, respectively).
- E138A/K/Q in subtype C decreased RPV susceptibility 2.9-, 5.8-, and 5.4-fold, respectively.
- Taken together, these data suggest that E138A could impact treatment or prevention strategies that include RPV in geographic areas where subtype C infection is prevalent.

Sluis-Cremer et al., Antiviral Res 2014

Etravirine (ETR, TMC125, Intelence®): resistance profile

- 20 ETR resistance-associated mutations (genotype) were defined
- weight factors for each mutation present in a sample are added together to give a total weighted genotypic score, predicting treatment response to ETR

Weight factors for individual ETR RAMs

Y181I	3
Y181V	3
K101P	2.5
L100I	2.5
Y181C	2.5
M230L	2.5
E138A	1.5
V106I	1.5
G190S	1.5
V179F[§]	1.5
V90I	1
V179D	1
K101E	1
K101H	1
A98G	1
V179T	1
G190A	1
E138G	1
E138K	1
E138Q	1

Add together

ETR Weighted Genotypic Score

≤2 - highest response

2.5-3.5 - intermediate response

≥4 - reduced response

Note: presence of K103N did not affect virologic response in the phase III DUET studies

[§]V179F was never present as single ETR RAM (always with Y181C)

In case of a mixture of 2 ETR RAMs at the same position, the one with the highest weight only is counted.

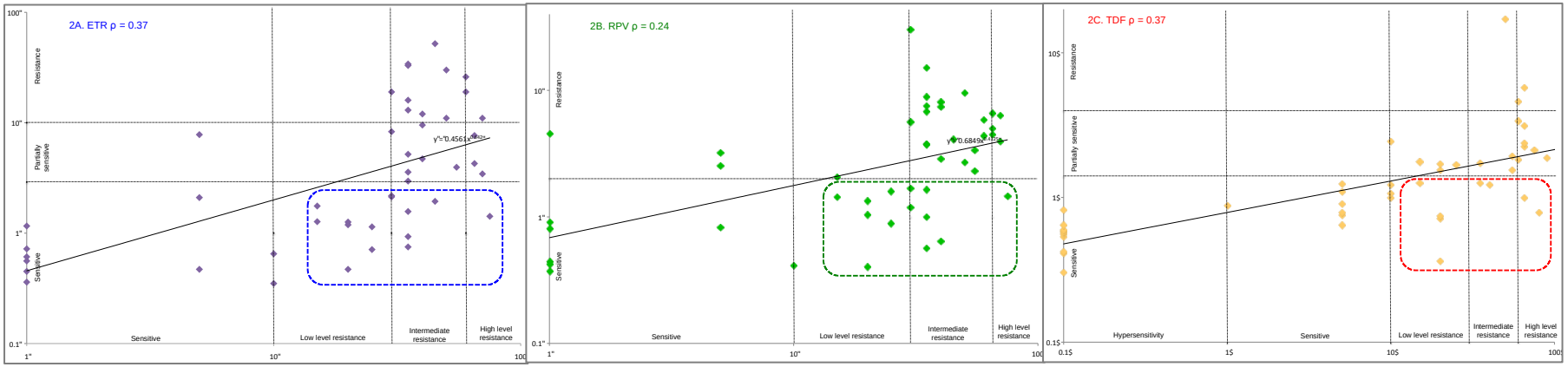
Vingerhoets, et al. AIDS 2010;24:503-514

Tambuyzer, et al. JAIDS 2011;58:18-22

Phenotyping and Subtype C

- Phenotypic analysis different for subtype C, when compared to genotyping prediction (either full RT or partial RT).
  - Concordance: NVP, EFV and 3TC
  - Differences: TDF, RPV and ETR misclassified 17, 30 and 30% respectively of isolates which demonstrated phenotypic susceptibility despite estimated genotypic resistance.

- This may result from the presence of compensatory and/or epistatic mutations in RT which increase susceptibility to ETR, RPV and TDF.



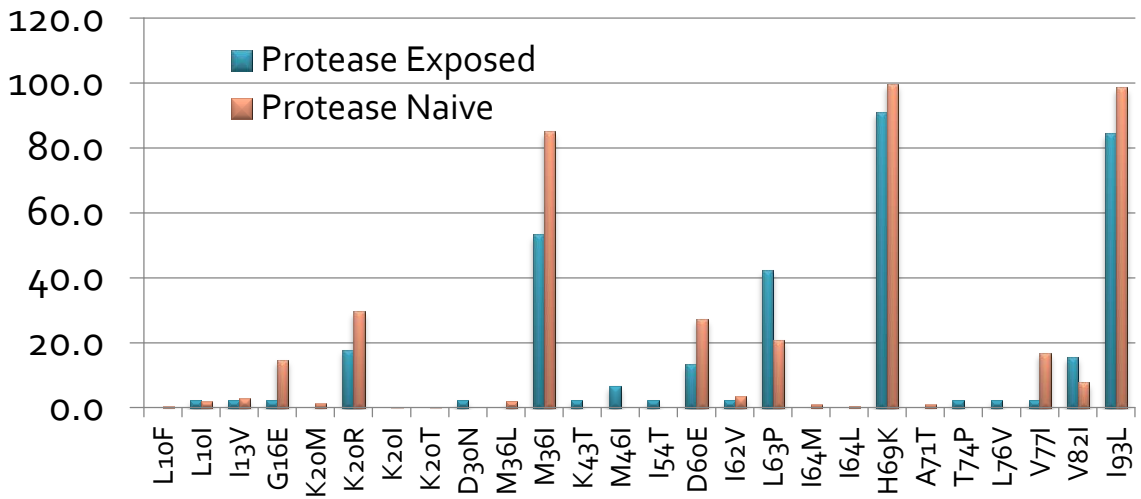
Derache et al., JID 2016

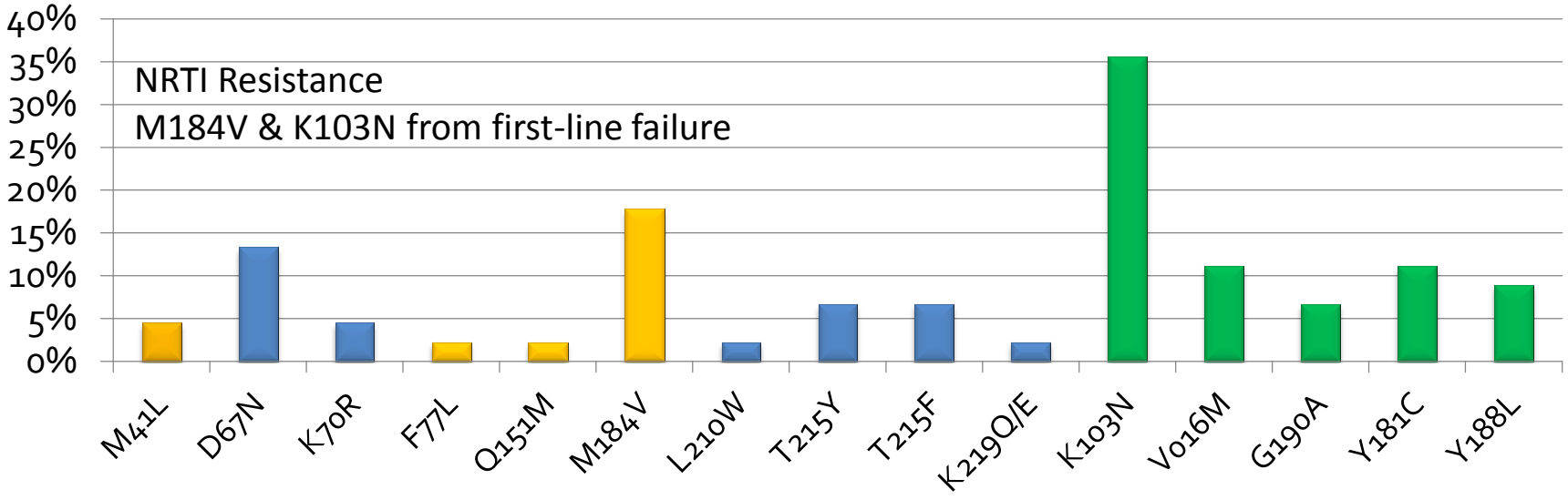
PR Mutations associated with different subtypes

- HIV subtype C viruses failing Nelfinavir have been shown to have subtype specific mutations;
- Baseline polymorphisms in subtype C in the protease regions (Cane, et al., 2001; Grossman, et al., 2001);
- HIV-1 subtype influences susceptibility and response to monotherapy with the protease inhibitor lopinavir/ritonavir (Sutherland et al., 2015).

LPV/r Mutation Profiles

- 45% of the patients had no mutations
- 3/45 patients had PI mutations present at time of failure: 2x L76V; 1x V82A

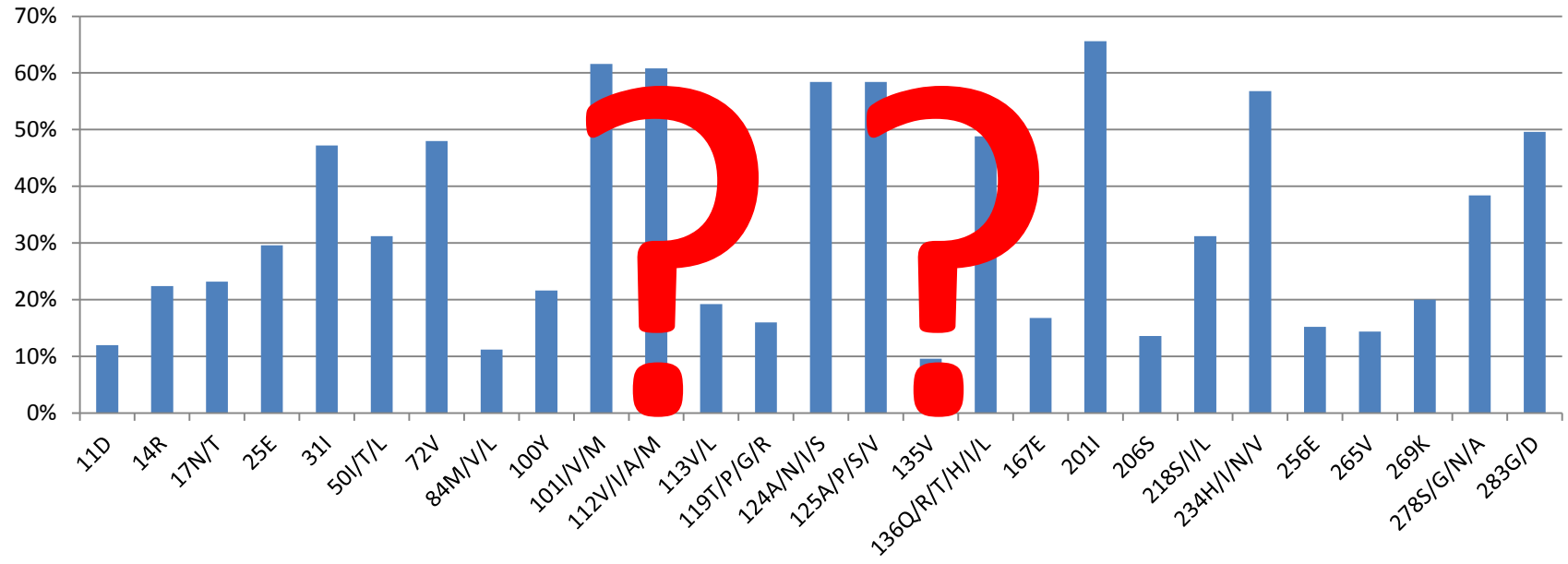




Wallis et al., AIDS Res Treat. 2011

Integrase Mutations associated with different subtypes

- Don’t really know hopefully A5273 and A5288 can contribute to this information



Integrase Polymorphisms (differences from HXB2) in HIV Subtype C Integrase Naïve subjects. To date, none of these polymorphisms have been linked to reducing integrase activity.

Conclusion

- Time on failing regimen could be magnifying the subtype specific mutations.

- Treatment:
  - Don’t think subtype matters for NRTI and PI
  - Might matter for next generation NNRTIs
  - Integrase ???

- PrEP:
  - NRTI: unlikely low viral fitness of K65R
  - NNRTI: Yes…E138A??

Acknowledgments

Team Members for both A5273 and A5288

Participating Sites

Site ID	SiteName
11101	Wits HIV CRS
11201	Durban Adult HIV CRS
11301	IMPACTA Barranco, CRS
11302	IMPACTA San Miguel, CRS
11501	Chiang Mai Univ. ACTG CRS
11601	NARI Pune CRS
11701	YRG CARE Medical Ctr., VHS CRS
12001	University of North Carolina Lilongwe CRS
12101	Instituto de Pesquisa Clínica Evandro Chagas
12301	Soweto ACTG CRS
12601	Moi University International CRS
12901	Kilimanjaro Christian Medical CRS
30301	College of Med. JHU CRS - Blantyre
30313	UZ-Parirenyatwa CRS - Harare
31441	BJ Medical College CRS

Study participants

HIV Genotyping Labs/Staff

Univ. of Pittsburgh
Lancet/BARC Labs
YRGCare
FIOCRUZ

Industry Collaborators

AbbVie
Gilead Sciences, Inc
GlaxoSmithKline
Merck and Company

What else do we need to know about HIVDR virology?

- Is archived resistance transmitted?
- Should HIVDR testing of archived variants be considered?
- Lessons learned from Prevention of mother-to-child transmission.
- What are kinetics of laying down resistance in the archived reservoir?
- Subtleties of K65R testing; what is role of prep?
- Are we missing important PI mutations? What about INSTI? When should INSTI resistance be part of usual genotyping?