AIDS RESEARCH AND HUMAN RETROVIRUSES
Volume 27, Number 9, 2011

DOI: 10.1089/aid.2010.0291

The Role of Toxicity-Related Regimen Changes in the Development of Antiretroviral Resistance

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Abstract

In an effort to evaluate factors associated with the development of antiretroviral (ARV) resistance, we assessed the prevalence of toxicity-related regimen changes and modeled its association to the subsequent development of ARV resistance in a cohort of treatment-naive individuals initiating ARV therapy (ART). A retrospective analysis of patients initiating ART was conducted at the UAB 1917 Clinic from 1 January 2000 to 30 September 2007. Cox proportional hazards models were fit to identify factors associated with the development of resistance to ≥1 ARV drug class. Among 462 eligible participants, 14% ($n=64$) developed ARV resistance. Individuals with ≥1 toxicity-related regimen change (HR = 3.94, 95% CI = 1.09–14.21), initiating ART containing ddI or d4T (4.12, 1.19–14.26), and from a minority race (2.91, 1.16–7.28) had increased risk of developing resistance. Achieving virologic suppression within 12 months of ART initiation (0.10, 0.05–0.20) and higher pretreatment CD4 count (0.85 per 50 cells/mm^3, 0.75–0.96) were associated with decreased hazards of resistance. Changes in ART due to drug intolerance were associated with the subsequent development of ARV resistance. Understanding the role of ARV drug selection and other factors associated with the emergence of ARV resistance will help inform interventions to improve patient care and ensure long-term treatment success.

Introduction

Despite marked improvements in HIV-related morbidity and mortality with antiretroviral therapy (ART), the emergence of drug resistance remains a threat capable of rendering these lifesaving drugs ineffective.[1–3] The development of antiretroviral (ARV) resistance is associated with poor clinical outcomes, including virologic failure and death.[4–6] As use of ARVs continues to expand throughout the world, and the life expectancy of HIV-infected individuals increases, furthering our understanding of factors contributing to the development of ARV resistance is critical to ensure the long-term success of antiretroviral therapy (ART).

Toxicity often leads to premature changes in ARV regimens and has been associated with poor adherence to ART.[7–13] The impact of such toxicity-associated intermittent adherence on the development of subsequent ART resistance remains understudied. In an effort to contribute to the extant literature on factors associated with the development of ARV resistance, we assessed the prevalence of toxicity-related regimen changes and modeled its association to the subsequent development of ART resistance in a cohort of treatment-naive individuals initiating ART. We hypothesized that individuals initiating ART with agents known to have more frequent side effects, and individuals who underwent regimen changes due to toxicity would be more likely to intermittently adhere to treatment and to subsequently develop ARV resistance. These data are particularly important as the treatment of HIV with older, more toxic ARVs continues to expand in resource-poor settings and as the role of such agents in the developed world is reexamined as cost-saving, generic formulations become available.

Materials and Methods

Setting

This study is nested in the University of Alabama at Birmingham (UAB) 1917 HIV/AIDS Clinic Cohort, a 100% quality-controlled, prospective cohort study that collects detailed sociodemographic, psychosocial, and clinical information (www.uab1917cliniccohort.org). Currently, over 1700 patients receiving primary HIV care at the UAB 1917 HIV/AIDS clinic (1917 Clinic) participate in the Institutional Review Board (IRB) approved observational, clinical cohort

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project. The process put in place by the cohort to assure data quality was recently recognized by the information integrity coalition for excellence in information integrity (http://www.eiiaward.org/).

Sample and procedures

Data from all ART-naive patients initiating therapy from 1 January 2000 to 30 September 2007 were reviewed to evaluate eligibility for study inclusion. Patients initiating therapy with single or dual drug regimens were excluded from all analyses, as were patients who did not have at least two viral load measures within the first 12 months following ART initiation since initial virologic suppression could not be measured. The analytic dataset was generated in September 2008. Enrollment stopped in September 2007 to ensure all patients had at least a 12-month period of observation following ART initiation.

Patients were followed from the time of ART initiation until the end of the study period (September 2008) or until resistance to ARVs was documented, whichever occurred first. Detailed chart abstraction was performed whenever an elevation in plasma HIV viral load (VL) occurred to determine whether or not a resistance test was performed. Additional chart abstraction was performed when ≥1 ARV was added to or subtracted from the ART regimen. Provider responses to VL elevations and reasons for regimen changes were recorded. All regimen changes were classified into the following categories: toxicity, unable to afford, regimen simplification, noncompliance, contraindicated medication/medical condition, other, or unknown. Changes due to toxicity that occurred prior to the detection of resistance or the end of the study period were quantified and subsequently used in statistical models.

Independent variables

Patient level variables. Age, gender, race, HIV risk factor, baseline plasma HIV RNA (copies/ml), baseline CD4 cell count (cells/μl), achievement of virologic suppression (<50 copies/ml) on at least 1 occasion within 12 months of ART initiation (yes/no), and health insurance status (private, public, uninsured) were included. Several clinical variables including history of affective mental health disorders (depression and/or anxiety), substance abuse (cocaine, opiate, and amphetamine use), alcohol abuse, hepatitis C infection, and opportunistic infections were also collected.[14]

Regimen level variables. Nucleoside reverse transcriptase inhibitor (NRTI) [didanosine or stavudine (ddI or d4T), zidovudine (AZT), and tenofovir or abacavir (TDF or ABC)] and third drug strategy [NRTI, nonnucleoside reverse transcriptase inhibitor (NNRTI), protease inhibitor (PI), or boosted-PI (PI plus ritonavir)] were identified. Because nearly all (98.9%) NRTIs were paired with either lamivudine (3TC) or emtricitabine (FTC), only one component of the NRTI backbone pair was evaluated. If a regimen contained NRTIs from more than one group, the regimen was assigned to one NRTI group using a standardized hierarchy previously used in the literature: ddI or d4T, ZDV, and finally TDF or ABC.[15]

Dependent variables

ARV resistance. The primary outcome of interest was documented resistance to ≥1 ARV drug class. Resistance was defined as ≥1 significant mutation as categorized in the spring 2008 International AIDS Society-USA (IAS-USA) drug mutation listing and/or "Reduced susceptibility" or "Resistance" to an ARV per phenotypic assessment.[16] Those who underwent resistance testing but had pan-sensitive virus were not considered to have met this outcome.

Statistical analysis

Descriptive statistics were performed to evaluate patient and regimen level characteristics of the overall study population and to ensure assumptions of statistical tests were met. Frequencies of identified resistance mutations per genotypic assays were calculated. Bivariate analysis (chi-square, *t*-test) was performed to evaluate differences between those who developed resistance during the study period and those who did not. Univariate and multivariable Cox proportional hazard models to evaluate factors associated with time to the development of resistance to ≥1 drug class were completed. Cox proportional hazards (survival methods) were selected to account for time on antiretroviral therapy. Sensitivity analyses were performed using differing censoring strategies to account for loss to follow-up and missed visits (≥1 year without a primary provider appointment) and starting analysis of time to resistance 12 months after ART initiation. All statistical analyses were performed using SAS software, version 9.1.3 (SAS Institute).

Results

Overall, 462 patients initiated ART during the study period and met criteria for inclusion. The mean age was 38.5 ± 9.8 years and the majority were males (76%) and of black/other (53%) race. The average pretreatment CD4 cell count was 173 ± 160 cells/μl and 57% (n = 244) of patients had a baseline plasma HIV viral load ≤100,000 copies/ml. The most commonly used NRTIs were TDF or ABC (46%) and AZT (45%), while NNRTIs (68%) were the most commonly employed third drug. A majority of patients (82%) achieved virologic suppression (VL <50 copies/ml) within 12 months of initiating ART. Affective mental health disorders were present in over half (52%) of patients, whereas alcohol (17%) and substance abuse (14%) were less common.

Most patients did not experience a toxicity-related regimen change during the study period (82%). A total of 79 toxicity-related regimen changes took place among the remaining 18% (n = 62) of study participants. Anemia (n = 16), nausea (n = 13), neuropathy (n = 8), lipodystrophy/lipoatrophy (n = 7), and other/unspecified (n = 11) toxicities were most commonly found (Table 1). Statistically significant differences (p < 0.05) in race, health insurance status, history of opportunistic infection, baseline CD4 cell count, baseline HIV viral load, HIV RNA suppression (<50 copies/ml) within 12 months of ART initiation, number of toxicity-related regimen changes, NRTI backbone, and third drug were seen among the study groups (Table 1).

A total of 184 patients experienced virologic failure during the study period. Resistance testing was ordered for 77 (42%) of these patients; 50% (n = 38) underwent genotypic testing (GeneSeq), 14% (n = 11) phenotypic testing (Phenosense), and 36% (n = 28) had a combination of both (Phenosense GT). Pan-sensitive virus was reported for 13 patients, while virologic failure with resistance was detected in 64 individuals. The most commonly found reverse transcriptase mutations were

Table 1. Overall and Group-Specific Characteristics of Treatment Naive Patients Starting Antiretroviral Therapy at the UAB 1917 HIV/AIDS Clinic January 1, 2000–September 30, 2007 (n = 462).

Characteristic	*Overall (n = 462)*	*Group 1: Virologic failure with resistance*[a] *(n = 64)*	*Group 2: Virologic failure without documented resistance*[a] *(n = 120)*	*Group3: No virologic failure*[a] *(n = 278)*	p-*value*
Age at ART initiation (years)	38.5 ± 9.8	36.7 ± 10.8	37.7 ± 9.2	39.3 ± 9.8	0.08
Gender					0.34
Male	351 (76.0%)	44 (68.8%)	92 (76.7%)	63 (22.7%)	
Female	111 (24.0%)	20 (31.2%)	28 (23.3%)	215 (77.3%)	
Race					**0.008**
White	216 (46.8%)	19 (29.7%)	55 (45.8%)	142 (51.1%)	
Black/other	246 (53.2%)	45 (70.3%)	65 (54.2%)	136 (48.9%)	
HIV risk factor					0.70
MSM	248 (54.0%)	33 (51.6%)	62 (51.7%)	153 (55.6%)	
Heterosexual	211 (46.0%)	31 (48.4%)	58 (48.3%)	122 (44.4%)	
Health insurance					**0.002**
Private	202 (43.7%)	20 (31.3%)	45 (37.5%)	137 (49.3%)	
Public	147 (31.8%)	31 (48.4%)	46 (38.3%)	70 (25.2%)	
Uninsured	113 (24.5%)	13 (20.3%)	29 (24.2%)	71 (25.5%)	
History of affective mental health disorder					0.55
No	224 (48.5%)	27 (42.2%)	60 (50.0%)	137 (49.3%)	
Yes	238 (51.5%)	37 (57.8%)	60 (50.0%)	141 (50.7%)	
History of substance abuse					0.12
No	398 (86.1%)	58 (90.6%)	97 (80.8%)	243 (87.4%)	
Yes	64 (13.9%)	6 (9.4%)	23 (19.2%)	35 (12.6%)	
History of alcohol abuse					0.94
No	385 (83.3%)	53 (82.8%)	99 (82.5%)	233 (83.8%)	
Yes	77 (16.7%)	11 (17.2%)	21 (17.5%)	45 (16.2%)	
History of hepatitis C infection					0.68
No	420 (90.9%)	60 (93.8%)	108 (90.0%)	252 (90.7%)	
Yes	42 (9.1%)	4 (6.3%)	12 (10.0%)	26 (9.3%)	
History of opportunistic infection					**<0.001**
No	278 (60.2%)	21 (32.8%)	67 (55.8%)	190 (68.4%)	
Yes	184 (39.8%)	43 (67.2%)	53 (44.2%)	88 (31.7%)	
Pretreatment CD4 cell count (cells/mm^3)	173 ± 160	110 ± 123	174 ± 181	187 ± 155	**0.004**
Pretreatment plasma HIV RNA (copies/ml)					0.12
≤ 100,000 copies/ml	244 (56.7%)	23 (44.2%)	63 (55.8%)	158 (59.6%)	
> 100,000 copies/ml	186 (43.3%)	29 (55.8%)	50 (44.2%)	107 (40.4%)	
VL < 50 within 12 months of ART initiation					**<0.001**
No	84 (18.2%)	33 (51.6%)	34 (28.3%)	17 (6.1%)	
Yes	378 (81.8%)	31 (48.4%)	86 (71.7%)	261 (93.9%)	
Toxicity-related regimen change					**<0.001**
0	400 (86.6%)	43 (67.2%)	120 (100.0%)	237 (85.3%)	
1	48 (10.4%)	16 (25.0%)	0 (0%)	32 (11.5%)	
≥ 2	14 (3.0%)	5 (7.8%)	0 (0%)	9 (3.2%)	
Death					**0.006**
No	432 (93.5%)	54 (84.4%)	113 (94.2%)	265 (95.3%)	
Yes	30 (6.5%)	10 (15.6%)	7 (5.8%)	13 (4.7%)	
NRTI backbone					**<0.001**
TDF or ABC	211 (45.7%)	11 (17.2%)	37 (30.8%)	163 (58.6%)	
AZT	208 (45.0%)	41 (64.1%)	67 (55.8%)	100 (46.0%)	
ddI or d4T	43 (9.3%)	12 (18.7%)	16 (13.3%)	15 (5.4%)	
Third drug					**<0.001**
Boosted PI	73 (15.8%)	5 (7.8%)	16 (13.3%)	52 (18.7%)	
PI	32 (6.9%)	9 (14.1%)	11 (9.2%)	12 (4.3%)	
NNRTI	315 (68.2%)	38 (59.4%)	77 (64.2%)	200 (71.9%)	
NRTI	42 (9.1%)	12 (18.7%)	16 (13.3%)	14 (5.1%)	

[a]Data presented as mean ± standard deviation or n (%).

ART, antiretroviral treatment; MSM, men who have sex with men; VL, viral load; NRTI, nucleoside reverse transcriptase inhibitor; NNRTI, nonnucleaside reverse transcriptase inhibitor; PI, protease inhibitor; TDF, tenofovir; ABC, abacavir; AZT, zidovudine; ddI, didanosine; dHT, stavudine. Figures in bold are statistically significant ($p < 0.05$).

M184V/I ($n=50$, 65.8%) followed by K103N ($n=45$, 59.2%) (Table 2). Other reverse transcriptase mutations found in >10% of cases included the K70R/E, T215F, D67N, M41L, P225H, V108I, Y181C/I, and Y188C/L. Mutations to PIs were rare, with the D30N being most common (Table 2). Provider rationale for not ordering a resistance test among the remaining patients ($n=107$, 58%) with documented high HIV viral loads included perceived noncompliance ($n=56$), viral load blip ($n=26$), adverse event ($n=12$), lost to follow-up ($n=5$), scheduled treatment interruption ($n=5$), and unknown ($n=3$).

In multivariable Cox proportional hazards analysis, individuals who experienced ≥1 toxicity-related regimen change were at significantly greater risk of developing resistance [hazard ratio (HR) 3.94, 95% confidence interval (CI) 1.09–14.21]. Individuals initiating ART regimens with ddI or d4T (HR 4.12, 95% CI 1.19-–14.26) as an NRTI and those patients who were black/other race also had increased risk of developing resistance (HR 2.91, 95% CI 1.16–7.28). Higher pretreatment CD4 cell count (HR 0.85 per 50 cells/mm^3, 95% CI 0.65–0.96) and achieving viral load suppression (<50 copies/ml) within 12 months of ART initiation (HR 0.10, 95% CI 0.05–0.20) were associated with a decreased risk of developing ARV resistance (Table 3). Analyses using different censoring strategies (see Materials and Methods) did not significantly alter results.

Table 2. Frequency of Selected Resistance Mutations in the Reverse Transcriptase and Protease Genes Among Treatment Naive Patients Initiating ART Between January 2000 and September 2007 Who Underwent Genotypic Testing (n=64)

Mutation	*No. (%) of patients*
NRTI resistance	
M41L	8 (10.5)
A62V	1 (1.3)
K65R	8 (10.5)
D67N	11 (14.5)
K70R/E	14 (18.4)
L74V	3 (4.0)
V75I	1 (1.3)
F77L	0 (0)
Y115F/Y	0 (0)
F116Y	0 (0)
Q151M	0 (0)
M184V/I	50 (65.8)
L210W	1 (1.3)
T215F	12 (15.8)
K219Q/E/N/R	5 (6.6)
Total NRTI resistance mutations	114
NNRTI resistance	
L100I	4 (5.3)
K103N	45 (59.2)
V106A/M	2 (2.6)
V108I	8 (10.5)
Y181C/I	8 (10.5)
Y188C/L	8 (10.5)
G190A/S	7 (9.2)
P225H	21 (27.6)
Total NNRTI resistance mutations	103
PI resistance	
D30N	2 (2.6)
V32I	1 (1.3)
L33F/I	1 (1.3)
M46I/L	1 (1.3)
I47V/A	1 (1.3)
G48V	0 (0)
I50V	0 (0)
I54M/L	1 (1.3)
L76V	0 (0)
V82A/T/F/S	0 (0)
I84V	0 (0)
N88S	1 (1.3)
L90M	0 (0)
Total PI resistance mutations	8

Discussion

In our cohort of treatment-naive patients initiating ART between 2000 and 2007, 14% developed antiretroviral medi-

Table 3. Unadjusted and Adjusted Cox PH Model of Factors Associated with Time Development of ≥1 Resistance Mutations Among Treatment Naive Patients Initiating ART Between January 2000 and September 2007

Patient Characteristics	*Unadjusted HR (95% CI)*	*Adjusted HR (95% CI)*
Age at ART initiation (per 10 years)	0.98 (0.95–1.01)	0.99 (0.95–1.03)
Gender		
Male	1.0	1.0
Female	1.42 (0.79–2.54)	0.47 (0.20–1.14)
Race		
White	1.0	1.0
Black/other	**2.42 (1.36–4.33)**	**2.91 (1.16–7.28)**
Health insurance		
Uninsured	1.0	1.0
Private	0.67 (0.31–1.43)	0.82 (0.33–2.04)
Public	1.52 (0.76–3.06)	1.17 (0.50–2.73)
History of affective mental health disorder		
No	1.0	1.0
Yes	1.42 (0.83–2.42)	1.50 (0.73–3.06)
Pretreatment CD4 cell count (per 50 cells/mm^3)	**0.85 (0.76–0.95)**	**0.85 (0.75–0.96)**
VL <50 within 12 months of ART initiation		
No	1.0	1.0
Yes	**0.14 (0.08–0.23)**	**0.10 (0.05–0.22)**
Toxicity-related regimen change		
0	1.0	1.0
≥1	2.42 (0.86–6.77)	**3.94 (1.09–14.21)**
NRTI backbone		
TDF or ABC	1.0	1.0
AZT	1.69 (0.81–3.49)	2.18 (0.87–5.47)
ddI or d4T	2.36 (0.96–5.80)	**4.12 (1.19–14.26)**
Other drug		
Boosted-PI	1.0	1.0
PI	3.06 (0.94–10.02)	2.09 (0.45–9.64)
NNRTI	1.42 (0.50–4.02)	2.12 (0.58–7.78)
NRTI	2.54 (0.80–8.04)	2.20 (0.51–9.53)

HR, hazard ratio; CI, confidence interval. Figures in bold are statistically significant ($p<0.05$).

cation resistance mutations. Existing literature points to associations between pretreatment patient characteristics (e.g., low CD4 and high pretreatment viral load) and ART regimen composition (e.g., inclusion of NNRTIs, inadequate number of active drugs) and the development of ARV resistance, but none investigated the role of prior toxicity-related regimen changes.[17–22] In our study, we found, for the first time in the published literature that prior regimen change owing to toxicity was associated with a significant risk of developing resistance. Individuals who experienced toxicity-related regimen changes had over a 3-fold increased risk of developing ARV resistance than those who did not undergo toxicity-related regimen changes.

Another potentially related finding in our study was that those initiating ART with ddI or d4T as part of the NRTI backbone had over four times the risk of developing resistance than individuals starting therapy with TDF or ABC. Previous studies have reported on the various side effects and long-term toxicity of ddI, d4T, and AZT, as well as the decreased durability of regimens containing these drugs.[11,23–26] In our sample, among individuals ($n=62$) who underwent toxicity-related regimen changes, the most common NRTI backbone was ddI or d4T (43%) followed by AZT (30%) and finally TDF or ABC (27%). We postulate that initiation of ART with agents more likely to result in toxicity more commonly leads to intermittent adherence and increases the risk of subsequent ARV. Further research is needed, however, to confirm this relationship.

Though the use of many of the agents included in these analyses has declined in the United States and other developed nations, they continue to be utilized frequently as first-line agents throughout the world. Generic coformulations of agents such as ddI, d4T, and AZT are increasingly available in resource-limited settings, in large part owing to their reduced costs and convenient administration. As the patents on these older agents expire, generic formulations for these ARVs will be available in the developed world as well, offering potential savings in the cost of HIV therapy. However, despite lower costs and similar efficacy, these agents exhibit side effect profiles more significant than many of the contemporary ARVs for which generic formulations are not yet available.[27–29] The difficult balance of short-term cost benefits versus maintenance of long-term therapeutic success must be weighed when making individual and programmatic decisions regarding the selection of initial ART both in the United States and abroad. Further study is needed in larger numbers of patients to determine the true cost effectiveness of utilizing generic formulations of older agents to inform policy decisions.

HIV viral load has been used as a surrogate measure of therapeutic success since the mid-1990s and virologic suppression is associated with decreased morbidity and mortality.[30–32] In our study, achieving virologic suppression (VL <50 copies/ml) within 12 months of ART initiation was associated with a dramatically reduced risk for the emergence of drug resistance (HR 0.10, 95% CI 0.05–0.22). This is consistent with previous studies and clinical experience in which incomplete suppression of plasma HIV viral load results in ARV resistance and treatment failure.[31–33] These findings suggest that HIV viral load monitoring is particularly critical in the first year of treatment and failure to achieve suppression in this timeframe indicates substantial risk for the development of resistance. This finding may be of particular importance in regions of the world where HIV VL testing is not readily accessible and the frequency and timing of virologic testing must be apportioned carefully to achieve maximal benefit.

Minority patients had nearly a 3-fold increased risk of developing resistance mutations. In addition, patients with lower pretreatment CD4 cell counts had a decreased time to the development of resistance. Both minority race and pretreatment CD4 cell counts have been previously associated with an increased risk for virologic failure and poor clinical outcomes, including disease progression and death.[11,31,32,34–39] In our study, we find that minority race and low pretreatment CD4 cell counts are also associated with an increased risk of the development of ARV resistance. The implementation of interventions targeting those individuals at greatest risk for the development of ARV resistance is important to maximizing the effectiveness and durability of initial ART regimens.

The findings of our study should be interpreted with respect to its limitations. As a single-site, observational cohort study, our experiences may not be applicable to other national or international settings. However, given our broad patient sample, time period, and the high quality of our data, our findings may prove useful in other settings. As with all observational studies, we are only able to ascertain associations, but not establish causation. The study period overlaps the implementation of guidelines recommending routine baseline resistance testing for treatment-naive individuals and we were unable to determine the impact of baseline resistance on subsequent ART failure. However, baseline ARV resistance has been previously reported to be $<10\%$ in settings such as ours, likely diminishing its impact on our results.[40] Finally, we were unable to measure self-reported adherence to ART in this retrospective analysis as it was not captured in a consistent, analyzable format by providers and patients use multiple pharmacies, precluding the use of adherence measures such as medication possession ratio.

In summary, our findings underscore the importance of the selection of ARV agents with reduced toxicity profiles, virologic monitoring in the first year after ART initiation, and timely HIV diagnosis as it relates to the development of resistance to ART. Understanding the role of ARV drug selection and other factors associated with the emergence of ARV resistance will help inform interventions to improve patient care and ensure long-term treatment success. These findings may be of particular use in settings in which long-term success of initial ART is critical due to limited drug formularies and reduced access to viral load testing.

Acknowledgments

The authors would like to thank the University of Alabama at Birmingham Center for AIDS Research (Grant P30-AI27767), the Mary Fisher CARE Fund, and the CFAR Network of Integrated Clinical Sites (CNICS; Grant 5R24-AI 067039). M.J.M. is supported by K23MH082641 from the National Institute of Mental Health.

We would also like to thank the UAB 1917 Clinic Cohort Team for their extensive assistance through all stages of the elaboration of this manuscript: *Steering Committee:* Michael S. Saag, Michael J. Mugavero, James H. Willig, James L. Raper, Paul Goepfert, Jeroan J. Allison, Mirjam-Colette Kempf,

Joseph E. Schumacher, and Inmaculada B. Aban. *Faculty Investigators:* Maria Pisu, Linda Moneyham, David Vance, Susan L. Davies, Eta Berner, Edward Acosta, Jennifer King, Richard A. Kaslow, Eric Chamot, Karen Cropsey, and Andrew O. Westfall. *Research Support Team:* Karen Savage, Christa Nevin, Frances B. Walton, Malcolm L. Marler, Sarah Lawrence, Sara-Anne Wilkins, Anne Zinsky, Barbara Files-Kennedy, and D. Scott Batey. *Informatics Team:* Mohit Varshney, Eugene Gibson, Suneetha Thogaripally, Alfredo Guzman, Dustin Rinehart, Sunil Adusumili, Allen Kelly, and Ridha T. Bagana. *Current Trainees:* Justin S. Routman, Paula Seal, Noah Godwin, Mary Orr, Michael Kozak, Tyler Tate, Sarika Modi, and Tyler Wahl.

Data were presented in part at the 13th International Workshop on HIV Observational Databases, Lisbon, Portugal, March 26–28, 2009.

Author Disclosure Statement

M.J. Mugavero has received research funding and/or consulted for Tibotec Therapeutics, Bristol-Myers Squibb, and Gilead. M.S. Saag has received research funding and/or consulted for Adrea Pharmaceuticals, Avexa, Boehringer Ingelheim, Bristol-Myers Squibb, Gilead, GlaxoSmithKline, Merck, Monogram Biosciences, Panacos, Pfizer, Progencis, Roche, Serono, Tanox, Tibotec, Trimeris, and Vertex. J.H. Willig has received research funding and/or consulted for Bristol-Myers Squibb, Gilead, Merck, and Tibotec.

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