EDITORIAL COMMENTARY

Assessments of HIV Drug Resistance Mutations in Resource-Limited Settings

Michael R. Jordan[1,2,3]

[1]Department of HIV/AIDS, World Health Organization, Geneva, Switzerland; [2]Division of Infectious Disease and Geographic Medicine, and [3]Department of Public Health and Community Medicine, Tufts University School of Medicine, Boston, Massachusetts

(See the brief report by Sungkanuparph et al, on pages 1053–1057.)

At the end of 2009, 5.25 million persons were receiving antiretroviral therapy (ART) worldwide, representing an ~10-fold increase over a period of 5 years [1]. The global scale-up of ART has led to an inevitable increase in HIV drug resistance (HIVDR) and a pool of resistant virus available to establish new infections. The report by Sungkanuparph et al in this issue highlights the need for strengthened national, regional, and global surveillance of HIVDR for the purpose of informing public health policy [2]. Because >739,000 persons are receiving ART in East, South, and Southeast Asia [3], the paucity of data on emergence of HIVDR in populations taking ART in this region is striking.

Broadly, there are 3 categories of HIVDR. Acquired HIVDR occurs when resistance mutations are selected for by drug selective pressure in individuals receiving ART. In individuals receiving ART, acquired HIVDR may emerge because of suboptimal adherence, treatment interruptions, inadequate plasma drug concentrations, or the use of suboptimal drug or drug combinations. Transmitted HIVDR occurs when previously uninfected individuals are infected with drug-resistant virus. The term "transmitted HIVDR" is appropriately applied only to HIVDR detected in recently infected individuals. The third category is HIVDR detected in individuals with chronic infection in which drug resistance can be either transmitted or acquired. This last category is important because it is the focus of the analysis presented by Sungkanuparph et al.

Transmitted HIVDR may persist for many months or years in the absence of drug selective pressure (ie, in individuals naive to ART), although duration varies by mutation. For example, the reverse transcriptase (RT) mutation M184V, which confers resistance to the nucleoside reverse-transcriptase inhibitors (NRTI) lamivudine and emtricitabine, reduces viral fitness, whereas the K103N and Y181C mutations that cause resistance to the nonnucleoside reverse transcriptase inhibitors (NNRTIs) nevirapine (NVP) and efavirenz (EFV) have little impact on viral fitness [4]. In an individual infected with a virus with drug resistance mutations that only modestly reduce fitness, most but not all mutant species are likely to persist over long periods. Specifically, M41L, T69N, K103N, and some T215 variants show little tendency to revert to wild-type over time. However, it is theoretically possible that some transmitted drug-resistant HIV strains may have reverted to wild-type before genotypic assessment [5–7] or have decreased to levels below the threshold of detection by population-based sequencing, persisting as minority variants or archived resistance in proviral DNA [8]. Sungkanuparph et al rightly indicate that this may result in an underestimation of transmitted resistance in chronically infected patients. However, some HIVDR detected in chronically infected patients may be acquired because of previous ART exposure not elicited at the time of testing because of social desirability bias, desire of individuals to participate in a particular study, or interviewer bias. Nonetheless, there is value in surveying HIVDR in populations starting ART in settings where transmitted drug resistance is known to occur at high levels, and results provide data about the likely efficacy of currently available regimens in patients starting ART.

An important consideration in determining the prevalence of HIVDR is the method used to classify mutations. When assessing transmitted HIVDR, the

Received 17 January 2011; accepted 25 January 2011.
Correspondence: Michael Jordan, MD, MPH, Division of Geographic Medicine and Infectious Disease, Tufts Medical Center, 800 Washington St, Box 41, Boston, MA 02111 (mjordan@tuftsmedicalcenter.org).

Clinical Infectious Diseases 2011;52(8):1058–1060

1058-4838/2011/528-0017$14.00
DOI: 10.1093/cid/cir093

World Health Organization recommends use of the World Health Organization surveillance drug resistance mutations list [9]. Mutations included on this list are recognized as (1) causing or contributing to HIVDR, (2) nonpolymorphic, (3) subtype independent, and (4) emerging under drug selective pressure. Surveys of transmitted resistance using this list may be compared over time and between regions. When assessing acquired HIVDR or HIVDR in chronically infected patients, clinical-based algorithms, such as the Stanford HIV Drug Resistance database [10, 11], which considers the contribution of polymorphisms and mutation combination to overall drug susceptibility, or the International AIDS Society (IAS)–USA HIV mutations list, are used [12].

Sungkanuparph et al assessed HIVDR in 682 patients with chronic HIV infection (median CD4 cell count, 100 cells/mm^3) who started ART at 8 sites in Hong Kong, Malaysia, and Thailand and reported a 13.8% prevalence among patients of $\geqslant$1 HIVDR mutation. The report is a baseline analysis of a study designed to assess individual patient and ART clinical factors associated with viral suppression 12 and 24 months after initiation of ART. In this analysis, the authors used the IAS-USA 2008 mutations list [12] and reported no association between HIVDR and patient age, sex, location, ethnicity, risk exposure, HIV-1 subtype, hepatitis B or C coinfection, and HIV load. Of interest, the median CD4 cell count was observed to be lower in patients with HIVDR than in patients without it (66 cells/mm^{3}vs 108; $P = .009$). The authors are correct to assert that patients may have been infected with a drug-resistant strain during an earlier era when mono- or dual therapy was being used in Asia. However, because the population studied had advanced disease, it raises the possibility of previous undisclosed exposures to ART, including prevention of mother to child transmission, resulting in acquired HIVDR, which makes interpretation and development of subsequent public health recommendations challenging.

A total of 8.4% of patients were reported to have NRTI resistance. The most frequently observed mutation, K70R (7.6%), confers resistance to zidovudine and potential low-level resistance to stavudine. T69S, present in .7% of specimens, is selected by NRTIs, but its effect on NRTI susceptibility is unknown. Although the overall reported prevalence of NNRTI resistance was 6.5%, it is reassuring that only 4 patients (0.6%) had HIVDR to EFV and NVP, because they are the NNRTIs used in the region's first-line regimens. V108I, associated with low-level resistance to all NNRTIs except etravirine (ETR), was observed in only 0.1% and A98G, associated with NVP and delavirdine resistance in only .1%. The surprisingly high prevalence of reported NNRTI resistance was driven by the inclusion of the naturally occurring polymorphism conferring potential low level resistance to all NNRTIs (V179D; 3.2%) and by the inclusion of the polymorphic V90I (0.7%), A98G (0.1%), and V106I (1.9%), which were associated with ETR response in the DUET studies designed to evaluate ETV efficacy [13] but have little effect on ETR susceptibility. Because ETR is not widely used in the region, it is unlikely that these mutations had been selected for therapy. Furthermore, because the population is susceptible to EFV, NVP, and protease inhibitors, potential low-level ETR resistance is unlikely to be of significant public health importance. Nevertheless, documentation of polymorphisms associated with decreased response to ETV before the start of ART is important in light of recent studies demonstrating association between HIV-1 CR01_AE, the predominant HIV-1 subtype reported in this cohort, and ETV cross-resistance in patients experiencing NVP and EFV treatment failure [14]. As expected, protease inhibitor resistance was low, detected in only .1% of patients.

On the basis of previous reports classifying transmitted drug-resistant HIV at $<$5% in Vietnam and Thailand, the authors concluded that HIVDR is increasing in the region. However, it is important to clarify that the surveys referred to by Sungkanuparph et al that were performed in Hanoi, Vietnam, and Bangkok, Thailand, classified transmitted resistance in very specific populations of recently infected individuals in a defined geographical region with use of the World Health Organization surveillance drug resistance mutations list, which excludes naturally occurring polymorphisms [9, 11, 15, 16]. These surveys use very different methods, and therefore their use as a baseline comparator of HIVDR may be misleading. Although it may be difficult to infer an increase of HIVDR in the region based on their findings, the findings by Sungkanuparph et al are important and highlight the need for continued vigilance and routine surveillance of HIVDR at the population level in the region.

Sungkanuparph et al suggest the need for individual HIVDR testing before initiation of ART in the region. However, this study with patients drawn from 8 sites in 3 countries documents low levels of HIVDR to the major components of first-line ART regimens; thus, the results do not support a recommendation for individual patient drug resistance testing. The article by Sungkanuparph et al suggests that the currently available standard first-line regimens used in the region are likely to be effective and durable at the population level. Of importance, in most if not all resource-limited settings, HIVDR testing is neither routinely available nor recommended for individual patient management. Genotyping is expensive and complex; moreover, the limited availability of alternate regimens permits little change based on genotyping results.

Although, in the future, HIVDR testing may become more accessible as technology gaps are reduced and lower cost tests and point-of-care assays, new specimen technologies, and point mutation assays become available, we have a collective responsibility to use available resources wisely to maximize treatment optimization and minimize HIVDR.

The lack of accessible individual HIVDR testing need never limit optimization of patient care and global efforts to minimize HIVDR. Care may be optimized and HIVDR minimized through the strengthening of health care systems informed by robust programmatic evaluation of factors known to be associated with the emergence of HIVDR and by routine, standardized, population-based surveillance of transmitted and acquired HIVDR. Focusing available resources on optimizing retention of patients in care (both those receiving ART and pre-ART), supporting adherence to therapy, minimizing toxicities by improved pharmacovigilance, and ensuring a continuous supply of quality assured drugs are critical to the success of global ART scale-up. Failure to proactively identify and address programmatic challenges associated with HIVDR is likely to lead to inadequate response of available first- and second-line regimens. As ART continues to be scaled-up rapidly, it is a global imperative that programmatic assessment informed by routine surveillance of transmitted and acquired HIVDR be performed to best inform national, regional, and global ART policy. Greater funding and infrastructure are urgently needed to support ongoing routine surveillance of HIVDR and increased efforts in supporting national and regional ART programs in optimizing care and treatment of HIV infected patients, which has the added value of minimizing HIVDR.

Acknowledgments

The author alone is responsible for the views expressed in this publication and they do not necessarily represent the decision or stated policy of the World Health Organization.

Potential conflicts of interest. Author certifies no potential conflicts of interest.

References

1. WHO. Towards universal access. scaling up priority HIV/AIDS interventions in the health sector. Progress report 2010. Geneva, **2010.**
2. Sungkanuparph S, Oyomopito R, Sirivichayakul S, et al. HIV-1 Drug Resistance Mutations among Antiretroviral-naÿve HIV-1-infected Patients in Asia: Results from the TREAT Asia Studies to Evaluate Resistance-Monitoring Study (TASER-M). Clin infect Dis. **2011**; 52:1046–50.
3. WHO. Towards universal access: scaling up priority HIV/AIDS interventions in the health sector. Progress report 2010. (WHO, UNICEF, UNAIDS). Geneva, **2010**:53.
4. Nicastri E, Sarmati L, d'Ettorre G, et al. Replication capacity, biological phenotype, and drug resistance of HIV strains isolated from patients failing antiretroviral therapy. J Med Virol **2003**; 69:1–6.
5. Pao D, Andrady U, Clarke J, et al. Long-term persistence of primary genotypic resistance after HIV-1 seroconversion. J Acquir Immune Defic Syndr **2004**; 37:1570–3.
6. Little SJ, Frost SD, Wong JK, et al. Persistence of transmitted drug resistance among subjects with primary human immunodeficiency virus infection. J Virol **2008**; 82:5510–8.
7. Johnson JA, Li JF, Wei X, 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:e158.
8. Palmer S, Boltz V, Maldarelli F, et al. Selection and persistence of non-nucleoside reverse transcriptase inhibitor-resistant HIV-1 in patients starting and stopping non-nucleoside therapy. AIDS **2006**; 20:701–10.
9. 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:e4724 Epub 2009 Mar 6.
10. Rhee S-Y, Gonzales MJ, Kantor R, Betts BJ, Ravela J, Shafer RW. Human immunodeficiency virus reverse transcriptase and protease sequence database. Nucleic Acids Res **2003**; 31:298–303.
11. Shafer RW. Rationale and uses of a public HIV drug-resistance database. J Infect Dis **2006**; 194(Suppl 1):S51–8.
12. Johnson VA, Brun-Vezinet F, Clotet B, et al. Update drug resist mutations HIV-1. Top HIV Med **2008**; 16:138–45.
13. Tambuyzer L, Vingerhoets J, Azijn H, et al. Characterization of genotypic and phenotypic changes in HIV-1-infected patients with virologic failure on an etravirine-containing regimen in the DUET-1 and DUET-2 clinical studies. AIDS Res Hum Retroviruses **2010**; 26:1197–205 Epub 2010 Sep 20.
14. Manosuthi W, Butler DM, Chantratita W, Sukasem C, Richman DD, Smith DM. Patients infected with HIV type 1 subtype CRF01_AE and failing first-line nevirapine- and efavirenz-based regimens demonstrate considerable cross-resistance to etravirine. AIDS Res Hum Retroviruses **2010**; 26:609–11.
15. Nguyen HT, Duc NB, Shrivastava R, et al. HIV drug resistance threshold survey using specimens from voluntary counselling and testing sites in Hanoi, Vietnam. Antivir Ther **2008**; 13(Suppl 2):115–21.
16. Sirivichayakul S, Phanuphak P, Pankam T, O-Charoen R, Sutherland D, Ruxrungtham K. HIV drug resistance transmission threshold survey in Bangkok, Thailand. Antivir Ther **2008**; 13(Suppl 2):109–13.