Published in final edited form as:

Infect Disord Drug Targets. 2011 April 1; 11(2): 124–133.

The Global Status of HIV Drug Resistance: Clinical and Public-Health Approaches for Detection, Treatment and Prevention

Steven Y. Hong, MD, MPH^{*,1,2}, Jean B. Nachega, MD, PhD^{3,4}, Karen Kelley, MPH⁵, Silvia Bertagnolio, MD⁵, Vincent C. Marconi, MD⁶, and Michael R. Jordan, MD, MPH⁵

¹Tufts University School of Medicine, Boston, USA ²Division of Geographic Medicine and Infectious Diseases, Tufts Medical Center, Boston, USA ³Department of International Health and Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland, USA ⁴Centre for Infectious Diseases, Stellenbosch University, Cape Town, South Africa ⁵World Health Organization, Geneva, Switzerland ⁶Emory University School of Medicine, Atlanta, GA, USA

Abstract

Antiretroviral therapy (ART) scale-up in resource limited settings (RLS) has been successful, utilizing a standardized population-based approach to ART delivery. An unintended consequence of treatment scale-up is the inevitable emergence of HIV drug resistance (HIVDR) in populations even when patient adherence to ART is optimally supported. HIVDR has the potential to undermine the dramatic gains that ART has had in reducing the morbidity and mortality of HIV-infected patients in RLS. Sustaining and expanding ART coverage in RLS will depend upon the ability of ART programs to deliver ART in a way that minimizes the emergence of HIVDR. Fortunately, current evidence demonstrates that HIVDR in RLS has neither emerged nor been transmitted to the degree that had initially been feared. However, due to a lack of standardized methodologies, HIVDR data from RLS can be difficult to interpret and may not provide the programmatic evidence necessary for public health action. The World Health Organization has developed simple, standardized surveys that generate comparable results to assess acquired and transmitted HIVDR for routine public health implementation in RLS. These HIVDR surveys are designed to be implemented in conjunction with annual monitoring of program and site factors known to be associated with the emergence of HIVDR.

Keywords

HIV; antiretroviral therapy; drug resistance; adherence; epidemiology

A. INTRODUCTION

As of December 2009, approximately 5.25 million adults and children were estimated to be receiving antiretroviral therapy (ART) globally, representing an increase of approximately 1 million patients on therapy compared to the previous year. [1] The rapid scale-up of ART programs has been made possible by the availability of inexpensive, generic, fixed-dose ART combinations in the early 2000's, the creation of the Global Fund to fight AIDS, Tuberculosis and Malaria, the initiation by the United States of the President's Emergency Plan for AIDS Relief (PEPFAR), the 3 by 5 Initiative implemented by the World Health

*Corresponding Author: Steven Y. Hong MD, MPH, Division of Geographic Medicine and Infectious Diseases, Tufts Medical Center, Tufts University School of Medicine, 150 Harrison Avenue, Jaharis 2, Boston, MA 02111, USA, Telephone: 917-951-2488, Fax: 617-636-1580, shong@tuftsmedicalcenter.org.

Organization (WHO) and the Joint United Nations Programme on HIV/AIDS (UNAIDS), and other private donors. ART scale-up has been made possible because of a standardized population-based approach to ART delivery [1,2] involving the use of standardized and simplified ART regimens that are consistent with international standards and appropriate to local circumstances [1,3]. This approach allows for healthcare workers with basic training to administer HIV/AIDS care to large numbers of patients using minimal resources. In most of the ART sites in low- and middle-income countries, only one first-line ART regimen is available such as two nucleoside reverse transcriptase inhibitors (NRTI) combined with a non-nucleoside reverse transcriptase inhibitor (NNRTI) (e.g. zidovudine or tenofovir + lamivudine (or FTC) + efavirenz or nevirapine). While second-line ART regimens consisting of 2 NRTIs with a ritonavir-boosted protease inhibitor (PI) (e.g. tenofovir + lamivudine (or FTC) or abacavir + didanosine or zidovudine + lamivudine (or FTC) + lopinavir/ritonavir) are available in most low- and middle-income countries, they are not readily accessible in most of the ART treatment sites in these countries [4–6].

Sustaining scale-up of ART in resource-limited settings (RLS) will depend largely upon the ability of ART programs to deliver ART in a way that minimizes treatment interruptions through drug continuity and support for patient adherence, thereby maximizing durability of first- and second-line regimens. Adherence to ART is a predictor of virological suppression [7–12], emergence of HIV drug resistance (HIVDR) [13,14], disease progression [15], and death [16–18]. Fortunately, some of the highest levels of patient adherence have been reported from sub-Saharan Africa, and data have shown that adherence in developing countries is often equal to or higher than that in developed countries [19–22].

Scale-up of ART in RLS will inevitably be accompanied by emergence of some HIVDR, as has been observed in countries where ART has been available for many years [23]. Rapid or uncontrolled emergence of HIVDR is a feared consequence of ART scale-up, which could lead to failure of ART programs and of HIV prevention programs that are based on pre- or post-exposure prophylaxis or ART-based topical microbicides [24]. Thus, the worldwide effort to improve treatment outcomes and reduce HIV transmission through optimal delivery of ART and HIV prevention programs must be coordinated with and enlightened by ongoing national, regional, and global evaluations of HIVDR. HIVDR can be acquired or transmitted. Acquired HIVDR occurs when mutations develop to drugs in individuals who have received ARVs, often because of poor adherence, treatment interruptions, inadequate drug concentrations, or use of sub-optimal drug combinations. The transmission of drug-resistant HIV may occur when previously uninfected individuals become infected with a drug-resistant virus.

The development of resistance to NNRTIs, the backbone of first-line regimens in RLS [1], is associated with unplanned treatment interruptions of ≥ 48 hours [25–26]. Treatment interruptions in RLS may largely be due to financial difficulty in securing ARVs and drug stock-outs, rather than suboptimal adherence at an individual patient level. Studies have documented drug stock outs [26–28] and lack of access to medication [29] as reasons for missed ARV doses in RLS. These data have important implications for addressing HIVDR in RLS. To minimize emergence of HIVDR in RLS, emphasis should be placed on continuous ARV supply and access. With unbroken supply and access to all routinely prescribed ARVs at all times and at all sites within countries, patients in RLS will be able to achieve the adherence patterns needed to prevent HIVDR.

HIV providers in developed countries routinely perform viral load and HIVDR testing to monitor virological response and to assess for the presence of acquired HIVDR in patients receiving therapy or baseline HIVDR prior to the start of therapy. In RLS, viral load and HIVDR testing are not routinely available primarily because of their cost and a lack of local

capacity. In these settings, population-based monitoring of program factors known to be associated with the emergence of HIVDR should be implemented, and results used to optimize site and program functioning to minimize the emergence of preventable HIVDR. In addition, HIVDR testing should be used in targeted population-based surveys to assess for acquired and transmitted HIVDR.

B. GLOBAL EPIDEMIOLOGY OF HIV DRUG RESISTANCE

a) Transmitted HIV Drug Resistance

When an individual is infected with an HIV strain containing drug resistance mutations, the donor has “transmitted” drug resistant HIV to the recipient. Depending upon the number and type of mutations, transmitted HIVDR can significantly compromise virological response to therapy, even for individuals with maximal adherence to combination ART [30–32]. The prevalence of transmitted HIVDR is highest in developed countries, estimated between 8.4% and 22.7% [30,33–36]. Data from the United States Centers for Disease Control and Prevention (US-CDC) showed that between 1998–2000, resistance to any drug class was present in 3.8–10.0% of patients and <2% had resistance to >1 drug class [37]. Between 2003–2006, this rate had stabilized at 10.4% [38]. In 2006, the prevalence estimate increased to 14.6% [39] and to 16% in 2007, with 13% of sequences exhibiting transmitted resistance for a single drug class, 2% for two drug classes, and <1% for three drug classes [40]. Very recent data from a large cohort of ART-naïve patients in the United States demonstrate that the prevalence of major HIVDR mutations in ART-naïve individuals peaked between 2006–2008 and decreased slightly in 2009. Notably the prevalence of key specific NNRTI mutations, K103N and Y181I/C/V decreased in 2009 compared with preceding years, and detection of double or triple class resistance in HIV-infected ART-naïve patients also appeared to be decreasing [41].

To date most reports from RLS have described low rates of transmitted resistance to NRTIs and NNRTIs, which may reflect the limited availability of ARVs until recently. The WATCH study (Worldwide Analysis of Resistance Transmission over Time of Chronically and Acute Infected HIV-1 infected persons) found that the rate of resistance (to any drug) among treatment naïve individuals was 5.5% in Africa [42]. Hamers et al [43] reported on 19 studies completed among treatment-naïve populations in Africa between 2002 and 2007. Studies were conducted in South Africa, Zambia, Côte d’Ivoire, Malawi, Senegal, Botswana, Cameroon, Djibouti, Democratic Republic of Congo, Burundi, Mozambique, Burkina Faso and Tanzania. NNRTI resistance rates ranged from 0% to 5.6%, NRTI resistance ranged from 0% to 3.7% and transmitted PI mutations were rare.

A subsequent review of studies [44] from seven sub-Saharan African countries and three Asian countries reported that prevalence of transmitted HIVDR varied widely from 1.6% in Angola [45] to 18.4% in China [46], with higher prevalence of 10.7% and 11.5% reported in Togo [47] and Mali [48], respectively. The ability to compare published studies assessing transmitted drug resistant virus is limited by the use of different methodologies to estimate prevalence, including variations in sample size, mixing of population risk groups, long sampling time frames, and the inclusion of chronically infected individuals whose resistance may in fact be acquired. In addition, studies frequently reference different mutation interpretation algorithms that include mutations that are not markers of transmitted drug resistance but rather that are polymorphic in certain subtypes. Although, in general, the prevalence of transmitted HIVDR remains low in RLS, it is anticipated that incidence rates may increase if acquired HIVDR is not kept to a minimum [49].

b) Acquired HIV Drug Resistance

HIV-1 is a pseudo-diploid RNA virus characterized by rapid and error-prone replication, and viral recombination. Additionally, HIV's high mutation rate in the presence of drug selective pressure and the need for lifelong treatment in patients infected with HIV, make the emergence of some degree of HIVDR inevitable even when optimal adherence to therapy is supported [50]. Drug resistance mutations reduce viral susceptibility to individual ARVs, and ongoing viral replication in the presence of ARVs may result in the accumulation of additional resistance mutations, leading to multi-drug resistant virus refractory to many potent combinations of ARVs. For nearly a decade in the developed world, drug resistance testing along with expert interpretation has been used routinely in the management of patients with virological failure, and a substantial body of evidence has supported its use in specific circumstances [51–61] (Table 1). In a large, longitudinal study conducted in the United Kingdom [62], the cumulative risk of virological failure for patients starting combination ART after 1997 was 28% for those remaining on ART through the follow-up period of eight years. The risk of developing at least one resistance mutation was 17%. However, in North America, Europe and Australia, the greater efficacy, convenience, and tolerability of current first-line regimens, along with the rarity of drug resistance at failure of ritonavir-boosted PI regimens, have kept the rates at which triple-class resistance develops relatively low. Indeed, only 10% of patients followed in several clinics in the London area had triple-class resistance after a decade of ART [63]. A significant body of evidence [64–73] has demonstrated the relationship between the presence of acquired HIVDR and AIDS/death outcomes. In addition, data from the US-CDC's HIV Outpatient Study demonstrated that patients who had resistance testing survived longer than those who did not [74]. However, it is unlikely that genotypic testing per se was life-saving but served as an indicator for better care and access to newer drugs or drugs from different classes. A recent survey in France has demonstrated a decrease in drug resistance in patients failing therapy in 2009 compared to 2004, and importantly only 9.3% of failing patients could contribute to the transmission of resistant virus [75].

Recent data indicate that the success of first-line therapy in RLS is encouraging. Barth et al [76] reviewed rates of virological suppression and drug-resistance outcomes in 89 studies conducted in sub-Saharan Africa. In on-treatment analysis, 10,351 (78%) of 13,288 patients showed virological suppression after 6 months of therapy, 7,413 (76%) of 9,794 after 12 months, and 3,840 (67%) of 5,690 after 24 months. Importantly, the proportion of patients with on-treatment success after 6–24 months of first-line therapy was comparable to those from developed countries. Other studies in RLS reporting HIVDR acquired during ART demonstrate failure rates similar to those seen in developed countries [77,78].

A recent review by Hamers et al [43] of HIVDR in sub-Saharan Africa summarized twelve studies on acquired HIVDR conducted in Botswana, Cameroon, Côte d'Ivoire, Rwanda, Senegal, Tanzania, Uganda, and Zimbabwe. Patients receiving first-line ART showed large variations in the rate of reported resistance, 3.7%–49% after 24–163 weeks of therapy. Earlier studies showed that the use of non-suppressive regimens (mono or dual-therapy) with inappropriate therapeutic monitoring rapidly led to high levels of resistance [79–81]. Importantly, the review concluded that, despite the lack of full comparability among the studies because of different drug regimens prescribed, variable exposure to ARVs by patients prior to start of ART, differing follow-up periods, and different HIV-1 subtypes, reported resistance rates did not appear to exceed rates reported in developed countries, where the prevalence of resistance mutations has been estimated at 9% in patients after 2 years on ART, rising to 27% after 6 years.

De Luca et al [44] reviewed studies from sub-Saharan Africa and India and reported a high frequency of resistance mutations among patients failing first-line therapy, ranging from

47% to 93% for NNRTIs, 32% to 60% for thymidine analog NRTIs and 3% to 4% for K65R, with one study showing 24% for K65R or K70E [82]. Importantly, variations in study designs, including a range of sample sizes, drug regimens used, previous use of antiretroviral drugs, and duration of follow-up, substantially limit the comparability of these study results.

C. WORLD HEALTH ORGANIZATION HIV DRUG RESISTANCE GLOBAL STRATEGY

In order to address some of the methodological limitations and lack of comparability in studies assessing transmitted and acquired HIVDR while optimizing available resources in RLS, the WHO has developed a global strategy for the prevention and assessment of HIVDR. This strategy was developed by WHO and the US-CDC, in collaboration with WHO/HIV ResNet, a global network of over 50 institutions, laboratories, clinicians, epidemiologists, and HIVDR experts [24]. To date the strategy has been adopted by non governmental organizations including TREAT Asia and PharmAccess, and WHO actively encourages its adoption by national and international research institutions for the purposes of contributing minimal yet vital standardized national and global datasets to national ART programs and global policies.

WHO recommends that countries develop a multi-sectoral strategy for HIVDR prevention and assessment, including the implementation of three key assessment elements. Results from these assessment elements are used to inform the optimal selection of ARV regimens on a population-basis, and to provide an evidence base for making programmatic adjustments, if necessary, to optimize the quality of patient care and improve overall programmatic functioning. These three assessment elements are: (1) routine monitoring of HIVDR "Early Warning Indicators" (EWI) [24], factors known to be associated with the emergence of HIVDR at site and program levels; (2) surveys to assess transmitted HIVDR [83] in recently infected populations; and (3) surveys to monitor the emergence of HIVDR [84] and related programmatic factors in populations receiving ART. WHO HIVResNet also coordinates a global network of accredited laboratories that perform quality-assured genotyping for HIVDR surveillance and monitoring at the country level.

a) World Health Organization HIV Drug Resistance Strategy Assessment Elements

HIVDR EWIs assess site-specific and national ART program factors known to be associated with the emergence of HIVDR (Table 2), which can be adjusted to increase the efficiency of ART delivery and minimize emergence of HIVDR [24]. EWI monitoring is a minimum-resource, sustainable strategy that uses data routinely collected in patient medical and pharmacy records to assess site and program success in minimizing HIVDR. EWIs form the foundation of a national HIVDR evidence base that can be used to take corrective programmatic action at the level of an individual site or at the national level to minimize the emergence of HIVDR and improve the quality of patient care and retention. Additionally, EWI results provide the necessary programmatic context to interpret and apply data from laboratory-based surveys assessing transmitted or acquired HIVDR.

The WHO survey to assess transmitted HIVDR in recently infected populations [83] was developed for the purpose of implementation in RLS as a routine public health activity to produce comparable results in multiple countries and areas within countries. The survey focuses on geographic areas where HIVDR is most likely to be transmitted first, (i.e. areas with widespread ART for > 3 years) since transmitted HIVDR is unlikely to be seen at the population level until ART has been available in a city or health planning area for several years. The survey methodology supports categorization of the prevalence of transmitted

drug resistant HIV in a specific geographic area into one of three categories. LOW prevalence: < 5%; HIGH prevalence: > 15%; or MODERATE prevalence: 5% – 15%. Classification of transmitted HIVDR into three categories using WHO's binomial sequential sampling methodology permits the categorization of transmitted HIVDR using small sample sizes of ≤ 47 specimens from one geographic area. [85] To maximize ARV-drug naïveté and increase the likelihood of recent HIV infection (<3 years), the WHO methodology uses surrogate epidemiologic criteria to identify recently-infected populations. Additionally, surveys to assess transmitted HIVDR use a standard drug resistance mutation list based on four criteria [86,87]: 1) mutations should be recognized as causing or contributing to drug resistance, defined as being present on three or more of five expert lists of drug resistance mutations; 2) mutations should be non-polymorphic and should not occur at highly polymorphic positions; 3) the mutation list has to be applicable to the eight most common HIV-1 subtypes; and 4) the list should be parsimonious, excluding mutations resulting exceedingly rarely from drug pressure. Surveys of transmitted drug resistant HIV are designed to generate data that will inform evidence-based decisions regarding the future selection of national and global ART regimens.

WHO surveys to monitor the emergence of HIVDR [84] assess the success of ART programs in preventing HIVDR emergence during the first year of ART and identify programmatic factors that can be adjusted to minimize the emergence of HIVDR. Specifically, this methodology estimates the proportion of patients initiating ART at each site who achieve HIVDR prevention, as measured by viral load <1000 copies/ml, 12 months after starting first-line ART. HIVDR mutations and mutation patterns are identified among survey participants not achieving prevention of HIVDR after 12 months on first-line ART, or who switch to second-line ART before 12 months. Drug resistance mutations are identified using the Stanford HIVDR algorithm [88].

b) World Health Organization Strategy Implementation

With technical support provided by WHO and its partners, 40 countries had implemented one or more elements of the WHO HIVDR prevention and assessment strategy as of mid-2010 (Figure 1). Additionally, 24 laboratories had been accredited: 7 specialized, 7 regional, and 10 national. 36 countries implemented HIVDR EWI monitoring by mid-2010. An early publication on the results of HIVDR EWI monitoring in Malawi in 2008 [89] reported that all sites reached the WHO targets for prescribing practices and drug supply continuity. The target for adherence was achieved by 85% of sites and 84% of sites achieved the target for minimizing loss to follow-up during the 12 months after starting ART. Fewer than half of all sites reached the WHO target for patient retention. Namibia's 2010 EWI publication [90] reported that all sites reached the WHO targets for prescribing practices, 89% of sites met the target for lost to follow-up, and 67% of sites met the target for patients on first-line ART at 12 months. These results highlighted the need for defaulter tracing.

By mid-2010, ten countries began implementation of surveys to monitor the prevention of HIVDR and associated factors in sentinel antiretroviral therapy sites using the WHO protocol; one country expanded to additional sites and five countries completed data collection. Nine additional countries are developing protocols or have submitted protocols to the WHO for review.

Through mid-2010, 21 countries had completed or were in the process of implementing WHO HIVDR surveys to evaluate transmitted drug resistance. In 2009, one country implemented the survey for the first time while five additional countries initiated a new round of sampling, or expanded implementation into new areas. Studies classifying the prevalence of transmitted HIVDR using WHO methodology have been published from Swaziland [91], Tanzania [92], Chad [93], Cameroon [93], South Africa [94,95], Ethiopia

[96], Malawi [97], Uganda [98], Vietnam [99], Thailand [100], and Indonesia [101] (Table 3). The majority of surveys (9 of 11) were conducted in primigravid woman aged less than 25 with no previous history of ARV exposures. All surveys were performed between 2002 and 2007. Following the standardized WHO approach, which generates population, time and geographic specific results, the prevalence of transmitted HIVDR reported remains low (<5%) with the exception of one published report from Douala, Cameroon, where the estimated drug resistance prevalence was moderate, between 5 and 15% for NRTIs and NNRTIs [94].

D. CONCLUSIONS

ART scale-up utilizing a standardized population-based approach to ART delivery in RLS has been hugely successful and has saved countless lives. Fortunately, HIVDR in RLS has not emerged to the degree that has been observed in developed countries. Although, currently published population-based assessments of HIVDR are reassuring that available first-line regimens are likely to remain effective for some time, ongoing vigilance is required, and global scale-up of ART should be accompanied by robust programmatic assessment informed by routine surveillance of transmitted and acquired HIVDR.

Acknowledgments

Funding Sources: SYH was supported by the National Institute for Allergy and Infectious Disease: T32 AI007438-16 and L30 AI080268-02. MRJ was supported by the National Institute for Allergy and Infectious Disease: K23 AI074423-04.

Some of the authors are staff members of the World Health Organization. The authors alone are responsible for the views expressed in this publication and they do not necessarily represent the decision or stated policy of the World Health Organization.

References

1. WHO, UNAIDS, UNICEF. [Accessed October 29, 2010] Towards universal access: scaling up priority HIV/AIDS interventions in the health sector. Progress Report 2010. <http://www.who.int/hiv/pub/2010progressreport/report/en/index.html>
2. WHO, UNAIDS, UNICEF. [Accessed October 29, 2010] Towards universal access: scaling up priority HIV/AIDS interventions in the health sector. Progress Report 2009. <http://www.who.int/hiv/pub/2009progressreport/en/>
3. Gilks CF, Crowley S, Ekpini R, Gove S, Perriens J, Souteyrand Y, Sutherland D, Vitoria M, Guerna T, De Cock K. The WHO Public-Health Approach to Antiretroviral Treatment Against HIV in Resource-Limited Settings. *Lancet*. 2006; 368:505–510. [PubMed: 16890837]
4. Boyd MA, Cooper DA. Second-Line Combination Antiretroviral Therapy in Resource-Limited Settings: Facing the Challenges through Clinical Research. *AIDS*. 2007; 21 Suppl. 4:S55–S63. [PubMed: 17620754]
5. Bartlett JA, Shao JF. Successes, Challenges, and Limitations of Current Antiretroviral Therapy in Low-Income and Middle-Income Countries. *Lancet Infect. Dis*. 2009; 9:637–649. [PubMed: 19778766]
6. Ford N, Wilson D, Costa Chaves G, Lotrowska M, Kijtiwatchakul K. Sustaining Access to Antiretroviral Therapy in the Less-Developed World: Lessons from Brazil and Thailand. *AIDS*. 2007; 21 Suppl 4:S21–S29. [PubMed: 17620749]
7. Lucas GM, Chaisson RE, Moore RD. Highly Active Antiretroviral Therapy in a Large Urban Clinic: Risk Factors for Virologic Failure and Adverse Drug Reactions. *Ann. Intern. Med*. 1999; 131:81–87. [PubMed: 10419445]
8. Paterson DL, Swindells S, Mohr J, Brester M, Vergis EN, Squier C, Wagener MM, Singh N. Adherence to Protease Inhibitor Therapy and Outcomes in Patients with HIV Infection. *Ann. Intern. Med*. 2000; 133:21–30. [PubMed: 10877736]

9. Arnsten JH, Demas PA, Farzadegan H, Grant RW, Gourevitch MN, Chang CJ, Buono D, Eckholdt H, Howard AA, Schoenbaum EE. Antiretroviral Therapy Adherence and Viral Suppression in HIV-Infected Drug Users: Comparison of Self-Report and Electronic Monitoring. *Clin. Infect. Dis.* 2001; 33:1417–1423. [PubMed: 11550118]
10. Nachega JB, Hislop M, Dowdy DW, Chaisson RE, Regensberg L, Maartens G. Adherence to Nonnucleoside Reverse Transcriptase Inhibitor-Based HIV Therapy and Virologic Outcomes. *Ann. Intern. Med.* 2007; 146:564–573. [PubMed: 17438315]
11. Shuter J, Sarlo JA, Kanmaz TJ, Rode RA, Zingman BS. HIV-Infected Patients Receiving lopinavir/ritonavir-Based Antiretroviral Therapy Achieve High Rates of Virologic Suppression Despite Adherence Rates Less than 95%. *J. Acquir. Immune Defic. Syndr.* 2007; 45:4–8. [PubMed: 17460469]
12. Martin M, Del Cacho E, Codina C, Tuset M, De Lazzari E, Mallolas J, Miro JM, Gatell JM, Ribas J. Relationship between Adherence Level, Type of the Antiretroviral Regimen, and Plasma HIV Type 1 RNA Viral Load: A Prospective Cohort Study. *AIDS Res. Hum. Retroviruses.* 2008; 24:1263–1268. [PubMed: 18834323]
13. Bangsberg DR, Acosta EP, Gupta R, Guzman D, Riley ED, Harrigan PR, Parkin N, Deeks SG. Adherence-Resistance Relationships for Protease and Non-Nucleoside Reverse Transcriptase Inhibitors Explained by Virological Fitness. *AIDS.* 2006; 20:223–231. [PubMed: 16511415]
14. Harrigan PR, Hogg RS, Dong WW, Yip B, Wynhoven B, Woodward J, Brumme CJ, Brumme ZL, Mo T, Alexander CS, Montaner JS. Predictors of HIV Drug-Resistance Mutations in a Large Antiretroviral-Naive Cohort Initiating Triple Antiretroviral Therapy. *J. Infect. Dis.* 2005; 191:339–347. [PubMed: 15633092]
15. Bangsberg DR, Perry S, Charlebois ED, Clark RA, Roberston M, Zolopa AR, Moss A. Non-Adherence to Highly Active Antiretroviral Therapy Predicts Progression to AIDS. *AIDS.* 2001; 15:1181–1183. [PubMed: 11416722]
16. Hogg RS, Heath K, Bangsberg D, Yip B, Press N, O'Shaughnessy MV, Montaner JS. Intermittent use of Triple-Combination Therapy is Predictive of Mortality at Baseline and After 1 Year of Follow-Up. *AIDS.* 2002; 16:1051–1058. [PubMed: 11953472]
17. Nachega JB, Hislop M, Dowdy DW, Lo M, Omer SB, Regensberg L, Chaisson RE, Maartens G. Adherence to Highly Active Antiretroviral Therapy Assessed by Pharmacy Claims Predicts Survival in HIV-Infected South African Adults. *J. Acquir. Immune Defic. Syndr.* 2006; 43:78–84. [PubMed: 16878045]
18. Wood E, Hogg RS, Yip B, Moore D, Harrigan PR, Montaner JS. Impact of Baseline Viral Load and Adherence on Survival of HIV-Infected Adults with Baseline CD4 Cell Counts > Or = 200 cells/microl. *AIDS.* 2006; 20:1117–1123. [PubMed: 16691062]
19. Oyugi JH, Byakika-Tusiime J, Charlebois ED, Kityo C, Mugerwa R, Mugenyi P, Bangsberg DR. Multiple Validated Measures of Adherence Indicate High Levels of Adherence to Generic HIV Antiretroviral Therapy in a Resource-Limited Setting. *J. Acquir. Immune Defic. Syndr.* 2004; 36:1100–1102. [PubMed: 15247564]
20. Orrell C, Bangsberg DR, Badri M, Wood R. Adherence is Not a Barrier to Successful Antiretroviral Therapy in South Africa. *AIDS.* 2003; 17:1369–1375. [PubMed: 12799558]
21. Nachega JB, Stein DM, Lehman DA, Hlatshwayo D, Mothopeng R, Chaisson RE, Karstaedt AS. Adherence to Antiretroviral Therapy in HIV-Infected Adults in Soweto, South Africa. *AIDS Res. Hum. Retroviruses.* 2004; 20:1053–1056. [PubMed: 15585095]
22. Mills EJ, Nachega JB, Buchan I, Orbinski J, Attaran A, Singh S, Rachlis B, Wu P, Cooper C, Thabane L, Wilson K, Guyatt GH, Bangsberg DR. Adherence to Antiretroviral Therapy in Sub-Saharan Africa and North America: A Meta-Analysis. *JAMA.* 2006; 296:679–690. [PubMed: 16896111]
23. Richman DD, Morton SC, Wrin T, Hellmann N, Berry S, Shapiro MF, Bozzette SA. The Prevalence of Antiretroviral Drug Resistance in the United States. *AIDS.* 2004; 18:1393–1401. [PubMed: 15199315]
24. Bennett DE, Bertagnolio S, Sutherland D, Gilks CF. The World Health Organization's Global Strategy for Prevention and Assessment of HIV Drug Resistance. *Antivir. Ther.* 2008; 13 Suppl. 2:1–13. [PubMed: 18578063]

25. Parienti JJ, Massari V, Descamps D, Vabret A, Bouvet E, Larouze B, Verdon R. Predictors of Virologic Failure and Resistance in HIV-Infected Patients Treated with Nevirapine- Or Efavirenz-Based Antiretroviral Therapy. *Clin. Infect. Dis.* 2004; 38:1311–1316. [PubMed: 15127346]
26. Oyugi JH, Byakika-Tusiime J, Ragland K, Laeyendecker O, Mugerwa R, Kityo C, Mugenyi P, Quinn TC, Bangsberg DR. Treatment Interruptions Predict Resistance in HIV-Positive Individuals Purchasing Fixed-Dose Combination Antiretroviral Therapy in Kampala, Uganda. *AIDS.* 2007; 21:965–971. [PubMed: 17457090]
27. Marcellin F, Boyer S, Protopopescu C, Dia A, Ongolo-Zogo P, Koulla-Shiro S, Abega S-C, Abe C, Moatti J-P, Spire B, Carrieri MP. EVAL Study Group. Determinants of unplanned antiretroviral treatment interruptions among people living with HIV in Yaoundé, Cameroon. (EVAL survey, ANRS 12-116). *Tropical Medicine and International Health.* 2009; 13:1470–1478. [PubMed: 19000156]
28. Eholie SP, Tanon A, Polneau S, Ouiminga M, Djadji A, Kangah-Koffi C, Diakite N, Anglaret X, Kakou A, Bissagnene E. Field Adherence to Highly Active Antiretroviral Therapy in HIV-Infected Adults in Abidjan, Cote d'Ivoire. *J. Acquir. Immune Defic. Syndr.* 2007; 45:355–358. [PubMed: 17438479]
29. Tuller DM, Bangsberg DR, Senkungu J, Ware NC, Emenyonu N, Weiser SD. Transportation Costs Impede Sustained Adherence and Access to HAART in a Clinic Population in Southwestern Uganda: A Qualitative Study. *AIDS. Behav.* 2010; 14:778–784. [PubMed: 19283464]
30. Little SJ, Holte S, Routy JP, Daar ES, Markowitz M, Collier AC, Koup RA, Mellors JW, Connick E, Conway B, Kilby M, Wang L, Whitcomb JM, Hellmann NS, Richman DD. Antiretroviral-Drug Resistance among Patients Recently Infected with HIV. *N. Engl. J. Med.* 2002; 347:385–394. [PubMed: 12167680]
31. Grant RM, Hecht FM, Warmerdam M, Liu L, Liegler T, Petropoulos CJ, Hellmann NS, Chesney M, Busch MP, Kahn JO. Time Trends in Primary HIV-1 Drug Resistance among Recently Infected Persons. *JAMA.* 2002; 288:181–188. [PubMed: 12095382]
32. Violin M, Cozzi-Lepri A, Velleca R, Vincenti A, D'Elia S, Chiodo F, Ghinelli F, Bertoli A, d'Arminio Monforte A, Perno CF, Moroni M, Balotta C. Risk of Failure in Patients with 215 HIV-1 Revertants Starting their First Thymidine Analog-Containing Highly Active Antiretroviral Therapy. *AIDS.* 2004; 18:227–235. [PubMed: 15075540]
33. Wensing AM, van de Vijver DA, Angarano G, Asjö B, Balotta C, Boeri E, Camacho R, Chaix ML, Costagliola D, De Luca, Derdelinckx I, Grossman Z, Hamouda O, Hatzakis A, Hemmer R, Hoepelman A, Horban A, Korn K, Kücherer C, Leitner T, Loveday C, MacRae E, Maljkovic I, de Mendoza C, Meyer L, Nielsen C, Op de Coul EL, Ormaasen V, Paraskevis D, Perrin L, Puchhammer-Stöckl E, Ruiz L, Salminen M, Schmit JC, Schneider F, Schuurman R, Soriano V, Stanczak G, Stanojevic M, Vandamme AM, Van Laethem K, Violin M, Wilbe K, Yerly S, Zazzi M, Boucher CA. SPREAD Programme. Prevalence of Drug-Resistant HIV-1 Variants in Untreated Individuals in Europe: Implications for Clinical Management. *J. Infect. Dis.* 2005; 192:958–966. [PubMed: 16107947]
34. Vercauteren J, Wensing AM, van de Vijver DA, Albert J, Balotta C, Hamouda O, Kücherer C, Struck D, Schmit JC, Asjö B, Bruckova M, Camacho RJ, Clotet B, Coughlan S, Grossman Z, Horban A, Korn K, Kostrikis L, Nielsen C, Paraskevis D, Poljak M, Puchhammer-Stöckl E, Riva C, Ruiz L, Salminen M, Schuurman R, Sonnerborg A, Stanekova D, Stanojevic M, Vandamme AM, Boucher CA. Transmission of Drug-Resistant HIV-1 is Stabilizing in Europe. *J. Infect. Dis.* 2009; 200:1503–1508. [PubMed: 19835478]
35. Little SJ, May S, Hecht F, Markowitz M, Daar ES, Kaldor J, Grant RM, Bates M, Woelk C, Kosakovsky Pond SL, Liu L, Degruittola V, Frost SDW, Richman DD. Increase in transmitted NNRTI drug resistance among recently HIV infected patients from North America and Australia. *Antivir. Ther.* 2006; 11 Suppl 1:S110.
36. Ross LL, Florance A, Wine B, Craig C, Vavro C, McClernon D, Tisdale M, Baul R, Lancaster T, Shaefer M, Lanier ER. Prevalence of HIV-1 drug resistance-associated mutations in a large cohort of antiretroviral therapy (ART) naïve HIV-infected individuals in the United States from 2000–2004. *Antivir. Ther.* 2006; 11 Suppl 1:S120.
37. Bennett, D.; Zaidi, I.; Heneine, W.; Woods, T.; García-Lerma, G.; Kaplan, J.; Weinstock, H. Prevalence of mutations associated with antiretroviral drug resistance among recently diagnosed

- persons with HIV, 1998–2000. 9th Conference on Retroviruses & Opportunistic Infections; Seattle, Wash., USA: 2002 February 24–28. Abstract 372-M.
38. Wheeler, W.; Mahle, K.; Bodnar, U.; Kline, R.; Hall, I.; McKenna, M. the US Variant, Atypical and Resistant HIV Surveillance (VARHS) Group. Antiretroviral Drug-resistance Mutations and Subtypes in Drug-naïve Persons Newly Diagnosed with HIV-1 Infection, US, March 2003 to October 2006. 14th Conference on Retroviruses & Opportunistic Infections; Los Angeles, CA, USA: 2007 February 25–28. Abstract 648
 39. Wheeler WH, Ziebell RA, Zabina H, Pieniazek D, Prejean J, Bodnar UR, Mahle KC, Heneine W, Johnson JA, Hall HI. Variant, Atypical, and Resistant HIV Surveillance Group Prevalence of Transmitted Drug Resistance Associated Mutations and HIV-1 Subtypes in New HIV-1 Diagnoses, U.S.-2006. *AIDS*. 2010; 24:1203–1212. [PubMed: 20395786]
 40. Kim, D.; Wheeler, W.; Zieball, R.; Johnson, J.; Prejean, J.; Heneine, W.; Hall, I. and US Variant, Atypical, and Resistant HIV Surveillance Coordinators. Prevalence of transmitted antiretroviral drug resistance among newly-diagnosed HIV-1-infected persons, US, 2007. 17th Conference on Retroviruses & Opportunistic Infections; San Francisco, CA, USA: 2010 February 16–19. Abstract 580
 41. Ross LL, Wine B, Horton JH, Vavro C, St Clair M, Ha BF, Pappa KA, Schaefer M. Prevalence of HIV-1 drug resistance-associated mutations in a large cohort of antiretroviral naïve HIV-infected individuals in the USA from 2000–2009. *Antivir. Ther.* 2010; 15 Suppl. 2:A50.
 42. Bowles, E.; Wensing, AMJ.; van de Vijver, DAMC.; Boulme, R.; Schuurman, R.; Boucher, C. on behalf of all WATCH investigators. WATCH: a worldwide database for collecting and analyzing data on transmission of drug resistant HIV using standardized methods. XVIth International AIDS Conference; Toronto, Canada: 2006 August 3–8. Abstract MOPE0388
 43. Hamers RL, Derdelinckx I, van Vugt M, Stevens W, Rinke de Wit TF, Schuurman R. PharmAccess African Studies to Evaluate Resistance Programme The Status of HIV-1 Resistance to Antiretroviral Drugs in Sub-Saharan Africa. *Antivir Ther.* 2008; 13:625–639. [PubMed: 18771046]
 44. De Luca A, Prosperi M, Bracciale L. Resistance Considerations in Sequencing of Antiretroviral Therapy in Low-Middle Income Countries with Currently Available Options. *Curr. Opin. HIV. AIDS*. 2010; 5:27–37. [PubMed: 20046145]
 45. Bartolo I, Rocha C, Bartolomeu J, Gama A, Fonseca M, Mendes A, Cristina F, Thamm S, Epalanga M, Silva PC, Taveira N. Antiretroviral Drug Resistance Surveillance among Treatment-Naïve Human Immunodeficiency Virus Type 1-Infected Individuals in Angola: Evidence for Low Level of Transmitted Drug Resistance. *Antimicrob. Agents Chemother.* 2009; 53:3156–3158. [PubMed: 19433560]
 46. Tu YQ, Wang MJ, Yao J, Zhu XM, Pan PL, Xing WG, Zhang GH, Yang RG, Zheng YT, Jiang Y. Human Immunodeficiency Virus-1 Genotypic Drug Resistance among Volunteer Blood Donors in Yunnan, China. *Transfusion*. 2009; 49:1865–1873. [PubMed: 19453981]
 47. Yaotse DA, Nicole V, Roch NF, Mireille PD, Eric D, Martine P. Genetic Characterization of HIV-1 Strains in Togo Reveals a High Genetic Complexity and Genotypic Drug-Resistance Mutations in ARV Naïve Patients. *Infect. Genet. Evol.* 2009; 9:646–652. [PubMed: 19460333]
 48. Derache A, Maïga AI, Traore O, Akonde A, Cisse M, Jarrousse B, Koita V, Diarra B, Carcelain G, Barin F, Pizzoccolo C, Pizarro L, Katlama C, Calvez V, Marcelin AG. Evolution of Genetic Diversity and Drug Resistance Mutations in HIV-1 among Untreated Patients from Mali between 2005 and 2006. *J. Antimicrob. Chemother.* 2008; 62:456–463. [PubMed: 18556706]
 49. Blower S, Bodine E, Kahn J, McFarland W. The Antiretroviral Rollout and Drug-Resistant HIV in Africa: Insights from Empirical Data and Theoretical Models. *AIDS*. 2005; 19:1–14. [PubMed: 15627028]
 50. Coffin JM. HIV Population Dynamics in Vivo: Implications for Genetic Variation, Pathogenesis, and Therapy. *Science*. 1995; 267:483–489. [PubMed: 7824947]
 51. Durant J, Clevenbergh P, Halfon P, Delgiudice P, Porsin S, Simonet P, Montagne N, Boucher CA, Schapiro JM, Dellamonica P. Drug-Resistance Genotyping in HIV-1 Therapy: The VIRADAPT Randomised Controlled Trial. *Lancet*. 1999; 353:2195–2199. [PubMed: 10392984]
 52. Baxter JD, Mayers DL, Wentworth DN, Neaton JD, Hoover ML, Winters MA, Mannheimer SB, Thompson MA, Abrams DI, Brizz BJ, Ioannidis JP, Merigan TC. A Randomized Study of

Antiretroviral Management Based on Plasma Genotypic Antiretroviral Resistance Testing in Patients Failing Therapy. CPCRA 046 Study Team for the Terry Bein Community Programs for Clinical Research on AIDS. AIDS. 2000; 14:F83–F93. [PubMed: 10894268]

53. Tural C, Ruiz L, Holtzer C, Schapiro J, Viciano P, Gonzalez J, Domingo P, Boucher C, Rey-Joly C, Clotet B. Havana Study Group Clinical Utility of HIV-1 Genotyping and Expert Advice: The Havana Trial. AIDS. 2002; 16:209–218. [PubMed: 11807305]
54. Cohen CJ, Hunt S, Sension M, Farthing C, Conant M, Jacobson S, Nadler J, Verbiest W, Hertogs K, Ames M, Rinehart AR, Graham NM. VIRA3001 Study Team A Randomized Trial Assessing the Impact of Phenotypic Resistance Testing on Antiretroviral Therapy. AIDS. 2002; 16:579–588. [PubMed: 11873001]
55. Cingolani A, Antinori A, Rizzo MG, Murri R, Ammassari A, Baldini F, Di Giambenedetto S, Cauda R, De Luca A. Usefulness of Monitoring HIV Drug Resistance and Adherence in Individuals Failing Highly Active Antiretroviral Therapy: A Randomized Study (ARGENTA). AIDS. 2002; 16:369–379. [PubMed: 11834948]
56. Meynard JL, Vray M, Morand-Joubert L, Race E, Descamps D, Peytavin G, Matheron S, Lamotte C, Guiramand S, Costagliola D, Brun-Vezinet F, Clavel F, Girard PM. Narval Trial Group Phenotypic Or Genotypic Resistance Testing for Choosing Antiretroviral Therapy After Treatment Failure: A Randomized Trial. AIDS. 2002; 16:727–736. [PubMed: 11964529]
57. Haubrich RH, Kemper CA, Hellmann NS, Keiser PH, Witt MD, Tilles JG, Forthal DN, Leedom J, Leibowitz M, McCutchan JA, Richman DD. California Collaborative Treatment Group A Randomized, Prospective Study of Phenotype Susceptibility Testing Versus Standard of Care to Manage Antiretroviral Therapy: CCTG 575. AIDS. 2005; 19:295–302. [PubMed: 15718840]
58. Wegner SA, et al. Long-Term Efficacy of Routine Access to Antiretroviral-Resistance Testing in HIV Type 1-Infected Patients: Results of the Clinical Efficacy of Resistance Testing Trial. Clin. Infect. Dis. 2004; 38:723–730. [PubMed: 14986258]
59. The European HIV Drug Resistance Guidelines Panel. [Accessed October 30, 2010] The European HIV Drug Resistance Guidelines 2009 Update. <http://www.europeanaidscinicalsociety.org/The>
60. Panel on Antiretroviral Guidelines for Adults and Adolescents. [Accessed October 30, 2010] Department of Health and Human Services. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. <http://www.aidsinfo.nih.gov/contentfiles/AdultandAdolescentGL.pdf>
61. Hirsch MS, Günthard HF, Schapiro JM, Brun-Vézinet F, Clotet B, Hammer SM, Johnson VA, Kuritzkes DR, Mellors JW, Pillay D, Yeni PG, Jacobsen DM, Richman DD. International AIDS Society-USA. Antiretroviral drug resistance testing in adult HIV-1 infection: 2008 recommendations of an International AIDS Society-USA panel. Top. HIV Med. 2008 Aug.–Sept.; 16(3):266–285. [PubMed: 19856548]
62. UK Collaborative Group on HIV Drug Resistance: UK CHIC Study Group. Long-term probability of detecting drug-resistant HIV in treatment-naïve patients initiating combination antiretroviral therapy. Clin. Infect. Dis. 2010; 50(9):1275–1285. [PubMed: 20353366]
63. Phillips AN, et al. Risk of Extensive Virological Failure to the Three Original Antiretroviral Drug Classes Over Long-Term Follow-Up from the Start of Therapy in Patients with HIV Infection: An Observational Cohort Study. Lancet. 2007; 370:1923–1928. [PubMed: 18068516]
64. Cozzi-Lepri A, Phillips AN, Clotet B, Mocroft A, Ruiz L, Kirk O, Lazzarin A, Wiercinska-Drapalo A, Karlsson A, Lundgren JD. EuroSIDA Study Group Detection of HIV Drug Resistance during Antiretroviral Treatment and Clinical Progression in a Large European Cohort Study. AIDS. 2008; 22:2187–2198. [PubMed: 18832882]
65. Zaccarelli M, Tozzi V, Lorenzini P, Trotta MP, Forbici F, Visco-Comandini U, Gori C, Narciso P, Perno CF, Antinori A. Collaborative Group for Clinical Use of HIV Genotype Resistance Test (GRT) at National Institute for Infectious Diseases Lazzaro Spallanzani Multiple Drug Class-Wide Resistance Associated with Poorer Survival After Treatment Failure in a Cohort of HIV-Infected Patients. AIDS. 2005; 19:1081–1089. [PubMed: 15958840]
66. Di Giambenedetto S, Colafigli M, Pinnetti C, Bacarelli A, Cingolani A, Tamburrini E, Cauda R, de Luca A. Genotypic Resistance Profile and Clinical Progression of Treatment-Experienced HIV Type 1-Infected Patients with Virological Failure. AIDS Res. Hum. Retroviruses. 2008; 24:149–154. [PubMed: 18240962]

67. Ormaasen V, Sandvik L, Asjo B, Holberg-Petersen M, Gaarder PI, Bruun JN. An Algorithm-Based Genotypic Resistance Score is Associated with Clinical Outcome in HIV-1-Infected Adults on Antiretroviral Therapy. *HIV. Med.* 2004; 5:400–406. [PubMed: 15544691]
68. Napravnick S, Keys J, Stalzer B, Eron JJ. Extensive HIV-1 antiretroviral drug class resistance is associated with inferior virological and clinical outcomes. *Antivir. Ther.* 2007; 12 Suppl. 1:S68.
69. Lohse N, Jorgensen LB, Kronborg G, Moller A, Kvinesdal B, Sorensen HT, Obel N, Gerstoft J. Danish HIV Cohort Study Genotypic Drug Resistance and Long-Term Mortality in Patients with Triple-Class Antiretroviral Drug Failure. *Antivir. Ther.* 2007; 12:909–917. [PubMed: 17926645]
70. Lucas GM, Gallant JE, Moore RD. Relationship between Drug Resistance and HIV-1 Disease Progression Or Death in Patients Undergoing Resistance Testing. *AIDS.* 2004; 18:1539–1548. [PubMed: 15238772]
71. Lucas GM. Antiretroviral Adherence, Drug Resistance, Viral Fitness and HIV Disease Progression: A Tangled Web is Woven. *J. Antimicrob. Chemother.* 2005; 55:413–416. [PubMed: 15722389]
72. Hogg RS, Bangsberg DR, Lima VD, Alexander C, Bonner S, Yip B, Wood E, Dong WW, Montaner JS, Harrigan PR. Emergence of Drug Resistance is Associated with an Increased Risk of Death among Patients First Starting HAART. *PLoS Med.* 2006; 3:e356. [PubMed: 16984218]
73. Kozal MJ, Hullsiek KH, Macarthur RD, Berg-Wolf M, Peng G, Xiang Y, Baxter JD, Uy J, Telzak EE, Novak RM. Terry Bein Community Programs for Clinical Research on AIDS (CPCRA) The Incidence of HIV Drug Resistance and its Impact on Progression of HIV Disease among Antiretroviral-Naive Participants Started on Three Different Antiretroviral Therapy Strategies. *HIV. Clin. Trials.* 2007; 8:357–370. [PubMed: 18042501]
74. Palella FJ Jr, Armon C, Buchacz K, Cole SR, Chmiel JS, Novak RM, Wood K, Moorman AC, Brooks JT. HOPS (HIV Outpatient Study) Investigators The Association of HIV Susceptibility Testing with Survival among HIV-Infected Patients Receiving Antiretroviral Therapy: A Cohort Study. *Ann. Intern. Med.* 2009; 151:73–84. [PubMed: 19620160]
75. Assoumou L, Descamps D, Yerly S, Dos Santos G, Marcelin AG, Delaguerre C, Ruffault A, Izopet J, Plantier J-C, Pakianather S, Montes B, Chaix ML, Calvez V, Costagliola D, Masquelier B. the ANRS AC11 Resistance Study Group. Prevalence of HIV-1 drug resistance in treated patients with viral load >50 copies/ml in 2009: a French nationwide study. *Antivir. Ther.* 2010; 15 Suppl 2:A185.
76. Barth RE, van der Loeff MF, Schuurman R, Hoepelman AI, Wensing AM. Virological Follow-Up of Adult Patients in Antiretroviral Treatment Programmes in Sub-Saharan Africa: A Systematic Review. *Lancet Infect. Dis.* 2010; 10:155–166. [PubMed: 20185094]
77. Gupta RK, Pillay D. HIV Resistance and the Developing World. *Int. J. Antimicrob. Agents.* 2007; 29:510–517. [PubMed: 17346940]
78. Marconi VC, Sunpath H, Lu Z, Gordon M, Koranteng-Apeagyei K, Hampton J, Carpenter S, Giddy J, Ross D, Holst H, Losina E, Walker BD, Kuritzkes DR. South Africa Resistance Cohort Study Team Prevalence of HIV-1 Drug Resistance After Failure of a First Highly Active Antiretroviral Therapy Regimen in KwaZulu Natal, South Africa. *Clin. Infect. Dis.* 2008; 46:1589–1597. [PubMed: 18419495]
79. Weidle PJ, Malamba S, Mwebaze R, Sozi C, Rukundo G, Downing R, Hanson D, Ochola D, Mugenyi P, Mermin J, Samb B, Lackritz E. Assessment of a Pilot Antiretroviral Drug Therapy Programme in Uganda: Patients' Response, Survival, and Drug Resistance. *Lancet.* 2002; 360:34–40. [PubMed: 12114039]
80. Adje C, et al. High Prevalence of Genotypic and Phenotypic HIV-1 Drug-Resistant Strains among Patients Receiving Antiretroviral Therapy in Abidjan, Cote d'Ivoire. *J. Acquir. Immune Defic. Syndr.* 2001; 26:501–506. [PubMed: 11391173]
81. Vergne L, Malonga-Mouellet G, Mistoul I, Mavoungou R, Mansaray H, Peeters M, Delaporte E. Resistance to Antiretroviral Treatment in Gabon: Need for Implementation of Guidelines on Antiretroviral Therapy use and HIV-1 Drug Resistance Monitoring in Developing Countries. *J. Acquir. Immune Defic. Syndr.* 2002; 29:165–168. [PubMed: 11832686]
82. Tebit DM, Sangare L, Makamtse A, Yameogo S, Somlare H, Bado G, Kouliaty BG, Sathiandee K, Tiba F, Sanou I, Ouedraogo-Traore R, Zoungrana L, Diallo I, Drabo JY, Krausslich HG. HIV Drug Resistance Pattern among HAART-Exposed Patients with Suboptimal Virological Response

- in Ouagadougou, Burkina Faso. *J. Acquir. Immune Defic. Syndr.* 2008; 49:17–25. [PubMed: 18667925]
83. Bennett DE, Myatt M, Bertagnolio S, Sutherland D, Gilks CF. Recommendations for surveillance of transmitted HIV Drug resistance in countries scaling up antiretroviral treatment. *Antivir. Ther.* 2008; 13 Suppl 2:25–36. [PubMed: 18575189]
 84. Jordan MR, Bennett DE, Bertagnolio S, Gilks CF, Sutherland D. World Health Organization Surveys to Monitor HIV Drug Resistance Prevention and Associated Factors in Sentinel Antiretroviral Treatment Sites. *Antivir Ther.* 2008; 13 Suppl 2:15–23. [PubMed: 18575188]
 85. Myatt M, Bennett DE. A Novel Sequential Sampling Technique for the Surveillance of Transmitted HIV Drug Resistance by Cross-Sectional Survey for use in Low Resource Settings. *Antivir Ther.* 2008; 13 Suppl 2:37–48. [PubMed: 18575190]
 86. Bennett DE, Camacho RJ, Otelea D. Drug resistance mutations for surveillance of transmitted HIV-1 drug resistance: 2009 update. *PLoS ONE.* 2009; 4:e4724. [PubMed: 19266092]
 87. Shafer RW, Rhee SY, Bennett DE. Consensus Drug Resistance Mutations for Epidemiological Surveillance: Basic Principles and Potential Controversies. *Antivir Ther.* 2008; 13 Suppl 2:59–68. [PubMed: 18575192]
 88. [Accessed October 30, 2010] Stanford HIV Drug Resistance Database. <http://hivdb.stanford.edu/>
 89. Hedt BL, Wadonda-Kabondo N, Makombe S. Early warning indicators for HIV Drug resistance in Malawi. *Antivir. Ther.* 2008; 13 Suppl 2:69–75. [PubMed: 18575193]
 90. Hong SY, Jonas A, Dumeni E, Badi A, Pereko D, Blom A, Muthiani VS, Shiningavamwe AN, Mukamba J, Andemichael G, Barbara R, Bennett DE, Jordan MR. Population-Based Monitoring of HIV Drug Resistance in Namibia with Early Warning Indicators. *J. Acquir. Immune Defic. Syndr.* 2010
 91. Maphalala G, Okello V, Mndzebele S, Gwebu P, Mulima N, Dlamini S, Nhlabatsi B, Ginindza T, Ghebrenegus Y, Ntlivamunda A, Mwanyumba F, Ledwaba J, Pillay V, Bennett DE. Surveillance of Transmitted HIV Drug Resistance in the Manzini-Mbabane Corridor, Swaziland, in 2006. *Antivir. Ther.* 2008; 13 Suppl. 2:95–100. [PubMed: 18575197]
 92. Somi GR, Kibuka T, Diallo K, Tuhuma T, Bennett DE, Yang C, Kagoma C, Lyamuya EF, Swai RO, Kassim S. Surveillance of Transmitted HIV Drug Resistance among Women Attending Antenatal Clinics in Dar Es Salaam, Tanzania. *Antivir. Ther.* 2008; 13 Suppl. 2:77–82. [PubMed: 18575194]
 93. Aghokeng AF, Vergne L, Mpoudi-Ngole E, Mbangue M, Deoudje N, Mokondji E, Nambei WS, Peyou-Ndi MM, Moka JJ, Delaporte E, Peeters M. Evaluation of Transmitted HIV Drug Resistance among Recently-Infected Antenatal Clinic Attendees in Four Central African Countries. *Antivir. Ther.* 2009; 14:401–411. [PubMed: 19474474]
 94. Pillay V, Ledwaba J, Hunt G, Rakgotho M, Singh B, Makubalo L, Bennett DE, Puren A, Morris L. Antiretroviral Drug Resistance Surveillance among Drug-Naive HIV-1-Infected Individuals in Gauteng Province, South Africa in 2002 and 2004. *Antivir. Ther.* 2008; 13 Suppl. 2:101–107. [PubMed: 18575198]
 95. Ledwaba J, Hunt G, Rakgotho M, El-Khatib Z, Singh B, Makubalo L, Puren A, Morris L. HIV-1 transmitted drug resistance surveillance in three provinces in South Africa during 2002–2007. *Antivir. Ther.* 2009; 14 Suppl 1:A182.
 96. Abegaz WE, Grossman Z, Wolday D, Ram D, Kaplan J, Sibide K, Wuhib T, Ismael S, Nkengasong J, Mekonen T, Berhanu H, Messele T, Lulseged S, Maayan S, Mengistu Y. Threshold Survey Evaluating Transmitted HIV Drug Resistance among Public Antenatal Clinic Clients in Addis Ababa, Ethiopia. *Antivir. Ther.* 2008; 13 Suppl 2:89–94. [PubMed: 18575196]
 97. Kamoto K, Aberle-Grasse J. Malawi HIV Drug Resistance Task Force Surveillance of Transmitted HIV Drug Resistance with the World Health Organization Threshold Survey Method in Lilongwe, Malawi. *Antivir. Ther.* 2008; 13 Suppl 2:83–87. [PubMed: 18575195]
 98. Ndemi N, Lyagoba F, Nanteza B, Kushemererwa G, Serwanga J, Katongole-Mbidde E, Grosskurth H, Kaleebu P. Uganda HIV Drug Resistance Working Group Transmitted Antiretroviral Drug Resistance Surveillance among Newly HIV Type 1-Diagnosed Women Attending an Antenatal Clinic in Entebbe, Uganda. *AIDS Res. Hum. Retroviruses.* 2008; 24:889–895. [PubMed: 18544019]

99. Nguyen HT, et al. HIV Drug Resistance Threshold Survey using Specimens from Voluntary Counselling and Testing Sites in Hanoi, Vietnam. *Antivir. Ther.* 2008; 13 Suppl. 2:115–121. [PubMed: 18575200]
100. 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. 2:109–113. [PubMed: 18575199]
101. World Health Organization. [Accessed October 30, 2010] HIV Drug Resistance Prevention, Surveillance and Monitoring in the Western Pacific Region.
<http://www.wpro.who.int/internet/resources.ashx/HSI/docs/HIV+Drug+Resistance+Surveillance.pdf>

FIGURE 1.
Countries implementing the WHO HIVDR Strategy (September 2010)

TABLE 1
Summary of clinical trials to assess the utility of genotypic and phenotypic resistance testing for clinical care

Study Name <i>Author, Journal</i>	Number Enrolled	Study Duration (months)	Study Randomizations	Change in Plasma HIV-1 RNA	% Plasma Virus Below Detection	Change CD4 Cell Number
<i>VIRADAPT Durant, Lancet 1999 [51]</i>	108	6	Genotype SOC	-1.15 -0.67 (P=0.05)	32 14 (P=0.07)	+21 +33
<i>CPCRA 046 Baxter, AIDS 2000 [52]</i>	153	3	Genotype SOC	-0.94 -0.47 (P=0.003)	34 22(P=0.10)	+25 +18
<i>Havana Tural, AIDS 2002 [53]</i>	326	6	Genotype No genotype	-0.84 -0.63 (P<0.05)	49 36 (P=0.03)	Not reported
<i>VIRA 3001 Cohen, AIDS 2002 [54]</i>	272	4	Phenotype SOC	-1.23 -0.87 (P=0.005)	46 34 (P=0.08)	+27 +40
<i>ARGENTA Cingolani, AIDS 2002 [55]</i>	174	6	Genotype SOC	-0.62/-0.38 -0.57 (P=NS)	21 17 (P=0.47)	+15 +22
<i>NARVAL Meynard, AIDS 2002 [56]</i>	541	4	Geno v. pheno SOC	-0.95/-0.93 -0.76 (P=NS)	44/35 36 (P=NS)	+14/+40 +27
<i>CCTG575 Haubrich, AIDS 2005 [57]</i>	238	12	Phenotype SOC	-0.71 -0.71 (P=NS)	45 46 (P=NS)	+39 +42
<i>CERT Wegner, CID 2004 [58]</i>	450	12	Geno v. pheno SOC	Not reported	63/55 59 (P=NS)	Not reported

Standard of Care(SOC),Not significant (NS)

Genotype resistance testing utilizes viral sequence data to infer drug susceptibility by applying rules-based algorithms or algorithms based upon pattern matching of genotype-phenotype correlations
Phenotype resistance testing determines the direct antiviral susceptibility of a patient's virus

TABLE 2

WHO Early Warning Indicator Definitions and Targets

Indicator	Definition and Target
EWI 1: ART Prescribing Practices	Percentage of patients initiating ART at the site who are initially prescribed, or who initially pick up from the pharmacy, an appropriate first-line ART regimen. Suggested target: 100%
EWI 2: Patients lost to follow-up at 12 months	Percentage of patients initiating ART at the site who are lost to follow-up during the 12 months after starting ART. Suggested target: ≤20%
EWI 3: Patient retention on first-line ART at 12 months	<p>a. Percentage of patients initiating ART at the site who are taking an appropriate first-line ART regimen 12 months later. Suggested target: ≥70%</p> <p>b. Percentage of patients initiating ART at the site who are still on ART after 12 months, and whose initial ART regimen was changed during the first 12 months of ART to another regimen involving a different drug class. Suggested target: 0%</p>
EWI 4: On-time ARV drug pick-up	<p>a. Percentage of patients picking up all prescribed ARV drugs on time. Suggested target: ≥90%</p> <p>b. Percentage of patients initiating ART at the site who picked up all prescribed ARV drugs on time during their first 12 months of ART. Suggested target: ≥90%</p>
EWI 5: ART clinic appointment keeping	<p>a. Percentage of ART patients who attending all clinical consultations on time. Suggested target: ≥80%</p> <p>b. Percentage of patients initiating ART at the site who attended all clinical consultations on time during the first 12 months of ART. Suggested target: ≥80%</p>
EWI 6: ARV drug-supply continuity	<p>a. Percentage of months in a designated year in which there were no ARV drug stock-outs. Suggested target: 100%</p> <p>b1. Percentage of patients on first-line ART whose regimen was stopped, modified or incompletely dispensed at the pharmacy due to stock-outs or shortages during a designated year. Suggested target: 0%</p> <p>b2. Percentage of patients initiating ART at the site whose regimen was stopped, modified, or incompletely dispensed at the pharmacy during the first 12 months of ART due to ARV stock-outs or shortages. Suggested target: 0%</p>
Optional EWI 7: Patient adherence to ART	<p>a. Percentage of patients who demonstrate 100% adherence by pill count. Suggested target 100%</p> <p>b. Percentage of patients who demonstrate 100% adherence by other standardized measure of adherence. Suggested target 100%</p>
Optional EWI 8: Viral load suppression 12-months after ART initiation	Percentage of patients initiating ART at the site whose viral load is <1000 copies/ml after 12 months of ART. Suggested target ≥70%

TABLE 3

Published WHO HIVDR Threshold Surveys

Study	Country (geographic region)	Sample type	Year of survey	Prevalence classification	Subtypes
Maphalala et al. [91]	Swaziland (Manzini- Mbabane corridor)	<25 year old antenatal clinic	July-August 2006	<5% to all drug classes	98% C, 2% B
Somi et al [92]	Tanzania (Dares Salaam)	<25 year old antenatal clinic	November 2006- February 2005	<5% to all drug classes	33.3% A1, 33.3% C, 10.3% D
Aghokeng et al [93]	Chad (NDjamena)	<25 year old antenatal clinic	2006-2007	<5% to all drug classes	30.5% CRF11_cpx, 11.1% G, 11.1% A-Cam, 8.3% A, 11.0% D, 5.5% CRF01_AE, 5.5% CRF02_AG, 5.5% CRF06_cpx, 5.5% CRF13_cpx
Aghokeng et al [93]	Cameroon (Yaoundé, Douala)	<25 year old antenatal clinic	2006-2007	Between 5% and 15% NRTI, NNRTI	Yaoundé: 8.2% D, 2.0% F2, 4.1% G, 2.0% A, 4.1% A-Cam, 2.0% CRF01_AE, 4.1% CRF11_cpx, 2.0% CRF18_cpx, 2.0% CRF25_cpx, 2.0% 01.A, 2.0% 02.A1, 4.1% 01.DU Douala: 2.0% A, 2.0% D, 4.0% F2, 2.0% G, 6.0% CRF11_cpx, 2.0% CRF13_cpx, 4.0% CRF18_cpx, 6.0% CRF37_cpx, 2.0% 01.A, 4.0% 02.25
Pillay et al [94]	South Africa (Gauteng Province)	<25 year old antenatal clinic	October 2002, October 2004	<5% to all drug classes	100% C
Ledwaba et al [95]	South Africa (Kwa-Zulu Natal, Gauteng, Western Cape)	<25 year old antenatal clinic	2002-2007	<5% to all drug classes	NA
Abegaz et al [96]	Ethiopia (Addis Ababa)	<25 year old antenatal clinic	April-August 2005	<5% to all drug classes	97.4% C, 2.6% recombinant CRF02_AG
Kamoto et al [97]	Malawi (Lilongwe City)	<25 year old antenatal clinic	October-December 2006	<5% to all drug classes	100% C
Ndambi et al [98]	Uganda (Entebbe)	<25 year old antenatal clinic	2006-2007	<5% to all drug classes	48% A1, 39% D, 2% A2, 2% C, 99% intersubtype recombinant A1/D
Nguyen et al [99]	Vietnam (Hanoi)	<25 year old antenatal clinic	February-August 2006	<5% to all drug classes	34.7% CRF01, 20.4% CRF15, 44.9% CRF01 and CRF15
Sirivichayakul et al [100]	Thailand (Bangkok Metropolitan Area)	Blood donors, voluntary counseling and testing	July 2005-April 2006	<5% to all drug classes	80% CRF01_AE, 17% B, 2% CRF01_AG
WHO [101]	Indonesia (Jakarta)	Injection drug use		<5% to all drug classes	NA

Circulating recombinant forms (CRF)
Not available (NA)