

increase in protease resistance and a decrease in reverse transcriptase resistance mutations in primary HIV-1 infection

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Introduction

The development of drug resistance is one of the major challenges confronting the continued administration of effective therapy against infectious pathogens. The increasing prevalence of drug resistant virus among HIV-1 infected patients on therapy has increased the probability of transmission of virus resistant to one or more classes of antiretroviral drugs. Estimates of rates the number of new cases infected with resistant virus vary markedly from study to study. Reports demonstrate that rates of resistance in certain populations especially those late in the disease, who have been heavily pre-treated, in the region of 17-75%. Some recent studies have suggested significant recent increases in the rates of transmission of drug resistant HIV-1 with in excess of 25% of newly infected individuals carrying virus with at least one primary mutation. Transmission of resistant virus has implications for the management of HIV-infection both on an individual and on a population basis.

Aim

To describe the prevalence and epidemiologic correlates of changes in prevalence of drug resistance mutations in patients with early HIV-1 primary infection.

Hypothesis

- > The widespread use of antiretroviral drugs will result in the increased transmission of drug-resistant virus
- > This will result in an increased prevalence of resistant variants in newly infected patients

Method

> A retrospective analysis was performed on all subjects with acute primary HIV-1 infection who had plasma samples stored at the Centre for Immunology, St Vincent's Hospital, Sydney, Australia

Results

Baseline characteristics of 185 subjects with Primary HIV infection

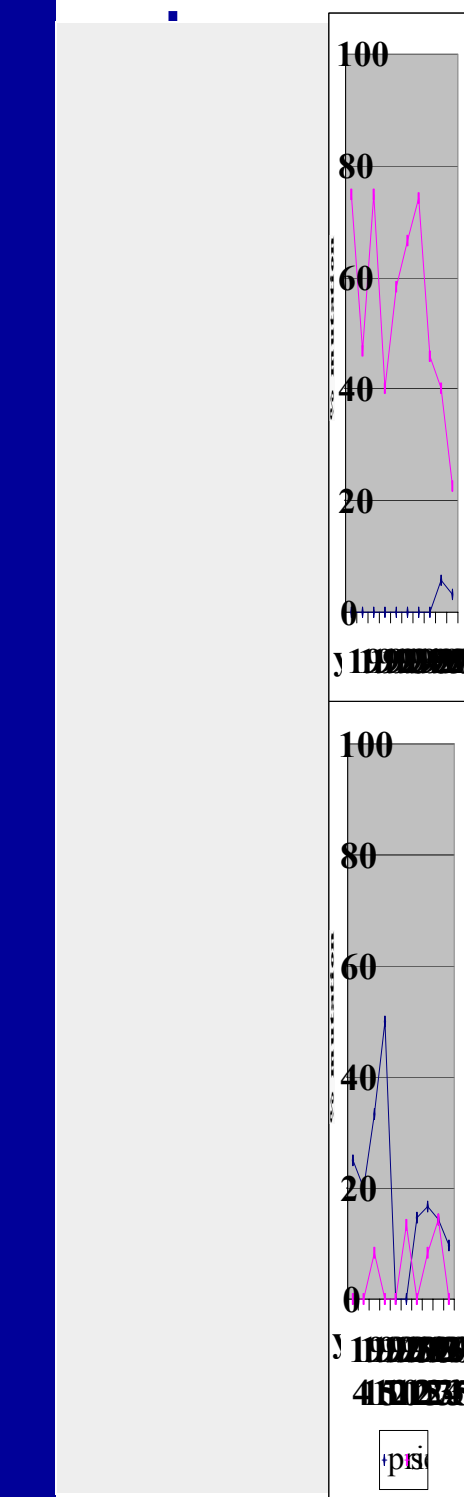
Age, mean (range)	37 (23-72)
Sex, No. (%)	
Male	180 (97.3)
Female	3 (1.6)
Unknown	2 (1.1)
HIV risk factor, No. (%)	
Homosexual contact	160 (86.5)
Heterosexual contact	4 (2.2)
Injection drug use	1 (0.5)
Unspecified	20 (10.8)
Mean Initial plasma HIV RNA level, copies/ml (range)	3,485,781 (3,600-63,641,000)
Mean Initial CD4 cell count, cells/ml (range)	539 (136-1,440)
Interval between positive diagnosis and collection of sample for resistance testing, days (mean)	2.1

Frequency of amino acid substitutions associated with drug resistance RT

Mutation	Substitution	Reverse Transcriptase	
		Drug	No (%) of study subject
1°	M41L	AZT	8.1
	T69N	ddC	2.2
	K70R	AZT	3.2
	K103N/R	NVP,DLV,EFV	2.2
	M184V	3TC,ABC,ddl,ddC,AZT	0.5
	T215Y	AZT	3.2
2°	I50N		1.1
	D67N	AZT	1.1
	A98S	NVP	1.1
	V106A	Protease Inhibitors	0.5
	E164L	Protease Inhibitors	0.5
1°	V179D	EFV	0.5
	D30N	AZT	0.5
	D30W	NFV	0.5
	K87Q	IDV,RTV,SQV	0.5
	K87R	IDV,RTV,SQV	0.5
	L90M	IDV,RTV,SQV,NFV	0.5

Frequency of amino acid substitutions associated with drug resistance in PR

Frequency of primary



Significant

Substitution	Drug	Pre 1995	Post 1995	P value
M41L	AZT	17.2%	5.6%	< 0.0008
D67N		4.9%	0%	< 0.03
K70R		12.2%	0.7%	< 0.0008
T215Y		12.2%	0.7%	< 0.0008
Any NRTIs		29.3%	15.3%	< 0.008
1°				
D30N	NFV	0%	0.7%	NS
V82I	IDV,RTV,SQV	0%	0.7%	NS
L90M	IDV,RTV,SQV,NFV	0%	0.7%	NS
2°				
L101V	IDV			

Sequencing kits were provided by Visible Genetics Inc.

185 blood samples were taken during acute primary infection prior to full seroconversion and prior to initiation of any therapy

HIV viral RNA extracted, RT-PCR performed, followed by bi-directional sequencing

Sequences aligned and assembled, compared with HIV-LAV1 consensus sequence

Phylogenetic analysis performed

- > Population divided into those collected pre and post introduction of protease inhibitors into parent population (pre and post 31/12/1995)
- > Change in frequency of mutations assessed by Fischer's exact test