

Changing Patterns of Transmitted Resistance Among Patients with Primary HIV Infection in North Carolina from 1998 to 2003: Evidence for the Importance of HAART

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ABSTRACT

Background: Antiretroviral resistance transmitted to newly infected patients impairs efficacy of HAART. Transmitted resistance implies source patients are receiving incompletely suppressive antiretroviral therapy. Studies in urban populations indicate increasing rates of resistance in patients with primary HIV infection (PHI), suggesting transmission by patients in care but on non-suppressive therapy.

Methods: The Duke-UNC-Emory PHI Consortium has identified and enrolled patients with acute HIV infection since Jan 1998. PHI is defined by a negative HIV ELISA within 30 days of diagnosis. Phenotypic (PT) HIV resistance testing was done by Virco Antivirogram. Phenotypic resistance was defined by the following levels of reduced susceptibility: ZDV (4.0); 3TC (4.5); ddI (3.5); ddC (3.5); d4T (3.0); ABC (3.0) NVP (8.0); EFV (6.0); DLV (10.0); RTV (3.5); IDV (3.0); SAQ (2.5); NFV (4.0); APV (2.5). To assess patterns of transmitted resistance from a non-urban setting, we studied patients living in North Carolina identified with PHI between Jan 98 and May 03. Statistical comparisons were by 2-sided Fisher's Exact Test.

Results: 30 patients with PHI had PT resistance testing during the study. Between Jan 98 and Jun 00, 4/12 PHI patients (33%) had PT resistance [10 males (6 white, 3 black, 1 Latino), 2 females (2 white)]. Since Jun 00 there have been no cases of PT resistance in 18 PHI patients [13 males (4 white, 8 black, 1 Latino), 5 females (4 black, 1 Latina)], [p=0.018 for comparison of rates of resistance in the 2 time periods]. Transmission risks were: Jan 98 to Jun 00: 8 MSM, 4 heterosexuals; Jun 00 to May 03 - 8 MSM, 8 heterosexuals, 2 unknown. All 4 samples with resistance were in white MSM. Rates of resistance by transmission risk: MSM 4/16 (25%) vs. heterosexuals 0/12 [p-value 0.11] and by race: white 4/12 (33%) vs. black or Latino 0/18 [p-value 0.018].

Conclusion: Among patients diagnosed with PHI in North Carolina, resistance was significantly more common in whites than in non-whites and occurred significantly more often before Jun 00 than afterwards. No cases of transmitted resistance have been observed over the past 3+ years. These data suggest that new HIV infections are being acquired either from patients without significant antiretroviral resistance (perhaps because fewer patients on therapy have transmissible levels of HIV viremia) or that new infections are transmitted most often by persons not in care or unaware of their HIV status.

BACKGROUND

Transmission of HIV resistant to antiretroviral agents has been reported to be occurring with increasing frequency among patients with acute HIV infection.

- A consecutive case series of 225 patients from San Francisco with recently acquired HIV infection demonstrated increases in transmitted NNRTI resistance from 0% in 1996-97 to 13.2% in 2000-01 and in PI resistance from 2.5% to 7.7% during the same time period.¹

- A study of 377 newly infected patients from 10 cities showed increased frequency of high-level resistance over time. Between 1995-98 3.4% of patients had such resistance while 12.4% had high-level resistance between 1999-2000.²

More contemporary approaches to antiretroviral therapy (such as ritonavir boosting) and increased emphasis on adherence may reduce the likelihood of resistance being generated and subsequently transmitted.

Lower levels of HIV viremia with improved therapy and reduced viral fitness among patients with incomplete viral suppression may also alter transmission risks.

We assessed rates of and trends in HIV drug resistance in a cohort of patients diagnosed with primary HIV infection (PHI) in North Carolina between 1998 and 2003

STUDY DESIGN

This work represents data from a subset of patients enrolled in the Duke-UNC-Emory Acute HIV Infection Research Consortium. Members of this consortium include:

- Duke University Medical Center - Charles Hicks, Amy Weintrob, Julia Giner, Guido Ferrari, Kent Weinhold
- University of North Carolina, Chapel Hill - Joseph Eron, Chris Pilcher, Prema Menezes, Susan Fiscus
- Emory University - Jeffrey Lennox, Carlos del Rio, Beth Dean

The parent study is designed to investigate the virologic and immunologic events occurring during acute HIV infection. Some patients only provided baseline samples and did not participate in the treatment study.

Persons thought to have primary HIV infection were screened by standard techniques. Patients determined to be HIV antibody negative within 30 days of diagnosis were eligible for inclusion.

Informed consent was obtained from all study participants prior to enrollment.

At the screening and/or baseline visit, a pre-treatment specimen was obtained for HIV resistance testing.

Phenotypic HIV resistance testing was done by the Virco Antivirogram™ method (LabCorp, Burlington, NC)

To assess patterns of transmitted resistance from patients with HIV infection acquired in a non-urban setting, we studied the subset of patients who were living in North Carolina when they were diagnosed with PHI between January 1998 and May 2003.

The study was approved by the Institutional Review Boards at all three participating institutions.

Statistical comparisons were made by 2-sided Fisher's Exact Test.

Phenotypic resistance was defined by the following levels of reduced susceptibility

NRTI		NNRTI		PI	
ZDV	4.0-fold	EFV	6.0-fold	RTV	3.5-fold
3TC	4.5-fold	NVP	8.0-fold	IDV	3.0-fold
ddI	3.5-fold	DLV	10.0-fold	SAQ	2.5-fold
ddC	3.5-fold			NFV	4.0-fold
d4T	3.0-fold			APV	2.5-fold
ABC	3.0-fold				

RESULTS

- 30 patients living in North Carolina were diagnosed with PHI between January 1998 and July 2003. All had phenotypic resistance testing completed on baseline samples (table 1).
- Between January 1998 and June 2000, 10 males (6 white, 3 black, 1 Latino) and 2 females (2 white) from North Carolina were diagnosed with PHI.
- The last patient with phenotypic resistance was identified on June 30, 2000.

Table 1 - Demographics and Risk Factors

	Jan 98 - Jun 00 (n=12)			Jul 00 - May 03 (n=18)			
	White	Black	Latino	White	Black	Latino	
Male (10)	6	3	1	Male (13)	4	8	1
Female (2)	2			Female (5)	1	4	
MSM	8			MSM	8		
Hetero-sexual	4			Hetero-sexual*	8		

* Risk unknown for 2 patients

- Between July 2000 and May 2003, 13 males (4 white, 8 black, 1 Latino) and 5 females (4 black, 1 Latina) were diagnosed with PHI.
- Overall, 4 of the first 12 North Carolina PHI patients (33%) diagnosed between Jan 1998 and June 2000 had PT resistance (table 2) compared to none of 18 patients diagnosed after June 2000 [p=0.018].

Table 2 - Phenotypic Resistance

Patient	Diagnosis Date	Baseline VL	PT Resistance
Z03	8/13/98	184,670	d4T 9.7-fold EFV 6.3-fold DLV 16.7-fold
Z06	10/19/98	470,476	NVP 9.3-fold DLV 4.5-fold
Z17	4/12/00	2,553,350	RTV 6.6-fold APV 5.1-fold
Z18	6/30/00	2,845,823	NFV 5.0-fold

Transmission Risks

- Reported HIV transmission risks for patients diagnosed before June 2000: 8 MSM, 4 heterosexual.
- Reported HIV transmission risks for patients diagnosed after June 2000: 8 MSM, 8 heterosexual, 2 unknown.
- All 4 samples with resistance were from white MSM.
- Rates of resistance by transmission risk and race (Table 3):
 - MSM 4/16 (25%) vs. heterosexuals 0/12 [p-value 0.11]
 - Race: white 4/12 (33%) vs. black or Latino 0/18 [p-value 0.018].

Table 3 - Factors Associated with Resistance

Infection before 7/00 vs. after 7/00	4/12 vs. 0/18	p=0.018
White vs. non-white ethnicity	4/12 vs. 0/18	P=0.018
MSM vs. heterosexual	4/16 vs. 0/12	P=0.11

Rates of Phenotypic Resistance by Drug Class and Agent

Baseline phenotypic resistance to NRTI [total = 1/30 (3.3%)]

Zidovudine	none	0%
Lamivudine	none	0%
Didanosine	none	0%
Zalcitabine	none	0%
Stavudine	1 [9.7-fold change]	3.3%
Abacavir	none	0%

Baseline phenotypic resistance to NNRTI [total = 2/30 (6.7%)]

Nevirapine	1 [9.3-fold change]	3.3%
Delavirdine	1 [16.7-fold change]	3.3%
Efavirenz	1 [6.3-fold change]	3.3%

Baseline phenotypic resistance to Protease Inhibitors [total = 2/30 (6.7%)]

Indinavir	none	0%
Ritonavir	1 [6.6-fold change]	3.3%
Nelfinavir	1 [5.0-fold change]	3.3%
Saquinavir	none	0%
Amprenavir	1 [5.1-fold change]	3.3%

Conclusions

- In contrast to reports of patients with recently acquired HIV infection in urban settings, our study shows rates of transmitted HIV resistance among persons diagnosed with acute HIV infection in North Carolina are low and decreasing.**
- Among patients diagnosed with PHI in North Carolina, resistance was significantly more common in whites than in non-whites and occurred significantly more often before June 2000 than afterwards.**
- No cases of transmitted resistance have been observed over the past 3+ years.**

Discussion

Reasons for the low rates of transmitted resistance and for the absence of resistance over the last 3 years in our cohort are uncertain but may include the following:

- Transmission of HIV in North Carolina (and likely in the Southeast in general) is most often occurring from persons not on therapy, either because their HIV infection is undiagnosed or because those who are diagnosed are not in care.
- Patterns of sexual partnerships may be different in non-urban settings and among heterosexuals compared to MSM. As the HIV epidemic becomes an increasingly heterosexual one involving non-white populations, new resistance patterns may be identified.
- Improvements in antiretroviral therapy, more frequent use of ritonavir boosting, and a stronger emphasis on adherence mean fewer patients receiving HAART have viral load sufficient for transmission to be likely.
- Patterns of management of HIV virologic failure may be more often generating virus with reduced fitness which in turn may be less transmission-competent than wild type HIV virus.

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