Transmission of Antiretroviral Drug Resistance and Potential Impact on Selection of First-Line Therapy

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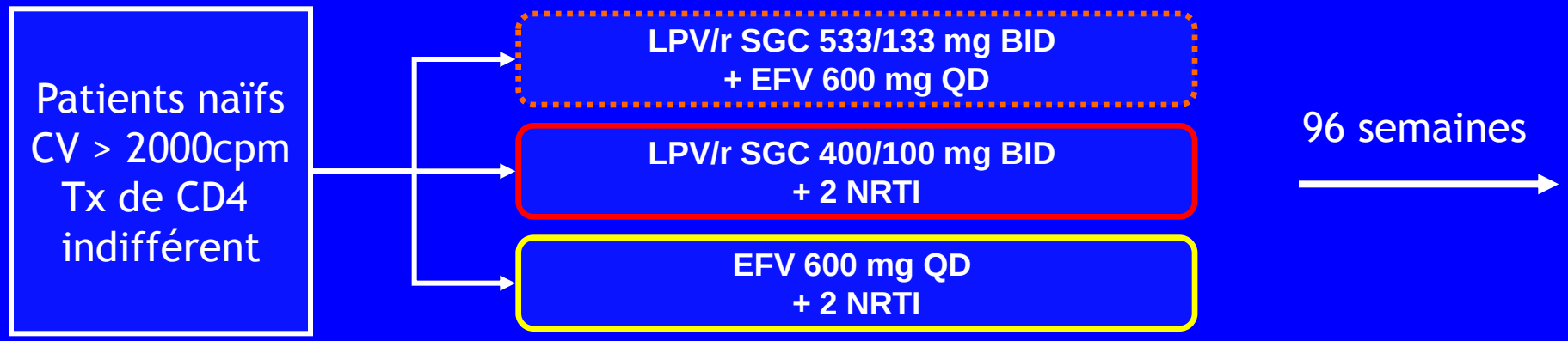
Lessons from ACTG 5142

ACTG 5142 : EFV vs LPV/r chez le patient naïf

Etude ouverte, multicentrique, randomisé chez des patients naïfs



3TC + TDF ou d4T XR ou ZDV (choix investigateur)

Stratification :
CV > 5log;
co-infection hépatique,
sélection NRTI

Significativité statistique = 0,016 après ajustement sur :
la comparaison des bras 2 à 2
les deux co-objectifs principaux
analyse intermédiaire

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ACTG 5142 : résultats (1)

Objectif primaire : comparer les bras deux à deux :
-le délai avant l'échec virologique
-précoce (Δ CV < 1 log ou rebond avant S32)
-tardif (CV non < 200 cpm ou rebond après S32)
-Arrêt de ttt pour échec virologique ou EI.

Caractéristiques BL :

	LPV/EFV n = 250	LPV n = 253	EFV n = 250	Total n = 753
Female (%)	18	23	19	20
Non-White (%)	65	65	60	64
Age (median)	38	37	39	38
CD4 (median)	181	178	190	182
HIV RNA >10^3 (%)	51	51	52	51
Selected NRTI (%) **ZDV** **d4T XR** **TDF**	 42 24 34	 42 25 34	 42 24 34	 42 24 34

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ACTG 5142 : résultats (2)

Gain de CD4

2 NRTI + LPV/r : + 285
2 NRTI + EFV : + 241 } 0,01
LPV/r + EFV : + 258 } 0,01

	LPV/EFV	LPV	EFV
# Observed VF	73	94	60
# Genotypic assays*	39	52	33
# NRTI mutations **M184I/V** **K65R**	4 (10%) 1 0	8(15%) 7 0	11(33%) 8 3
#NNRTI mutations **K103N**	27(69%) 21	2(4%) 0	16(48%) 9
#Major PI mutations**	2	0	0
Mutation in 2 classes	2	2	10

** 30N, 32I, 46I, 47A/V, 48V, 50L/V, 82A/F/L/S/T, 84V, 90M

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Conclusion

NNRTIs have a very low genetic barrier for resistance. LPV/r has a very high genetic barrier for resistance

Other evidence in support of the low genetic barrier for resistance for NNRTIs:

1. Development of the K103N mutation after single-dose use of NVP in MTCT studies.
2. Evidence for development of K103N and other NNRTI mutations after treatment interruption. This results in compromise regarding future use of NNRTIs.

3. Patients to whom NNRTI mutations have been transmitted have diminished responsiveness to NNRTIs that are employed in subsequent therapy.

4. Patients who have NNRTI mutations detected by ultrasensitive assays rather than genotyping may be more likely to fully express such mutations when NNRTI therapy is introduced.

Baseline Samples with Detectable Minority Mutations and Treatment Outcomes

Sample ID	Baseline Minority Mutations	Regimen	Outcome	Treatment Week of Failure	Bulk Genotype Mutations at Failure
1	M184V	ABC -3TC+EFV	Failure	48	Unk
2	M184V	ABC -3TC+EFV	Failure	12	M184V
3	K103N	ABC -3TC+EFV	Failure	8	K103N, M184V
4	K103N, M148V	ABC -3TC+EFV	Failure	8	K103N, M184V
5	K103N	ZDV+3TC+EFV	Failure	24	K103N
6	K103N	ZDV+3TC+EFV	Failure	48	Unk
7	Y181C	ABC -3TC+EFV	Failure	12	WT
8	Y181C	ABC -3TC+EFV	Success	—	NA
9	K103N	ABC -3TC+EFV	Success	—	NA

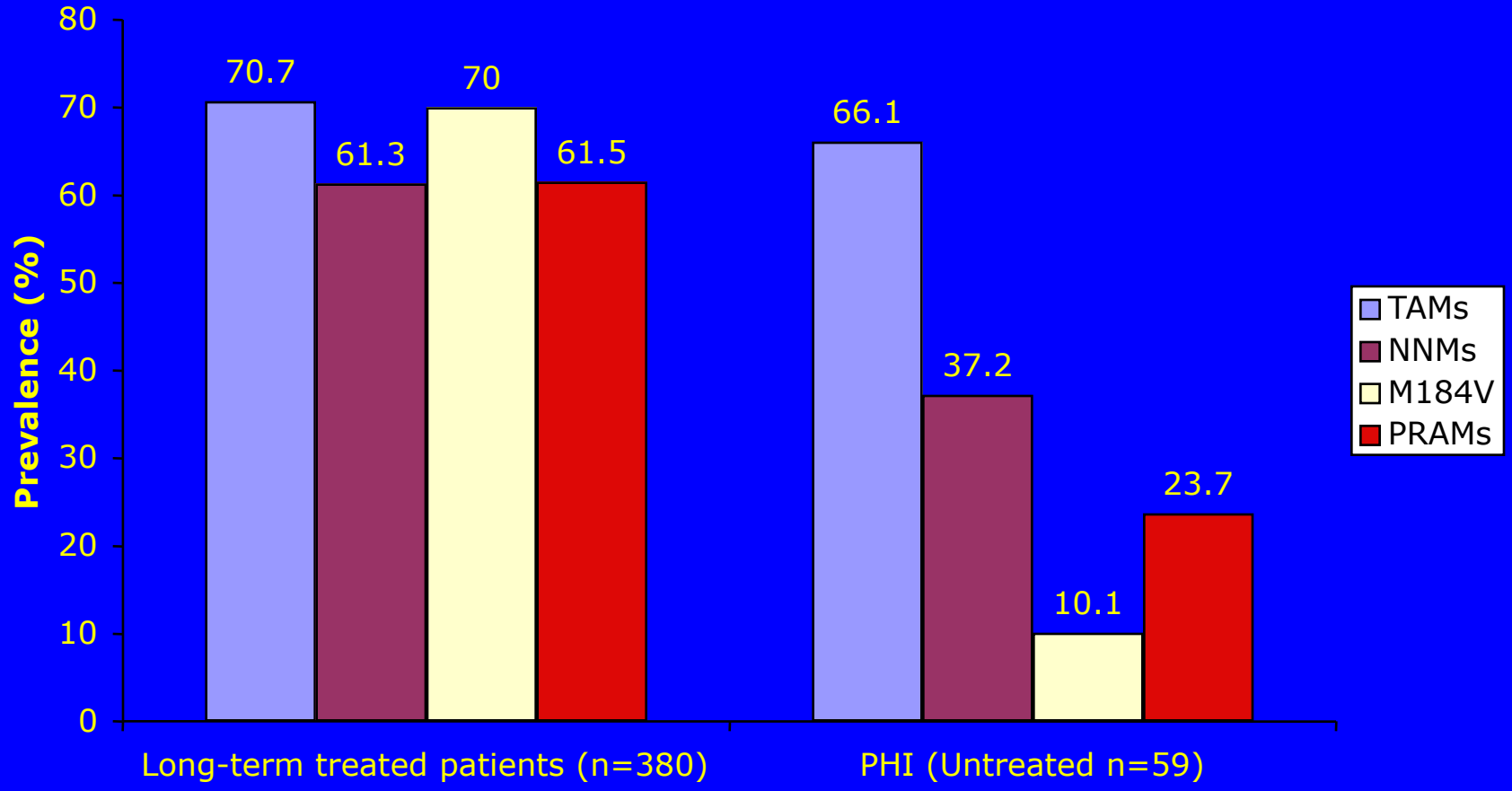
Johnson et al., *PLos Medicine* 2008. 5:e158.

Fraction of Treatment Success or Failure Versus Presence of Detectable Minority Drug Resistance Mutations

Mutation Status	Treatment Success (n = 221)	Treatment Failure (n = 95)
No detectable drug Resistance mutation	219 (99.1%)	88 (92.6%)
Minority drug Resistance mutation	2 (0.9%)	7 (7.4%)

Johnson et al., *PLos Medicine* 2008. 5:e158.

Differential Presence of Select Drug Resistance Mutations in Patient Populations



Minority Drug-Resistant Populations in Primary Infection (n=30)

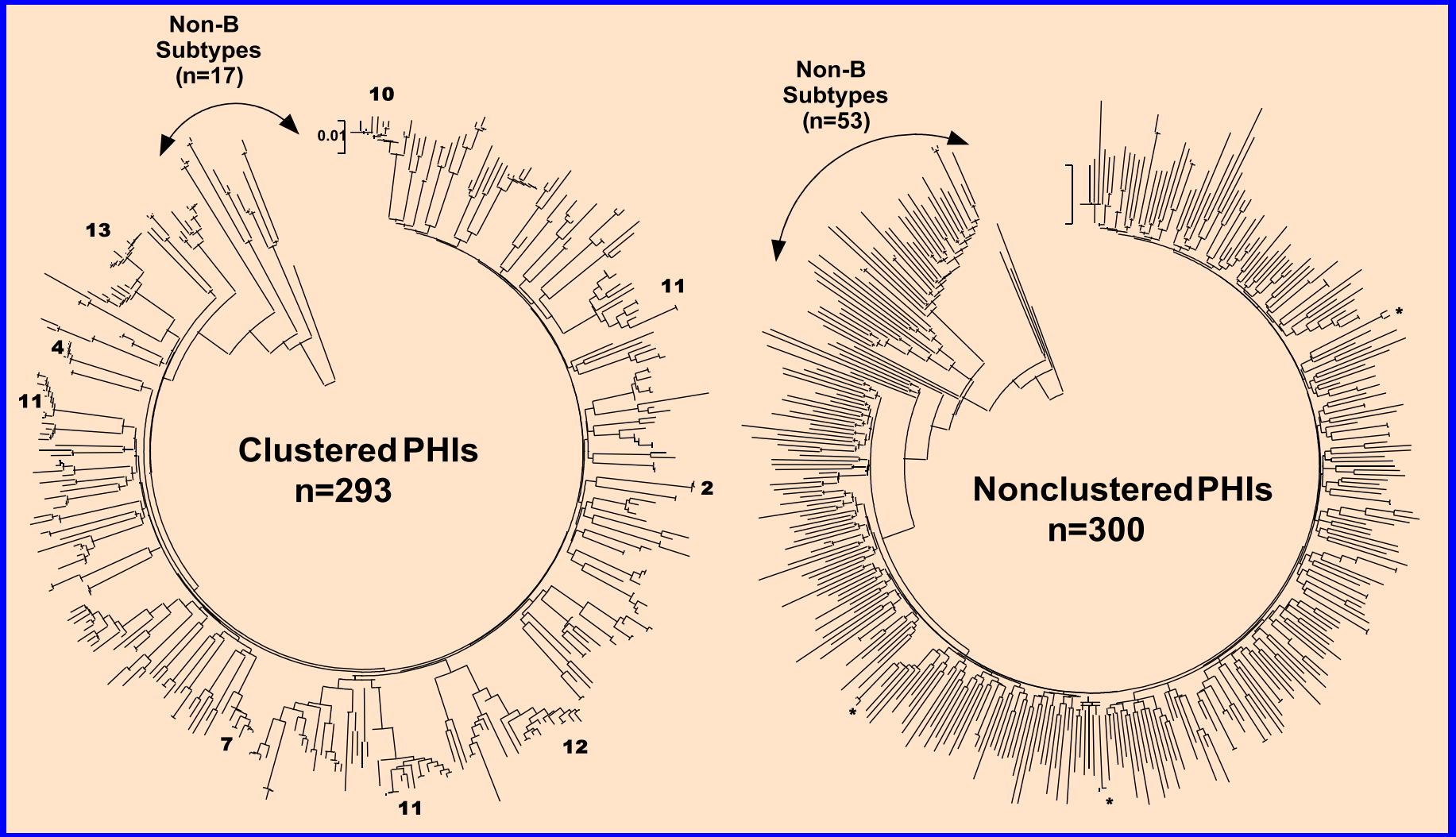
	Number positive by sequence-based genotyping	Number positive by allele-specific PCR
Presence of K103N	0	3
Presence of M184V	0	4

Population-based surveillance shows transmission cascades of HIV-1 variants harbouring drug resistance

Pol gene sufficient to reconstruct transmission events

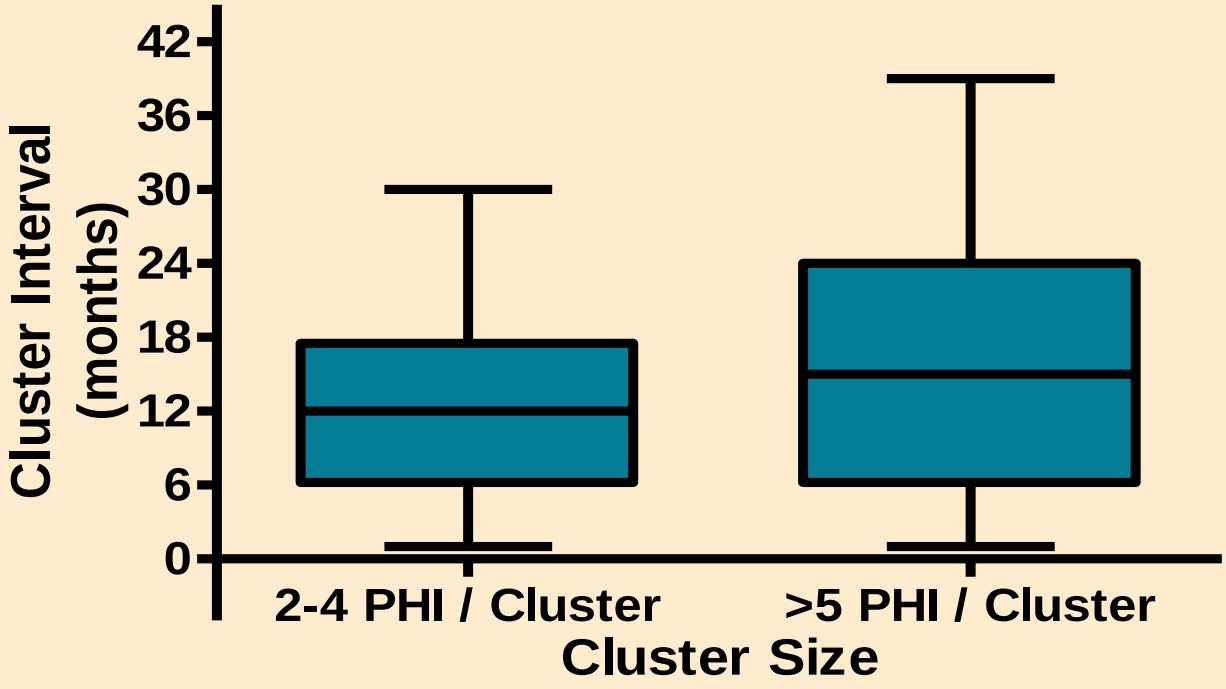
- RT and protease sequences are conserved
- A single dominant viral species is transmitted & persists
- Sequence clustering infers viral inter-relationships
  - Hué S, AIDS 2004

Clustering of PHI transmission events



Brenner B, et al, JID April, 2007

Time intervals for onward PHI:PHI transmission



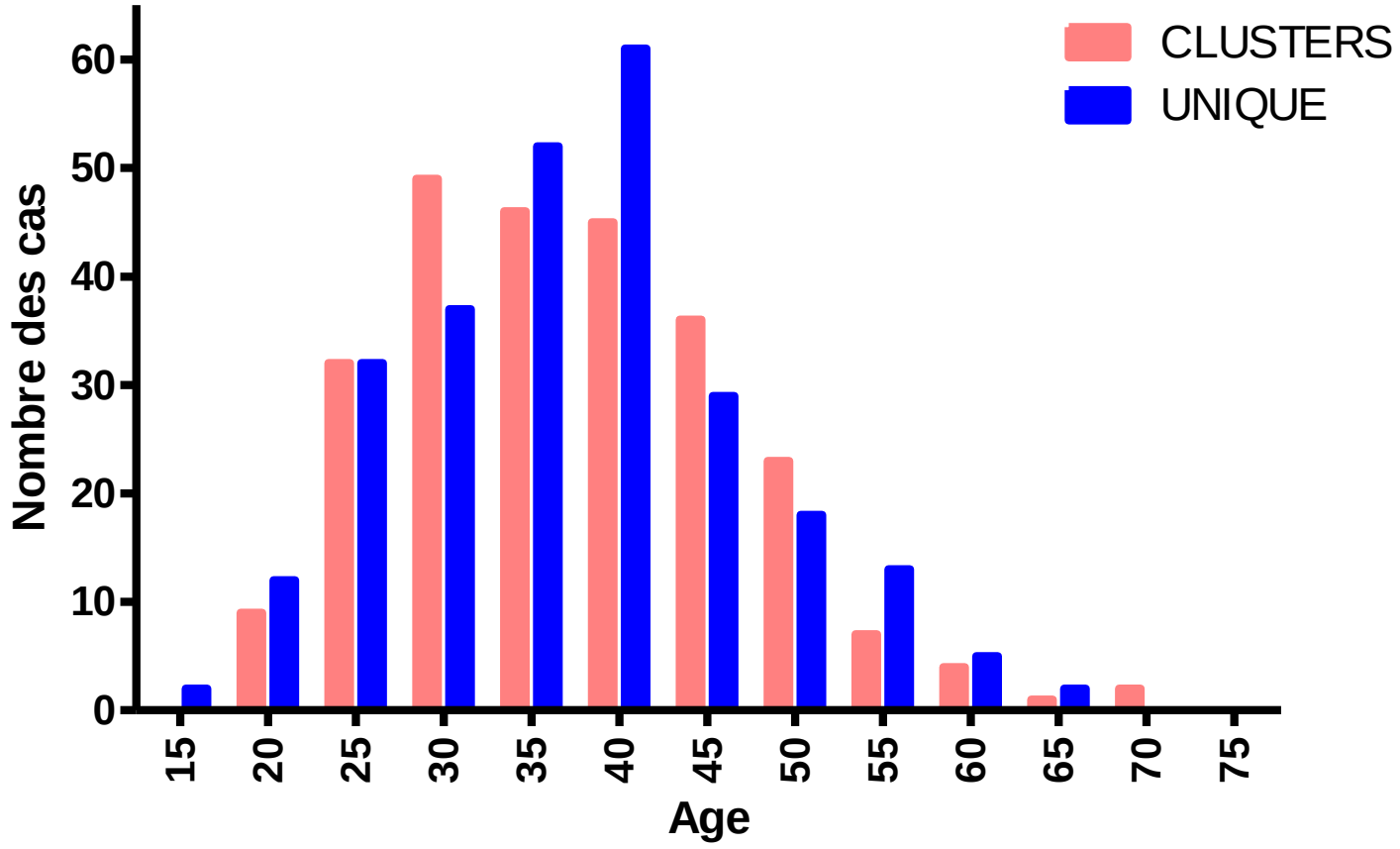
64 clusters
(n=158)
12 ± 6 months

20 clusters
(n=168)
15 ± 9 months

Drug resistance in clustered and nonclustered PHI, in relation to CI potential transmitters

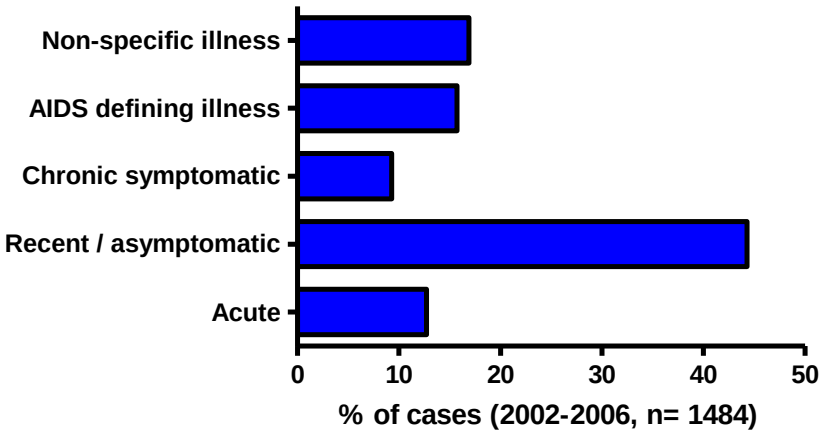
Drug class	CI - Treated	PHI Cluster	PHI Unique	P values
Any NRTI	64.4%	3.8%	9.0%	0.009
Any NNRTI	37.8%	10.2%	9.0%	n.s
Any PI	42.2%	2.4%	5.0%	0.092

Age distribution of PHI in clustered and unique transmissions

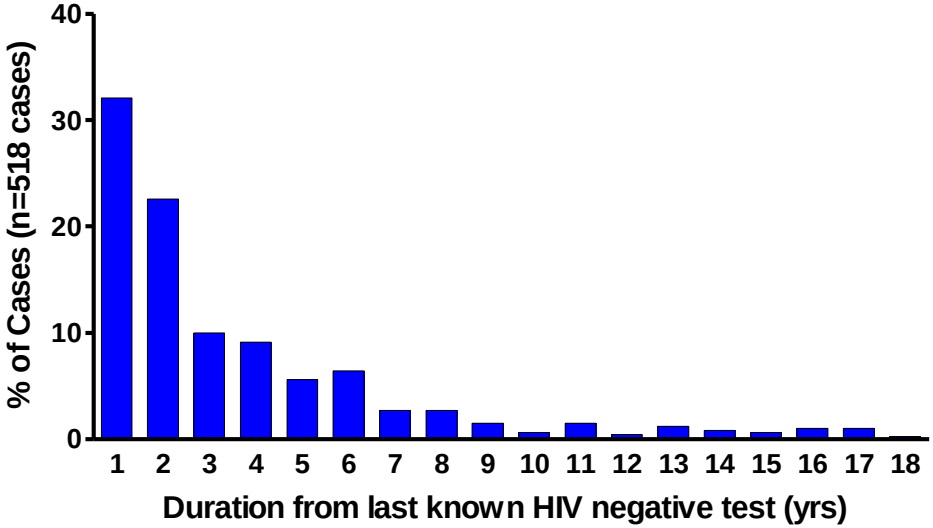


The potential impact of rapid testing in HIV-1 prevention

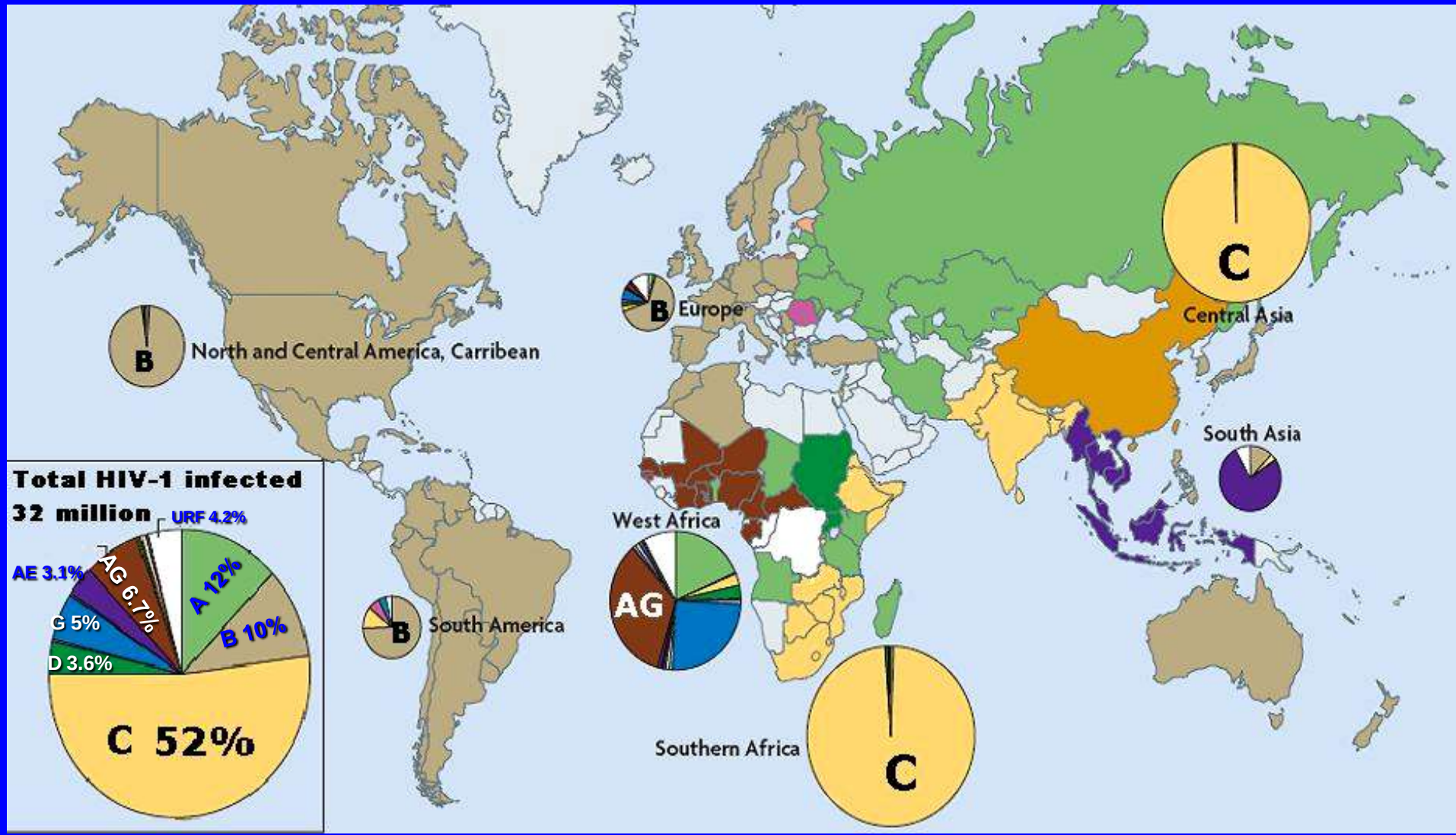
Disease stage at diagnosis (2002-2006)



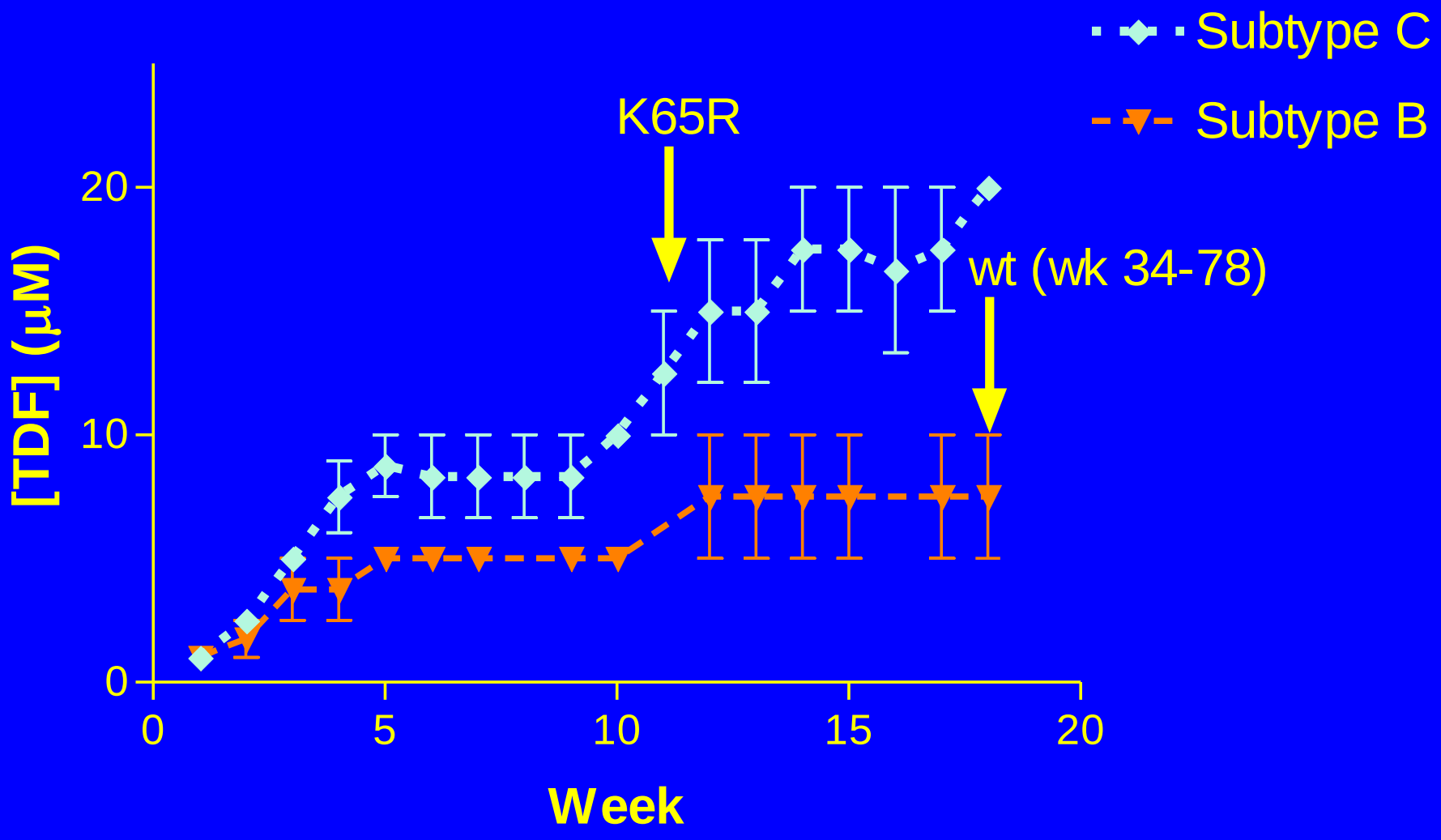
Time from last reported HIV negative test at diagnosis



Global distribution of HIV-1 subtypes



Rapid Selection of K65R Resistance in Subtype C Isolates



History of 23 Botswana Patients Treated with ddI/d4T plus 3TC or NVP

No. Patients	23
No. Patients failing	15
No. Patients with K65R	7
No. Patients with L74V	0

Do We Need to Worry About the K65R Mutation?

- Similar results have now been described in Malawi, South Africa, and India
- We know nothing about the relative fitness of the K65R mutation in Subtype C compared to SubtypeB
- Will K65R be sexually transmitted?
- Why are we still using d4T in resource-limited settings?

RESULTATS :
Sous-types VIH prédominants à baseline, provenant des 28 pays de l'étude CASTLE

18 sous-types VIH :

A, A/C, A/H, A/K, A1, AE, AG, B, BC, BF, C, CD, Complex, D, F, F1, F2, G

SOUSTYPE	ATV/r n = 434 n (%)	LPV/r n = 431 n (%)	TOTAL* n = 865 n (%)
AE	28 (6)	28 (6)	56 (6)
B	291 (67)	283 (66)	574 (66)
BF	27 (6)	38 (9)	65 (8)
C	73 (17)	65 (15)	138 (16)

Total incluant seulement les sous-types prédominants

Substitutions IP IAS-USA à baseline par sous-types VIH

Soustype B	ATV/r n = 291	LPV/r n = 282
>10%	I13, D60	L10, I13, D60
>20%	L10, M36, I62, I64, A71, V77, I93	M36, I62, I64, A71, V77, I93
>50%	L63	L63
>90%	--	--

Soustype BF	ATV/r n = 27	LPV/r n = 38
>10%	I13, G16, V77	G16, D60, I64, V77
>20%	K20, D60, I62, L63, I93	L10, L63
>50%	--	I93
>90%	M36	M36

Soustype AE	ATV/r n = 27	LPV/r n = 28
>10%	G16, I62,V77	L10, I62, V77
>20%	L10, K20, L63	G16, K20
>50%	I13	I13
>90%	M36, H69	M36, H69

Soustype C	ATV/r n = 73	LPV/r n = 64
>10%	I13, V82	D60, I62, V77
>20%	K20, L63	K20, L63
>50%	--	--
>90%	M36, H69, I93	M36, H69, I93

- Les substitutions IP multiples classées mineures par la classification IAS-USA (positions d'acides aminés listées ci-dessus) surviennent naturellement à baseline chez plusieurs soustypes VIH chez les patients naïfs d'IP.

- La fréquence de certaines substitutions IP à baseline varie largement selon les soustypes:
  - L63 > 50% chez soustype B, <30% chez AE, BF, C.
  - M36 > 90%, chez soustype BF vs. <30% chez soustype B.
  - H69, M36 >90% chez soustype AE vs. <1%, <30% chez soustype B respectivement
  - M36, I93 > 90% chez soustype C vs. < 30% chez soustype B.

Réponse à la semaine 48 selon la région et le soustype VIH : CV<50c/mL

Région	ATV/r n/N (%)	LPV/r n/N (%)
AFRIQUE	47/67 (70)	52/65 (80)
ASIE	32/39 (82)	36/40 (90)
EUROPE	53/65 (82)	49/66 (74)
AMERIQUE DU NORD	46/67 (69)	50/69 (72)
AMERIQUE DU SUD	165/202 (82)	151/203 (74)

Soustype	ATV/r n/N (%)	LPV/r n/N (%)
B	230/291 (79)	210/283 (74)
Non-B	107/143 (75)	121/148 (82)
AE	23/28 (82)	25/28 (89)
BF	21/27 (78)	31/38 (82)
C	51/73 (70)	52/65 (80)
AUTRE	12/15 (80)	13/17 (76)

Summary

- NNRTIs that are now approved for use in first-line therapy may be more fragile than some long-term clinical trials may suggest.
- It is only logical that the transmission of NNRTI mutations will continue to increase in settings in which NNRTIs have been used extensively in first-class therapy.
- This problem is further exacerbated by data on clustering of NNRTI mutations in new transmissions, which reflects the high fitness of viruses that carry NNRTI mutations.

Quebec PHI Study Group

Actuel

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Réseau SIDA/MI du FRSQ

CIHR

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T H A N K Y O U