

High Rates of Forward Transmission Events after Acute/Early HIV-1 Infection

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(See the editorial commentary by Pillay and Fisher, on pages 924–6.)

Background. A population-based phylogenetic approach was used to characterize human immunodeficiency virus (HIV)–transmission dynamics in Quebec.

Methods. HIV-1 *pol* sequences included primary HIV infections (PHIs; <6 months after seroconversion) from the Quebec PHI cohort (1998–2005; *n* = 215) and the provincial genotyping program (2001–2005; *n* = 481). Phylogenetic analysis determined sequence interrelationships among unique PHIs (*n* = 593) and infections from untreated (*n* = 135) and treated (*n* = 660) chronically infected (CI) potential transmitter populations (2001–2005). Clinical features, risk factors, and drug resistance for clustered and nonclustered transmission events were ascertained.

Results. Viruses from 49.4% (293/593) of PHIs cosegregated into 75 transmission chains with 2–17 transmissions/cluster. Half of the clusters included 2.7 ± 0.8 (mean \pm SD) transmissions, whereas the remainder had 8.8 ± 3.5 transmissions. Maximum periods for onward transmission in clusters were 15.2 ± 9.5 months. Coclustering of untreated and treated CIs with PHIs were infrequent (6.2% and 4.8%, respectively). The ages, viremia, and risk factors were similar for clustered and nonclustered transmission events. Low prevalence of drug resistance in PHI supported amplified transmissions at early stages.

Conclusions. Early infection accounts for approximately half of onward transmissions in this urban North American study. Therapy at early stages of disease may prevent onward HIV transmission.

An understanding of HIV-transmission dynamics is important in the design of effective prevention and treatment interventions. A number of recent studies suggest

that early stages of HIV infection may disproportionately contribute to viral transmission and spread of the epidemic [1–3]. Primary HIV infection (PHI) and early stages of infection are associated with high viral burden and viral set points in blood and semen, a major determinant of HIV transmission [1, 2, 4–6]. The Reka-Uganda surveillance study showed that 43.8% (10/23) of new transmissions occurred in discordant partners at 6–15 months subsequent to seroconversions of source partners [6].

In contrast, other groups have used viral load/epidemiological/behavioral data to contend that the role of PHIs in HIV transmission may be overestimated [7–9]. Many cofactors influence transmission, including access to antiretroviral therapy and medical care, high risk behaviors, sexually transmitted diseases, and coinfections [7–9]. The findings of the North Carolina program Screening and Tracing of Active Transmission

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(STAT) suggest that as many as half of identified source partners were chronically infected (CI) and that 37% of these were on antiretroviral therapy [9].

Phylogenetic analysis of viral gene sequences has been used as a molecular epidemiological approach to reconstruct transmission events in early/acute infection [10–15]. Data from the Swiss and UK PHI cohort studies have reported significant clustering of viral sequences from 24% and 34% of recent infections, respectively [13, 14]. Clustering of transmitted drug resistance has also been reported in 10 PHI cases within the San Francisco cohort [15].

These findings underscore the importance of tracing the etiology of new HIV transmissions in different patient population settings. Quebec is a unique venue for population-based molecular surveillance of HIV-1 transmission based on 2 major initiatives of recent years. The provincial genotypic testing program, recommended for drug-resistance testing in PHI, has been in place since 2001. In addition, the Quebec PHI cohort, established in 1997, is a large prospective longitudinal study of viral evolution, drug resistance, transmission risk factors, and disease progression after PHI [16, 17]. These initiatives offer a unique opportunity to assess the role of the early phase of infection in total HIV transmission and drug resistance in Quebec, a province with free universal access to health care, including antiretroviral therapy.

The present study involved phylogenetic analysis on all genotyped recent infections <6 months after seroconversions ($n = 593$), to estimate the relative importance of acute/early infection in onward transmission chains. Comparative analysis was performed on the treatment-naïve and treated CI potential transmitter populations ($n = 135$ and 660, respectively). In addition, data from the PHI cohort study were used to examine the clinical and sociodemographic characteristics associated with the features of transmission clusters in early infection. Our findings underscore that acute/early infection accounts for approximately half of all HIV transmissions in Quebec.

PATIENTS AND METHODS

Study populations. The PHI study population is drawn from 2 PHI initiatives involving subjects having acute/early infection (<6 months after seroconversion). Sequence data were available from all participants in the Quebec cohort with confirmed PHI (<6 months after seroconversion; 1997–2005; $n = 215$) [16–18]. Participants provided informed consent for blood collection and resistance testing; they completed standardized nurse-administered questionnaires describing risk factors, mode of transmission, age, and estimated date of infection [16–18]. Viral loads, drug-resistance profiles, and clinical epidemiological data were included in the analysis.

The remainder of acute/early stage infections were identified through the provincial genotyping program, at either of 2 Que-

bec reference laboratories (2001–2005; Hôpital Notre-Dame [HND; $n = 269$] and Jewish General Hospital [JGH; $n = 233$]). The clinical indication of PHI (<6 months after documented seroconversions) was noted on the laboratory requisitions by prescribing physicians and validated by laboratory personnel. On the basis of published data from l'Actuel, the largest HIV clinic in Montreal, this PHI study population ($n = 180$) had been infected for an average of 4.9 months [17]. Test requisitions also provided information on age, sex, viral load, and date of first genotypic sampling.

Sequence and epidemiologic data compiled from these 2 initiatives were made anonymous by the assignment of irretrievable patient identifiers. A total of 717 sequences from primary/early infections included 593 unique subtype B infections, 3 identified source partners, 65 non-subtype B infections, and 56 repeat samplings. The sample repeats of participants genotyped through both initiatives were useful tools to validate clustering. Non-subtype B infections, largely from the recent immigrant populations, were included on trees for comparative purposes but excluded from all analyses [19].

There are an estimated 58,000 persons HIV-infected persons in Canada. HIV became a reportable disease in Quebec in 2004 and includes ~13,000–15,000 infected persons, of whom ~3000 persons have been genotyped to date (viral load >400 copies/mL). Sequence data were obtained from a representative CI potential transmitter population that included all genotyped CIs from the JGH site (2001–2005), performing 40% of all provincial genotyping. The treatment-naïve and treated CIs included single sequence determinations for all persons genotyped with clinical indications of CI (>6 months after seroconversions; $n = 135$) and first or subsequent treatment failure on an antiretroviral regimen ($n = 660$), respectively. All study initiatives were approved by clinic and hospital ethics committees, as well as by the Quebec Ministry of Health committee on confidentiality and access of information.

Phylogenetic analysis. Genotyping was performed at either HND or JGH using the same procedures as described above to generate sequences for the HIV *pol* region spanning the protease gene and reverse transcriptase (RT) codons 1–400 or 38–250 using Virco primers (Virco Lab) or the Bayer TRUGENE HIV-1 assay (Bayer Diagnostics) protocols, respectively. All sequences were aligned to consensus HXB2 sequences, removing gaps and cutting to identical sequence lengths using BioEdit software [20]. Genotypic data identified minor and major resistance mutations, based on the March/April 2005 International AIDS Society–USA resistance panel guidelines [21].

Phylogenetic interrelationships among viral sequences were estimated using neighbor joining trees and maximum likelihood methods with BioEdit and MEGA2 integrated molecular evolutionary genetics analysis software [20, 22]. The existence of clusters was ascertained using the statistical robustness of

the maximum likelihood topologies assessed by high bootstrap values (>98%) with 1000 resamplings and short branch lengths (genetic distances >0.015%) [10, 22]. Infections in clusters were validated for congruent polymorphisms and mutational motifs.

Comparative phylogenetic analysis evaluated coclustering of unique subtype B genotyped primary/early infections ($n = 593$) with the representative potential transmitter population of treatment-naive ($n = 135$) or treated ($n = 660$) CIs. To minimize any potential bias of nonclustering between the PHI and CI patient population infection due to drug resistance, phylogenetic analysis was repeated after modifying CIs to wild-type ancestral forms, changing protease codons 30, 50, 54, 82, 84, and 90 and RT codons 41, 65, 67, 69, 70, 74, 103, 106, 151, 181, 184, and 215 to the wild-type codons present in the consensus B sequence.

Statistical analysis. The maximum window period for transmissions within clusters was estimated as the maximum difference in time between the earliest and latest infections within clusters. Differences in the viral load (\log_{10} copies/mL), age, risk behaviors, and drug motifs among clustered and non-clustered PHI transmissions and CI groups were ascertained

using Fisher's exact tests and analysis of variance (ANOVA), with GraphPad Prism software (version 4.0; available at: <http://www.graphpad.com>).

Sequence data. All sequences included in figure 1 were deposited into GenBank under the sequential accession numbers EF011572–EF011609.

RESULTS

Clustering of PHIs. Sequence data (HIV-1 *pol* region) were compiled from all PHIs (<6 months after seroconversion) identified through the provincial genotyping program ($n = 502$; 2001–2005) and the Quebec PHI cohort study ($n = 215$; 1998–2005). A phylogenetic approach was used to identify the sequence interrelationships of these early/acute stage infections.

A region within this tree is presented in figure 1. As illustrated, many PHIs segregated into clusters having sequence similarity based on the established criteria of high bootstrap values (>98%) and short branch lengths (genetic distances >0.015%) [10, 22]. Manual assessment of similarities in resistance and polymorphism mutational motifs of sequences was

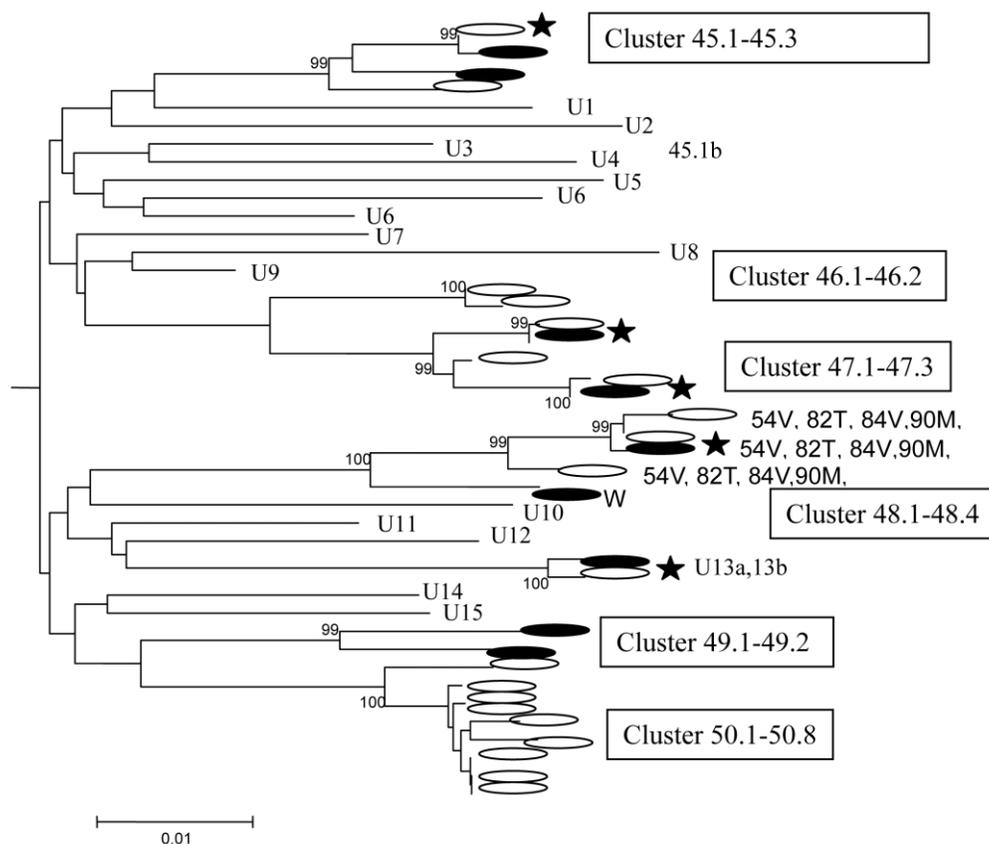


Figure 1. Region of the primary HIV infection (PHI) phylogenetic tree, showing unique PHIs (U1–U15), clustered transmissions ($n = 22$), and repeat patient samplings ($n = 5$). Cluster 48 depicts a transmission chain harboring drug resistance. Bootstrap values higher than 98% are indicated on the branches.

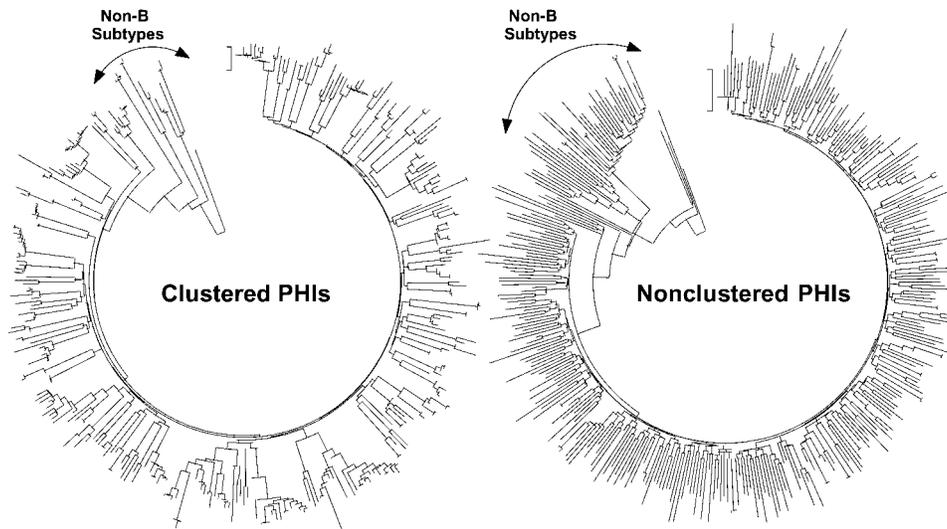


Figure 2. Phylogenetic tree, showing clustered B ($n = 293$) and non-subtype B ($n = 12$) primary infections, and the corresponding phylogenetic analysis, showing nonclustered B ($n = 300$) and non-subtype B ($n = 53$) infections.

evaluated to validate clusters. As an example, viruses in cluster 48 harbored transmitted drug resistance (figure 1). Irretrievable nonnominative cross-identifiers identified repeat samplings of viral sequences ($n = 56$) within clusters sequenced through both genotyping initiatives. Four repeat samplings of infections in transmission clusters are illustrated in figure 1. Non-subtype B infections ($n = 65$), composing 9.8% of all recent infections, were included on trees but excluded from subsequent analysis. All together, 593 unique subtype B infections were identified.

Tree topology revealed that half (293/593) of all PHIs grouped into 75 different transmission clusters, whereas the remaining (300/593) infections represented unique sequences. The entire phylogenetic tree, stratified according to clustered and non-clustered transmissions is shown in figure 2. As shown in figures 2 and 3, clustered transmission events included between 2 and 17 infections per transmission cluster. Of note, 49% of clustered transmission chains had 2–4 infections per cluster (i.e., 2.7 ± 0.8 [mean \pm SD]). The remaining 51% of clustered events segregated into large clusters including 8.8 ± 3.5 transmissions per cluster (figures 2 and 3).

Sequence interrelationships between CI and PHI populations.

The clustering profiles of PHI transmissions were compared with corresponding patterns observed for a representative potential transmitter population of CI persons genotyped at the JGH site (2001–2005). The treatment-naive CI population ($n = 135$) included persons genotyped for clinical indication of CI (>6 months after seroconversion, baseline before treatment). The treated CI population ($n = 660$) included patients genotyped for reasons of first or subsequent treatment failure.

Infections from untreated and treated CI patient populations rarely coclustered with PHIs (1% and 2.7%, respectively). Insofar as 70% of sequences from CI patients harbored drug

resistance, phylogenetic analysis was reevaluated after modifying CIs to wild-type ancestral sequences. As depicted in figure 4, clustering of CIs was infrequent (3.2% [21/660], of cases), with cluster sizes of 3.1 ± 1.6 (mean \pm SD).

Phylogenetic analyses were then performed to determine whether treatment-naive infections ($n = 135$) and ancestral sequences from CI treated persons ($n = 660$) coclustered with PHIs ($n = 593$). As depicted in figure 3, clustering of infections from treatment-naive ($n = 12$) and treated CI ($n = 17$) patients with PHIs was infrequent. However, 25 and 12 of treatment-naive and CI treated persons constituted new CI-PHI

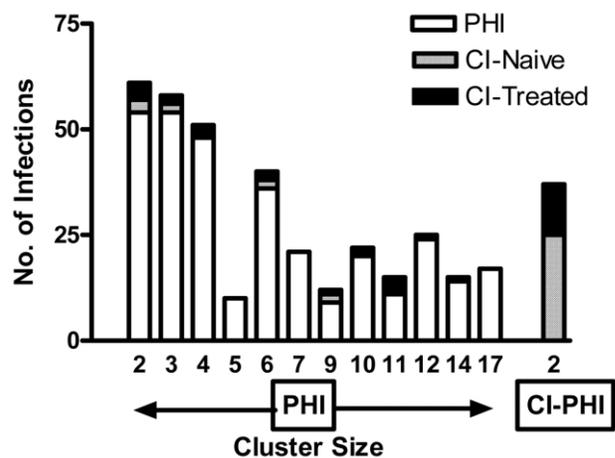


Figure 3. The distribution of patients with primary HIV infection (PHI) and chronically infected (CI) persons in and the 75 transmission clusters. Overall, half of the transmission chains have 2–4 persons/cluster, whereas the remaining individuals are in clusters having 5–17 persons/cluster. Single clustering of CIs and nonclustered PHIs is also depicted.

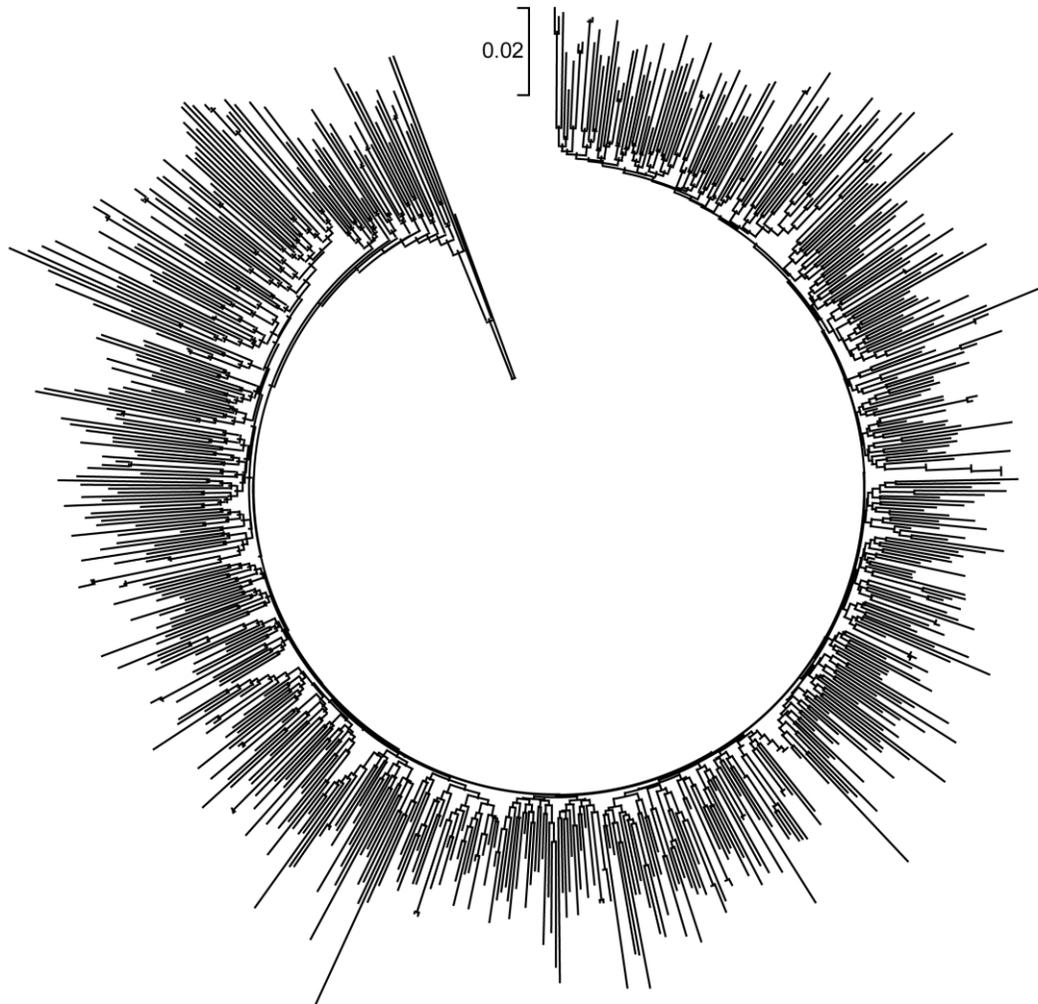


Figure 4. Phylogenetic tree showing the wild-type ancestral forms of treated chronic infections ($n = 660$)

coclusters containing 32 of the 300 nonclustered PHI transmissions (table 1).

The cumulative results of our phylogenetic results are summarized in table 1. Small and large transmission chains were largely attributable to onward transmission after recent infections, accounting for half of all transmission events. CIs, however, represented the source of new CI-PHI transmissions as well as the intermediate partners in forward PHI-PHI transmission events. Based on estimates that the JGH site performs 40% of all genotyping, untreated and treated CI populations may account for 15% and 12% of onward transmissions, respectively.

The viral loads for PHI and CI patient populations are also summarized in table 1. A mean viral load of 4.1 log copies/mL for the treated genotyped patient population is significantly lower than the corresponding viral loads of 4.6 and 4.7 observed for the PHI and treatment-naive populations, respectively

($F = 43.2$; $P < .0001$, ANOVA; and $P < .001$, post hoc Tukey tests). These results are similar to that reported by l'Actuel, the major clinical center in Montreal [18]. A mean viral load of 2.58 was observed for the nongenotyped CI patient population; this may be too low to facilitate forward transmission [18].

Time intervals for onward transmission. Because PHIs were genotyped over 9 years (1997–2005), it was important to further investigate whether early stages of infections were the source of the majority of onward transmissions. The maximum window periods for onward transmission after PIs were estimated by determining the time intervals between the first and last infections within each cluster. Forward transmission intervals ranged from 1 to 37 months with overall transmission intervals of 15.2 ± 9.5 (mean \pm SD) months. It is important to note that maximal transmission intervals are overestimated because there were only 27 of 293 infections in which the first infection was >24 months apart from other infections.

Table 1. Clinical and clustering features for the primary HIV-infected (PHI) and chronically infected (CI) patient populations.

Study population	Age, years	Viral load, copies/mL	No. of patients in the study population clustering with PHI transmission clusters (PHI transmissions, %)			Estimated transmissions, ^c %
			PHI small clusters ^a	PHI large clusters ^b	CI-PHI new cluster	
Genotyped PHI ^d	37 ± 10	4.64 ± 0.83	293 (24.2)	300 (25.1)	...	49.4
Genotyped naive CI ^e	41 ± 11	4.71 ± 0.70	5 (0.8)	7 (1.2)	25 (4.2)	~15.5
Genotyped treated CI ^f	43 ± 8	4.14 ± 0.76 ^g	9 (1.5)	8 (1.3)	17 (2.0)	~12.0
Nongenotyped CI ^h	43 ± 8	2.58 ⁱ

NOTE. Data are mean ± SD values, unless otherwise indicated.

^a 2–4 persons/cluster.

^b >5 persons/cluster.

^c Based on 40% of genotyped CIs.

^d *n* = 593.

^e *n* = 135.

^f *n* = 660.

^g *P* < .001, for treated CI compared with PHI and naive CI subjects.

^h *n* = 2328.

ⁱ Based on published findings [17].

Clinical characteristics of nonclustered and clustered transmissions. There were no differences in the viral load or age distributions in infections associated with clustered or non-clustered events (table 2). Epidemiologic data from the PHI cohort study show that clustering could not be attributed to differences in behavioral risk factors. The proportions of modes of transmission (male-male sex, intravenous drug use, and heterosexual sex) were similar in clustered and nonclustered trans-

mission events (table 2). The overall incidence of high risk sexual behavior with multiple partners was similar in non-clustered and clustered transmission chains (table 2).

Drug-resistance mutational profiles were compared in the genotyped PHI and CI patient populations (table 3). The genotyped CI potential transmitter population had single-class and multidrug resistance (MDR) in 17.5% and 52.5% of patients, respectively. This contrasts with the infrequent trans-

Table 2. Clinical characteristics of primary HIV infections (PHIs) in clustered transmission chains, compared with nonclustered unique infections.

Characteristic	Clustered transmissions ^a (<i>n</i> = 144)	Clustered transmissions ^b (<i>n</i> = 149)	Nonclustered unique PHIs (<i>n</i> = 300)
Viral load, mean ± SD, log copies/mL	4.70 ± 0.93	4.68 ± 0.80	4.66 ± 0.78
Age, mean ± SD, years	38.8 ± 9.9	34.8 ± 8.6	37.2 ± 9.8
Mode of transmission	(<i>n</i> = 63)	(<i>n</i> = 54)	(<i>n</i> = 89)
MMS	53.9 (34)	74.0 (40) ^c	57.0 (57)
IDU	34.9 (22)	13.0 (7)	28.0 (25)
HS	11.1 (7)	13.0 (7)	7.9 (7)
Sexual risk behavior	(<i>n</i> = 41)	(<i>n</i> = 47)	(<i>n</i> = 57)
0 partners	14.6 (6)	10.6 (5)	5.2 (3)
1–4 partners	68.2 (28)	68.0 (32)	66.6 (38)
5–9 partners	7.3 (3)	2.1 (1)	8.8 (5)
>10 partners	9.8 (4)	19.1 (9)	19.3 (11)

NOTE. Data are the percentage (no.) of subjects with characteristic, unless otherwise indicated. The viral load and age of the patients were determined on the date of genotypic testing. Information on mode of transmission and risk behavior was available through questionnaires completed by 195 participants in the PHI cohort study. The sexual risk behavior of the population of men who have sex with men is the no. of sexual partners during the 3-month period before PHI diagnosis. HS, heterosexual sex; IDU, injection drug use; MMS, male-male sex.

^a 2–4 persons/cluster.

^b >5 persons/cluster.

^c The distribution of risk behavior in the chronic patient population is 57.5% for MMS, 28% for IDU, and 14% for HS [17].

Table 3. Drug-resistance profiles in clustered and nonclustered transmission events in genotyped primary HIV infection (PHI) patients, compared with the treated chronically infected (CI) potential transmitter population.

Drug-resistance mutations	Patient population			P ^a
	CI treated (n = 660)	PHI cluster (n = 293)	PHI unique (n = 300)	
Wild type	189 (30)	250 (85.3)	245 (81.7)	NS
Any resistance	461 (69.9)	43 (14.7)	55 (18.3)	NS
NRTI only	79 (12)	8 (2.7)	16 (5.3)	NS
NNRTI only	23 (3.5)	25 (8.5)	18 (6.0)	NS
PI only	13 (2)	5 (1.7)	10 (3.3)	NS
NRTI/NNRTI	81 (12.2)	3 (1.0)	6 (2.0)	NS
NRTI/PI	121 (18.3)	0	3 (1.0)	NS
NNRTI/PI	1 (0.1)	2 (0.7)	0	NS
NRTI/NNRTI/PI	145 (21.9)	0	2 (0.7)	NS
Any NRTI only	425 (64.4)	11 (3.8)	27 (9.0)	.009
Any NNRTI only	249 (37.8)	30 (10.2)	27 (9.0)	NS
Any PI	279 (42.2)	7 (2.4)	15 (5.0)	.092

NOTE. Data are no. (%) of subjects. The frequency of major and minor resistance mutations associated with nucleoside reverse transcriptase inhibitors (NRTIs) and nonnucleoside reverse transcriptase inhibitors (NNRTIs), as well as with protease inhibitors (PIs), were determined in the genotyped CI and clustered and nonclustered PHI patient populations. Polymorphisms associated with resistance to NNRTIs (codons 98 and 179) and PIs (codons 10, 20, 36, 63, 71, 73, and 77) were excluded from analysis because there is a high prevalence of these substitutions in treatment naive persons. NS, not significant.

^a PHI clustered vs. unique.

mission of drug resistance and MDR in PHI (~10% and ~3%, respectively) [16, 18].

At least half of transmitted drug resistance in PHI may reflect forward transmission events as shown by the presence of drug-resistance mutations in 14.7% of clustered transmissions (table 3). Clustering may lead to an overrepresentation of select resistance-related mutational motifs. For example, one cluster had 14 patients with the G190A mutation in RT. No significant differences emerged in regard to the overall incidence of resistance mutations within clustered and nonclustered isolates (table 3). It is, however, noteworthy that the transmission of mutations associated with resistance to nucleoside analogues and protease inhibitors appeared less prevalent in clustered transmissions (table 3).

DISCUSSION

Our results show that 49% of all PHI strains in the Quebec HIV population form phylogenetic clusters, indicating that early infection may account for a major proportion of onward transmissions. This contrasts with the relatively low frequency (<2%) of clustering observed within the CI genotyped population, mostly representing individuals receiving long-term therapy with antiretroviral drugs (ARVs). Thus, primary/early infection, representing <10% of the total sequenced samples

in the provincial genotyping program, disproportionately accounted for approximately half of onward transmission events.

Events surrounding acute/early infection may play a key role in the spread of HIV. Our findings represent broad population-based surveillance and are consistent with a recent report from the Rekaï study in Uganda in regard to primary/early infection [6]. The latter suggested that the majority of new transmissions may be due to contacts with individuals who were themselves in early stages of infection. In comparison with data previously reported in the Swiss and British cohort studies, the present study shows a higher incidence of PHI clustering (~50%) and larger sizes of clustered transmission events with ~50% of transmission chains having 8.8 ± 3.5 (mean \pm SD) infections per cluster [13, 14]. Indeed, the role of acute infection may be underestimated because ~30% of PHIs remain undiagnosed [17, 23, 24].

Some groups have postulated that cases of CI may be responsible for most HIV transmission and that early treatment will have only limited impact on the spread of HIV [7–9, 25]. In stark contrast, we have rarely observed PHIs that can be linked to CI transmitters. Our findings are different from those reported in the North Carolina STAT study, on the basis of partner identification after PHI [9]. The fact that all patients in Quebec benefit from universal free access to medical care and ARVs may reduce forward transmission from the treated potential transmitter population. Indeed, transmission of single-class and primary MDR remains stable and relatively rare in Quebec, representing 10% and 3% of all PHIs, respectively [16–18].

The potential benefits of highly active antiretroviral therapy (HAART) in early infection may therefore be 2-fold. HAART may lower the risk of onward transmission, and, in addition, patients may potentially benefit from better immune control and lower set points of viremia [1, 26, 27]. Initiation of HAART during acute infection may be associated with durable virologic and immunologic benefits for >72 weeks, compared with no treatment [26]. Although some people who have newly diagnosed HIV infection may have already transmitted the virus to others by the time of initiation of HAART, early treatment intervention may nonetheless prevent significant numbers of additional transmissions.

The high incidence of clustering of PHI-related transmission events might be due to high risk sexual behavior. According to the Quebec PHI cohort data, 23.8% of newly diagnosed men who have sex with men had engaged in high risk sexual behavior with ≥ 5 partners before becoming infected, and such behaviors did not significantly change subsequent to infection. These observations are consistent with those recently reported in regard to increased coincidence of HIV with sexually transmitted diseases and high risk sexual behavior [1, 7, 13, 14, 28]. However, the present study showed that patients with high risk behavior were found among small clusters, large clusters, and nonclus-

tered infections. This suggests that different infections may vary in transmissibility, and further study is necessary. However, concerns arise from potential bias associated with self-reporting of sensitive and stigmatized behavior and other factors.

The recent case report from New York City of a triple-class MDR transmission in a man who has sex with men has raised concerns as to the threat of transmission of replication-competent drug-resistant variants of HIV [29]. Drug resistance acquired in PHI is clonal and persists over time in the absence of drug pressure [16, 30]. It is noteworthy that approximately half of transmitted resistance can be attributed to clustered infections but that transmission of viruses containing mutations associated with resistance to nucleoside and protease inhibitors was diminished in clustered infections, possibly because of reduced viral fitness.

The cost effectiveness and relevance of genotypic resistance testing programs are often debated, because transmitted drug resistance in PHI is relatively rare and resistance algorithms for MDR in CI may be difficult to interpret. Our findings underscore the importance of genotypic testing in PHI, as well as of phylogenetic analysis, to evaluate evolving trends in HIV transmission.

Several limitations must be considered with respect to these results. Although some groups raise concerns in sequencing the conserved HIV *pol* domain [31], our results are consistent with those of other groups showing that there is adequate sequence diversity to identify clustered transmission events [10–15, 32, 33]. We have also modified viral sequences in CIs to their ancestral wild-type forms to eliminate any bias caused by resistance mutations.

Although the present study compiled data from 3 surveillance sites, we doubtless missed some PHIs in the Quebec population during the study period (1996–2004). The incidence of clustered transmission events in any given population depends on how effectively the local health care system diagnoses and tracks people with HIV infection. It is estimated that 30%–50% of newly infected persons in North America may be undiagnosed and unaware of their serological status [17, 23, 24]. The nongenotyped CI patient population may be a source of HIV-1 infection, although published findings by our group show that this population generally has low viremia [17].

Taken together, our findings indicate that PHI can account for a high proportion of HIV transmissions. Acute/early infection is characterized by high viremia and high viral set points in the absence of treatment [1]. Acute/early infections are often undiagnosed, leading to high risk behavior, and unprotected sex may facilitate transmission. Relatively homogeneous viral quaspecies exist at early stages of infection, enhancing the selective advantage of clonal transmissible species [16, 30]. Many multiresistant variants that arise in treated individuals show reduced viral replicative fitness and transmissibility [30].

HIV-1-specific immunity may not arise during the first 2–4 months after PHI, and early immune responses may decrease rapidly in the absence of treatment [34]. Treatment of CI patients reduces circulating viremia, a critical factor in HIV transmission.

It is important to actively seek out recently infected persons and to propose counselling to reduce high risk behavior during this critical period [1, 3, 35–37]. Our findings further underscore recommendations for genotyping in primary/early infection to document clustering of infection and to provide information on transmitted drug resistance, both as an issue in public health and as a guide to future therapy [37].

QUEBEC PRIMARY HIV INFECTION STUDY GROUP

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