Burden of Nonnucleoside Reverse Transcriptase Inhibitor Resistance in HIV-1-Infected Patients: A Systematic Review and Meta-Analysis

Sonya J. Snedecor,¹ Lavanya Sudharshan,¹ Katherine Nedrow,² Abhijeet Bhanegaonkar,¹ Kit N. Simpson,³ Seema Haider,² Richard Chambers,⁴ Charles Craig,⁵ and Jennifer Stephens¹

Abstract

The prevalence of HIV drug resistance varies with geographic location, year, and treatment exposure. This study generated yearly estimates of nonnucleoside reverse transcriptase inhibitor (NNRTI) resistance in treatment-naïve (TN) and treatment-experienced (TE) patients in the United States (US), Europe (EU), and Canada. Studies reporting NNRTI resistance identified in electronic databases and 11 conferences were analyzed in three groups: (1) TN patients in one of four geographic regions [US, Canada, EU countries with larger surveillance networks (“EU1”), and EU countries with fewer data (“EU2”)]; (2) TE patients from any region; and (3) TN patients failing NNRTI-based treatments in clinical trials. Analysis data included 158 unique studies from 22 countries representing 84 cohorts of TN patients, 21 cohorts of TE patients, and 8 trials reporting resistance at failure. From 1995 to 2000, resistance prevalence in TN patients increased in US and EU1 from 3.1% to 7.5% and 0.8% to 3.6%, respectively. Resistance in both regions stabilized in 2006 onward. Little resistance was identified in EU2 before 2000, and increased from 2006 (5.0%) to 2010 (13.7%). One TN Canadian study was identified and reported resistance of 8.1% in 2006. Half of TN clinical trial patients had resistance after treatment failure at weeks 48–144. Resistance in TE patients increased from 1998 (10.1%) to 2001 (44.0%), then decreased after 2004. Trends in NNRTI resistance among TN patients show an increased burden in the US and some EU countries compared to others. These findings signify a need for alternate first-line treatments in some regions.

Introduction

A COMBINATION OF THREE OR MORE antiretroviral (ARV) drugs, commonly known as highly-active antiretroviral therapy (HAART), is the mainstay of treatment in individuals infected with human immunodeficiency virus (HIV) and significantly reduces morbidity and mortality.¹ HAART typically includes a nonnucleoside reverse transcriptase inhibitor (NNRTI) or protease inhibitor (PI) in combination with at least two nucleoside reverse transcriptase inhibitors to minimize the likelihood that the virus will develop resistance to all three drugs simultaneously.^{2,3} HIV resistance mutations allow the virus to continue to replicate within a patient despite the presence of HAART. Without effective suppression of viral replication, patients progress

to a state of immunodeficiency followed by death. Thus, minimizing resistance is central to long-term management of HIV disease.

Many international guidelines recommend the first-generation NNRTI, efavirenz (EFV), as the preferred NNRTI-based treatment for first-line treatment.^{2–4} EFV was introduced in 1998 and is considered the gold standard for patients beginning therapy. Although the number of approved ARVs has increased in recent years, the number of available regimens to any given patient remains limited. This is due in part to cross-resistance, which can preclude use of treatments within the same class. Resistance can be transmitted or arise after virologic failure. For example, the two mutations most frequently selected by EFV, K103N and Y188L, also confer resistance to the other first-generation NNRTI, nevirapine

¹Pharmerit International, Bethesda, Maryland.

²Pfizer, Groton, Connecticut.

³Medical University of South Carolina, Charleston, South Carolina.

⁴Pfizer, Collegeville, Pennsylvania.

⁵Pfizer, Sandwich, Kent, United Kingdom.

(NVP), whereas second-generation NNRTIs available since 2008 may still remain active.⁵ One concern is that transmitted NNRTI resistance observed among treatment-naïve patients can be relatively persistent, with the potential to become endemic.⁶

NNRTI resistance has been found to vary by geographic location, patient observation year, and exposure to treatment.^{7,8} Given the importance of optimal selection of initial treatment regimens fully effective against patients' viral strains, understanding population-wide resistance prevalence can guide health policy makers by informing treatment recommendations and help clinicians prescribe treatments most likely to suppress viral replication. Therefore, the objective of this study was to understand the overall prevalence and recent trends of NNRTI resistance in European countries, the United States, and Canada.

Materials and Methods

Systematic search

A systematic literature review was conducted in EMBASE and PubMed to identify relevant citations containing estimates of the prevalence of NNRTI drug resistance. Database search terms included the following: ["HIV-1" (MeSH) OR "human immunodeficiency virus 1" (tiab)] AND ["reverse transcriptase inhibitor" (all fields) OR "reverse transcriptase inhibitors" (all fields)] AND ["nonnucleoside" (all fields) OR "nonnucleoside" (all fields) OR "NNRTI" (all fields)] AND ["resistance" (all fields) OR "resistant" (all fields)]. The search was restricted to studies with abstracts published between 2002 and July 2012 in English. Manual searching of references of systematic reviews and meta-analyses identified from the searches was also conducted to find additional relevant articles.

To identify more recent studies not yet published, we also searched abstracts presented at 11 research conferences (International HIV Drug Resistance Workshop, International HIV & Hepatitis Drug Resistance Workshop & Curative Strategies, Conference on Retroviruses and Opportunistic Infections, Annual Conference of the British HIV Association, IAS Conference on HIV Pathogenesis, Treatment and Prevention, International AIDS Conference, International Conference on Human Retroviruses: HTLV and Related Viruses, International Congress on Drug Therapy in HIV Infection, Infectious Disease Society of America, International Symposium on HIV & Emerging Infectious Diseases, and International Conference on Antimicrobial Agents and Infectious Diseases). Conference proceedings from 2009 to July 2012 were searched using text-based methods with the following search strings: "resistan," "NNRTI," "nonnucleoside," "nonnucleoside," "EFV," "efavirenz." These words were selected to correspond to the database search terms.

Study selection

Inclusion criteria consisted of clinical trials or observational cohort studies with explicit mention of patient type (treatment-naïve, treatment-experienced, or treatment-failing type) and reporting total number of patients and total number with NNRTI resistance, defined as the presence of any NNRTI mutation according to algorithm used in the study. Patient population of included studies was restricted to

patients from a European country, United States, Canada, or multicenter international randomized clinical trials (RCTs). Studies were excluded that did not report resistance specific to the NNRTI class, reported prevalence of individual point mutations, and/or reported prevalence proportions without total number of patients sampled.

Titles and abstracts of each record identified from the search process were independently assessed by two researchers for further review. Selected full-text articles were also independently assessed for potential data extraction by two researchers using the aforementioned criteria. Inconsistencies were resolved by consensus. Manual searching of references of published systematic reviews and meta-analyses was also conducted to identify additional studies. Conference abstracts were searched by one reviewer for potential relevance. A second reviewer made the final selection for potential study inclusion. Authors of selected conference abstracts were contacted to request associated posters/presentations, if contact information could be obtained. Posters and full-text articles obtained directly from the authors were then evaluated for inclusion into the study.

Data extraction

Variables including country of data collection, year of sample, sample size, and number of patients with NNRTI

TABLE 1. COUNTRIES (AND NUMBER OF PATIENT COHORTS) IDENTIFIED IN THE LITERATURE FOR EACH REGION

<i>Country/region</i>	<i>Number of cohorts</i>
EU countries with more data (EU1) ^a	
Multiple EU countries	6
France	5
Germany	2
Italy	9
Spain	7
Switzerland	1
UK	5
Total	35
United States ^a	33
Canada	1
EU countries with fewer data (EU2)	
Belarus	1
Bulgaria	1
Cyprus	1
Denmark	1
Estonia	1
Greece	2
Latvia	1
Luxembourg	1
Netherlands	1
Poland	1
Portugal	2
Romania	1
Slovenia	1
Sweden	2
Total	17

^aTwo studies reported data from European and North American (assigned to the United States) patients,^{8,39} which were recorded separately.

resistance were extracted from all relevant studies into a structured Microsoft Access database designed for this study. Relevant data from each study were extracted by three reviewers, and results were compared to ensure accuracy.

Data analysis

Analyses were stratified by patient type and geographic location: (1) treatment-naïve patients in European countries with well-developed surveillance programs and large cohort studies providing data with larger sample sizes ("EU1"; Italy, Germany, Spain, France, United Kingdom, and the EuroSIDA, SPREAD, CASCADE, and Swiss HIV cohort studies); (2) treatment-naïve patients in other European countries providing data from two or fewer studies ("EU2"; Belarus, Bulgaria, Cyprus, Denmark, Estonia, Greece, Hungary, Latvia, Luxembourg, The Netherlands, Poland, Romania, Slovenia, and Sweden) (Table 1); (3) treatment-naïve patients in the United States; (4) treatment-naïve patients in Canada; (5) treatment-experienced patients from any region; and (6)

treatment-naïve patients failing NNRTI treatments in randomized clinical trials.

Stratified resistance data were visualized using scatter plots of the reported resistance prevalence versus data collection year. The median year of data collection was used for studies reporting resistance measured over multiple years. For purposes of quantitative meta-analyses, median years ending in "0.5" (from a collection period of 2000–2001, for example) were rounded to the nearest even year.

Generalized linear mixed models (GLMMs) with the logit link function were used to generate a random effects estimate of overall resistance prevalence for each year in the United States and EU1 treatment-naïve analyses and the treatment-experienced analysis. A random effects model has two components of variation: (1) random variation across the different studies due to differences in sampling methods, patient population, etc. and (2) the random variation resulting from the collection of the data from year to year. These two sources of variation are commonly known as between-study variability and within-study variability, respectively. The model

FIG. 1. Published article and conference abstract literature search results.

of within-study variability was developed because several studies report data over multiple time periods and year-to-year variability and inherent correlation among multiple observations within the same study needed to be captured within the statistical model.

EU2 data were insufficient for a GLMM, and a generalized linear model (GLM) with the logit link function was used instead. The distinction between the GLMM and GLM is analogous to the distinction between the fixed-effect and random-effects model. The use of the GLM model is reasonable if no or few studies include data over multiple years and there is no need to account for within-study correlations.

GLMM/GLM analyses generated overall estimates and 95% confidence intervals (CIs) of the proportion of patients with NNRTI resistance by year for the treatment-naïve and treatment-experienced strata. Overall resistance in patients failing treatment in RCTs was determined using the weighted average of the reported prevalence estimates; 95% CIs were generated using the pooled variance.

Results

Systematic search results

Study search results are shown in Fig. 1. Conference screening using EMBASE and keyword searches identified 149 abstracts, of which 77 were selected for potential inclusion and authors of 58 were contacted successfully by e-mail, from whom some full conference presentations were obtained. Forty-six abstracts or presentations were selected for extraction after which four were later excluded due to insufficient data, resulting in a total of 17 conference posters/presentations and 25 abstracts in the analysis. Full-text database searching identified 1,287 hits from which 170 full-text articles were evaluated for potential inclusion. These articles included 14 references identified from supplementary searching or received from authors of conference abstracts and 8 systematic reviews, which were screened for relevant references. Ultimately, 143 full-text articles and 42 conference posters were extracted for potential inclusion in the study (Table 2).

Several articles reported data from the same cohort of patients. Each extracted study was reviewed to identify like patient cohorts among the different articles. Twenty-seven articles and/or abstracts were found to contain duplicate data (duplicate patient cohorts and study collection years); thus, 158 records remained for inclusion into the meta-analyses. Six of these studies were excluded because the patient type could not be identified⁹ or for reporting prevalence of resistance in a mixed population of treatment-naïve and treatment-experienced patients.^{10–14}

FIG. 2. Scatter plot of reported resistance and meta-analytic trends in (A) US, (B) EU1 countries, and (C) EU2 countries [Luxembourg (1992, 0%, *n* = 299) and Romania (2000, 30%, *n* = 10) data lie outside of the figure axes limits and are not shown]. The center of each circle represents the prevalence estimate for each study and time point. The size of each circle is proportional to the study's sample size. The solid line represents the overall estimates for each year and dotted lines describe each estimate's 95% confidence interval.

FIG. 3. Scatter plot of reported resistance and meta-analytic trends in treatment-experienced patients. The center of each circle represents the prevalence estimate for each study and time point. The size of each circle is proportional to the study's sample size. The solid line represents the overall estimates for each year and dotted lines describe each estimate's 95% confidence interval.

Among studies of treatment-naïve patients, those reporting resistance to specific second-generation NNRTIs (rilpivirine, etravirine, or lersivirine)^{15–19} were excluded from the quantitative analysis, but reported separately. Studies reporting resistance identified by ultrasensitive sequencing methods,^{20,21} or not reporting year of data collection,^{22–28} were also excluded, leaving 93 studies^{8,14,26,29–118} included in the treatment-naïve meta-analysis. These 93 studies represented 84 patient cohorts from 22 countries reporting data from 1992 to 2011. The majority of studies included patients from EU1 countries (35 cohorts) and the US (33 cohorts), with two studies presenting data from both regions. Seventeen cohorts were from EU2 countries and one cohort was from Canada. The overall treatment-naïve analysis consisted of data from 60,645 patient samples.

Five studies of treatment-experienced patients were excluded for reporting resistance specific to the second-generation NNRTI, etravirine (results reported separately).^{18,119–122} An additional 10 were excluded for not reporting years of data collection,^{55,123–131} leaving 23 studies^{14,58,59,94,132–150} representing 21 patient cohorts from nine countries reporting data from 1996 to 2010 for the quantitative analysis. These data included 12 EU1 cohorts, 5 US cohorts, 3 EU2 cohorts, and 1 Canadian cohort totaling 41,666 patient samples.

Of the 17 randomized controlled trials (RCTs) reporting resistance at time of treatment failure, nine were not included into the quantitative analyses due to not reporting the total number of patients failing treatment,^{151,152} trial not conducted in treatment-naïve patients,^{153,154} both,^{140,155–157} or not reporting the time point of assessment.⁵⁶ The remaining eight studies^{158–165} included 613 treatment-naïve patients failing treatment by weeks 48, 96, or 144 of the trials.

FIG. 4. Prevalence of nonnucleoside reverse transcriptase inhibitor (NNRTI) resistance and 95% confidence intervals after failure of efavirenz (EFV)-, rilpivirine (RPV)-, and ritonavir-boosted lopinavir (LPV/r)+EFV-based first-line treatment identified from clinical trials.

First-generation NNRTI resistance

Overall prevalence estimates by year and geographic region are shown in Fig. 2 superimposed onto scatter plots of the reported data. NNRTI resistance was more prevalent in treatment-naïve US patients than treatment-naïve EU1 patients for nearly all observation years. From 1995 to 2000, the prevalence of TN-associated resistance increased in US and EU1 from 3.1% to 7.5% and from 0.8% to 3.6%, respectively. The estimated mean prevalence was more stable from 2006 to 2009 in the US (range: 8.3–9.1%) and from 2006 to 2011 in EU1 (range: 3.2–3.9%). From 1995 to 2000, data identified from EU2 countries included a longitudinal study from the Netherlands and a Greek study, both containing samples from fewer than 25 patients and reporting 0% prevalence of resistance. TN-associated resistance in EU2 increased from 2006 (5.0%) to 2010 (13.7%), driven by data from Greece and Portugal. One Canadian cohort was identified reporting a prevalence of 8.1% in 2006, consistent with US findings.

Data of reported resistance in patients previously exposed to treatment from all geographic areas were analyzed together due to the relatively small number of studies. These results showed an increasing trend from 1998 to 2001 (10.1–44.0%), followed by a decrease in resistance prevalence after 2004 (44.8–36.8% in 2009) (Fig. 3).

Second-generation NNRTI resistance

Etravirine (ETR) resistance in treatment-naïve patients was reported to be 9.5%¹⁸ in Switzerland, 10.3%¹⁶ in France, and 11.8%⁴⁸ in an international RCT. Rilpivirine resistance was reported to be 4.9% in France,¹⁵ 6.3% in Portugal,¹⁷ and 20.7% in the treatment-naïve screening population of a clinical trial.¹⁹ Lersivirine resistance was reported to be 1.4% at baseline of an international clinical trial.⁴⁸

Four studies reported ETR resistance in patients exposed to or failing NNRTI treatment^{18,120–122} ranging from 22.1% to 64.9%. The overall prevalence of at least one ETR resistance mutation among those data was 53.6% [95% CI (31.5%,

TABLE 2. STUDIES AND PREVALENCE DATA

<i>Country</i>	<i>Reference</i>	<i>Study cohort (if provided)</i>	<i>Year(s)</i>	<i>NNRTI resistance (n)/N</i>
Belarus	Ilyenkova EUDRW 2012 ⁶⁸		2011	0/82
Bulgaria	Santoro 2008 ⁹⁴		2002–2006	2/22
Canada	Jayaraman 2006 ⁷⁰		2000–2001	10/715
Canada,	Masquelier 2005 ⁸¹		1996–1998	1/145
European countries			1999–2003	14/224
Cyprus	Kousiappa 2009 ⁷⁴		2003–2006	1/37
Denmark	Audelin 2011 ³⁰	Danish HIV cohort study	2001–2009	18/1405
Estonia	Avi 2011 ³¹	Estonia HIV Reference Laboratory	2008	3/145
European countries	Vercauteren 2009 ¹⁰⁷	SPREAD	2002–2005	62/2687
	Frentz EUDRW 2011 ⁵⁷		2006–2007	64/1630
European countries	Wensing 2005 ¹¹²	SPREAD-CATCH	1996–1998	5/217
			1999–2000	14/454
			2001–2002	8/87
International	Bannister 2008 ³⁴	EuroSIDA	1994–2004	5/525
France	Chaix 2009 ⁴³	ANRS CO4	1996–1998	1/156
			1999–2000	10/249
			2001–2002	8/299
			2003–2004	19/327
			2005–2006	19/415
			2005–2006	20/415
France	Chaix 2003 ⁴²		1999–2000	10/249
France	Descamps 2010 ⁵²	Odyssee	2001	1/363
			2006–2007	13/466
France	Descamps 2005 ⁵¹	Primo/Odyssee	2001–2002	13/664
France	Clevenberg 2002 ⁴⁴	ADDIS	1996–1999	6/268
Germany	Bartmeyer 2010 ³⁵	German HIV-1 seroconverter cohort	1996	0/18
			1997	0/30
			1998	1/34
			1999	0/32
			2000	1/36
			2001	4/74
			2002	1/83
			2003	4/169
			2004	5/206
			2005	12/235
			2006	12/207
			2007	5/176
Germany	Sagir 2007 ⁹²	RESINA Study	2001	0/83
			2002	3/123
			2003	5/138
			2004	8/242
			2005	9/245
Greece	Skoura 2011 ⁹⁶	Greek National AIDS Reference Laboratory	2000–2003	3/118
			2004–2005	5/109
			2006–2007	12/142
Greece	Magiorkinis 2002 ⁷⁹		1999–2000	0/24
Greece	Skoura EUDRW 2012 ⁹⁷	Greek National AIDS Reference Laboratory	2009–2011	45/238
Italy	Corvasce 2006 ⁴⁷		1997–2004	7/152
Italy	Biagetti 2009 ³⁷		2006–2007	1/56
Italy	Lai 2012 ⁷⁶		2002–2008	24/510
Italy	Lapadula 2008 ⁷⁷		2001–2006	32/569
Italy	Bracciale 2009 ⁴¹	ARCA database	1996–2001	13/350
			2002–2004	35/464
			2005	17/326
			2006–2007	32/550
Italy	Violin 2002 ¹⁰⁹	ICoNA	1996–1998	1/347
	Violin 2004 ¹¹⁰		1996–2001	1/112

(continued)

TABLE 2. (CONTINUED)

<i>Country</i>	<i>Reference</i>	<i>Study cohort (if provided)</i>	<i>Year(s)</i>	<i>NNRTI resistance (n)/N</i>
Italy	Alteri 2009 ²⁹	SENDIH	2004–2007	9/255
Italy	Bonura 2010 ³⁸		2004–2008	11/108
Latvia	Balode 2010 ³³	SPREAD/HER—Latvia	2005–2006	1/117
Luxemburg	Deroo 2002 ⁵⁰		1983–2000	0/299
Netherlands	Bezemer 2004 ³⁶		1994	1/13
			1995	0/12
			1996	0/13
			1997	0/12
			1998	0/7
			1999	0/10
			2000	0/7
			2001	1/10
			2002	0/16
			2008	1/95
Poland	Stanczak 2010 ⁹⁸			
Portugal	Cortez EUDRW 2012 ⁴⁶	Centro Hospitalar de Coimbra	2004–2011	12/92
Portugal	Correia EUDRW 2012 ⁴⁵		2009–2011	7/142
Romania	Manolescu IAS 2010 ²⁶		1992–2009	3/10
Slovenia	Babic 2006 ³²	Slovenian AIDS Reference Center	2000–2004	0/77
Spain	Gallego 2003 ⁵⁸		1999	2/47
			2001	6/47
Spain	Garcia-Guerrero 2006 ⁵⁹		2002	3/43
Spain	Monge EUDRW 2012 ⁸³		2007–2011	72/1864
Spain	de Mendoza 2005 ⁴⁹	Spanish HIV Seroconverter group	1998	1/17
			2002	1/28
			2003	2/50
			2004	4/52
Spain	Yebra 2011 ¹¹⁵		1996–2010	15/292
Spain	Romero 2011 ⁹⁰		2003–2005	7/182
Sweden	Maljkovic 2003 ⁸⁰		1998–2001	3/100
Sweden	Eiros 2004 ⁵³		1996–2003	2/145
Switzerland	Yang CROI 2012 ¹⁷⁷	Swiss HIV Cohort Study	1996	0/85
			1997	1/123
			1998	2/96
			1999	1/143
			2000	3/131
			2001	0/126
			2002	2/143
			2003	3/144
			2004	3/183
			2005	7/221
			2006	10/220
			2007	10/185
			2008	7/175
			2009	7/152
			2010	3/91
			2011	1/36
			≤1995	0/38
	Yerly 2007 ¹¹⁶		1996	0/44
			1997	2/75
			1998	3/69
			1999	0/77
			2000	2/87
			2001	0/93
			2002	2/100
			2003	1/88
			2004	0/89
			2005	6/100

(continued)

TABLE 2. (CONTINUED)

<i>Country</i>	<i>Reference</i>	<i>Study cohort (if provided)</i>	<i>Year(s)</i>	<i>NNRTI resistance (n)/N</i>
United Kingdom	Booth 2007 ³⁹		2004–2006	4/239
United Kingdom	Kahn BHIVA 2009 ⁷²		2004–2008	6/355
United Kingdom	Payne 2008 ⁸⁸		2005–2007	7/392
United Kingdom	Street 2008 ¹⁰¹		2006	1/99
United Kingdom	UK Collaborative Group on HIV Drug Resistance 2007 ¹⁰⁶	UK HIV Drug Resistance Database	1996–1997 1998 1999 2000 2001 2002 2003 2004 2005 2006 2007 2008 2009	4/310 7/340 18/358 24/458 27/517 29/548 42/766 58/1363 84/2054 91/2455 100/2525 120/2651 80/2221
United States	Shet 2006 ⁹⁵	Aaron Diamond AIDS Research Center	1995–1998 1999–2000 2001–2002 2003–2004 2005–2009	2/76 4/71 8/102 15/112 30/393
United States	Goodwin-Fernandez IDSA 2011 ⁶⁰		2004–2009	1/54
United States	Nathavitharana IDSA 2011 ⁸⁵			
United States	Grubb 2006 ⁶²	Washington University Clinic, St. Louis	2003–2005	13/192
United States	Juethner 2003 ⁷¹		2000–2001	3/18
United States	Hanna 2003 ⁶³		1999	4/88
United States	Iarikov 2010 ⁶⁷		2004–2008	4/99
United States	Nannini 2002 ⁸⁴		1999	2/44
United States	Grant 2002 ⁶¹	Options Project	1996–1997 1998–1999 2000–2001 2001–2009	0/40 6/94 12/91 7/325
United States	Salama IHDRW 2009 ⁹³			
United States	Little IHDRW 2011 ⁷⁸	AIEDRP	1995–2007	135/1927
United States	Novak 2005 ⁸⁶	FIRST	1999 2000 2001	3/156 6/170 6/165
United States	Hightow-Weidman 2010 ⁶⁴		2006–2009	18/145
United States	Huang 2008 ⁶⁵		2005–2007	22/228
United States	Hurt 2009 ¹⁷⁸		1998–2000 2001–2002 2003–2004 2005–2007	0/18 2/16 14/153 8/67
United States	Jain CROI 2009 ⁶⁹	Options Project	2003 2004 2005 2006 2007 2008	1/58 3/54 4/43 3/29 3/40 2/42
United States	Parker 2007 ⁸⁷		2000–2004	8/151
United States	Holodniy 2004 ¹⁴	REACH cohort	1996–1997 1999–2000	8/143 11/124

(continued)

TABLE 2. (CONTINUED)

Country	Reference	Study cohort (if provided)	Year(s)	NNRTI resistance (n)/N
United States	Stekler 2011 ⁹⁹		1996–2002	2/99
United States	Stone 2002 ¹⁰⁰		2000–2001	0/25
United States	Sullivan 2002 ¹⁰²		1997–1999	2/69
United States	Vibhakkar IAS 2009 ¹⁰⁸		2004–2008	13/113
United States	Weinstock 2004 ¹¹¹		1997–2001	18/1082
United States	Yanik IHDRW 2011 ¹¹⁴		1999–2010	40/720
United States	Mena AIDS 2011 ⁸²		2005–2008	91/746
United States	Truong 2011 ¹⁰⁴	San Francisco municipal STI clinic	2004	11/136
			2005	8/112
			2006	9/114
United States	Kim CROI 2010 ⁷³	VARHS	2007–2008	202/2480
	Prejean CROI 2010 ⁸⁹		2006–2007	132/1626
United States	Youmans 2011 ¹¹⁸		2005	22/243
			2006	25/299
			2007	26/239
			2008	31/283
			2009	22/213

NNRTI, nonnucleoside reverse transcriptase inhibitor.

75.7%)). Studies providing these data were conducted in Switzerland (years 1999–2008), Portugal (2000–2010), Italy (up to 2010), and Spain (2000–2009). As ETR was approved in the US in early 2008 and in Europe in late 2008, it is unlikely that any of the patients in these treatment-exposed cohorts are ETR-experienced.

Eight studies reported the prevalence of NNRTI resistance after failure of EFV-based^{48,159–164,166} or rilpivirine (RPV)-based^{161,162,166} treatment regimens in clinical trials. Approximately 50% of patients had resistance to these agents after failure (Fig. 4). One of these studies also examined ritonavir-boosted lopinavir (LPV/r) in combination with EFV without cotreatment with NRTIs, where approximately two-thirds of patients failing treatment by week 144 had at least one NNRTI mutation.¹⁶⁴

Discussion

In this analysis of the published prevalence of NNRTI resistance, increased resistance was observed in the US and EU1 countries (those with larger surveillance networks and more available data) from the mid to late 1990s. This increase later stabilized in EU1 countries around 2000, but did not do so in the US until the late 2000s. Prevalence data in EU2 countries (those providing fewer data) were very limited prior to the year 2000 and studies reported very low to no levels of NNRTI resistance among treatment-naïve patients. In contrast, EU2 data after the year 2000 showed a rapid and sustained increase in prevalence.

The resistance observed in treatment-naïve patients will have arisen mostly through transmission either from a treated person with suboptimal viral suppression or from a person who in turn was infected by an individual with transmitted resistance.¹⁶⁷ However, the nature of the information reviewed here did not permit an assessment of the prevalence of

transmitted resistance using designated mutations.¹⁶⁸ Thus, the overall prevalence of resistance transmission (or transmission of potential resistance) is likely greater than the prevalence of resistance reported here.

The reason for different trends for resistance prevalence over time among the US, EU1, and EU2 regions is complex. Different and changing availability of therapies and prescribing patterns in the populations during and prior to the period reviewed may be key factors in determining the prevalence of resistance. The stabilization of resistance in EU1 countries near the year 2000 coincides with the introduction of more potent ritonavir-boosted PIs. The data examined here primarily include surveillance periods prior to 2008 when newer second-generation NNRTIs were unavailable. The introduction of these and other novel drug classes into routine clinical practice could change future resistance trends, as has been observed previously.¹⁶⁹

Studies have shown that transmission of drug resistance correlates with population-level ARV utilization.¹⁶⁹ Thus, the more widespread use of NNRTIs in the United States compared to some European countries could have contributed to the greater prevalence of resistance and slower stabilization observed here. Furthermore, variation in NNRTI usage among European countries could also lead to differences in resistance prevalence noted between the EU1 and EU2 regions, or even unobserved differences within those regions not explored within this analysis. These factors would be best explored with patient-level data of transmitted resistance at the country level.

The goal of this research was to quantify the prevalence of transmitted NNRTI resistance over time in the geographic regions of interest. Thus, no attempt was made to identify causes or correlates of resistance, such as patient management practices, modes of transmission, surveillance infrastructure, or social attitudes, which might be contributory. Viral subtype

differences have also been linked to differential transmitted drug resistance (TDR); however, some suggest this difference is better attributed to location of infection.^{107,170,171} Another possible factor contributing to differential TDR prevalence is the level of population-wide virologic control in the HIV-infected populations of interest. Poor population-level viral suppression in regions of the US and the EU2 countries is a possible consideration as TDR prevalence has been shown to be linked to the proportion of HIV-infected individuals with detectable HIV RNA.⁴⁹

Data were sparse for the EU2 countries, and the analysis was limited to a small number of studies published in different countries where the patient populations and HIV treatment patterns may not be comparable. Publication bias must be considered, where the data were taken from countries in which HIV was endemic and patients in other EU2 countries were not represented. The recent increase in treatment-naïve resistance in EU2 countries was driven, in part, by Greek data. In a recent publication, Skoura *et al.* (2013)¹⁷² discuss the high rates of resistance among newly diagnosed patients in Greece from 2009 to 2011. The authors note that the rise in all-class TDR was driven by increases in NRTI and NNRTI resistance and that it coincided with an HIV outbreak affecting intravenous drug users and the profound Greek financial crisis, which resulted in drastic cuts in health expenditures. Other factors affecting adherence to therapy and retention to HIV care, as well as high-risk sexual behaviors, were also hypothesized to be responsible for the spread of TDR in this population.

It is interesting to note that while all-region NNRTI resistance in treatment-experienced patients decreased in recent years, no region showed a simultaneous decrease in resistance among treatment-naïve patients. This observation supports the possibility of a scenario where, despite good control of the local epidemic through good antiretroviral drug use, transmission of resistance can be perpetuated by treatment-naïve patients who were infected with resistant strains themselves.⁶ This highlights the importance of early diagnosis and control of viral replication in these patients with fully active treatment regimens.

Reported resistance to the second-generation NNRTIs ETR and rilpivirine in treatment-naïve patients was equal to or higher than the reported prevalence of first-generation NNRTIs. Additionally, reported data showed that prior exposure to NNRTIs results in a substantial prevalence of ETR resistance mutations. The data presented here include the prevalence of one or more mutations against these treatments, but it is not known whether the presence of only one mutation has the same impact on drug efficacy as is possible with a single first-generation NNRTI mutation. One study reports that at least three ETR mutations may be required to impair drug efficacy.^{173,174}

The results of our study are consistent with previous reports of HIV drug resistance. The study of patients screened for clinical trial participation by Rahim *et al.*⁸ reported a higher prevalence of transmitted NNRTI resistance in North America compared to Western Europe. Frentz *et al.*⁷ conducted a systematic review and meta-analysis of global resistance prevalence up to 2009. The authors found NNRTI resistance to be higher in North America than in Europe and an increasing time-based trend among North American studies for the year strata <2001, 2001–2003, and >2003.

The corresponding NNRTI resistance trend for Europe was more stable.

Meta-analytic results in treatment-experienced patients are also consistent with a recent study identifying a decreasing trend in Western EU countries.¹⁷⁵ Gupta *et al.* (2008)¹⁷⁶ conducted a systematic literature review and meta-analysis of patients failing HAART treatment among clinical trials to estimate resistance to the NNRTI third agent occurred in 53% of patients after 48 weeks of follow-up, consistent with our study.

This study provides an assessment of the published literature and conference abstracts identifying reports of the prevalence of NNRTI resistance in several patient populations in 22 countries in Europe and North America. Resistance data were statistically aggregated by year of data collection to provide year-by-year trends of the prevalence of resistance in treatment-naïve and treatment-experienced patients from three geographic regions, not previously found in the published literature. Understanding the magnitude and direction of TDR is important for public health officials to quantify the burden of drug resistance in the HIV population, which could call for the development of new treatment guidelines, changed patient monitoring practices, or identification of novel therapies not affected by NNRTI TDR.

Acknowledgments

The authors would like to thank Jing Li for statistical assistance and John A. Carter and Varun Ektare of Pharmerit International for manuscript review and critical appraisal. This work was presented at the 2013 IAS Conference on HIV Pathogenesis, Treatment and Prevention in Kuala Lumpur, Malaysia.

Author Disclosure Statement

This study was funded by Pfizer Inc and funded by ViiV Healthcare.

References

1. Palella FJ Jr, Delaney KM, Moorman AC, *et al.*: Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. HIV Outpatient Study Investigators. *N Engl J Med* 1998;338(13):853–860.
2. DHHS: Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. www.aidsinfo.nih.gov/contentfiles/lvguidelines/adultandadolescentgl.pdf.
3. IAS: Antiretroviral treatment of adult HIV infection: 2012 recommendations of the International Antiviral Society-USA panel. *JAMA* 2012;308(4):387–402.
4. EACS: European AIDS Clinical Society (EACS) guidelines. 2012. Available at www.europeanaidsclinicalsociety.org/images/stories/EACS-Pdf/EACSGuidelines-v6.1-English-Nov2012.pdf.
5. Johnson VA, Calvez V, Gunthard HF, *et al.*: 2011 update of the drug resistance mutations in HIV-1. *Top Antivir Med* 2011;19(4):156–164.
6. Smith RJ, Okano JT, Kahn JS, Bodine EN, and Blower S: Evolutionary dynamics of complex networks of HIV drug-resistant strains: The case of San Francisco. *Science* 2010;327(5966):697–701.

7. Frentz D, Boucher CA, and van de Vijver DA: Temporal changes in the epidemiology of transmission of drug-resistant HIV-1 across the world. *AIDS Rev* 2012;14(1):17–27.
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. Brennan CA, Yamaguchi J, Devare SG, Foster GA, and Stramer SL: Expanded evaluation of blood donors in the United States for human immunodeficiency virus type 1 non-B subtypes and antiretroviral drug-resistant strains: 2005 through 2007. *Transfusion* 2010;50(12):2707–2712.
10. Faruki H: Increased Prevalence of Drug Resistance in Pediatric HIV Isolates as Compared with Adult Isolates in the United States. International Workshop on HIV and Hepatitis Virus Drug Resistance and Curative Strategies, 2011. Abstract #118.
11. Franzetti M, Lai A, Simonetti FR, *et al.*: High burden of transmitted HIV-1 drug resistance in Italian patients carrying F1 subtype. *J Antimicrob Chemother* 2012;67(5):1250–1253.
12. Goldsamt LA, Clatts MC, Parker MM, Colon V, Hallack R, and Messina MG: Prevalence of sexually acquired antiretroviral drug resistance in a community sample of HIV-positive men who have sex with men in New York City. *AIDS Patient Care STDS* 2011;25(5):287–293.
13. Hirsch HH, Drechsler H, Holbro A, *et al.*: Genotypic and phenotypic resistance testing of HIV-1 in routine clinical care. *Eur J Clin Microbiol Infect Dis* 2005;24(11):733–738.
14. Holodniy M, Charlebois ED, Bangsberg DR, Zolopa AR, Schulte M, and Moss AR: Prevalence of antiretroviral drug resistance in the HIV-1-infected urban indigent population in San Francisco: A representative study. *Int J STD AIDS* 2004;15(8):543–551.
15. Lambert-Niclot S: Prevalence of pre-existing resistance associated mutations to rilpivirine (TMC278), emtricitabine, and tenofovir in antiretroviral-naïve patients. *IHDRW*, 2012.
16. Maiga AI, Descamps D, Morand-Joubert L, *et al.*: Resistance-associated mutations to etravirine (TMC-125) in antiretroviral-naïve patients infected with non-B HIV-1 subtypes. *Antimicrob Agents Chemother* 2010;54(2):728–733.
17. Pereira-Vaz J: Resistance associated mutations to rilpivirine in HIV-1 subtypes C and G strains isolated from antiretroviral treatment-naïve individuals. *EUDRW*, 2012.
18. Scherrer AU, Hasse B, von Wyl V, *et al.*: Prevalence of etravirine mutations and impact on response to treatment in routine clinical care: The Swiss HIV Cohort Study (SHCS). *HIV Med* 2009;10(10):647–656.
19. Vingerhoets J, Rimskey L, Van Eygen V, *et al.*: Preexisting mutations in the rilpivirine Phase III trials ECHO and THRIVE: Prevalence and impact on virologic response. *Antivir Ther* 2013;18(2):253–256.
20. Kozal M: Low frequency NNRTI-resistant HIV-1 variants and mutational load relationship in ART-naïve subjects. *IHDRW*, 2011.
21. Lataillade M: Prevalence and clinical significance of transmitted drug resistance (TDR) HIV mutations by ultra deep sequencing (UDS) in HIV-infected ARV-naïve subjects in a CASTLE study. *IHDRW*, 2009.
22. Barbour JD, Hecht FM, Wrin T, *et al.*: Persistence of primary drug resistance among recently HIV-1 infected adults. *AIDS* 2004;18(12):1683–1689.
23. Perno CF, Cozzi-Lepri A, Balotta C, *et al.*: Low prevalence of primary mutations associated with drug resistance in antiviral-naïve patients at therapy initiation. *AIDS* 2002;16(4):619–624.
24. Ji H: National HIV Drug Resistance Surveillance Using Tagged Pooled Pyrosequencing. *CROI*, 2011.
25. Kanizsai S, Ghidan A, Ujhelyi E, Banhegyi D, and Nagy K. Monitoring of drug resistance in therapy-naïve HIV infected patients and detection of African HIV subtypes in Hungary. *Acta Microbiol Immunol Hung* 2010;57(1):55–68.
26. Manolescu L: Analysis of transmitted drug resistance, resistance mutations and future antiretroviral efficacy in HIV-1 subtype F infected-patients prior to therapy. *IAS*, 2010.
27. Nicot F, Saliou A, Raymond S, *et al.*: Minority variants associated with resistance to HIV-1 nonnucleoside reverse transcriptase inhibitors during primary infection. *J Clin Virol* 2012;55(2):107–113.
28. Paraschiv S, Otelea D, Dinu M, Maxim D, and Tinischi M: Polymorphisms and resistance mutations in the protease and reverse transcriptase genes of HIV-1 F subtype Romanian strains. *Int J Infect Dis* 2007;11(2):123–128.
29. Alteri C, Svicher V, Gori C, *et al.*: Characterization of the patterns of drug-resistance mutations in newly diagnosed HIV-1 infected patients naïve to the antiretroviral drugs. *BMC Infect Dis* 2009;9:111.
30. Audelin AM, Gerstoft J, Obel N, *et al.*: Molecular phylogenetics of transmitted drug resistance in newly diagnosed HIV Type 1 individuals in Denmark: A nation-wide study. *AIDS Res Hum Retroviruses* 2011;27(12):1283–1290.
31. Avi R, Huik K, Pauskar M, *et al.*: Emerging transmitted drug resistance in treatment-naïve human immunodeficiency virus-1 CRF06_cpx-infected patients in Estonia. *Scand J Infect Dis* 2011;43(2):122–128.
32. Babic DZ, Zelnikar M, Seme K, *et al.*: Prevalence of antiretroviral drug resistance mutations and HIV-1 non-B subtypes in newly diagnosed drug-naïve patients in Slovenia, 2000–2004. *Virus Res* 2006;118(1–2):156–163.
33. Balode D, Westman M, Kolupajeva T, Rozentale B, and Albert J: Low prevalence of transmitted drug resistance among newly diagnosed HIV-1 patients in Latvia. *J Med Virol* 2010;82(12):2013–2018.
34. Bannister WP, Cozzi-Lepri A, Clotet B, *et al.*: Transmitted drug resistant HIV-1 and association with virologic and CD4 cell count response to combination antiretroviral therapy in the EuroSIDA Study. *J Acquir Immune Defic Syndr* 2008;48(3):324–333.
35. Bartmeyer B, Kuecherer C, Houareau C, *et al.*: Prevalence of transmitted drug resistance and impact of transmitted resistance on treatment success in the German HIV-1 Seroconverter Cohort. *PLoS One* 2010;5(10):e12718.
36. Bezemer D, Jurriaans S, Prins M, *et al.*: Declining trend in transmission of drug-resistant HIV-1 in Amsterdam. *AIDS* 2004;18(11):1571–1577.
37. Biagetti C, Bon I, Vitone F, *et al.*: Prevalence of antiretroviral drug resistance in untreated persons newly diagnosed with HIV-1 infection. *New Microbiol* 2009;32(2):129–134.
38. Bonura F, Tramuto F, Vitale F, Perna AM, Viviano E, and Romano N: Transmission of drug-resistant HIV type 1 strains in HAART-naïve patients: A 5-year retrospective

- study in Sicily, Italy. *AIDS Res Hum Retroviruses* 2010; 26(9):961–965.
39. Booth CL, Garcia-Diaz AM, Youle MS, Johnson MA, Phillips A, and Geretti AM: Prevalence and predictors of antiretroviral drug resistance in newly diagnosed HIV-1 infection. *J Antimicrob Chemother* 2007;59(3): 517–524.
 40. Borroto-Esoda K, Waters JM, Bae AS, *et al.*: Baseline genotype as a predictor of virological failure to emtricitabine or stavudine in combination with didanosine and efavirenz. *AIDS Res Hum Retroviruses* 2007;23(8): 988–995.
 41. Bracciale L, Colafigli M, Zazzi M, *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.
 42. Chaix ML, Descamps D, Harzic M, *et al.*: Stable prevalence of genotypic drug resistance mutations but increase in non-B virus among patients with primary HIV-1 infection in France. *AIDS* 2003;17(18):2635–2643.
 43. Chaix ML, Descamps D, Wirten M, *et al.*: Stable frequency of HIV-1 transmitted drug resistance in patients at the time of primary infection over 1996–2006 in France. *AIDS* 2009;23(6):717–724.
 44. Clevenbergh P, Cua E, Dam E, *et al.*: Prevalence of nonnucleoside reverse transcriptase inhibitor (NNRTI) resistance-associated mutations and polymorphisms in NNRTI-naïve HIV-infected patients. *HIV Clin Trials* 2002; 3(1):36–44.
 45. Correia C: Prevalence of HIV-1 drug resistance mutations in naïve patients in Oporto (Portugal) from 2009 to 2011. European Meeting on HIV and Hepatitis, Barcelona, Spain, 2012.
 46. Cortez J, Pereira-Vaz J, Valente C, and Duque V: Resistance associated mutations in antiretroviral treatment-naïve HIV-1 infected individuals in portuguese centre: A retrospective analysis. *Rev Antivir Ther Infect Dis* 2012; 28(8):944–948.
 47. Corvasce S, Violin M, Romano L, *et al.*: Evidence of differential selection of HIV-1 variants carrying drug-resistant mutations in seroconverters. *Antivir Ther* 2006; 11(3):329–334.
 48. Craig C: Non-nucleoside reverse transcriptase inhibitor (NNRTI) resistance-associated mutations (rams) detection in HIV-infected patients screened for entrance into ongoing clinical studies of Maraviroc and Lersivirine. IHDRW, 2010.
 49. de Mendoza C, Rodriguez C, Colomina J, *et al.*: Resistance to nonnucleoside reverse-transcriptase inhibitors and prevalence of HIV type 1 non-B subtypes are increasing among persons with recent infection in Spain. *Clin Infect Dis* 2005;41(9):1350–1354.
 50. Deroo S, Robert I, Fontaine E, *et al.*: HIV-1 subtypes in Luxembourg, 1983–2000. *AIDS* 2002;16(18):2461–2467.
 51. Descamps D, Chaix ML, Andre P, *et al.*: French national sentinel survey of antiretroviral drug resistance in patients with HIV-1 primary infection and in antiretroviral-naïve chronically infected patients in 2001–2002. *J Acquir Immune Defic Syndr* 2005;38(5):545–552.
 52. Descamps D, Chaix ML, Montes B, *et al.*: Increasing prevalence of transmitted drug resistance mutations and non-B subtype circulation in antiretroviral-naïve chronically HIV-infected patients from 2001 to 2006/2007 in France. *J Antimicrob Chemother* 2010;65(12):2620–2627.
 53. Eiros JM, Blanco R, Labayru C, *et al.*: Prevalence of genotypic resistance in untreated HIV-infected patients. *Rev Esp Quimioter* 2004;17(3):250–256.
 54. Eshleman SH, Husnik M, Hudelson S, *et al.*: Antiretroviral drug resistance, HIV-1 tropism, and HIV-1 subtype among men who have sex with men with recent HIV-1 infection. *AIDS* 2007;21(9):1165–1174.
 55. Falloon J, Ait-Khaled M, Thomas DA, *et al.*: HIV-1 genotype and phenotype correlate with virological response to abacavir, amprenavir and efavirenz in treatment-experienced patients. *AIDS* 2002;16(3):387–396.
 56. Ferrer E, Podzamczek D, Arnedo M, *et al.*: Genotype and phenotype at baseline and at failure in human immunodeficiency virus-infected antiretroviral-naïve patients in a randomized trial comparing zidovudine and lamivudine plus nelfinavir or nevirapine. *J Infect Dis* 2003;187(4): 687–690.
 57. Frentz D: Recent dynamics of transmitted drug resistance in Europe: SPREAD programme 2006–2007. EUDRW, 2011.
 58. Gallego O, Corral A, De Mendoza C, Gonzalez-Lahoz J, and Soriano V: High rate of resistance to antiretroviral drugs among HIV-infected prison inmates. *Med Sci Monit* 2003;9(6):CR217–CR221.
 59. Garcia-Guerrero J, Saiz de la Hoya P, Portilla J, *et al.*: Prevalence of HIV-1 drug resistance mutations among Spanish prison inmates. *Eur J Clin Microbiol Infect Dis* 2006;25(11):695–701.
 60. Goodwin-Fernandez: Prevalence of Antiretroviral Drug Resistance Mutations in Antiretroviral-Naïve HIV-1 Infected Persons in Newark, New Jersey. IDSA, 2011.
 61. Grant RM, Hecht FM, Warmerdam M, *et al.*: Time trends in primary HIV-1 drug resistance among recently infected persons. *JAMA* 2002;288(2):181–188.
 62. Grubb JR, Singhatiraj E, Mondy K, Powderly WG, and Overton ET: Patterns of primary antiretroviral drug resistance in antiretroviral-naïve HIV-1-infected individuals in a midwest university clinic. *AIDS* 2006;20(16):2115–2116.
 63. Hanna GJ, Balaguera HU, Freedberg KA, *et al.*: Drug-selected resistance mutations and non-B subtypes in antiretroviral-naïve adults with established human immunodeficiency virus infection. *J Infect Dis* 2003;188(7): 986–991.
 64. Hightow-Weidman LB, Hurt CB, Phillips G, 2nd, *et al.*: Transmitted HIV-1 drug resistance among young men of color who have sex with men: A multicenter cohort analysis. *J Adolesc Health* 2011;48(1):94–99.
 65. Huang HY, Daar ES, Sax PE, *et al.*: The prevalence of transmitted antiretroviral drug resistance in treatment-naïve patients and factors influencing first-line treatment regimen selection. *HIV Med* 2008;9(5):285–293.
 66. Hurt CB, McCoy SI, Kuruc J, *et al.*: Transmitted antiretroviral drug resistance among acute and recent HIV infections in North Carolina from 1998 to 2007. *Antivir Ther* 2009;14(5):673–678.
 67. Iarikov DE, Irizarry-Acosta M, Martorell C, Hoffman RP, and Skiest DJ: Low prevalence of primary HIV resistance in western Massachusetts. *J Int Assoc Physicians AIDS Care (Chic)* 2010;9(4):227–231.
 68. Ilyenkova V: Transmitted HIV drug resistance (T HIVDR) in treatment naïve patients in Belarus. EUDRW, 2012.
 69. Jain V, Pilcher CD, Deeks SG, and Liegler T: Increasing Prevalence of NNRTI-Associated Drug Resistance Mutations in Patients with Acute/Early HIV in San Francisco.

- Conference on Retroviruses and Opportunistic Infections, 2009. Poster #673.
70. Jayaraman GC, Archibald CP, Kim J, *et al.*: A population-based approach to determine the prevalence of transmitted drug-resistant HIV among recent versus established HIV infections: Results from the Canadian HIV strain and drug resistance surveillance program. *J Acquir Immune Defic Syndr* 2006;42(1):86–90.
 71. Juethner SN, Williamson C, Ristig MB, Tebas P, Seyfried W, and Aberg JA: Nonnucleoside reverse transcriptase inhibitor resistance among antiretroviral-naïve HIV-positive pregnant women. *J Acquir Immune Defic Syndr* 2003;32(2):153–156.
 72. Khan P: Low prevalence of transmitted drug resistance (TDR) in an inner London genito-urinary medicine (GUM) clinic cohort with predominantly heterosexually transmitted, non-B subtype infection. BHIVA, 2009.
 73. Kim D: Prevalence of transmitted antiretroviral drug resistance among newly-diagnosed HIV-1 infected persons, United States, 2007D. CROI, 2010.
 74. Kousiappa I, van de Vijver DA, Demetriades I, and Kostrikis LG: Genetic analysis of HIV type 1 strains from newly infected untreated patients in Cyprus: High genetic diversity and low prevalence of drug resistance. *AIDS Res Hum Retroviruses* 2009;25(1):23–35.
 75. Kuritzkes DR, Lalama CM, Ribaud HJ, *et al.*: Preexisting resistance to nonnucleoside reverse-transcriptase inhibitors predicts virologic failure of an efavirenz-based regimen in treatment-naïve HIV-1-infected subjects. *J Infect Dis* 2008;197(6):867–870.
 76. Lai A, Violin M, Ebranati E, *et al.*: Transmission of resistant HIV type 1 variants and epidemiological chains in Italian newly diagnosed individuals. *AIDS Res Hum Retroviruses* 2012;28(8):857–865.
 77. Lapadula G, Izzo I, Gargiulo F, *et al.*: Updated prevalence of genotypic resistance among HIV-1 positive patients naïve to antiretroviral therapy: A single center analysis. *J Med Virol* 2008;80(5):747–753.
 78. Little S: Prevalence and treatment implications of transmitted drug resistance among subjects with primary HIV infection. IHDRW, 2011.
 79. Magiorkinis E, Paraskevis D, Magiorkinis G, *et al.*: Mutations associated with genotypic resistance to antiretroviral therapy in treatment naïve HIV-1 infected patients in Greece. *Virus Res* 2002;85(1):109–115.
 80. Maljkovic I, Wilbe K, Solver E, Alaeus A, and Leitner T: Limited transmission of drug-resistant HIV type 1 in 100 Swedish newly detected and drug-naïve patients infected with subtypes A, B, C, D, G, U, and CRF01_AE. *AIDS Res Hum Retroviruses* 2003;19(11):989–997.
 81. Masquelier B, Costagliola D, Schmuck A, *et al.*: Prevalence of complete resistance to at least two classes of antiretroviral drugs in treated HIV-1-infected patients: A French nationwide study. *J Med Virol* 2005;76(4):441–446.
 82. Mena I: Prevalence of drug resistance among persons with newly diagnosed HIV infection in Mississippi, United States, 2005–2008. AIDS Conference, 2011.
 83. Monge S: Transmitted drug resistance and subtype distribution in 2007–2010 in the Spanish cohort of antiretroviral naïve adults (CoRIS). EUDRW, 2012.
 84. Nannini EC, Han X, O'Brien WA, and Arduino RC: Genotypic HIV-1 drug resistance testing in antiretroviral-naïve subjects in Houston, Texas. *J Acquir Immune Defic Syndr* 2002;29(3):317–319.
 85. Nathavitharana R: 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. IDSA, 2011.
 86. Novak RM, Chen L, MacArthur RD, *et al.*: Prevalence of antiretroviral drug resistance mutations in chronically HIV-infected, treatment-naïve patients: Implications for routine resistance screening before initiation of antiretroviral therapy. *Clin Infect Dis* 2005;40(3):468–474.
 87. Parker MM, Gordon D, Reilly A, *et al.*: Prevalence of drug-resistant and nonsubtype B HIV strains in antiretroviral-naïve, HIV-infected individuals in New York State. *AIDS Patient Care STDS* 2007;21(9):644–652.
 88. Payne BA, Nsutebu EF, Hunter ER, *et al.*: Low prevalence of transmitted antiretroviral drug resistance in a large UK HIV-1 cohort. *J Antimicrob Chemother* 2008;62(3):464–468.
 89. Prejean J: Prevalence of Mutations Associated with Transmitted Drug-Resistant HIV among BED Recent versus Long-term Infections, 10 U.S. States and 1 County, 2006. CROI, 2010.
 90. Romero A, Sued O, Puig T, *et al.*: Prevalence of transmitted antiretroviral resistance and distribution of HIV-1 subtypes among patients with recent infection in Catalonia (Spain) between 2003 and 2005. *Enferm Infecc Microbiol Clin* 2011;29(7):482–489.
 91. Ross L, Lim ML, Liao Q, *et al.*: Prevalence of antiretroviral drug resistance and resistance-associated mutations in antiretroviral therapy-naïve HIV-infected individuals from 40 United States cities. *HIV Clin Trials* 2007;8(1):1–8.
 92. Sagir A, Oette M, Kaiser R, *et al.*: Trends of prevalence of primary HIV drug resistance in Germany. *J Antimicrob Chemother* 2007;60(4):843–848.
 93. Salama C: Comparison of the prevalence of HIV resistance mutations b/w US and foreign-born naïve chronically infected patients NYC. IHDRW, 2009.
 94. Santoro MM, Ciccozzi M, Alteri C, *et al.*: Characterization of drug-resistance mutations in HIV type 1 isolates from drug-naïve and ARV-treated patients in Bulgaria. *AIDS Res Hum Retroviruses* 2008;24(9):1133–1138.
 95. Shet A and Markowitz M: Transmitted multidrug resistant HIV-1: New and investigational therapeutic approaches. *Curr Opin Investig Drugs* 2006;7(8):709–720.
 96. Skoura L, Metallidis S, Buckton AJ, *et al.*: Molecular and epidemiological characterization of HIV-1 infection networks involving transmitted drug resistance mutations in Northern Greece. *J Antimicrob Chemother* 2011;66(12):2831–2837.
 97. Skoura L: High rates of transmitted drug resistance among newly-diagnosed antiretroviral naïve HIV patients in Northern Greece: Preliminary results. EUDRW, 2012.
 98. Stanczak GP, Stanczak JJ, Marczyńska M, *et al.*: Evolving patterns of HIV-1 transmitted drug resistance in Poland in the years 2000–2008. *J Med Virol* 2010;82(7):1291–1294.
 99. Stekler JD, Ellis GM, Carlsson J, *et al.*: Prevalence and impact of minority variant drug resistance mutations in primary HIV-1 infection. *PLoS One* 2011;6(12):e28952.
 100. Stone DR, Corcoran C, Wurcel A, *et al.*: Antiretroviral drug resistance mutations in antiretroviral-naïve prisoners. *Clin Infect Dis* 2002;35(7):883–886.
 101. Street EJ, Armstrong NR, Monteiro EF, and Hale AD: An audit of baseline HIV-1 genotypic resistance testing in a UK provincial city. *Int J STD AIDS* 2008;19(6):416–417.

102. Sullivan PS, Buskin SE, Turner JH, *et al.*: Low prevalence of antiretroviral resistance among persons recently infected with human immunodeficiency virus in two US cities. *Int J STD AIDS* 2002;13(8):554–558.
103. Torti C, Quiros-Roldon E, Regazzi M, *et al.*: Early virological failure after tenofovir + didanosine + efavirenz combination in HIV-positive patients upon starting antiretroviral therapy. *Antivir Ther* 2005;10(4):505–513.
104. Truong HM, Kellogg TA, McFarland W, *et al.*: Sentinel surveillance of HIV-1 transmitted drug resistance, acute infection and recent infection. *PLoS One* 2011;6(10):e25281.
105. U. K. Collaborative Group on HIV Drug Resistance, Dolling D, Sabin C, *et al.*: Time trends in drug resistant HIV-1 infections in the United Kingdom up to 2009: Multicentre observational study. *BMJ* 2012;345:e5253.
106. U. K. Collaborative Group on HIV Drug Resistance, U. K. Collaborative HIV Cohort Study, U. K. Register of HIV Seroconverters: Evidence of a decline in transmitted HIV-1 drug resistance in the United Kingdom. *AIDS* 2007;21(8):1035–1039.
107. Vercauteren J, Wensing AM, van de Vijver DA, *et al.*: Transmission of drug-resistant HIV-1 is stabilizing in Europe. *J Infect Dis* 2009;200(10):1503–1508.
108. Vibhakkar S: Prevalence of transmitted drug resistance and AIDS diagnosis at baseline among adolescents and young adults presenting to an urban clinic. *IAS*, 2009.
109. Violin M, Forbici F, Cozzi-Lepri A, *et al.*: Primary HIV-1 resistance in recently and chronically infected individuals of the Italian Cohort Naive for Antiretrovirals. *J Biol Regul Homeost Agents* 2002;16(1):37–43.
110. Violin M, Velleca R, Cozzi-Lepri A, *et al.*: Prevalence of HIV-1 primary drug resistance in seroconverters of the ICoNA cohort over the period 1996–2001. *J Acquir Immune Defic Syndr* 2004;36(2):761–764.
111. Weinstock HS, Zaidi I, Heneine W, *et al.*: The epidemiology of antiretroviral drug resistance among drug-naïve HIV-1-infected persons in 10 US cities. *J Infect Dis* 2004;189(12):2174–2180.
112. Wensing AM, van de Vijver DA, Angarano G, *et al.*: Prevalence of drug-resistant HIV-1 variants in untreated individuals in Europe: Implications for clinical management. *J Infect Dis* 2005;192(6):958–966.
113. Yang W: 15-Year Prevalence Data of Transmitted Drug Resistance Shows a Positive Association with Mean Population Viral Load of Treatment-Failing Patients from the Previous Year. Paper presented at the Conference on Retroviruses and Opportunistic Infections, 2012.
114. Yanik E: Differences in prevalence of transmitted drug resistance mutations between acutely and chronically HIV-infected, antiretroviral-naïve patients. *IHDRW*, 2011.
115. Yebra G, de Mulder M, Perez-Elias MJ, *et al.*: Increase of transmitted drug resistance among HIV-infected sub-Saharan Africans residing in Spain in contrast to the native population. *PLoS One* 2011;6(10):e26757.
116. Yerly S, von Wyl V, Ledergerber B, *et al.*: Transmission of HIV-1 drug resistance in Switzerland: A 10-year molecular epidemiology survey. *AIDS* 2007;21(16):2223–2229.
117. Yerly S, Junier T, Gayet-Ageron A, *et al.*: The impact of transmission clusters on primary drug resistance in newly diagnosed HIV-1 infection. *AIDS* 2009;23(11):1415–1423.
118. Youmans E, Tripathi A, Albrecht H, Gibson JJ, and Duffus WA: Transmitted antiretroviral drug resistance in individuals with newly diagnosed HIV infection: South Carolina 2005–2009. *South Med J* 2011;104(2):95–101.
119. Charpentier C, Roquebert B, Colin C, *et al.*: Resistance analyses in highly experienced patients failing raltegravir, efavirenz and darunavir/ritonavir regimen. *AIDS* 2010;24(17):2651–2656.
120. Pereira-Vaz J, Duque V, Pereira B, *et al.*: Prevalence of efavirenz resistance associated mutations in HIV-1 strains isolated from infected individuals failing efavirenz: Comparison between subtype B and non-B genetic variants. *J Med Virol* 2012;84(4):551–554.
121. Poveda E, Anta L, Blanco JL, *et al.*: Efavirenz resistance associated mutations in HIV-infected patients failing efavirenz or nevirapine in the Spanish antiretroviral resistance database. *AIDS* 2010;24(3):469–471.
122. Rusconi S: Prevalence of efavirenz (ETR)-RAMs at NNRTI failure and predictors of resistance to ETR in a large Italian resistance database (ARCA). *EUDRW*, 2011.
123. Ait-Khaled M, Rakik A, Griffin P, *et al.*: HIV-1 reverse transcriptase and protease resistance mutations selected during 16–72 weeks of therapy in isolates from antiretroviral therapy-experienced patients receiving abacavir/efavirenz/amprenavir in the CNA2007 study. *Antivir Ther* 2003;8(2):111–120.
124. Antinori A, Zaccarelli M, Cingolani A, *et al.*: Cross-resistance among nonnucleoside reverse transcriptase inhibitors limits recycling efavirenz after nevirapine failure. *AIDS Res Hum Retroviruses* 2002;18(12):835–838.
125. Bannister WP, Ruiz L, Cozzi-Lepri A, *et al.*: Comparison of genotypic resistance profiles and virological response between patients starting nevirapine and efavirenz in EuroSIDA. *AIDS* 2008;22(3):367–376.
126. Cohen CJ, Berger DS, Blick G, *et al.*: Efficacy and safety of efavirenz (TMC125) in treatment-experienced HIV-1-infected patients: 48-week results of a phase IIb trial. *AIDS* 2009;23(3):423–426.
127. Ochoa de Echaguen A, Arnedo M, Xercavins M, *et al.*: Genotypic and phenotypic resistance patterns at virological failure in a simplification trial with nevirapine, efavirenz or abacavir. *AIDS* 2005;19(13):1385–1391.
128. Di Vincenzo P, Rusconi S, Adorni F, *et al.*: Prevalence of mutations and determinants of genotypic resistance to efavirenz (TMC125) in a large Italian resistance database (ARCA). *HIV Med* 2010;11(8):530–534.
129. Gonzalez de Requena D, Gallego O, Corral A, Jimenez-Nacher I, and Soriano V: Higher efavirenz concentrations determine the response to viruses carrying non-nucleoside reverse transcriptase resistance mutations. *AIDS* 2004;18(15):2091–2094.
130. Margot NA, Isaacson E, McGowan I, Cheng AK, Schooley RT, and Miller MD: Genotypic and phenotypic analyses of HIV-1 in antiretroviral-experienced patients treated with tenofovir DF. *AIDS* 2002;16(9):1227–1235.
131. Vallejo A, Olivera M, Rubio A, Sanchez-Quijano A, Lissen E, and Leal M: Genotypic resistance profile in treatment-experienced HIV-infected individuals after abacavir and efavirenz salvage regimen. *Antiviral Res* 2004;61(2):129–132.
132. Aldous J: Decreasing Prevalence of Drug Resistance Mutations over a 7-Year Period in the CFAR Network of Integrated Clinical Systems. Conference on Retroviruses and Opportunistic Infections, 2010: 585.
133. Assoumou L: Prevalence of HIV-1 resistance in treated patients with viral load > 50 copies/ml in 2009: A French

- nationwide study. International Workshop on HIV & Hepatitis Virus Drug Resistance and Curative Strategies, 2010: A185.
134. Bangsberg DR, Acosta EP, Gupta R, *et al.*: Adherence-resistance relationships for protease and non-nucleoside reverse transcriptase inhibitors explained by virological fitness. *AIDS* 2006;20(2):223–231.
 135. Bannister WP, Cozzi-Lepri A, Kjaer J, *et al.*: Estimating prevalence of accumulated HIV-1 drug resistance in a cohort of patients on antiretroviral therapy. *J Antimicrob Chemother* 2011;66(4):901–911.
 136. Campo RE, Lichtenberger PN, Rosa I, *et al.*: Differences in the frequency of resistance to antiretroviral drug classes among human immunodeficiency virus type 1 clinical isolates. *J Clin Microbiol* 2003;41(7):3376–3378.
 137. de Mendoza C, Rodriguez C, Corral A, del Romero J, Gallego O, and Soriano V: Evidence for differences in the sexual transmission efficiency of HIV strains with distinct drug resistance genotypes. *Clin Infect Dis* 2004;39(8):1231–1238.
 138. de Mendoza C, Garrido C, Corral A, *et al.*: Changing rates and patterns of drug resistance mutations in antiretroviral-experienced HIV-infected patients. *AIDS Res Hum Retroviruses* 2007;23(7):879–885.
 139. Di Giambenedetto S, Zazzi M, Corsi P, *et al.*: Evolution and predictors of HIV type-1 drug resistance in patients failing combination antiretroviral therapy in Italy. *Antivir Ther* 2009;14(3):359–369.
 140. Duong M, Buisson M, Peytavin G, *et al.*: Low trough plasma concentrations of nevirapine associated with virologic rebounds in HIV-infected patients who switched from protease inhibitors. *Ann Pharmacother* 2005;39(4):603–609.
 141. Gange SJ, Schneider MF, Grant RM, *et al.*: Genotypic resistance and immunologic outcomes among HIV-1-infected women with viral failure. *J Acquir Immune Defic Syndr* 2006;41(1):68–74.
 142. Gardner EM, Hullsiek KH, Telzak EE, *et al.*: Antiretroviral medication adherence and class-specific resistance in a large prospective clinical trial. *AIDS* 2010;24(3):395–403.
 143. Lapadula G, Calabresi A, Castelnovo F, *et al.*: Prevalence and risk factors for efavirine resistance among patients failing on non-nucleoside reverse transcriptase inhibitors. *Antivir Ther* 2008;13(4):601–605.
 144. Pauskar M: Drug resistance mutations in HIV-1 CRF06_cpx viruses from anti-retroviral-treated patients in Estonia. ESCMID, 2011.
 145. Rodes B, Garcia F, Gutierrez C, *et al.*: Impact of drug resistance genotypes on CD4+ counts and plasma viremia in heavily antiretroviral-experienced HIV-infected patients. *J Med Virol* 2005;77(1):23–28.
 146. Santoro MM, Svicher V, Gori C, *et al.*: Temporal characterization of drug resistance associated mutations in HIV-1 protease and reverse transcriptase in patients failing antiretroviral therapy. *New Microbiol* 2006;29(2):89–100.
 147. Scott P, Arnold E, Evans B, *et al.*: Surveillance of HIV antiretroviral drug resistance in treated individuals in England: 1998–2000. *J Antimicrob Chemother* 2004;53(3):469–473.
 148. Tam LW, Chui CK, Brumme CJ, *et al.*: The relationship between resistance and adherence in drug-naïve individuals initiating HAART is specific to individual drug classes. *J Acquir Immune Defic Syndr* 2008;49(3):266–271.
 149. Tamalet C, Fantini J, Tourres C, and Yahi N: Resistance of HIV-1 to multiple antiretroviral drugs in France: A 6-year survey (1997–2002) based on an analysis of over 7000 genotypes. *AIDS* 2003;17(16):2383–2388.
 150. von Wyl V, Yerly S, Burgisser P, *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.
 151. Margot NA, Enejosa J, Cheng AK, Miller MD, McColl DJ, and Study T: Development of HIV-1 drug resistance through 144 weeks in antiretroviral-naïve subjects on emtricitabine, tenofovir disoproxil fumarate, and efavirenz compared with lamivudine/zidovudine and efavirenz in study GS-01-934. *J Acquir Immune Defic Syndr* 2009;52(2):209–221.
 152. Pozniak AL, Morales-Ramirez J, Katabira E, *et al.*: Efficacy and safety of TMC278 in antiretroviral-naïve HIV-1 patients: Week 96 results of a phase IIb randomized trial. *AIDS* 2010;24(1):55–65.
 153. Roge BT, Barford TS, Kirk O, *et al.*: Resistance profiles and adherence at primary virological failure in three different highly active antiretroviral therapy regimens: Analysis of failure rates in a randomized study. *HIV Med* 2004;5(5):344–351.
 154. van den Berg-Wolf M, Hullsiek KH, Peng G, *et al.*: Virologic, immunologic, clinical, safety, and resistance outcomes from a long-term comparison of efavirenz-based versus nevirapine-based antiretroviral regimens as initial therapy in HIV-1-infected persons. *HIV Clin Trials* 2008;9(5):324–336.
 155. Langmann P, Weissbrich B, Desch S, *et al.*: Efavirenz plasma levels for the prediction of treatment failure in heavily pretreated HIV-1 infected patients. *Eur J Med Res* 2002;7(7):309–314.
 156. Arasteh K, Rieger A, Yeni P, *et al.*: Short-term randomized proof-of-principle trial of TMC278 in patients with HIV type-1 who have previously failed antiretroviral therapy. *Antivir Ther* 2009;14(5):713–722.
 157. Dunn DT, Green H, Loveday C, *et al.*: A randomized controlled trial of the value of phenotypic testing in addition to genotypic testing for HIV drug resistance: Evaluation of resistance assays (ERA) trial investigators. *J Acquir Immune Defic Syndr* 2005;38(5):553–559.
 158. Craig C: 48-Week Results from the Phase 3 Study A4001026 (MERIT) –“Time to Loss of Virologic Response” Virology Analysis of Failures in the Enhanced Trofile™-Censored Subpopulation. XVIII International HIV Drug Resistance Workshop: Basic Principles and Clinical Implications, 2009.
 159. DeJesus E, Herrera G, Teofilo E, *et al.*: Abacavir versus zidovudine combined with lamivudine and efavirenz, for the treatment of antiretroviral-naïve HIV-infected adults. *Clin Infect Dis* 2004;39(7):1038–1046.
 160. Gallant JE, DeJesus E, Arribas JR, *et al.*: Tenofovir DF, emtricitabine, and efavirenz vs. zidovudine, lamivudine, and efavirenz for HIV. *N Engl J Med* 2006;354(3):251–260.
 161. Orkin C: Pooled week 96 efficacy, resistance and safety results from the double-blind, randomised, Phase III trials comparing rilpivirine (RPV, TMC278) versus efavirenz (EFV) in treatment-naïve, HIV-1 infected adults. BHIVA, 2012.
 162. White K: Week 96 resistance analysis of the pooled ECHO and THRIVE Truvada subset in treatment-naïve

- HIV-infected adults with = <100,000 c/ml baseline viral load. BHIVA, 2012.
163. Gallant JE, Staszewski S, Pozniak AL, *et al.*: Efficacy and safety of tenofovir DF vs. stavudine in combination therapy in antiretroviral-naïve patients: A 3-year randomized trial. *JAMA* 2004;292(2):191–201.
 164. Riddler SA, Haubrich R, DiRienzo AG, *et al.*: Class-sparing regimens for initial treatment of HIV-1 infection. *N Engl J Med* 2008;358(20):2095–2106.
 165. Rimsky L, Vingerhoets J, Van Eygen V, *et al.*: Genotypic and phenotypic characterization of HIV-1 isolates obtained from patients on rilpivirine therapy experiencing virologic failure in the phase 3 ECHO and THRIVE studies: 48-week analysis. *J Acquir Immune Defic Syndr* 2012;59(1):39–46.
 166. Rimsky L: Similar prevalence of baseline HIV-1 minority variants among responders and virologic failures, as well as increased detection of HIV-1 minority variants at treatment failure, in rilpivirine patients from the ECHO and THRIVE Phase III studies. *AIDS* 2013;27(6):939–950.
 167. Brenner BG, Roger M, Moisi DD, *et al.*: Transmission networks of drug resistance acquired in primary/early stage HIV infection. *AIDS* 2008;22(18):2509–2515.
 168. Bennett DE, Camacho RJ, Otelea D, *et al.*: Drug resistance mutations for surveillance of transmitted HIV-1 drug-resistance: 2009 update. *PLoS One* 2009;4(3):e4724.
 169. Kagan R, Winters M, Merigan T, and Heseltine P: HIV type 1 genotypic resistance in a clinical database correlates with antiretroviral utilization. *AIDS Res Hum Retroviruses* 2004;20(1):1–9.
 170. Snedecor SJ, Khachatryan A, Nedrow K, *et al.*: The prevalence of transmitted resistance to first-generation non-nucleoside reverse transcriptase inhibitors and its potential economic impact in HIV-infected patients. *PLoS One* 2013;8(8):e72784.
 171. Booth CL and Geretti AM: Prevalence and determinants of transmitted antiretroviral drug resistance in HIV-1 infection. *J Antimicrob Chemother* 2007;59(6):1047–1056.
 172. Skoura L, Metallidis S, Pilalas D, *et al.*: High rates of transmitted drug resistance among newly-diagnosed antiretroviral naïve HIV patients in Northern Greece, data from 2009–2011. *Clin Microbiol Infect* 2013;19(3):E169–172.
 173. Picchio G, Vingerhoets J, and Staes M: Prevalence of TMC125 Resistance-associated Mutations in a Large Panel of Clinical Isolates. 15th Conference on Retroviruses and Opportunistic Infections, 2008.
 174. Marcelin AG, Flandre P, Descamps D, *et al.*: Factors associated with virological response to etravirine in non-nucleoside reverse transcriptase inhibitor-experienced HIV-1-infected patients. *Antimicrob Agents Chemother* 2010;54(1):72–77.
 175. De Luca A, Dunn D, Zazzi M, *et al.*: Declining prevalence of HIV-1 drug resistance in antiretroviral treatment-exposed individuals in Western Europe. *J Infect Dis* 2013; 207(8):1216–1220.
 176. Gupta R, Hill A, Sawyer AW, and Pillay D: Emergence of drug resistance in HIV type 1-infected patients after receipt of first-line highly active antiretroviral therapy: A systematic review of clinical trials. *Clin Infect Dis* 2008; 47(5):712–722.
 177. Yang WL: 15-Year Prevalence Data of Transmitted Drug Resistance Shows a Positive Association with Mean Population Viral Load of Treatment-Failing Patients from the Previous Year. Conference on Retroviruses and Opportunistic Infections, 2012. Abstract 735.
 178. Hurt CB, McCoy SI, Kuruc J, *et al.*: Transmitted antiretroviral drug resistance among acute and recent HIV infections in North Carolina from 1998 to 2007. *Antivir Ther* 2009;14(5):673–678.

Address correspondence to:

Sonya J. Snedecor

Pharmerit International

4350 East West Highway, Suite 430

Bethesda, Maryland 20814

E-mail: ssnedecor@pharmerit.com