Transmitted Drug-Resistant HIV Type 1 Remains Prevalent and Impacts Virologic Outcomes Despite Genotype-Guided Antiretroviral Therapy

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Abstract

Trends in transmitted drug resistance-associated mutations (TDRM) in HIV-1infection vary depending on geographic and cohort characteristics. The impact of TDRM among patients receiving fully active combination antiretroviral therapy (cART) is poorly characterized. This was a retrospective study of 801 HIV-1-infected treatment-naive patients from 2001 to 2009 who had pre-cART genotype resistance test results available. The prevalence of TDRM was compared for each year strata. Multivariate Cox proportional hazards regression models were used to assess factors associated with virologic failure at 48 weeks. TDRM was detected in 136 (17%) patients with ≥ 2 class TDRM in 20 patients. K103N/S was the most frequent ($n = 77$). There were no changes in the prevalence of mutations over time ($P_{\text{trend}} = 0.67$). Six hundred and eleven patients were started on cART. Virologic failure occurred in 38% of those with TDRM and 24% of those without ($p < 0.01$). In multivariate analysis, nonnucleoside reverse transcriptase inhibitor (NNRTI) resistance was associated with a 1.5-fold increased risk of virologic failure. TDRM remains common among treatment-naive HIV-1-infected patients, affecting one in six patients. Transmission of NNRTI drug resistance was associated with risk of virologic failure despite initiation of genotype-guided cART.

Introduction

THE USE OF POTENT COMBINATION antiretroviral therapy (cART) provides sustained virologic suppression for an individual living with HIV and substantially reducing the morbidity and mortality associated with HIV-1 infection.[1] Despite this advance in treatment, virologic failure can develop in 10–20% as a result of suboptimal medication adherence, the presence of preexisting drug resistance, or the emergence of drug resistance.[2,3] Transmitted drug resistance-associated mutations (TDRM) are of particular concern as they limit the choice of first-line cART, decrease efficacy of subsequent antiretroviral regimens and increase the risk of treatment failure.[4–6] TDRM have been documented among treatment-naive HIV-1-infected patients with a prevalence ranging from 3% to 24%, depending on the cohort and geographic characteristics; the highest prevalence is noted in countries with long-established use of antiretrovirals.[7–11] Studies on time trends in the prevalence of TDRM are inconsistent. In Belgium, the overall prevalence of TDRM was reported at 8.4% with no time trend.[12]

Bracciale *et al.* demonstrated that the transmission of nucleoside reverse transcriptase inhibitor (NRTI) and protease inhibitor (PI) resistance declined over time, but nonnucleoside reverse transcriptase inhibitor (NNRTI) resistance increased from 3.7% during 1996–2001 to 7.8% during 2002–2004 and remained stable thereafter (5.8% in 2006–2007).[13]

Previous data highlight that the presence of TDRM influences the outcome of initial cART and pre-cART genotype resistance testing improves clinical outcomes and is cost effective.[14,15] Therefore, routine genotype resistance testing is considered the standard of care for all newly diagnosed HIV-1-infected patients to guide the choice of initial treatment.[16] Yet there are few studies evaluating the impact of TDRM on virologic efficacy when patients initiate cART with at least three active agents chosen based on genotype resistance testing. We evaluated the prevalence and time trend of TDRM in a midwestern HIV outpatient clinic and the virologic outcomes of treatment-naive patients who were started on cART with at least three fully active agents guided by the result of genotype resistance testing.

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Materials and Methods

All adult (age ≥18 years), treatment-naive HIV-1-infected patients who were new to Washington University HIV Outpatient Clinic from January 1, 2001 to June 30, 2009 were screened for the study. Patients with HIV-1 genotype resistance testing performed prior to starting on cART were included in the study. This study was approved by the Washington University School of Medicine Human Research Protection Office.

The following data were abstracted from electronic medical record: baseline demographics (age, sex, race, and HIV risk factors), psychiatric comorbidity, substance use (history of marijuana, cocaine, heroin, or methamphetamine use), tobacco use, sexually transmitted diseases (STDs: history of syphilis, gonorrhea, *Chlamydia trachomatis* infection, or genital herpes simplex virus infection), hepatitis C virus (HCV) coinfection (positive anti-HCV antibody), longitudinal CD4 cell counts, longitudinal HIV RNA levels, pre-cART HIV-1 genotype, antiretroviral regimen, pre-cART opportunistic infections, and the first date of virologic suppression on the cART initiated. The definition of cART was receipt of at least three active antiretroviral medications as part of a regimen.

The prevalence and trends of TDRM during the study period were calculated. Genotypic assays were obtained from either Quest Diagnostics or the Washington University Retrovirus Laboratory (ViroSeq HIV-1 Genotyping System, Celera Corporation, Alameda, CA). The genotype results were interpreted with the standardized list of mutations for surveillance of transmitted drug resistance (DRM) established by the World Health organization (WHO list).[17] TDRM were noted individually and also grouped by antiretroviral class: NRTI, NNRTI, and PI resistance mutations. To assess the impact of TDRM, two groups (those with TDRM and those without) were compared in regards to virologic outcomes after initiating cART. Virologic suppression was defined as HIV RNA level <400 copies/ml at 48 weeks. This cutoff was used because some data predated the use of ultrasensitive HIV RNA assays.

Statistical analysis

Differences between the groups were compared using chi-square and Fisher exact test for categorical data and Mann–Whitney tests for continuous variables. HIV RNA levels were $\log_{10}$ transformed. Calculations of TDRM prevalence in each antiretroviral class were conducted by using the number of new cases of resistance detected in each year divided by the number of new antiretroviral-naive patients in each year. Time trends of prevalence in TDRM for each antiretroviral class were analyzed by logistic regression. To assess the virologic outcomes, univariate analyses with a Cox proportional hazards regression models with one predictor was conducted. Patients were censored as virologic failure when they did not achieve virologic suppression at 48 weeks. Variables associated with virologic failure at $p < 0.10$ in the univariate analyses were considered in the multivariate Cox proportional hazards regression models. All statistical calculations were performed using R 2.12.0 (R Foundation for Statistical Computing, Vienna, Austria), and statistical significance was defined as $p < 0.05$.

Results

Among the 801 patients who had pre-cART genotype resistance testing, 68% were male, 72% were black, and 35% had a CD4 cell count <200 cells/mm³ (Table 1). Based on the WHO list, TDRM was detected in 136 (17%) patients; NRTI

TABLE 1. BASELINE CHARACTERISTICS OF THE STUDY POPULATION

	All patients (N=801)		TDRM present (N=136)		No TDRM present (N=665)		p value
Age, years (median, IQR)	31	24–41	29	22–39	32	24–41	<0.05
Male sex	545	68%	82	60%	462	79%	<0.05
Race							
Black	575	72%	99	73%	476	72%	0.96
White	201	25%	33	24%	168	25%	
HIV risk factors							
Heterosexual	356	44%	70	51%	286	43%	0.45
MSM	346	43%	51	38%	295	44%	
IDU	29	4%	5	4%	24	4%	
Psychiatric comorbidity	262	33%	45	33%	217	33%	0.99
Substance use[a]	336	42%	60	47%	276	44%	0.64
Tobacco use	439	55%	77	62%	362	58%	0.47
STDs	299	37%	58	43%	241	36%	0.19
HCV	61	8%	12	9%	49	7%	0.69
CD4 cell count[b] (median, IQR)	308	99–467	328	109–505	299	98–463	0.32
CD4 cell count[b] ≤200 cells/mm³	277	35%	42	31%	235	35%	0.37
$\log_{10}$ HIV RNA[b] (median, IQR)	4.62	4.00–5.07	4.56	3.90–5.00	4.63	4.02–5.09	0.23
Initiated cART	611	76%	110	81%	501	75%	0.20

[a]Substance abuse, history of marijuana, cocaine, heroin, or methamphetamine use.
[b]Baseline CD4 cell count and HIV RNA level.
TDRM, transmitted drug-resistant mutation; IQR, interquartile range; MSM, men who have sex with men; IDU, injection drug use; STDs, sexually transmitted diseases within 1 year of initiating cART; HCV, chronic hepatitis C virus infection; cART, combination antiretroviral therapy; CD4 cell count, CD4 cell count (cells/mm³); $\log_{10}$ HIV RNA, $\log_{10}$ HIV RNA plasma level (copies/ml).

TABLE 2. FREQUENCY OF INDIVIDUAL RESISTANCE MUTATIONS

Drug class	Mutation	2001–2003 (N=188)	2004–2006 (N=301)	2007–2009 (N=312)	Total (N=801)	%
NRTI	M184 (V/I)	1	3	0	4	0.5
	M41L	1	7	5	13	1.6
	D67 (N/E/G)	3	2	4	9	1.1
	K70R	2	0	0	2	0.5
	L210W	0	2	0	2	0.5
	T215 (C/D/E/F/I/S/Y)	5	9	9	23	2.9
	K219 (E/Q/R)	2	4	3	9	1.1
	K65R	1	0	0	1	0.1
	Y115F	0	1	0	1	0.1
	T69D	0	2	3	5	0.6
	Q151M	0	1	0	1	0.1
	F77L	0	1	0	1	0.1
NNRTI	L100I	1	2	2	5	0.6
	K101E	0	1	1	12	1.5
	K103 (N/S)	16	27	34	77	9.6
	V106A	1	0	0	1	0.1
	Y181C	2	4	2	8	1.0
	Y188L	0	3	1	4	0.5
	G190 (A/S)	4	3	2	9	1.1
	P225H	0	1	3	4	0.5
PI	M46 (I/L)	1	2	4	7	0.9
	I50L	0	1	0	1	0.1
	I54 (T/V)	1	3	1	5	0.6
	G73S	0	0	1	1	0.1
	V82 (A/L)	1	5	2	8	1.0
	L90M	1	5	2	8	1.0

Drug resistance mutation based on the WHO list as described in the Materials and Methods section.
NRTI, nucleoside reverse transcriptase inhibitor; NNRTI, nonnucleoside reverse transcriptase inhibitor; PI, protease inhibitor.

resistance was identified in 6% ($n = 48$), NNRTI resistance in 12% ($n = 94$), and PI resistance mutation in 2% ($n = 18$). Mutations at T215 ($n = 23$, 2.9%) and M41 ($n = 13$, 1.6%) were the two most commonly found NRTI resistance and K103N/S ($n = 77$, 9.6%) was the most commonly found NNRTI resistance, comprising almost half of the entire prevalence of TDRM. L90M ($n = 8$, 1%), V82A/L ($n = 8$, 1%), and M46I/L ($n = 7$, 0.9%) were the three commonly found PI resistance mutations (Table 2). Among the 136 patients with TDRM, 20 (15%) patients had ≥ 2 class TDRM. There were no significant time trends in the prevalence of any specific TDRM ($P_{trend} = 0.67$), NRTI ($P_{trend} = 0.75$), NNRTI ($P_{trend} = 0.99$), and PI resistance ($P_{trend} = 0.76$) (Fig. 1).

Patients with TDRM and those without were compared. Those with TDRM were younger and less likely male (both $p < 0.05$), but other characteristics, race, and HIV risk factors were similar. There were no differences in proportion of patients with psychiatric comorbidities, substance use, tobacco use, or those with a history of STDs. Baseline CD4 cell counts and HIV RNA levels did not differ between the groups (Table 1).

Among the 801 treatment-naive patients with genotype resistance testing, 611 patients (76%) were started on cART. Pre-cART CD4 cell count and HIV RNA level did not differ between the two groups. Patients with TDRM were started more frequently on PI-based cART regimen ($p < 0.001$). Virologic failure was observed in 42 (38%) of patients in the TDRM group and 121 (24%) in those without ($p < 0.01$). Changes in CD4 cell count at 24 weeks (median increase of 136
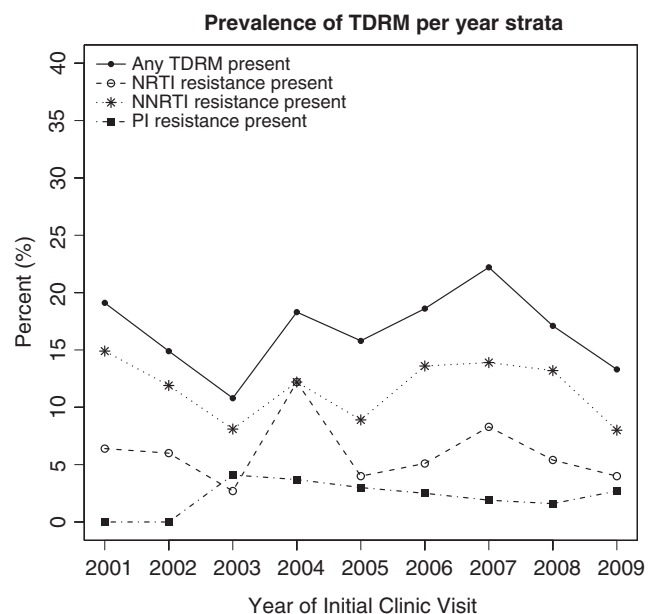

FIG. 1. Prevalence and trends of TDRM per year strata. TDRM, transmitted drug-resistant mutation; NRTI, nucleoside reverse transcriptase inhibitor; NNRTI, nonnucleoside reverse transcriptase inhibitor; PI, protease inhibitor.

TABLE 3. BIVARIATE ANALYSES OF PATIENTS STARTED ON cART

	All patients (N = 611)		TDRM present (N = 110)		No TDRM present (N = 501)		p value
Pre-cART CD4 cell count (median, IQR)	216	49–318	221	57–351	214	48–309	0.27
Pre-cART log₁₀ HIV RNA (median, IQR)	4.75	4.20–5.30	4.72	4.23–5.00	4.78	4.19–5.34	0.17
Choice of cART							
NNRTI + 2NRTI	353	58%	25	23%	328	66%	<0.001
PI + 2NRTI	237	39%	80	73%	157	31%	<0.001
Virologic failure at 48 weeks	163	27%	42	38%	121	24%	<0.01
Changes in CD4 cell count (median, IQR)							
At 24 weeks	124	60–205	136	55–194	121	61–211	0.85
At 48 weeks	156	86–269	159	70–292	156	88–265	0.78

cART, combination antiretroviral therapy; TDRM, transmitted drug-resistant mutation; IQR, interquartile range; pre-cART, prior to initiation of cART; CD4 cell count, CD4 cell count (cells/mm³); log₁₀ HIV RNA, log₁₀ HIV RNA plasma level (copies/ml); NNRTI, nonnucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor.

and 121 cell/mm³, $p=0.85$) and 48 weeks (median increase of 159 and 156 cell/mm³, $p=0.78$) did not differ between the two groups (Table 3).

By univariate analyses, those with pre-cART opportunistic infections (HR 0.68; 95% CI 0.56–0.84), the presence of any TDRM (HR 0.70; 95% CI 0.54–0.91), the presence of NNRTI resistance (HR 0.65; 95% CI 0.47–0.90), and plasma HIV RNA level of greater than 100,000 copies/ml (HR 0.64; 95% CI 0.52–0.78) were less likely to achieve virologic suppression at 48 weeks. Conversely, persons receiving a NNRTI -based regimen rather than a PI-based regimen (HR 1.24; 95% CI 1.02–1.51) and use of an efavirenz-based regimen rather than a boosted atazanavir-based regimen (HR 1.31; 95% CI 1.02–1.68) were more likely to achieve virologic suppression at 48 weeks.

The impact of NNRTI resistance on virologic outcomes was analyzed by multivariate analyses, adjusting by the presence of pre-cART opportunistic infections, a plasma HIV RNA level of greater than 100,000 copies/ml, and use of an NNRTI-based regimen rather than PI-based regimen. NNRTI resistance had HR of 0.67 (95% CI 0.47–0.94), conferring a 1.5-fold increased risk of virologic failure (Table 4).

Discussion

In this cohort, the prevalence of TDRM was 17%, affecting one in six newly diagnosed, treatment-naive HIV-infected patients. Those with NNRTI resistance had a 1.5-fold increased risk of virologic failure at 48 weeks. These data highlight that TDRM, especially NNRTI resistance mutations, have a meaningful negative impact on virologic outcomes when HIV-infected treatment-naive patients initiate even genotype guided cART.

TABLE 4. HAZARD RATIOS FOR ACHIEVING VIROLOGIC SUPPRESSION AT 48 WEEKS BY UNIVARIATE AND MULTIVARIATE ANALYSES

Predictors	Univariate HR (95% CI)	p value	Multivariate HR (95% CI)	p value
Age group, years				
>40	1.08 (0.88–1.33)	0.48		
Sex				
Male (ref. female)	0.99 (0.82–1.21)	0.99		
Race				
Black (ref. white)	1.02 (0.82–1.27)	0.85		
Pre-cART opportunistic infections	0.68 (0.56–0.84)	<0.001	0.76 (0.62–0.93)	<0.01
Any TDRM	0.70 (0.54–0.91)	<0.01		
NRTI resistance	0.99 (0.69–1.43)	0.97		
NNRTI resistance	0.65 (0.47–0.90)	<0.01	0.67 (0.47–0.94)	<0.01
PI resistance	1.22 (0.69–2.17)	0.49		
Pre-cART CD4 cell count				
≤200 cells/mm³	0.88 (0.73–1.07)	0.19		
Pre-cART HIV RNA level				
>100,000 copies/ml	0.64 (0.52–0.78)	<0.001	0.66 (0.54–0.80)	<0.001
NNRTI-based regimen (ref. PI-based regimen)	1.24 (1.02–1.51)	0.03	1.18 (0.96–1.45)	0.12
EFV-based regimen (ref. ATV/r -based regimen)	1.31 (1.02–1.68)	0.03		

Virologic suppression was defined as HIV RNA level <400 copies/ml at 48 weeks.
HR, hazard ratio; CI, confidence interval; TDRM, transmitted drug-resistant mutation; cART, combination antiretroviral therapy; pre-cART, prior to initiation of cART; NRTI, nucleoside reverse transcriptase inhibitor; NNRTI, nonnucleoside reverse transcriptase inhibitor; PI, protease inhibitor; EFV, efavirenz; ATV/r, atazanavir boosted with ritonavir.

Our findings can be explained by three possibilities. The first is that NNRTI resistance mutations themselves confer a higher risk for virologic failure. Second, NNRTI-based regimens may simply be superior to PI-based regimens. In univariate analyses, patients initiating an NNRTI-based regimen were more likely to achieve virologic suppression at 48 weeks when compared to those initiating a PI-based regimen. A randomized clinical trial from the AIDS Clinical Trial Group (ACTG) A5142 study similarly demonstrated the superiority of an efavirenz-based regimen when compared to the PI-based regimen using lopinavir/ritonavir.[18] Conversely, other randomized controlled studies such as the ACTG A5202 study or the Altair study have demonstrated equivalent efficacy with efavirenz- versus boosted atazanavir-based regimens.[19,20] However, these studies excluded patients with known baseline NNRTI resistance and thus cannot specifically address the issue. A subanalysis of A5202 comparing the efficacy of efavirenz and boosted atazanavir between different males and females showed the inferiority of boosted atazanavir in in black race and females.[21] The third possibility is that the presence of NNRTI resistance may serve as a proxy for undetected drug resistance mutations. Ultradeep sequencing may provide more information about the presence of drug resistance mutations, but this technique is available only in research settings and is not clinically validated.[22]

The TDRM prevalence of 17% is comparable to the data from the Centers for Disease Control and Prevention (16% prevalence),[23] and confirms the importance of monitoring for TDRM. We were unable to confirm the decline in the prevalence of TDRM in our population over time despite the simpler and potentially more potent cART regimen of the later years. Factors that affect the prevalence of TDRM are not well described and require further evaluation, particularly given the relationship between TDRM and virologic outcomes and the limited number of antiretroviral classes that are currently available to treat HIV infection.

There are several limitations in our study. This was a retrospective, single site study. We did not distinguish between acute HIV infection and chronic HIV infection. Our results potentially underestimate the prevalence of "nonfit" drug-resistant mutations that will be difficult to detect after the wild-type strains predominate. Nevertheless, the goal of our study was to provide findings relevant to routine patient care and genotypic testing is most commonly done in patients presenting with established chronic HIV infection. Measurement of virologic outcome was HIV RNA suppression at 48 weeks, which did not take into account subsequent virologic failure. A previous study illustrated that short-term virologic failure within 24 weeks may not translate to differences in long-term clinical outcomes.[24] Therefore, longitudinal data should be collected for further analyses. Lastly, because this was a retrospective review of data we did not have formal measurements of cART adherence.

In summary, transmitted drug resistance mutations remain prevalent in our community, affecting one in six newly diagnosed, treatment-naive HIV-infected patients. The presence of TDRM negatively impacted virologic outcomes when cART was initiated, especially when NNRTI resistance mutations were present. Considering the significant effect of the TDRM, its prevalence should be monitored and intervention studies to lower the transmission of drug resistance should be further developed.

References

1. Palella FJ, Baker RK, Moorman AC, Chmiel JS, Wood KC, Brooks JT, et al.: Mortality in the highly active antiretroviral therapy era: Changing causes of death and disease in the HIV outpatient study. J Acquir Immune Defic Syndr 2006; 43(1):27–34.
2. Holmberg SD, Hamburger ME, Moorman AC, Wood KC, and Palella FJ: Factors associated with maintenance of long-term plasma human immunodeficiency virus RNA suppression. Clin Infect Dis 2003;37(5):702–707.
3. Robbins GK, Johnson KL, Chang Y, Jackson KE, Sax PE, Meigs JB, et al.: Predicting virologic failure in an HIV clinic. Clin Infect Dis 2010;50(5):779–786.
4. Johnson JA, Li J, Wei X, Lipscomb J, Irlbeck D, Craig C, et al.: Minority HIV-1 drug resistance mutations are present in antiretroviral treatment-naïve populations and associate with reduced treatment efficacy. PLoS Med 2008; 5(7):e158.
5. Metzner KJ, Giulieri SG, Knoepfel SA, Rauch P, Burgisser P, Yerly S, et al.: Minority quasispecies of drug-resistant HIV-1 that lead to early therapy failure in treatment-naive and -adherent patients. Clin Infect Dis 2009;48(2):239–247.
6. Pillay D, Bhaskaran K, Jurriaans S, Prins M, Masquelier B, Dabis F, et al.: The impact of transmitted drug resistance on the natural history of HIV infection and response to first-line therapy. AIDS 2006;20(1):21–28.
7. Jain V, Liegler T, Vittinghoff E, Hartogensis W, Bacchetti P, Poole L, et al.: Transmitted drug resistance in persons with acute/early HIV-1 in San Francisco, 2002–2009. PLoS ONE 2010;5(12):e15510.
8. Rahim S, Fredrick LM, da Silva BA, Bernstein B, and King MS: Geographic and temporal trends of transmitted HIV-1 drug resistance among antiretroviral-naïve subjects screening for two clinical trials in North America and Western Europe. HIV Clin Trials 2009;10(2):94–103.
9. Wheeler WH, Ziebell RA, Zabina H, Pieniazek D, Prejean J, Bodnar UR, et al.: Prevalence of transmitted drug resistance associated mutations and HIV-1 subtypes in new HIV-1 diagnoses, U.S.-2006. AIDS 2010;24(8):1203–1212.
10. von Wyl V, Yerly S, Burgisser P, Klimkait T, Battegay M, Bernasconi E, et al.: Long-term trends of HIV type 1 drug resistance prevalence among antiretroviral treatment-experienced patients in Switzerland. Clin Infect Dis 2009;48(7):979–987.

11. Costagliola D, Descamps D, Assoumou L, Morand-Joubert L, Marcelin A, Brodard V, *et al.:* Prevalence of HIV-1 drug resistance in treated patients: A French nationwide study. J Acquir Immune Defic Syndr 2007;46(1):12–18.

12. Vercauteren J, Wensing AMJ, van de Vijver DAMC, Albert J, Balotta C, Hamouda O, *et al.:* Transmission of drug-resistant HIV-1 is stabilizing in Europe. J Infect Dis 2009;200(10):1503–1508.

13. Bracciale L, Colafigli M, Zazzi M, Corsi P, Meraviglia P, Micheli V, *et al.:* Prevalence of transmitted HIV-1 drug resistance in HIV-1-infected patients in Italy: Evolution over 12 years and predictors. J Antimicrob Chemother 2009;64(3):607–615.

14. Sax PE, Islam R, Walensky RP, Losina E, Weinstein MC, Goldie SJ, *et al.:* Should resistance testing be performed for treatment-naive HIV-infected patients? A cost-effectiveness analysis. Clin Infect Dis 2005;41(9):1316–1323.

15. Weinstein MC, Goldie SJ, Losina E, Cohen CJ, Baxter JD, Zhang H, *et al.:* Use of genotypic resistance testing to guide HIV therapy: Clinical impact and cost-effectiveness. Ann Intern Med 2001;134(6):440–450.

16. Panel on Antiretroviral Guidelines for Adults and Adolescents: Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services. May 4, 2006; 1–112. [Accessed 2011 Jan 18.] Available from http://aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL05042006050.pdf

17. Bennett DE, Camacho RJ, Otelea D, Kuritzkes DR, Fleury H, Kiuchi M, *et al.:* Drug resistance mutations for surveillance of transmitted HIV-1 drug-resistance: 2009 update. PLoS ONE 2009;4(3):e4724.

18. Riddler SA, Haubrich R, DiRienzo AG, Peeples L, Powderly WG, Klingman KL, *et al.:* Class-sparing regimens for initial treatment of HIV-1 infection. N Engl J Med 2008;358(20):2095–2106.

19. Daar ES, Tierney C, Fischl MA, Sax PE, Mollan K, Budhathoki C, *et al.:* Atazanavir plus ritonavir or efavirenz as part of a 3-drug regimen for initial treatment of HIV type-1: A randomized trial. Ann Intern Med 2011;154(7):445–456.

20. Puls RL, Srasuebkul P, Petoumenos K, Boesecke C, Duncombe C, Belloso WH, *et al.:* Efavirenz versus boosted atazanavir or zidovudine and abacavir in antiretroviral treatment-naive, HIV-infected subjects: Week 48 data from the Altair Study. Clin Infect Dis 2010;51(7):855–864.

21. Kimberly S, Tiernney C, Daar E, Mollan K, Budhathoki C, Sax P, *et al.:* Association of Race/Ethnicity and Sex on Outcomes in ACTG Study A5202. [Abstract 536]. Presented at the 18th Conference on Retroviruses and Opportunistic Infections. February 27–March 2, 2011, Boston.

22. Simen BB, Simons JF, Hullsiek KH, Novak RM, Macarthur RD, Baxter JD, *et al.:* Low-abundance drug-resistant viral variants in chronically HIV-infected, antiretroviral treatment-naive patients significantly impact treatment outcomes. J Infect Dis 2009;199(5):693–701.

23. Kim D, Wheeler W, Ziebell R, *et al.:* Prevalence of transmitted antiretroviral drug resistance among newly-diagnosed HIV-1-infected persons, US, 2007. [Abstract 580]. Presented at the 17th Conference on Retroviruses and Opportunistic Infections. February 16–19, 2010, San Francisco.

24. Mugavero MJ, May M, Harris R, Saag MS, Costagliola D, Egger M, *et al.:* Does short-term virologic failure translate to clinical events in antiretroviral-naïve patients initiating antiretroviral therapy in clinical practice? AIDS 2008;22(18):2481–2492.

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