The prevalence of antiretroviral drug resistance in the United States

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Background: Antiretroviral therapy has dramatically reduced the morbidity and mortality of infection due to HIV. The emergence of drug-resistant virus has limited the usefulness of many drugs.

Objective: To determine the prevalence of HIV drug resistance in the population of adults receiving care in the United States.

Design and methods: HIV drug susceptibility assays were performed on plasma virus from a random sample representative of the 132 500 HIV-infected American adults who had received medical care in early 1996 yet were viremic with > 500 copies/ml of HIV RNA in late 1998. A blood sample was obtained from 1797 patients who comprised a representative sample of the 208 900 adults receiving urban care for HIV infection in early 1996 who survived to late 1998. The sampling procedure permitted weighting each evaluated patient to reflect demographic and other characteristics of the target population.

Results: We estimated that 132 500 (63%) of the target population had HIV viremia of > 500 copies/ml. Among viremic patients, an estimated 76% had resistance to one or more antiretroviral drugs. The odds of resistance were significantly higher in patients with a history of antiretroviral drug use, advanced HIV disease, higher plasma HIV viral load and lowest CD4 cell count by self-report.

Conclusions: The frequent selection for drug-resistant virus among viremic patients during the first 3 years of widespread use of potent antiretroviral combination therapy has significant implications for HIV treatment and transmission.

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Introduction

Drug-resistant HIV evolves as virus replicates in the presence of the selective pressure of drug treatment [1]. Resistance to a drug diminishes the efficacy of that drug and often of members of the same drug class as well, thus diminishing the probability of identifying an effective subsequent treatment regimen [2]. By diminishing the efficacy of antiretroviral therapy, HIV drug resistance has negative implications both for treatment of individuals, for whom effective therapy has been shown to reduce morbidity and mortality, and for

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public health, since effective therapy can reduce transmissibility. Transmitted drug-resistant virus also impairs the response to treatment in the newly infected patient [3].

Since the initial description of resistant virus during the phase II clinical trial of the first antiretroviral drug, zidovudine [4], drug resistance and testing for it have become a routine part of antiretroviral drug development and clinical management, particularly of patients with virologic failure [1,2,5]. Although the prevalence of resistance has been reported in selected cohorts of limited size and geographic representation, the true prevalence of HIV drug resistance has not been described in any large population [6]. The objective of this study was to estimate the prevalence of antiretroviral drug resistance in a large, well-characterized study population representing adults receiving care for HIV infection throughout the contiguous United States.

Methods

The study sample is a subset of the nationally representative HIV Cost and Service Utilization Study (HCSUS) cohort, which represents the 231 000 adults under care for HIV in the contiguous United States at the start of the era of highly active antiretroviral therapy (HAART) in January and February 1996 [7]. We located and contacted for interview 1919 patients from the HCSUS cohort, who were receiving care in urban clinics during January and February of 1996 and were alive in 1998. The patients were asked to provide an anonymous blood sample. Interviewers met the patients at the blood draw center to provide the laboratory with the patient's study ID number for matching with other study data. Interviewers also collected information about current and past antiretroviral therapies, HIV disease status, CD4 cell count and viral load history. Blood samples were shipped to Quest Diagnostics (San Juan Capistrano, California, USA), centrifuged to separate cells and plasma, which were divided into aliquots and frozen at −70°C. Blood was successfully obtained, and CD4 and viral load information could be determined for 1797 patients, representing the 208 900 adults under care who survived from early 1996 to late 1998 (Fig. 1). This study focuses on results of drug susceptibility assays performed on 1099 blood specimens representing the 132 500 (63.4% of survivors) adults in care with ⩾ 500 HIV RNA copies/ml plasma ('viremic' subset of the cohort population). The study procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional or regional) and with the Helsinki Declaration of 1975, as revised in 1983.

Quantitative CD4+ T-cell determinations were performed on blood samples by flow cytometric analysis

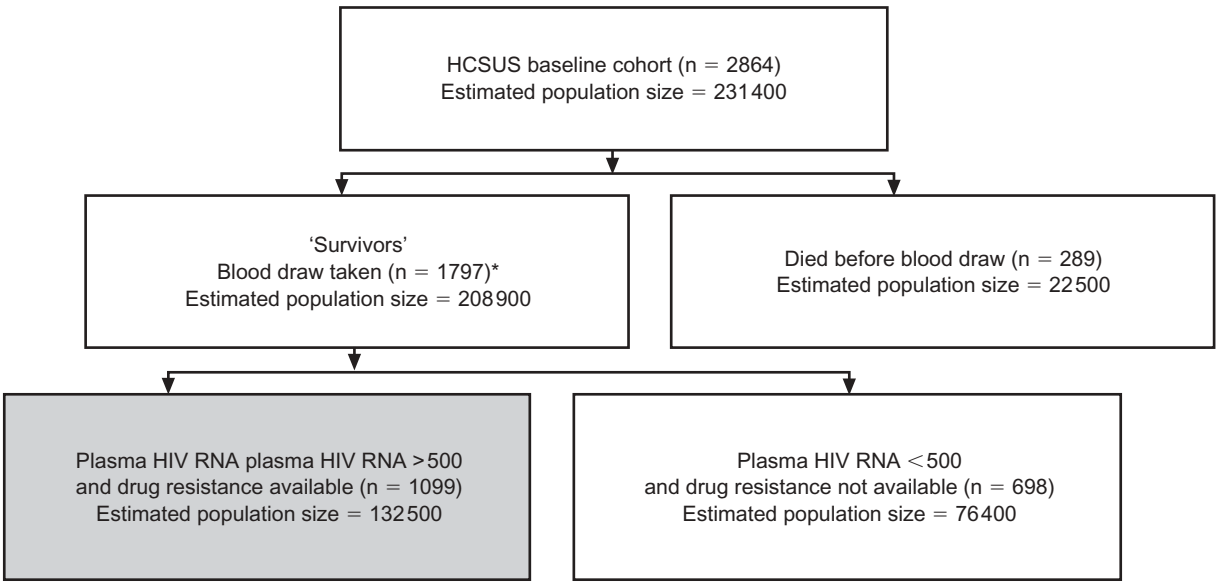

Fig. 1. The baseline HIV Cost and Service Utilization Study cohort consisted of 2864 randomly sampled members representing approximately 231 400 HIV-infected individuals who received care in early 1996 in the contiguous United States [7]. We focus on two subsamples of this cohort. The first consists of the 1797 who survived until blood specimens were drawn in 1998, and who represent approximately 208 900 'survivors'. The second consists of the 1099 who survived and had a viral load ⩾ 500 copies HIV RNA/ml plasma and who represent the 'detectable viral load' or 'viremic' subpopulation of approximately 132 500 individuals. The box representing this population on whom drug resistance assays were performed is shaded. *778 subjects are accounted for by analytic weights [10].

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by Quest Diagnostics. Aliquots of plasma were assayed for levels of HIV RNA by the Gen-Probe HIV-1 viral load assay [8]. Drug susceptibility assays were performed by the ViroLogic PhenoSense HIV assay which amplifies a *gag–pol* amplicon from plasma HIV RNA and inserts it into a resistance test vector [9]. Drug susceptibility is expressed as a ratio of the 50% inhibitory drug concentration (IC_{50}) of the patient's plasma virus in comparison with a standard reference HIV-1 strain, NL4-3. Drug susceptibility was measured against the 15 antiretroviral drugs approved by the FDA as of early 2001. Drug resistance was defined for each drug by the IC_{50} ratio associated with a significantly decreased clinical response to treatment with the drug in clinical trials (abacavir, didanosine, stavudine, and lopinavir) or, when clinically defined resistance levels were not available, by the greater of either the upper 95% confidence interval (CI) for reproducibility of IC_{50} ratios from repeated testing of clinical virus isolates or the upper 95% CI for drug susceptibility from >1400 wild-type, patient-derived virus isolates (number of tested isolates ranged from 1430 to 1515 per drug). Patient virus : reference virus IC_{50} ratios above the following values were considered to be indicative of drug resistance: abacavir 4.5; didanosine 1.7; lamivudine 1.8; stavudine 1.7; zalcitabine 1.7; zidovudine 2.3; delavirdine 4.7; efavirenz 2.2; nevirapine 3.4; amprenavir 1.9; indinavir 1.9; lopinavir 10; nelfinavir 3.0; ritonavir 2.3; and saquinavir 1.9.

We constructed analytic weights accounting for sampling and attrition to adjust the sample to represent the reference population [10]. To adjust standard errors and statistical tests for the differential weighting and complex sample design, we used the linearization method [11] implemented in the statistical package Stata [12]. For patient subgroups defined by covariates chosen *a priori*, such as key demographics and antiretroviral use history, we report estimated population sizes and weighted proportions. For each covariate, we present a chi-squared test of association, and a pairwise test for each subgroup versus a reference subgroup. We estimate adjusted odds ratios from a multivariate logistic regression model predicting drug resistance as a function of the covariates, and for each covariate present an *F*-test and a Wald pairwise *t*-test for each subgroup versus the reference subgroup.

Results

Drug resistance to one or more drugs was detected in virus from specimens representing an estimated 101 100 patients or 76.3% (95% CI, 73.0–79.2%) of the 132 500 surviving adults with more than 500 copies/ml HIV RNA plasma (Table 1). Among the viremic patients, the estimated prevalence of resistance to one or more drugs within each of the three drug classes ranged from 71.4% (95% CI, 67.6–74.9%) for nucleoside reverse transcriptase inhibitors (NRTI) to 40.5% (95% CI, 36.8–44.2%) for protease inhibitors and 25.2% (95% CI, 21.9–28.8%) for non-nucleoside reverse transcriptase inhibitors (Fig. 2). Lamivudine, an NRTI, was the single drug with the highest estimated prevalence of resistance (67.8%; 95% CI, 64.6–70.9%). Resistance to more than one class of drug, termed multiple drug resistance, was detected in an estimated 47.7% (95% CI, 43.6–51.8%) of the viremic population (63 200 patients). Resistance to all three drug classes was detected in an estimated 13.1% (95% CI, 10.6–16.1%) (17 300 patients). Details of resistance prevalence by drug, drug classes, and demographic group is provided in Table 2, and in more detail in Table 3.

Resistance was much more prevalent among patients who were very early adopters of HAART or who were taking nucleoside analogs at the start of the HAART era (1996) compared with patients who had not taken antiretroviral therapy up to that time. For example, 2 years later, resistance to any drug was estimated to be present in 87, 82, and 43% of these subpopulations, respectively, and resistance to all three drug classes was present in 27, 11, and 2%.

An estimated 88% of viremic survivors taking antiretroviral therapy when blood was collected had detectable resistance to one or more drugs compared with 30% of those not currently taking therapy ($P = 0.001$). A significantly higher prevalence of resistance was also associated with advanced disease stage [odds ratio (OR), 2.95; 95% CI, 1.04–8.35], lower current viral load (OR, 1.57; 95% CI, 1.18–2.09), and lowest self-reported CD4+ T-cell count (OR, 11.07; 95% CI,

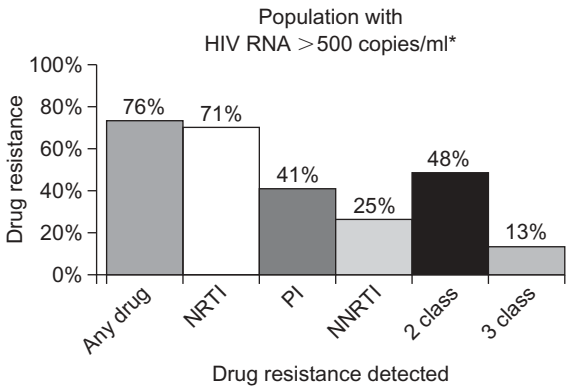

Fig. 2. Prevalence of estimated HIV drug resistance in the represented populations. *Represents 63% of total study population. PI, protease inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor.

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Table 1. Demographics of the study population.

	Plasma HIV RNA ⩾ 500	Plasma HIV RNA ⩾ 500 and resistant (%)	
Overall	132535	101078	(76.3%)
Lowest CD4 count (self-report)		*	
⩾ 500 cells × 10^6/l	6977	3054	(43.8%)†
200–499 cells × 10^6/l	41561	27251	(65.6%)†
50–199 cells × 10^6/l	46073	36792	(79.9%)†
0–49 cells × 10^6/l (R)	37924	33981	(89.6%)
CD4 count (based on blood draw)			
⩾ 500 cells × 10^6/l	25888	17910	(69.2%)
200–499 cells × 10^6/l	55807	42122	(75.5%)
50–199 cells × 10^6/l	35461	29733	(83.8%)†
0–49 cells × 10^6/l (R)	15380	11313	(73.6%)
Clinical stage of HIV disease		*	
Asymptomatic (R)	5572	3379	(60.6%)
Symptomatic	63551	45722	(71.9%)
Clinical AIDS	63413	51978	(82.0%)†
Age			
18–34 years	49466	35698	(72.2%)
35–49 years	73434	57648	(78.5%)
⩾ 50 years (R)	9636	7732	(80.2%)
Sex		*	
Male	98933	77777	(78.6%)†
Female (R)	33602	23301	(69.3%)
Race and ethnicity			
White (R)	58514	45653	(78.0%)
Black	50508	37329	(73.9%)
Hispanic	19195	14466	(75.4%)
Other	4319	3631	(84.1%)
HIV exposure group		*	
Injection drug use	33038	24926	(75.4%)
Male sex with men (R)	60657	48072	(79.3%)
Heterosexual sex	27819	20254	(72.8%)†
Other	11021	7826	(71.0%)†
Education		*	
Some high school (R)	35618	25161	(70.6%)
High school graduate	40568	30517	(75.2%)
Some college or more	56350	45400	(80.6%)†
Health Insurance		*	
None	21639	14661	(67.8%)†
Medicaid alone	41957	31721	(75.6%)
Private (R)	33430	26656	(79.7%)
Medicare with or without other insurance	35510	28040	(79.0%)
Region of country			
Northeast	34371	25945	(75.5%)
Midwest (R)	12305	9804	(79.7%)
South	53206	40946	(77.0%)
West	32654	24382	(74.7%)
Provider HIV practice size			
0–10	4154	3012	(72.5%)
11–100	25657	20637	(80.4%)
101–500	79577	61241	(77.0%)†
> 500 (R)	23149	16187	(69.9%)
Plasma viral load		*	
500–30 000 copies/mL	64586	51935	(80.4%)†
> 30 000 copies/mL (R)	67949	49143	(72.3%)
Current use of antiretroviral drug		*	
Yes	106241	93074	(87.6%)†
No (R)	26294	8004	(30.4%)
Past use of antiretroviral drug		*	
Yes	125035	99978	(80.0%)†
No (R)	7501	1101	(14.7%)
EVER use antiretroviral drug		*	
Yes	125967	100363	(79.7%)†
No (R)	6569	716	(10.9%)
Current use of protease inhibitor		*	
Yes	73085	65788	(90.0%)†
No (R)	58974	35291	(59.8%)

(*continued overleaf*)

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Table 1. (*continued*)

	Plasma HIV RNA ⩾ 500	Plasma HIV RNA ⩾ 500 and resistant (%)	
Past use of protease inhibitor		*	
Yes	98046	81651	(83.3%)†
No (R)	34490	19427	(56.3%)
EVER use protease inhibitor		*	
Yes	102339	85313	(83.4%)†
No (R)	30196	15765	(52.2%)
Current use of NNRTI		*	
Yes	21770	19839	(91.1%)†
No (R)	110288	81239	(73.7%)
Past use of NNRTI		*	
Yes	24865	22920	(92.2%)†
No (R)	107671	78158	(72.6%)
EVER use NNRTI		*	
Yes	35184	31665	(90.0%)†
No (R)	97352	69413	(71.3%)
Current use of NRTI drug		*	
Yes	100134	88154	(88.0%)†
No (R)	31925	12924	(40.5%)
Past use of NRTI drug		*	
Yes	122344	99226	(81.1%)†
No (R)	10192	1852	(18.2%)
EVER use NRTI drug		*	
Yes	123747	99936	(80.8%)†
No (R)	8789	1142	(13.0%)
Current use of lamivudine		*	
Yes	60004	53526	(89.2%)†
No (R)	72055	47552	(66.0%)
Past use of lamivudine		*	
Yes	102772	85422	(83.1%)†
No (R)	29763	15656	(52.6%)
EVER use lamivudine		*	
Yes	107407	89039	(82.9%)†
No (R)	25128	12039	(47.9%)

R represents the reference group for statistical comparisons. *Indicates demographic categories in which resistance is significantly different in a univariate analysis ($P < 0.05$). †Indicates that group was significantly different from the reference group ($P < 0.05$). NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor.

4.24–28.89), but not current CD4+ T-cell count (OR, 1.24; 95% CI, 0.59–2.60). A significantly higher resistance prevalence was also associated with male sex (OR, 1.63; 95% CI, 1.16–2.28), being a man who has sex with men (OR, > 1.25 with 95% CI, > 1 for all other risk groups), insurance coverage (OR, 1.87; 95% CI, 1.28–2.73), and more education (OR for college or more, 1.72, 95% CI, 1.20–2.48). However, among all these predictors in univariate analysis, only lowest reported CD4 count (OR, 7.51; 95% CI, 1.93–29.17) and current viral load (OR, 2.91; 95% CI, 1.93–4.39) were demonstrated to be persistent independent predictors of resistance in a multiple logistic regression. (Table 4).

As the cutoff criteria used to define resistance were not derived from treatment response criteria for all drugs, the study results may slightly over or under-estimate the true drug resistance prevalence, although the cutoffs utilized reflect the best current estimate of clinically significant criteria for impaired treatment responses due to drug resistance. When a much more conservative IC_{50} ratio of 10 is used to define resistance for all classes of drugs, despite the fact that with several drugs significantly impaired treatment responses have been documented with lower cutoff values, the prevalence of resistance to one or more drugs among the viremic population decreased slightly to 72.6%, whereas the prevalence of resistance to non-nucleoside reverse transcriptase inhibitors decreased to 21.8% and protease inhibitors to 27.4%. These small reductions in estimated prevalence of resistance did not substantially impact the results from analyses of drug resistance risk factors.

Discussion

These first estimates of the prevalence of HIV drug resistance in adults across the United States have several clinical and public health implications, mostly deriving from the fact that suppression of circulating HIV is an important goal for improving patient outcomes and

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Table 2. Characteristics of population represented by 1099 study specimens: the 132 500 American adults in care who survived to autumn of 1998 with Plasma HIV RNA > 500 copies/ml, and the proportion with any drug resistance.

	Estimated persons with HIV RNA > 500 copies/ml	Percentage of population subset with resistance to one or more drug
Age		
18–34	49500	72.2
35–49	73400	78.5
⩾ 50	9600	80.2
Sex		
Male	98900	78.6
Female	33600	69.3
Race/ethnicity		
Non-Hispanic white	58500	78.0
Non-Hispanic black	50500	73.9
Hispanic	19200	75.4
Other	4300	84.1
Education		
Some high school	35600	70.6
High school graduate	40600	75.2
College	56300	80.6
Plasma HIV RNA		
500–30 000 copies/ml	64600	80.4
> 30 000 copies/ml	67900	72.3
Lowest CD4 count (self report)		
⩾ 500 cells × 10^6/l	7000	43.8
200–499 cells × 10^6/l	41600	65.6
500–199 cells × 10^6/l	46100	79.9
0–49 cells × 10^6/l (R)	37900	89.6

reducing transmission. We found that most adult Americans who received medical care for HIV infection at urban clinics at the start of the HAART era, including essentially all urban residents and over half of the small number of rural residents receiving HIV care, survived until late 1998. However, even when considering all patients including those with early disease and those not on therapy, most survivors had viremia with > 500 copies HIV RNA/ml plasma, and most of these viremic patients had drug-resistant virus. Clinicians and policymakers need to be aware that this large population of patients with viral loads above 500 copies/ml while on therapy are likely to have more limited treatment options and a diminished probability of complete suppression of viral replication as a treatment outcome.

The drug resistance rates reported do not reflect the level of resistance among those with very low viral loads in whom resistance was not measured, and should not be generalized to that population. Even if all patients with < 500 copies HIV RNA/ml plasma were assumed to harbor no drug-resistant virus, then an estimated 48% of all 208 900 surviving adults would have drug resistance. Nevertheless we know that suppression of viremia with potent combination therapy in patients with drug-resistant virus can be attained, but the resistant virus can be archived indefinitely in the latently infected cell reservoir [13–15]. Thus the true rate in the total population regardless of plasma HIV RNA falls between the two values. The patient population characterized in this study represents a large reservoir for potential transmission of drug-resistant virus, consistent with the reports of increasing rates of transmission of drug-resistant HIV in North America with resulting impaired treatment responses and heightened urgency to prevention efforts targeted at this group [3]. An additional public health concern is that patients infected with resistant virus may not come to medical attention or receive specific prevention messages for a considerable period of time. Only about one-half of the between 850 000 and 950 000 Americans infected with HIV get regular care, and that an estimated one-quarter are unaware of their infection [7,16].

As the data were generated from specimens taken 3 years into the era of potent combination antiretroviral therapy with protease and reverse transcriptase inhibitors, factors have been in place that could potentially impact the prevalence of drug resistance either higher or lower. The more prolonged and wider utilization of the non-nucleoside reverse transcriptase inhibitors and protease inhibitors may have increased resistance to these drug classes as well as multiple class resistance. On the other hand the diminishing practice of sequential therapy and the availability of more effective and better tolerated combination regimens, especially for patients without prolonged nucleoside treatment experience, have been shown to increase the likelihood of suppression of viremia with resulting prevention of acquired resistance [17,18]. Active surveillance efforts will be required to monitor the trends of drug resistance among HIV-infected populations in order to assess the evolution of resistance patterns and to define optimum HIV treatment and prevention strategies. Nevertheless, these data indicate the magnitude of drug resistance that can be selected in a decade for nucleoside reverse transcriptase inhibitors in only 1 to 2 years for non-nucleoside reverse transcriptase and protease inhibitors.

Clinical approaches to address this growing drug resistance problem include the routine use of drug resistance testing to manage patients, development of new drugs active against drug-resistant virus, and the more careful and effective use of these drugs by both health care providers and patients. Because of the high rates of replication and mutation of HIV, the extensive use of antiretroviral therapy provides one of the most dramatic examples of the impact of human intervention on evolution in an ecological system [19]. HIV drug resistance frighteningly recapitulates the history of antimicrobial drug resistance in bacteria, with a pernicious twist: HIV is not curable and drug-resistant variants are archived within each patient for life. In addition, the ability of HIV to avoid inhibition by antiretroviral therapy through accumulating mutations

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Table 3. Estimated levels of resistance (%) among American adults with plasma HIV RNA ⩾ 500 copies/ml.

	Resistant to any drug		Resistant to NRTI		Resistant to NNRTI		Resistant to PI		Resistant to any two classes		Resistant to all three classes		Resistant to lamivudine ⩾ 1.8	
Overall %	76.3		71.4		25.2		40.5		47.7		13.1		67.8	
Lowest CD4 cell count (self-report)		*		*		*		*		*		*		
⩾ 500 × 10^6 cells/l	43.8	†	40.6	†	12.5	†	12.6	†	17.0	†	4.9		40.6	†
200–499 × 10^6 cells/l	65.6	†	59.9	†	16.6	†	22.9	†	30.1	†	3.8	†	57.3	†
50–199 × 10^6 cells/l	79.9	†	73.7	†	22.3	†	43.9	†	48.7	†	11.3	†	67.5	†
0–49 × 10^6 cells/l (R)	89.6		86.7		40.6		60.7		71.4		26.9		84.8	
CD4 cell count (based on blood draw)				*		*		*		*		*		
⩾ 500 × 10^6 cells/l	69.2		65.5		14.7	†	21.6	†	30.2	†	2.4	†	62.0	
200–499 × 10^6 cells/l	75.5		71.6		23.8	†	40.3		47.2		13.1	†	68.1	†
50–199 × 10^6 cells/l	83.8	†	77.5	†	28.6	†	52.6		57.8		17.0		75.1	†
0–49 × 10^6 cells/l (R)	73.6		66.2		40.4		44.8		55.7		22.0		60.2	
Clinical stage of HIV disease	*		*		*		*		*		*			
Asymptomatic (R)	60.6		60.6		8.2		36.2		36.2		8.2		58.1	
Symptomatic	71.9		66.9		21.1		32.2		39.4		9.0		63.2	
Clinical AIDS	82.0	†	76.7		30.8	†	49.1		57.0		17.6		73.3	
Age			*										*	
18–34 years	72.2		64.2		25.1		38.6		45.7		10.1		60.1	†
35–49 years	78.5		76.0		25.3		40.9		48.3		15.3		72.4	
⩾ 50 years (R)	80.2		73.0		25.3		47.0		53.5		11.7		73.0	
Sex	*		*		*		*		*		*		*	
Male	78.6	†	73.8	†	27.4	†	44.7	†	52.2	†	15.0	†	70.5	†
Female (R)	69.3		64.3		18.8		28.0		34.4		7.5		60.2	
Race and ethnicity							*|		|*		*			
White (R)	78.0		73.5		27.3		48.4		52.8		18.3		71.0	
Black	73.9	†	69.0		22.1		29.1	†	38.7	†	7.5	†	64.9	
Hispanic	75.4		71.1		26.9		45.5		55.0		13.1		67.7	
Other	84.1		71.0		26.9		44.2		51.3		6.8		59.9	
HIV exposure group	*		*				*		*				*	
Injection drug use	75.4		69.3		25.2		37.2	†	45.0	†	11.3		63.9	†
										†				
Male sex with men (R)	79.3		74.7		28.5		47.5		54.5		16.9		72.4	
Heterosexual sex	72.8	†	68.3	†	19.7		28.8	†	37.0	†	7.0	†	65.1	
Other	71.0	†	67.0		21.0		41.2		45.5		12.7		61.4	†
Education	*		*				*		*		*		*	
Some high school (R)	70.6		66.9		23.9		28.0		39.6		8.5		64.1	
High school graduate	75.2		69.6		24.9		41.0	†	46.2		14.0		64.2	
Some college or more	80.6	†	75.5	†	26.2		48.0	†	53.8	†	15.3	†	72.9	†
Health insurance	*		*		*		*		*		*			
None	67.8	†	63.9	†	23.8		32.4	†	39.8	†	12.6		59.5	†
Medicaid alone	75.6		68.6		18.9	†	32.5	†	37.2	†	7.2	†	63.7	†
Private (R)	79.7		76.5		26.6		47.6		54.5		16.4		74.5	
Medicare with or without other insurance	79.0		74.4		32.1		48.0		58.4		17.2		71.6	
Region of country					*									
Northeast	75.5		70.4		20.6	†	37.4		43.0		10.0	†	65.4	
Midwest (R)	79.7		70.5		40.9		39.0		52.9		17.8		68.2	
South	77.0		72.8		25.2	†	40.5		48.7		12.9		68.7	
West	74.7		70.4		24.1	†	44.2		49.0		15.0		69.0	
Provider HIV practice size														
0–10	72.5		72.5		24.2		51.7		55.6		20.2		69.2	
11–100	80.4		76.2		25.2		41.4		48.3		14.0		70.2	
101–500	77.0	†	71.6		25.9		40.2		48.3		12.4		68.4	
> 500 (R)	69.9		64.8		23.1		38.5		43.5		13.0		63.2	
Plasma viral load	*		*		*		*				*		*	
500–30 000 copies/ml	80.4	†	77.3	†	21.5	†	37.3	†	46.0		9.8	†	74.0	†
> 30000 copies/ml (R)	72.3		65.7		28.7		43.5		49.3		16.3		62.0	
Current use of antiretroviral drug	*		*		*		*		*		*		*	
Yes	87.6	†	83.4	†	28.8	†	47.7	†	56.7	†	15.6	†	79.7	†
No (R)	30.4		22.7		10.8		11.1		11.3		2.8		19.9	
Past use of antiretrovirals drug	*		*		*		*		*		*		*	
Yes	80.0	†	75.3	†	26.2	†	42.9	†	50.6	†	13.9	†	71.6	†
No (R)	14.7		6.5		8.2		0.0		0.0		0.0		5.1	
EVER use antiretrovirals drug	*		*		*		*		*		*		*	
Yes	79.7	†	75.0	†	26.0	†	42.6	†	50.2	†	13.8	†	71.4	†
No (R)	10.9		1.6		9.3		0.0		0.0		0.0		0.0	
Current use of PI drug	*		*				*		*		*		*	
Yes	90.0	†	85.9	†	25.6		58.7	†	63.2	†	17.0	†	82.4	†
No (R)	59.8		54.0		25.0		18.1		28.8		8.4		50.4	

(*continued overleaf*)

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Table 3. (*continued*)

	Resistant to any drug		Resistant to NRTI		Resistant to NNRTI		Resistant to PI		Resistant to any two classes		Resistant to all three classes		Resistant to lamivudine ⩾ 1.8	
Past use of PI drug	*		*				*		*		*		*	
Yes	83.3	†	78.2	†	27.2		52.0	†	57.5	†	16.6	†	74.8	†
No (R)	56.3		51.9		19.6		7.7		19.7		3.2		48.0	
EVER use PI drug	*		*		*		*		*		*		*	
Yes	83.4	†	78.5	†	27.5	†	51.2	†	57.1	†	16.7	†	75.1	†
No (R)	52.2		47.2		17.6		4.2		15.8		1.0		43.2	
Current use of NNRTI drug	*		*		*		*		*		*			
Yes	91.1	†	84.6	†	78.6	†	49.8	†	78.6	†	43.3	†	80.5	
No (R)	73.7		69.1		14.8		38.8		41.8		7.2		65.6	
Past use of NNRTI drug	*		*		*		*		*		*		*	
Yes	92.2	†	88.3	†	70.7	†	52.6	†	79.6	†	39.8	†	82.8	†
No (R)	72.6		67.5		14.7		37.7		40.3		6.9		64.4	
EVER use NNRTI drug	*		*		*		*		*		*		*	
Yes	90.0	†	84.5	†	68.0	†	51.7	†	75.2	†	39.0	†	80.1	†
No (R)	71.3		66.6		9.7		36.4		37.8		3.7		63.4	
Current use of NRTI drug	*		*		*		*		*		*		*	
Yes	88.0	†	83.8	†	27.7	†	46.6	†	55.7	†	14.4	††	80.3	†
No (R)	40.5		33.3		17.8		21.8		23.4		9.0		29.9	
Past use of NRTI drug	*		*		*		*		*		*		*	
Yes	81.1	†	76.6	†	26.6	†	43.4	†	51.3	†	14.2	†	72.9	†
No (R)	18.2		8.4		8.4		5.8		4.5		0.0		7.4	
EVER use NRTI drug	*		*		*		*		*		*		*	
Yes	80.8	†	76.2	†	26.4	†	43.1	†	51.0	†	14.0	†	72.6	†
No (R)	13.0		2.7		8.8		3.1		1.6		0.0		1.6	
Current use of lamivudine	*		*				*		*				*	
Yes	89.2	†	87.0	†	23.1		47.0	†	55.8	†	12.1		86.1	†
No (R)	66.0		58.8		27.1		35.3		41.2		14.0		53.1	
Past use of lamivudine	*		*				*		*		*		*	
Yes	83.1	†	79.6	†	26.7		45.5	†	53.8	†	14.9	†	76.5	†
No (R)	52.6		43.0		20.1		23.1		26.6		7.0		38.1	
EVER use lamivudine	*		*				*		*				*	
Yes	82.9	†	79.3	†	26.1		45.2	†	53.4	†	14.3		76.3	†
No (R)	47.9		37.5		21.3		20.2		23.3		7.7		31.6	

R represents the reference group for statistical comparisons. An asterisk (*) indicates demographic categories in which resistance is significantly different in a univariate analysis ($P < 0.05$). † after a percentage value indicates that group was significantly different from the reference group ($P < 0.05$). PI, protease inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor.

indicates that newer and more effective therapies will continue to be needed to control the pandemic.

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Table 4. Multivariate adjusted odds ratios.

	Any drug resistance among those with plasma HIV RNA = 500 copies/ml
Lowest CD4 cell count (self-report)	*
⩾ 500 × 10^6 cells/l	0.13 †
200–499 × 10^6 cells/l	0.22 †
50–199 × 10^6 cells/l	0.48 †
0–49 × 10^6 cells/l (R)	–
Clinical stage of HIV disease (based on blood draw)	
Asymptomatic (R)	–
Symptomatic	1.78
Clinical AIDS	1.29
Age	
18–34 years	0.70
35–49 years	0.90
⩾ 50 years (R)	–
Sex	
Male	1.43
Female (R)	–
Race and ethnicity	
White (R)	–
Black	1.13
Hispanic	1.03
Other	2.07
HIV exposure group	
Injection drug use	1.10
Male sex with men (R)	–
Heterosexual sex	0.88
Other	0.83
Education	
Some high school (R)	–
High school graduate	1.02
Some college or more	1.46 †
Health insurance	
None	0.90
Medicaid alone	1.16
Private (R)	–
Medicare with or without other insurance	0.83
Region of country	
Northeast	0.78
Midwest (R)	–
South	1.03
West	0.91
Provider HIV practice size	
0–10	2.04
11–100	2.32 †
101–500	1.55
> 500 (R)	–
Plasma viral load	*
500–30000 copies/ml	2.91 †
> 30000 copies/mL (R)	–
EVER use antiretrovirals drug	
Yes	1.42
No (R)	–
EVER use PI drug	*
Yes	1.75 †
No (R)	–
EVER use NNRTI drug	*
Yes	2.33 †
No (R)	–
EVER use NRTI drug	*
Yes	5.04 †
No (R)	–
EVER use lamivudine	*
Yes	2.12 †
No (R)	–

R represents the reference group for statistical comparisons. An asterisk (*) over a column indicates demographic categories in which resistance is significantly different in a multiple logistic regression analysis ($P < 0.05$). Symbol (†) after a percentage value indicates that group was significantly different from the reference group ($P < 0.05$).PI, protease inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor.

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