HIV Drug Resistance: Implications for Prevention and Therapy

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“Infidelity is one of the most important problems that confront America today”

Jesse Helms, U.S. Senator, 1996

George W Bush, United States President, 2004

These leaders were among the world's first politicians to attempt to understand the reverse transcriptase enzyme of HIV-1

Reasons for HIV Drug Resistance

- high viral replication rate
- high reverse transcriptase error rate ($5x10^{-5}$ mutations per replication event)

Therefore, HIV is capable of mutating at every possible locus on a daily basis, creating the potential for selection of resistant viruses

General Considerations in Drug Resistance re Prevention Research

The female is HIV-infected. She either does not know it or does but chooses to use a microbicide to protect a sexual partner. Will drug resistance be selected? In the case of microbicides, this will depend in large part on whether the microbicide is systemically absorbed and exerts the equivalent of monotherapy. But, inadequate absorption or only very low level absorption may be inadequate to apply antiviral drug pressure and select for drug resistance. e.g. UC-781, TMC-120

Is there enough HIV present and replicating in areas that are exposed to a topically applied microbicide to select for drug resistance? Probably not.

But, we do not know for sure. Will there be individual variability in this regard?

The male partner is infected with a drug-resistant variant of HIV-1. Can the presence of transmissible drug-resistant viruses in a population overcome whatever ARV block is in place through use of a microbicide or PREP?

There is scant data on this topic.

Will the Development of HIV Drug Resistance due to ARV-Based Microbicides Compromise Future Therapeutic Benefit for People Who Use such a Product?

- e.g. similar to the use of NVP in MTCT

Do Differences Exist among HIV Subtypes in the Development of Drug Resistance?

Silent Mutation at Codon 106 responsible for the V106M mutation in clade C RT with NNRTIs

HIV-1 RT	Clade B	Clade C
Wild type codon at position 106	V(GTA)	V(GTG)
In clade C, V106M arises	two codon changes	M(ATG)
In clade B, V106A occurs	A(GCA)	two codon changes

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

Time to Development of K65R in Botswana patients after initiation of ddI/d4T

Patient	Time (months)
3	18
6	4
7	4
10	4
13	6
15	12
16	11

Table 4. Selection of RT mutations after sequential passage with ddI and/or d4T

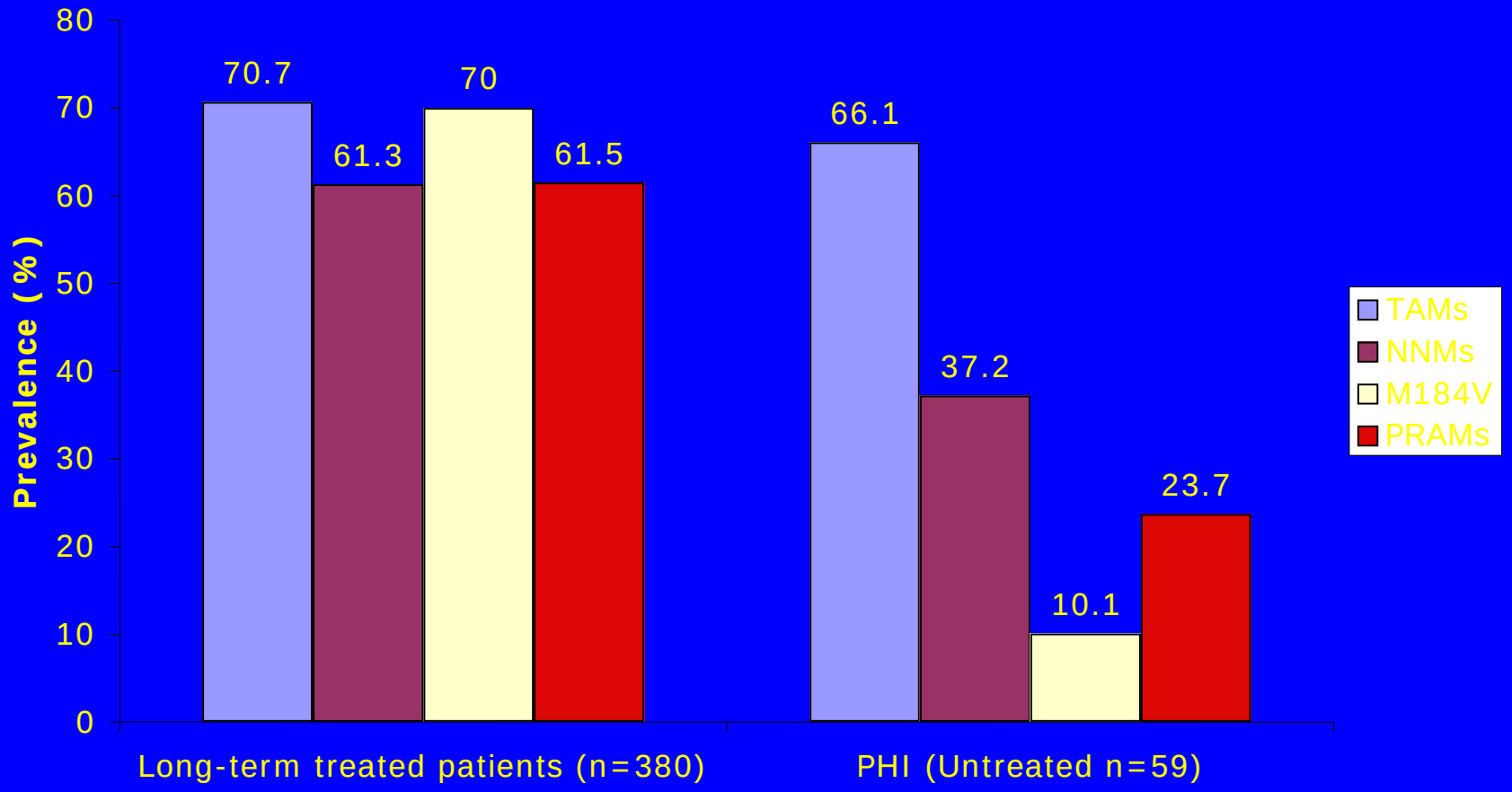
*clinical isolate	experiment nº	weeks of passage	highest drug concentration achieved	mutations selected
4742	1	28	40 µM ddI	K65R
	2	24	5 µM d4T	none
	3	17	10 µM ddI; 0.5 µM d4T	none
	4	17	10 µM TDF	K65R
4761	1	24	10 µM ddI	L74V
	2	22	2.5 µM d4T	D67N
	3	15	1 µM ddI; 0.1 µM d4T	K65R
	4	17	5 µM TDF	none
BG-05	1	28	30 µM ddI	K65R, D67N
	2	24	2.5 µM d4T	none
	3	28	10 µM ddI; 0.1 µM d4T	K65R
	4	24	10 µM TDF	K65R
BG-15	1	17	10 µM ddI	none
	2	17	0.5 µM d4T	none
	3	28	10 µM ddI; 0.5 µM d4T	K65R, V75I
	4	18	5 µM TDF	none
Mole 18	1	28	40 µM ddI	L74V
	2	22	0.5 µM d4T	none
	3	22	2.5 µM ddI; 0.1 µM d4T	none
	4	28	5 µM TDF	K65R

Nucleotide accession numbers: 4742 (AF492595), 4761(AF492597), BG-05 (AF492600), BG-15 (AF492601), Mole 18 (AF492607)

The development of K65R resistance to ddI and/or d4T was confirmed by tissue culture selection using 5 HIV-1 subtype C clinical isolates. The K65R mutation arose within 15-28 weeks in 2 of 5 subtype C selections under ddI pressure and 3 of 5 selections conducted using combinations of ddI and d4T. In some cases, ddI also selected for the appearance of the D67N or L74V substitutions in RT.

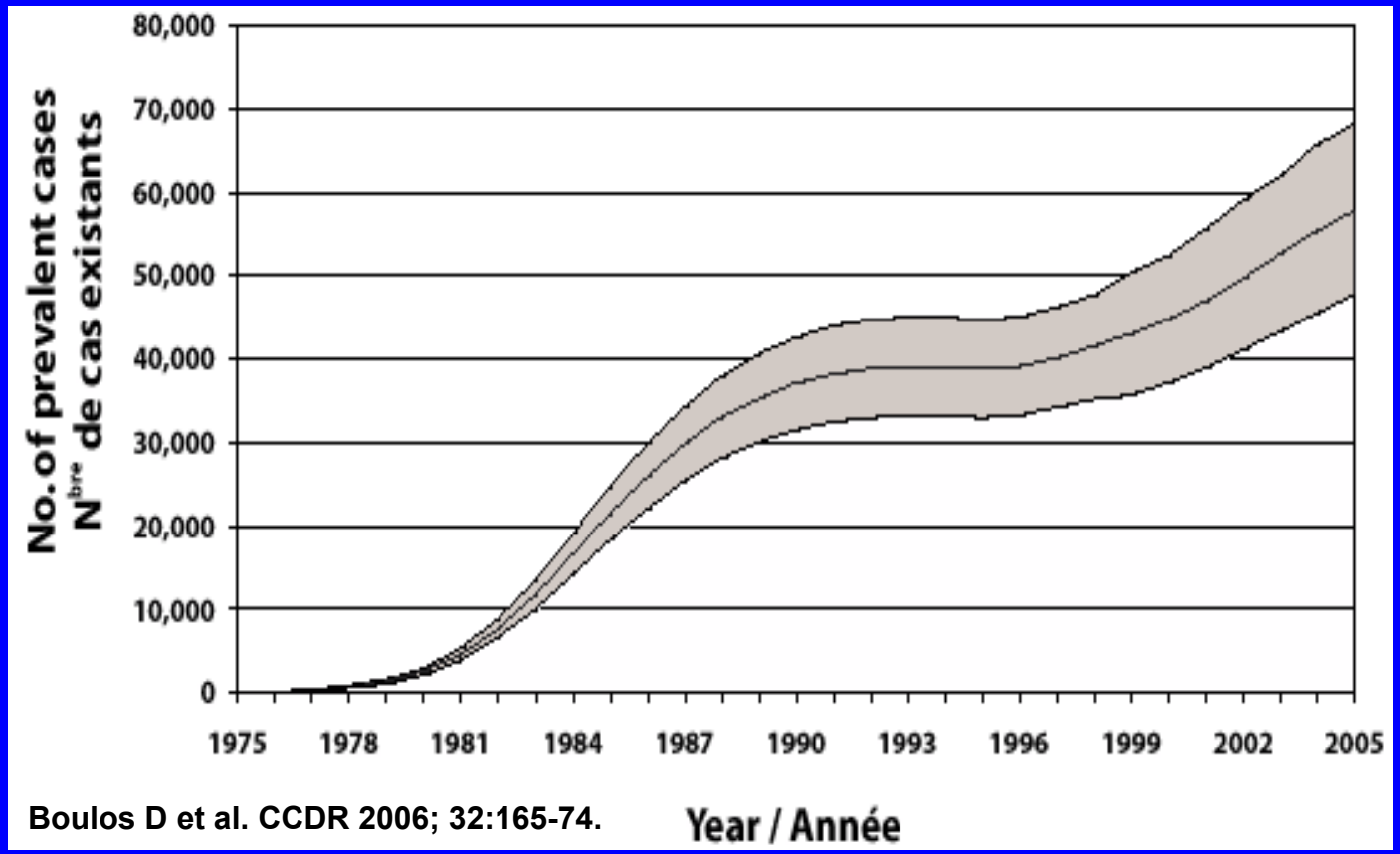
Are Drug-Resistant Viruses Transmitted with the Same Efficiency as Wild-Type Viruses?

Differential Presence of Select Drug Resistance Mutations in Patient Populations



HIV-1 Transmission Dynamics in an Urban North American Setting

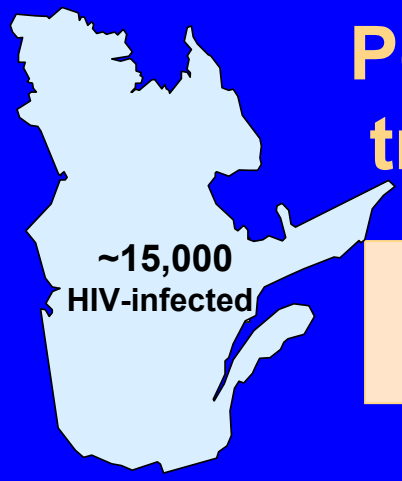
Evolving trends in the HIV-1 Epidemic in Canada



Boulos D et al. CCDR 2006; 32:165-74.

Integrating surveillance, prevention & treatment initiatives fundamental to control HIV/AIDS

Population-based surveillance of HIV transmission in Quebec (1997-2005)



Quebec Genotyping Program (2001-2006) n ~ 4000
PHI Cohort (1997-2006) n = 318

Potential Transmitter Populations

PHI (<6 mo)
n= 891

CI-Naïve

CI-
Treatment Failure

4.64 ± 0.83

4.71 ± 0.70

4.14 ± 0.76

HAART

0 | 6 mo | 2 yrs | 5 yrs | 10 yrs | >15 yrs

Undiagnosed
25-30%

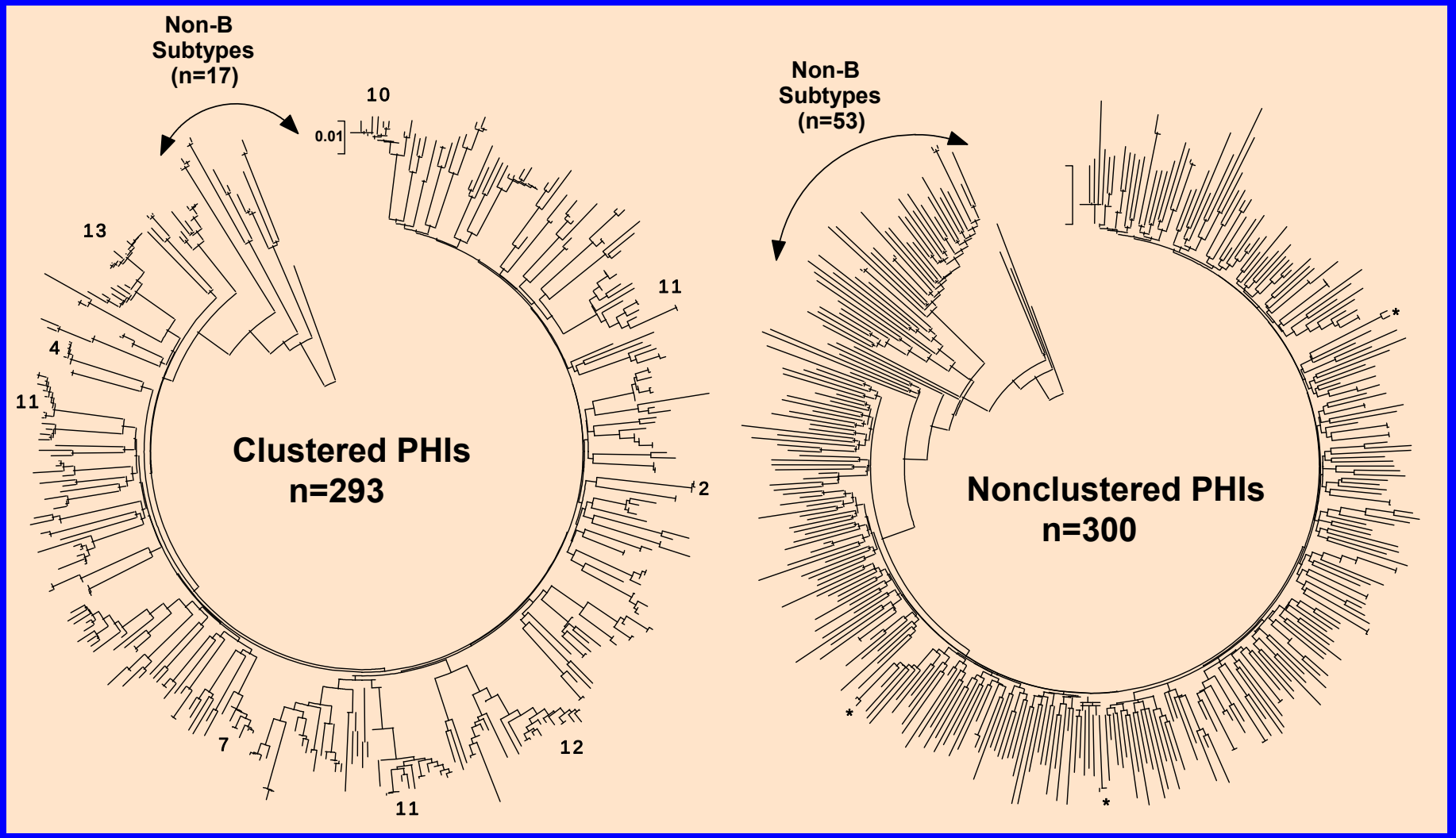
Non-genotyped CI

~2.58
n=2328

Genotypic surveillance of HIV transmission

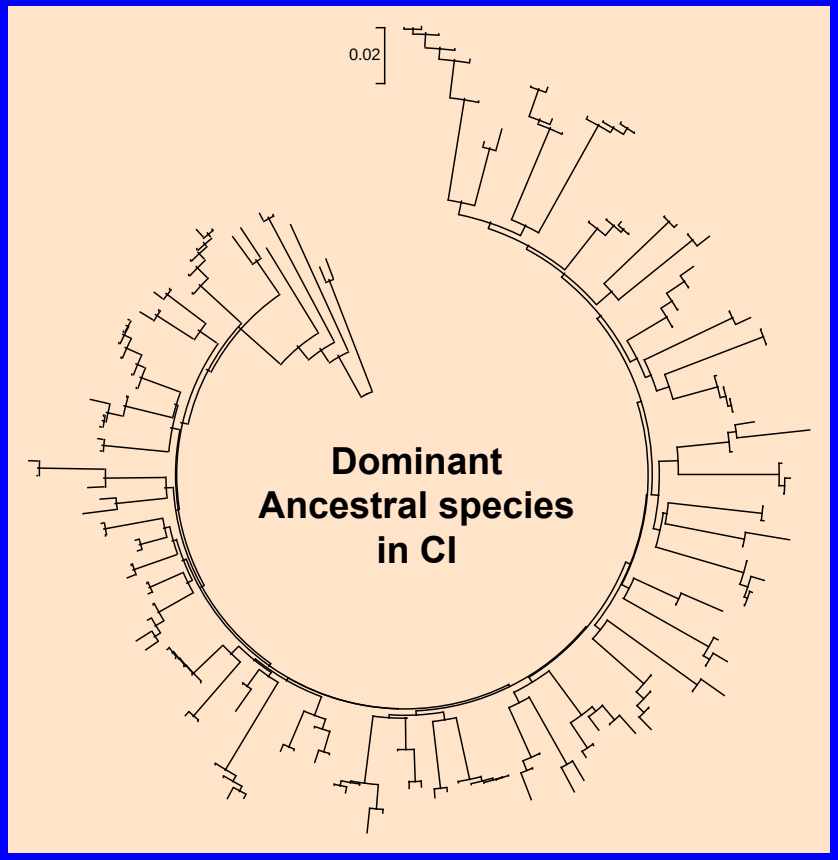
- ***Pol* gene sufficient to reconstruct transmission events**
  - RT and protease sequences are conserved
  - A single dominant viral species is transmitted & persists
  - Sequence clustering infers viral inter-relationships
    - Hué S, AIDS 2004
- **Non-subjective surveillance**
  - **Caveats:** Cannot identify time or direction of transmission
- **PHI cohort data can establish risk correlates**

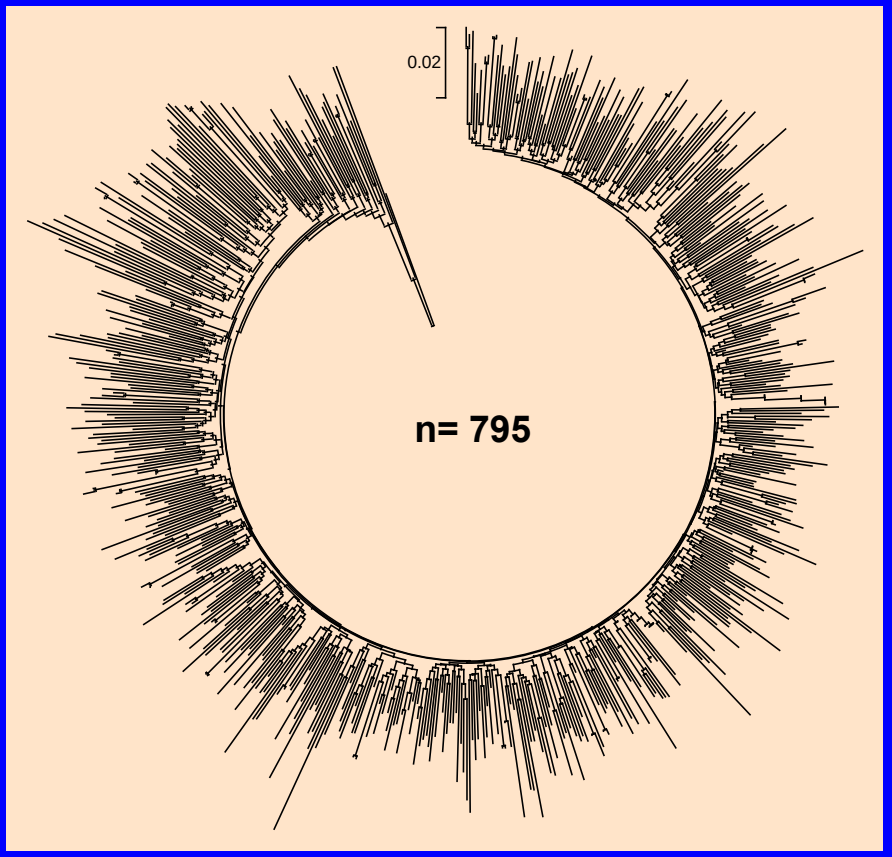
Clustering of PHI transmission events



Brenner B, et al, JID April, 2007

Chronic infections rarely co-cluster

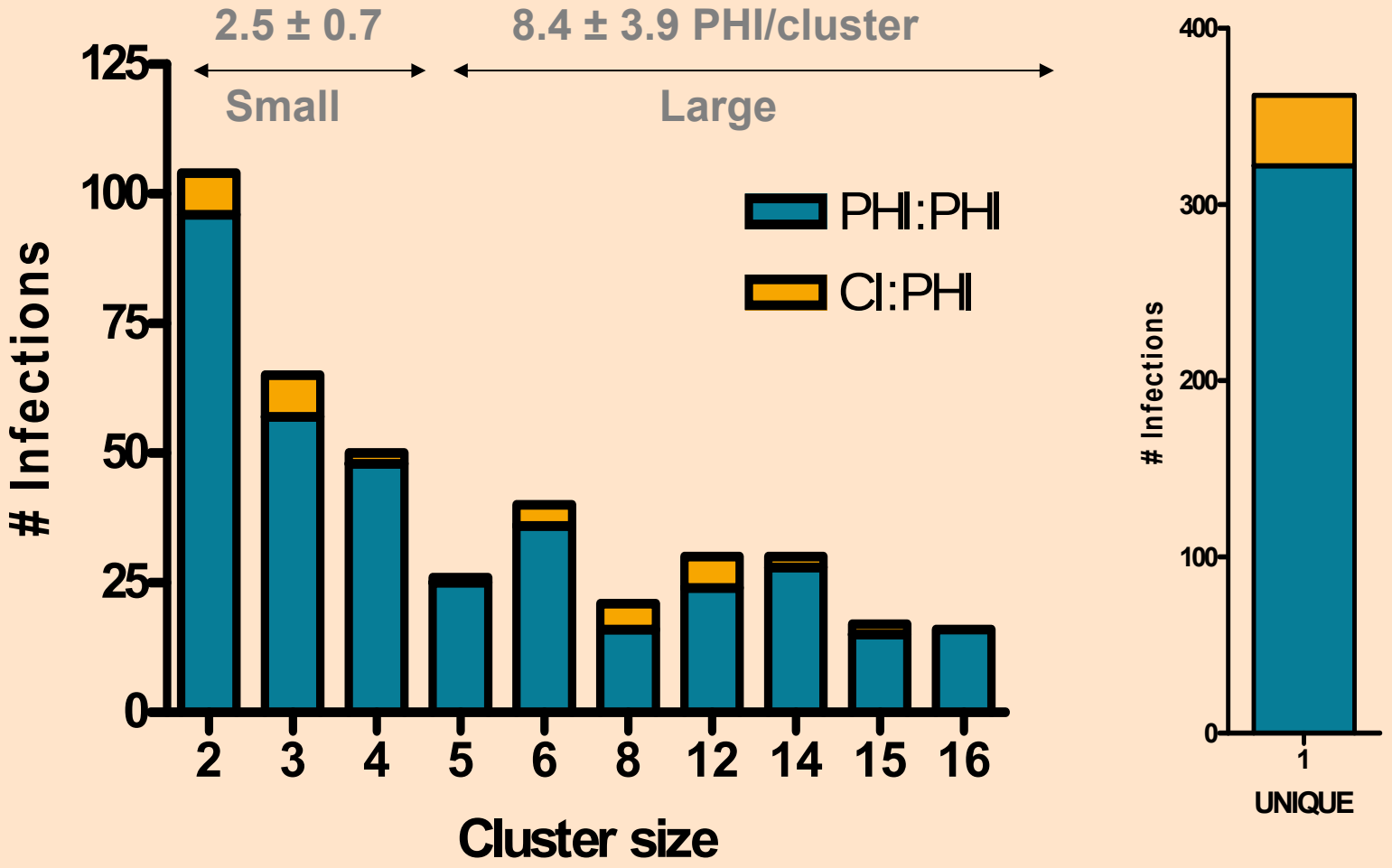




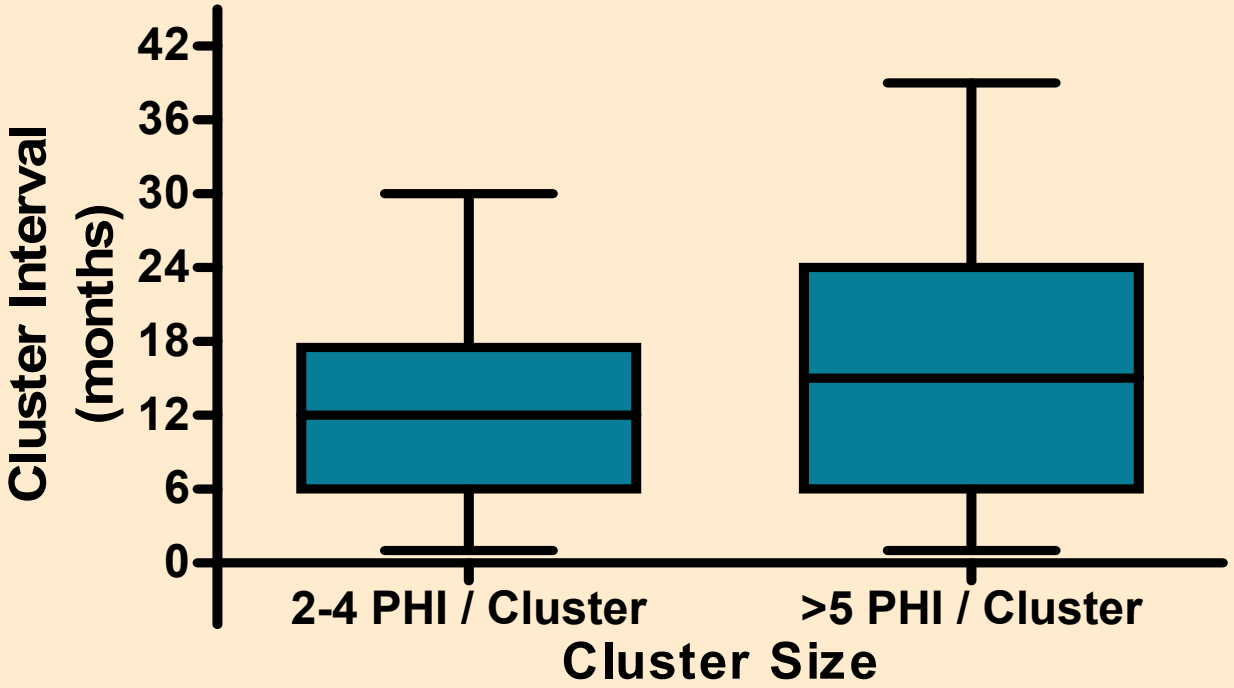
5 year follow-up of 54 HIV-infected individuals
Mutation reversal: PI: 30,50,54,82,84 and 90
RT: 41,65,67,69,70,74,103,106,151,181,184,215

CI:PHI
5.8%→14.4%

Co-Clustering of PHI and Chronic Infections



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 transmissions

Resistance profiles of CI within PHI clusters	PHI		
	Resistance Profiles in PHI	Small Clusters (1-4)	Large Clusters (>5)
wt (n=15)	wt	7	27
184V (n=6)	wt	6	15
67N,69R,70R,184V PI (n=1)	67N, 69N, 219Q	1	-
103N /PI (n=1)	103N 103N/PI	2 2	-
103N (n=1)	103N	2	
190A (n=1)	190A	-	14

Conclusions

- **Population-based genotypic surveillance complements epidemiological & behavioural cohort data**
- **Early/PHI disease stages linked to 50% of HIV transmissions**
- **Onward transmission of drug resistance may occur through transmission cascades**
- **Prevention initiatives should target early infection**
  - Enhanced behavioural approaches to reduce transmission
  - Increased sensitivity to early clinical diagnosis
  - Optimizing HIV testing methods for early detection
  - Earlier treatment initiation

Quebec PHI Study Group

Actuel

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T H A N K Y O U