Analysis of prevalence and characteristics of transmitted HIV-1 drug resistance in primary infections in a cohort of acute and recently infected men in New York

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ABSTRACT

The occurrence of transmitted HIV drug resistance (TDR) is a particularly important phenomenon since it is thought to be a more accurate reflection of the true prevalence of drug resistance within a community. The overall prevalence of TDR is estimated to be 14% and is thought to be increasing.

Three patients (5.5%) in our study had evidence of reverse transcriptase or protease gene mutations associated with drug resistance. One had a mutation associated with major protease inhibitor resistance and the other two had mutations associated with minor protease inhibitor resistance.

Our cohort consisted entirely of MSM and it is possible these patients with acute infection are acquiring the virus from others within this population that has a lower prevalence of resistance. Further work is needed to characterize the patterns of TDR locally & globally.

INTRODUCTION

HIV drug resistance is an important concern with varying trends observed geographically and in cohorts with different risk factors[1-2]. The overall prevalence of HIV drug resistance is thought to be around 14%[3]. The general trend suggests that the prevalence of HIV drug resistance is increasing, and that it is a particular problem among men who have sex with men (MSM)[1].

It can be difficult to assess the extent of transmitted resistance since diagnosed HIV infections are often not acute or recent with resistance developing after infection, and also because resistant strains may revert to wild type in the absence of drug selection pressures[2]. Some drug resistant viruses isolated during primary infection possess unique adaptive changes that allow for both high viral replication capacity and resistance. However the clinical significance of TDR remains unclear with some studies suggesting it is associated with impaired viral replicative capacity and poor virological suppression[1] and others refuting this.

During the past several years a consensus has emerged for starting drug treatment earlier in the disease, increasing the importance of knowing the prevalence of resistance in transmitted viruses[4]. It has been suggested that drug resistant viral strains in acute infection may greatly reduce the likelihood of long-term viral suppression[5]. Many previous studies have focused on small numbers of patients with infections of unknown duration obtained through convenience samples and high risk groups, leaving a need for studies looking at drug-naïve acutely infected patients.

METHODS

Study population: those enrolled in the clinical trial looking at immunologic control of acute and recent HIV infection performed at NYU Medical Center between 2004-2009.

Exclusion criteria: prior ART (including PEP during the previous 6 months, age < 18 years, pregnancy or breast feeding and other life-threatening illnesses.

Participants meeting the eligibility criteria were identified through **active case ascertainment** at clinics, counselling and testing in high risk venues, and print and web advertising. Patients were stratified by acute and recent infection.

All participants in the protocol were offered **ART**. Blood specimens for viral resistance testing were obtained from all consenting participants at entry, prior to the initiation of therapy.

Resistance testing

At baseline, plasma samples were analysed for drug resistance by nucleotide sequencing of the reverse transcriptase and protease genes of plasma virus **(genotyping)**.

RESULTS

Of the 54 patients infected between 2004-2009**, all were males whose risk factor for HIV transmission was sex with men**, with only one concurrent intravenous drug user (IVDU). **Considerable ethnic diversity** was seen with the predominant groups being white and Latino. **21 patients were referred with acute HIV infection and 33 with recent infection**. The mean time between estimated HIV infection and initial screening for all patients was 23.8 days for patients with acute infection and 71.3 days for recently infection. The median baseline entry CD4 count was 537 cells per cubic millimeter and the median entry plasma viral load was 27 789 copies per millimeter.

Three patients (5.5%) had evidence of reverse transcriptase or protease gene mutations associated with drug resistance (see table). Two of the three were successfully treated while one opted not to receive treatment. **One had a mutation associated with major protease inhibitor resistance and the other two had mutations associated with minor protease inhibitor resistance. One patient with resistant virus had acute infection and two had recent infections. There was no significant difference in age, ethnicity, entry CD4 count or viral load in patients with resistance mutations compared to the total study population.**

Patients with drug resistance mutations (status of Infection)	Key mutations associated with drug resistance	Drugs for which mutations compromise efficacy
Patient 1 (recent)	RT V108I	Low level resistance to EFV, NVP, DEL
	PR L63P	No associated resistance – common in persons receiving PIs
	PR A71T	**Minor PI resistance** – occur in 2-3% untreated persons, more commonly in persons receiving PIs
	PR V77I	No associated resistance – commonly associated with NFV therapy
	PR V82A	**Major PI resistance** - reduces susceptibility to IDV/r and LPV/r, with other mutations it is associated with reduced susceptibility to NFV, ATV/r, SQV/r, and FPV/r
Patient 2 (acute)	RT 211K	No associated resistance
	RT 215L	No associated resistance
	RT G333E	No associated resistance – occur more commonly in persons receiving NRTIs
	PR I13V	No associated resistance – more common in treated persons with subtype B isolates
	PR L33F	**Minor PI resistance** - selected by FPV/r, DRV/r, LPV/r, ATV/r, and TPV/r
	PR V77I	No associated resistance – commonly associated with NFV therapy
	PR N88D	**Minor PI resistance** – in combination with D30N increases NFV resistance
	PR L89M	No associated resistance
Patient 3 (recent)	RT R211K	No associated resistance
	RT G333D	No associated resistance – occur more commonly in persons receiving NRTIs
	PR L10I	**Minor PI resistance** – to most PIs if present with other mutations
	PR L63P	No associated resistance – common in persons receiving PIs

EFV: Efavirenz, NVP: Nevirapine, DEL: Delavirdine, NFV: Nelfinavir IND: Indinavir, , LPV: Lopinavir, ATV: Atazanavir, SQV: Saquinavir, FPV: Fosamprenavir, DRV: Darunavir, TPV: Tipranavir

DISCUSSION

It is unclear why the prevalence of TDR in our New York cohort of MSM presenting with acute or recent infection is lower than expected over the five year period between 2004-2009. Overall prevalence estimates (around 14%) are not specific to acute or early infection and it has been suggested that increases in the prevalence of TDR among patients with established HIV infection may result in more frequent transmission of resistant strains to newly infected members of their community[1].

Our cohort consisted entirely of MSM (with one concomitant intravenous drug user) and it may be that the pattern of TDR within this subset of the population is changing. It has previously been suggested that increases in risky behaviour in the MSM community may result in an increased incidence of both HIV infection and an increased frequency of drug resistant strains circulating[6]. A higher frequency of multivariant transmission has been demonstrated in the MSM population when compared with heterosexuals[7], although it is unclear what effect this has on the transmission of drug resistant strains. MSM are a risk group that has historically had greater access to HIV care than other groups and this could serve to explain the difference we observed. The changing patterns of transmitted drug resistance locally and globally are of great epidemiological interest.

TDR is an important concern as the utilization of HIV therapeutics continues to expand, with serious implications for individual patients and the wider public health community. Further work is required to elucidate the clinical significance of TDR at a local and global level. Efforts to improve adherence to antiretroviral treatment regimens must be escalated to decrease the selection of additional resistant strains.

REFERENCES

1. Little SJ, Holte S, Routy JP, et al. Antiretroviral-drug resistance among patients recently infected with HIV. N Engl J Med 2002;347:385-94.
2. Weinstock HS, Zaidi I, Heneine W, et al. The epidemiology of antiretroviral drug resistance among drug-naive HIV-1-infected persons in 10 US cities. J Infect Dis 2004;189:2174-80.
3. Wheeler WH, Ziebell RA, Zabina H, et al. Prevalence of transmitted drug resistance associated mutations and HIV-1 subtypes in new HIV-1 diagnoses, US. AIDS 2010; 24: 1203-12
4. Holmberg SD, Palella FJ, Jr., Lichtenstein KA, Havlir DV. The case for earlier treatment of HIV infection. Clin Infect Dis 2004;39:1699-704.
5. Little S, Holte S, Routy J-P, et al. Antiretroviral resistance and response to initial therapy among recently HIV-infected subjects in North America. Antivir Ther 2001;6.
6. HIV incidence among young men who have sex with men--seven U.S. cities, 1994-2000. MMWR Morb Mortal Wkly Rep 2001;50:440-4.
7. Li H, Bar KJ, Wang S, et al. High Multiplicity Infection by HIV-1 in Men Who Have Sex with Men. PLoS Pathog 2010;6:e1000890.