Human Immuno deficiency Virus Drug Resistance: 2018 Recommendations of the International Antiviral Society–USA Panel

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Background. Contemporary antiretroviral therapies (ART) and management strategies have diminished both human immunodeficiency virus (HIV) treatment failure and the acquired resistance to drugs in resource-rich regions, but transmission of drug-resistant viruses has not similarly decreased. In low- and middle-income regions, ART roll-out has improved outcomes, but has resulted in increased acquired and transmitted resistances. Our objective was to review resistance to ART drugs and methods to detect it, and to provide updated recommendations for testing and monitoring for drug resistance in HIV-infected individuals.

Methods. A volunteer panel of experts appointed by the International Antiviral (formerly AIDS) Society–USA reviewed relevant peer-reviewed data that were published or presented at scientific conferences. Recommendations were rated according to the strength of the recommendation and quality of the evidence, and reached by full panel consensus.

Results. Resistance testing remains a cornerstone of ART. It is recommended in newly-diagnosed individuals and in patients in whom ART has failed. Testing for transmitted integrase strand-transfer inhibitor resistance is currently not recommended, but this may change as more resistance emerges with widespread use. Sanger-based and next-generation sequencing approaches are each suited for genotypic testing. Testing for minority variants harboring drug resistance may only be considered if treatments depend on a first-generation nonnucleoside analogue reverse transcriptase inhibitor. Different HIV-1 subtypes do not need special considerations regarding resistance testing.

Conclusions. Testing for HIV drug resistance in drug-naive individuals and in patients in whom antiretroviral drugs are failing, and the appreciation of the role of testing, are crucial to the prevention and management of failure of ART.

Keywords. HIV; antiretroviral therapy; drug resistance; therapeutic failure; resource-rich; low and middle income countries; HIV-1 subtype; genotypic drug resistance; sanger sequencing; next generation sequencing.

This report [8] examines recent information regarding HIV drug resistance in resource-rich and LMIC, and provides updated recommendations [8, 9]. Drug-resistant mutations (DRMs) that impact treatment responses are updated regularly [9]. Implementation of next-generation sequencing methods is increasing and has changed approaches to drug resistance testing. These new approaches, and the insights they provide (eg, minority drug-resistant variants), are also addressed. Table 1 provides a summary of definitions of terms relevant for HIV drug resistance.

Epidemiology, Origin, and Effect of Transmitted Drug Resistance

Prevalence of Transmitted Drug Resistance in Resource-rich Countries

Recommendations are provided in Appendix Box 1. TDR has been observed in virtually all countries where drug-resistance testing has been performed [3]. Frequencies vary substantially over time and by country. The prevalence of TDR is highest for nucleoside analogue reverse transcriptase inhibitors (nRTIs) and nonnucleoside analogue reverse transcriptase

References

1. Department of Health and Human Services. Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents. https://www.aidsinfo.nih.gov/guidelines. Updated December 2017. Accessed May 18, 2018.
2. Dabis F, Mab NBC, Dabis F, et al. Antiretroviral treatment for HIV infection in low- and middle-income countries. Cochrane Database Syst Rev 2014; 8:CD005759. doi:10.1002/14651858.CD005759.pub4
3. De Wit S, Douek DC, Dustin ML, et al. The natural history of drug-resistant HIV-1 infection. Nat Med 2008; 14(1):128–34. doi:10.1038/nm1718
4. The WHO Collaborative Study of Drug Resistance in HIV-1. Estimating the global prevalence of antiretroviral drug resistance: a concentrated analytical approach. AIDS 2013; 27(18):2633–41. doi:10.1097/QAD.0000000000000119
5. Department of Health and Human Services. Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents. https://www.aidsinfo.nih.gov/guidelines. Updated December 2017. Accessed May 18, 2018.
inhibitors (NNRTIs); is lower for protease inhibitors (PIs); and, so far, is rare for integrase strand transfer inhibitors (InSTIs). Frequencies may vary by location and time of testing. Table 2 summarizes the prevalence of TDR in some recent studies in seroconverter cohorts or in drug-naive individuals.

The prevalence of TDR ranged from 6.6% to 11% and time trends seem to be rather stable, except in the United Kingdom, where TDR prevalence peaked in 2002 at 14% and dropped to 8% to 9% in 2009 [18, 19] and to 6.6% in 2013 [12]. In the Swiss HIV Cohort Study, the yearly TDR prevalence in recently infected patients fluctuated between 2.2% and 15.5% from 2000 to 2013, attributed in part to the introduction of new drugs (eg, boosted PIs in 2000 and InSTIs in 2008), after which substantial transient declines occurred [20]. Data on the transmission of InSTI resistances are scant. The larger studies, to date from the Swiss HIV Cohort Study and the United Kingdom, did not find any transmitted major InSTI DRMs since the class was introduced in 2007, despite the fact that thousands of patients are being treated with these drugs [12, 16, 17]. Anecdotal cases, however, have been reported [21, 22]. Thus, as seen for all drugs used at high frequency, InSTI TDR likely will increase over time.

### Prevalence of Transmitted or Pretreatment Drug Resistance in Low- and Middle-income Countries

With expanding use of ART in LMIC, acquired and transmitted drug resistance have increased [3–7]. It is increasingly recognized that a considerable proportion of detected DRMs in individuals in LMIC, previously assumed to be ART-naive, resulted from undisclosed exposure to earlier ART, rather than TDR [23]. Thus in LMIC, pretreatment drug resistance (PDR) data are more feasible to collect than TDR data, and remain important for treatment decisions.

Table 3 summarizes selected recent studies of PDR in LMIC. Surveillance conducted by the World Health Organization (WHO) between 2015 and 2016 in 11 countries from Africa, middle/south America, and Asia found that Uganda, Namibia,
### Table 2. Summary of Selected Prevalence Studies of TDR Mutations in Resource-rich Settings

| Study Name and Citation | Country/Region | Sample Size | Drug-naive Population (Years Studied) | Prevalence of TDR Against Any Respectively Specific Drug Classes [No. (%)] |
|-------------------------|----------------|-------------|--------------------------------------|---------------------------------------------------------------------|
| SPREAD Program [10]     | Europe         | 4140        | Chronically infected\(^a\) (2008–2010) | 344 (8.3) 120 (2.9)% 186 (4.5) 83 (2) NR |
| Robert Koch Institute [11] | Germany                | 809        | Recently infected (2013–2014)          | 87 (10.8)% 21 (2.6) 37 (4.6) 24 (3) NR |
| UK-CHIC [12]            | United Kingdom    | 3 527      | Chronically infected (2013)            | 233 (6.6) 116 (3.3) 124 (3.5) 60 (1.7) 0 (0) |
| ANRS PRIMO study [13]   | France           | 1318       | Recently infected (2007–2012)          | 154 (11.7) 51 (3.9) 69 (5.2) 33 (2.5) NR |
| START Trial [14]        | Europe/United States/ Australia | 1869\(^c\) | Chronically infected (2009–2013)       | 188 (10.1) 85 (4.5) 75 (4) 52 (2.8) NR |
| CASCADE [15]            | Europe (95%), Canada (1%), Australia 1%, sub-Saharan Africa (3%) | 4717    | Recently infected (1996–2012)          | 515 (11) 185 (3.9) 280 (5.9) 144 (3.1) NR |
| SHCS [16]               | Switzerland      | 1316       | Chronically infected                   | NR NR NR NR 0 (0) |
| Stekler et al., 2015 [17] | United States (Seattle) | 82          | Chronically infected (2007–2012)       | NR NR NR NR 0 (0) |

Abbreviations: ANRS PRIMO, French National Agency for Research on AIDS; CASCADE, concerted action on Seroconversion to AIDS and death in Europe; InSTI, integrase strand transfer inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; SHCS, the Swiss HIV cohort study; SPREAD, strategy to control SPREAD of HIV drug resistance; START, strategic timing of antiretroviral treatment; TDR, transmitted drug resistance; UK-CHIC, The UK collaborative HIV cohort.

\(^a\)Duration of infection was not known.

\(^b\)13% of patients were recently infected.

\(^c\)Pretreatment resistance tests were available for 41.5% of all patients enrolled. Resistance tests were from Europe (69%), the United States (21%), Australia (5%), Asia (4%), and South America (1%).

\(^d\)Enrollment for START was conducted on all continents.

### Table 3. Summary of Selected Prevalence Studies of Pretreatment Drug Resistance in Resource-limited Settings

| Study Name and Citation | Country/Region | Sample Size | Drug-naive Population (Years Studied) | Prevalence of PDR Against Any Respectively Specific Drug Classes [No. (%)] |
|-------------------------|----------------|-------------|--------------------------------------|---------------------------------------------------------------------|
| WHO [23]                | Cameroon       | 321         | Chronic (2015–2016)                  | 24 (8.3) 23 (8.1) 5 (2.4) 1 (0.2) NR |
| WHO [23]                | Namibia        | 383         | Chronic (2015–2016)                  | 56 (14.6) 52 (13.8) 6 (1.6) 2 (0.5) NR |
| WHO [23]                | Uganda         | 342         | Chronic (2016)                       | 48 (17.4) 43 (15.4) 11 (5.1) 2 (1.0) NR |
| WHO [23]                | Zimbabwe       | 353         | Chronic (2015–2016)                  | 34 (10.9) 34 (10.9) 3 (0.8) 0 (0) NR |
| WHO [23]                | Guatemala      | 241         | Chronic (2016)                       | 34 (15.1) 29 (13.2) 9 (3.2) 2 (0.6) NR |
| WHO [23]                | Mexico         | 290         | Chronic (2015–2016)                  | 34 (13.5) 22 (9.2) 14 (5.5) 7 (2.6) NR |
| WHO [23]                | Nicaragua      | 171         | Chronic (2015–2016)                  | 40 (23.4) 33 (19.3) 18 (10.5) 0 (0) NR |
| WHO [23]                | Argentina      | 294         | Chronic (2014–2016)                  | 41 (13.8) 33 (10.9) 10 (3.7) 6 (1.9) NR |
| WHO [23]                | Brazil         | 1391        | Chronic (2013–2016)                  | 137 (9.8) 94 (6.8) 50 (3.6) 13 (0.9) NR |
| WHO [23]                | Colombia       | 192         | Chronic (2016)                       | 19 (9.9) 12 (6.3) 7 (3.6) 0 (0) NR |
| WHO [23]                | Myanmar        | 327         | Chronic (2016)                       | 21 (6.4) 16 (3.9) 5 (1.4) 1 (0.2) NR |
| Metanalysis, Gupta et al. [5] | South Africa | 11 855   | Chronic (estimates for 2016)         | 11% [75–15.9] 10.7% [8.4–13.7] 5% [1.2–3.8] NR |
| Metanalysis, Gupta et al. [5] | Eastern Africa | 7169    | Chronic (estimates for 2016)         | 10.1% [5.1–19.4] 10.1% [8.2–12.4] 3.2% [3.3–8.5] NR |
| Metanalysis, Gupta et al. [5] | Western and Central Africa | 4924 | Chronic (estimates for 2016)         | 7.2% [2.9–16.5] 5.3% [3.3–8.5] 3.7% [2.0–6.5] NR |
| Metanalysis, Gupta et al. [5] | Latin America and Caribbean | 16 008 | Chronic (estimates for 2016)         | 9.4% [6.2–12.4] 8.8% [6.2–12.4] 4.1% [2.5–6.5] NR |
| Metanalysis, Gupta et al. [5] | Asia | 16 088 | Chronic (estimates for 2016)         | 3.2% [1.8–5.6] 4% [2.1–6.7] 1.5% [0.5–3.5] NR |

Abbreviations: InSTI, integrase strand transfer inhibitor; NNRTI, nonnucleoside reverse transcriptase inhibitor; PI, protease inhibitor; SHCS, the Swiss HIV cohort study; SPREAD, strategy to control SPREAD of HIV drug resistance; START, strategic timing of antiretroviral treatment; TDR, transmitted drug resistance; UK-CHIC, The UK collaborative HIV cohort.

\(^a\)Values are provided as either No. (%) or % [confidence interval].

\(^b\)Data published in supplementary appendix on page 18 of Gupta et al. [5].
Transmission of Minority Variants Harboring Drug-resistant Mutations

Recommendations are given in Appendix Box 2. In 70% to 90% of acute HIV-1 infections, single-virus variants are detected. However, in 10% to 30%, minority variants are transmitted, often at very low frequencies [36–38]. Minority variants harboring DRMs have been identified in drug-naive and primary infection populations [39–42].

Minority variants harboring DRMs have not been shown to negatively affect treatment responses in acutely-infected patients [41]; however, in some studies they modestly reduced treatment success in chronically-infected drug-naive patients receiving first-generation NNRTI (efavirenz or nevirapine)-based treatment [39, 42, 43]. More information on minority variants and the relevance of cut-offs to detect different frequencies of variants harboring DRMs is available in the Supplementary Data.

EMERGENCE OF RESISTANCE WITH LOW-LEVEL VIREMIA

Recommendations are given in Appendix Box 3. Suppression of HIV ribonucleic acid (RNA) below limits of quantification is the objective of ART [44]. Detectable viremia during ART between the limits of the assay quantification (20 to 50 copies/mL) and 1000 copies/mL is generally referred to as a low-level viremia (LLV). An LLV that is transient and only observed in a single measurement followed by subsequent undetectable viral load is termed a viral blip. A detectable viremia below the limit of quantification is referred to as a residual viremia or very LLV. The source and clinical relevance of very LLV and viral blips are unknown. LLV and blips may reflect technical variability or real biologic processes. A proposed mechanism is the release of a virus from activated, latently-infected cells that, in the presence of ART, does not result in active rounds of virus replication. Low levels of ongoing virus replication due to poor adherence or insufficient drug penetration in certain tissues and anatomical compartments may also occur [45–50].

Drug resistance can emerge in patients with an HIV-1 RNA below 1000 copies/mL. Studies have utilized different thresholds for LLV and different criteria for resistance; however, each confirmed that drug resistance can emerge at low levels of HIV replication, in the range of 50 to 200 copies/mL, with increased risk at higher levels in the presence of the selective pressure of ART [51–53].

Although resistance assay kits are only approved by the Food and Drug Administration for HIV RNA levels above 1000 copies/mL, resistance testing is feasible at lower ranges of viremia [44, 51, 53–55]. During polymerase chain reaction amplification, more plasma can be used to increase the amount of HIV RNA extracted. The Supplementary Data summarizes existing data on the relevance of LLV and blips in treated individuals in more detail.

EFFECT OF SUBTYPE ON HIV-1 DRUG RESISTANCE

Recommendations are given in Appendix Box 4. HIV-1 group M viruses have evolved into numerous subtypes and circulating recombinant forms, differing from each other by approximately 12% in HIV-1 pol. Subtype B viruses account for about 10% overall, but have been disproportionately studied, as they are the predominant subtype in North America and Europe. As ART has expanded globally, the effect of subtype on HIV-1 drug resistance has received increasing attention.

Virtually all amino acid differences between subtypes are polymorphisms: variants that occur commonly in the absence...
of therapy and have little, if any, phenotypic or clinical effect on antiretroviral drugs (ARVs). Thus, most studies suggest that individual ARVs and standard ART regimens are similarly active, regardless of subtype [56–63]. Increased risk of virologic failure has been associated with particular subtypes, but most studies are confounded by geographic location, treatment facilities, and clinical, social, and economic statuses that could affect outcome differences among individuals infected with different subtypes [64–67].

HIV-2 infects more than 1 million persons, most of whom reside in or have emigrated from West Africa [68]. It differs from HIV-1 by more than 50% of its genome. HIV-2 is intrinsically resistant to NNRTIs and is variably susceptible to PIs [69, 70]. The potential impact of different subtypes on ART outcomes is discussed in the Supplementary Data.

**METHODS FOR HIV-1 RESISTANCE TESTING**

**Resistance Test Options**

In most situations, genotypic testing for resistance is the test of choice because it is faster, less expensive, and sufficient to predict drug susceptibility. Phenotypic testing is more expensive, technically demanding, and requires a highly-specialized laboratory infrastructure, but is recommended in certain situations. Methodologic aspects and challenges of resistance testing are described in the Supplementary Data.

The bulk of evidence associating resistance with clinical outcomes has been generated with sequencing of plasma HIV RNA. For individuals with LLV (ie, <200 copies/mL), sequencing of peripheral blood mononuclear cell (PBMC) DNA is technically feasible and more likely to provide an HIV genotype than plasma. However, PBMCs contain HIV DNA that has been archived throughout the patient’s infection, and may be discordant with plasma testing. Clinicians should judge results from PBMC testing with caution [71, 72]. More detailed discussion on proviral DNA sequencing is provided in the Supplementary Data.

**Recommended Genomic Regions for Sequencing**

To determine what new regimen to use for patients in whom ART is failing, the protease and the first half of the reverse transcriptase (up to at least nucleotide 215) should be sequenced. If an InSTI-containing treatment has failed, integrase should be sequenced. Although of interest for better understanding of patterns at time of failure, baseline InSTI resistance testing is currently not cost-effective, as transmitted InSTI resistance is infrequent [73]. Baseline InSTI resistance testing should be considered, however, in select patients with evidence of TDR, such as those with nRTI- or multi-class resistances. In such patients, the risk of also having transmitted InSTI resistance is likely to be higher than in patients without TDR, and the consequences of virologic failure on an InSTI-containing initial regimen may be more severe.

Sequencing of other regions (C-terminus of reverse transcriptase, group-specific antigen) or even a near-full length of HIV-1 might be useful in research settings [74]. Sequencing of the third variable loop (V3) of the envelope glycoprotein, gp120, can determine whether a virus is R5 tropic, and thus might respond to inclusion of a chemokine receptor 5 (CCR5) antagonist in ART. Genotypic tropism testing performance might be comparable to phenotypic tropism assays, particularly when NGS is used [75–78]. However, testing for genotypic tropism from the PBMC compartment is less accurate than plasma testing [75]. A more detailed discussion of entry inhibitor resistance and novel drug formulations is available in the Supplementary Data.

**Genotypic Resistance Test Interpretation**

Genotypic test results require an interpretation, because there are many DRMs that often arise in complex patterns and cause varying levels of reduced drug susceptibilities [79, 80]. Genotypic test interpretation systems are either rule-based or machine-learning systems. Rule-based systems require a knowledge base and a set of derived rules. The knowledge base usually comprises studies of whether a drug selects a DRM in vitro or in patients, whether a DRM reduces drug susceptibility in site-directed mutants or clinical isolates, and whether a DRM is associated with reduced virologic response to a regimen containing a specific ARV. Virologic response studies have usually been performed in the context of clinical trials [81]. Such studies have assessed the effect of nRTI-associated DRMs on virologic responses to regimens containing abacavir or tenofovir disoproxil fumarate [82, 83]; PI-associated DRMs on responses to regimens containing lopinavir/ritonavir and darunavir/ritonavir [84, 85]; NNRTI-associated DRMs on responses to regimens containing etravirine [86]; and InSTI-associated DRMs on responses to regimens containing dolutegravir [87].

Rule-based systems are more commonly used for interpretation, because they consider diverse forms of data and incorporate expert opinions [80, 88–90]. These systems are reproducible, transparent, and educational, but subjective. Well-described rule-based systems include those from the French National Agency for Research on AIDS and Viral Hepatitis, Rega, HIV Genotypic Resistance-Algorithm Deutschland, and the Stanford HIV Drug Resistance Database [80, 91, 92]. Although these systems may produce somewhat different estimates of drug resistance for the same drug, their predictive ability generally has been similar [88, 89, 93]. An online system for interpreting HIV-2 sequences has also been developed [94].

Machine-learning systems use datasets containing large amounts of data; for example, correlating DRMs in a sequence with reduced susceptibility [95–97] or with virologic response to a new treatment regimen [98, 99]. With sufficiently large numbers of such correlations, these systems...
can use genotypic data to predict fold-reductions in susceptibility [95, 96] or the likelihood of virologic suppression with a new regimen [97–99].

Interpretation of Phenotypic Resistance Tests
Phenotypic test results require interpretation, because the clinical significance of fold-change reductions in susceptibility differs among drugs [98, 100]. Interpretation of these results usually requires studies that indicate cutoff values for each drug: the fold-reduction in drug susceptibility that exceeds the uppermost values for wild-type viruses (biologic cutoff) [100]; the lowest fold-reduction in susceptibility that indicates reduced likelihood of responding to therapy with a drug (lower clinical cutoff); and the lowest fold-reduction in susceptibility that indicates a drug will likely be completely inactive (upper clinical cutoff). Clinical cutoff values for an ARV are assay-dependent, and therefore need to be established for each phenotypic assay used in a clinical setting [98, 101].

Limitations of Drug Resistance Interpretation Systems
Genotypic and phenotypic test interpretations cannot provide specific treatment recommendations, because they do not integrate all data required for therapy selection, such as treatment history, previous resistance test results, minority variants harboring DRM archived in the latent reservoirs, plasma HIV-1 RNA level, CD4+ cell count, pharmacologic interactions, hepatic and renal status, or the likelihood of adherence. Interpretation systems vary in how they account for differences in potencies of different ARVs, and do not incorporate fundamental principles of how specific regimens should be constructed. Therefore, clinicians must either have a sound understanding of the principles of therapy to optimally use results of drug resistance tests or have access to expertise [33, 35]. An extended discussion on interpretation systems is available in the Supplementary Data.

CLINICAL APPLICATIONS AND RECOMMENDATIONS

Table 4 summarizes in whom and when genotypic resistance testing should be performed. With the recent recommendations to initiate therapy with an InSTI [33], the current likelihood of a compromising DRM is low. Regardless, even if treatment is initiated quickly, adjustments can be made within days if test results so indicate. The HIV-1 RNA threshold of 200 copies/mL is a technical limit; that is, the minimum copy number at which the likelihood of obtaining a test result is above 70% [53, 55, 102]. HIV genotyping below 200 copies/mL may produce clinically meaningful data, but the chance of obtaining an interpretable genotype may be too low for routine clinical use [53, 55, 102]. Access to drug resistance testing may be limited by economic constraints or local technical capacity.

USE OF GENETIC SEQUENCES FOR OTHER PURPOSES

With routine use of resistance testing for clinical purposes in the late 1990s [103], it became possible to establish large sequence databases [20, 104]. Linking sequences to clinical and epidemiologic data provides a public health infrastructure to monitor transmission of drug resistance and the risk conferred by the emergence of resistance on therapy. These approaches have also defined and validated clinical interpretations of drug resistance, such as those described earlier.

Large HIV genetic databases have also facilitated the application of increasingly sophisticated phylogenetic-based analyses to assess dynamics of virus spread, taking advantage of the inherent variation between sampled viral sequences [105]. This approach has uncovered key characteristics of the epidemic, particularly where the density of sampling (eg, the proportion of infected individuals represented by viral sequence) has been high. Use of large-scale viral sequences for purposes other than resistance testing is described in the Supplementary Data.

SUMMARY AND FUTURE DIRECTIONS

Despite the unprecedented global rollout and success of ART, drug resistance continues to emerge with treatment failure, and TDR persists. Divergent patterns of resistance between resource-rich and -limited settings have evolved. In the former, resistance testing, viral load monitoring, and access to care and to ART have resulted in a continuing decrease of acquired drug resistance and stable rates of TDR. In contrast, in LMIC, limited availability of drugs and inadequate monitoring of and acting on viral load and drug resistance has contributed to a steep increase in drug resistance. New strategies, such as starting with regimens with greater potency and genetic barriers (eg, with InSTIs), providing increased options for second- and third-line regimens, implementing viral load testing to identify virologic failures early, and raising capacities for resistance testing at baseline and after treatment failure are prerequisites to secure long-term global success of ART [106].

Since the last report [8], recommendations to initiate ART have fundamentally changed; all individuals with HIV infections should be treated as early as possible after infection, regardless of CD4+ count [2, 33, 35, 107–111]. Concerns that large-scale earlier treatment initiation would give rise to more resistance has not been confirmed in resource-rich settings; in fact, resistance emergence decreases with earlier treatment initiation [1, 112, 113].

This report is primarily written for settings that have access to resistance testing for HIV patient management, whereas most people with HIV live in LMIC, where most HIV drug resistance testing is applied to epidemiologic monitoring. Available data on prevalence and TDR or PDR in LMIC are limited and delayed, thus often underestimating those numbers.
In conclusion, testing for HIV drug resistance, and the appreciation of its role, is crucial to the prevention and management of failure of ART.

Supplementary Data
Supplementary materials are available at Clinical Infectious Diseases online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes
The panel designed and conducted the work; collected, managed, analyzed, and interpreted the data; and prepared, reviewed, and approved the manuscript.

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References

1. Scherrer AU, von Wyl V, Yang WL, et al.; Swiss HIV Cohort Study. Emergence of acquired HIV-1 drug resistance almost stopped in Switzerland: a 15-year prospective cohort analysis. Clin Infect Dis 2016; 62:1310–7.

2. World Health Organization. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection. Recommendations for a public health approach. Available at: http://www.who.int/hiv/pub/arv-2016/en/. Accessed 4 January 2017.

3. Rhee SY, Blanco JL, Jordan MR, et al. Geographic and temporal trends in the molecular epidemiology and genetic mechanisms of transmitted HIV-1 drug resistance: an individual-patient- and sequence-level meta-analysis. PLoS Med 2015; 12:e1001810.

4. Gupta RK, Jordan MR, Sultan BJ, et al. Global trends in antiretroviral resistance in treatment-naive individuals with HIV after rollout of antiretroviral treatment in resource-limited settings: a global collaborative study and meta-regression analysis. Lancet 2012; 380:1250–8.

5. Gupta RK, Gregson J, Parkin N, et al. HIV-1 drug resistance before initiation or re-initiation of first-line antiretroviral therapy in low-income and middle-income countries: a systematic review and meta-regression analysis. Lancet Infect Dis 2018; 18:346–55.

6. Stadeli KM, Richman DD. Rates of emergence of HIV drug resistance in resource-limited settings: a systematic review. Antivir Ther 2013; 18:115–23.

7. Hamers RL, Wallis CL, Kityo C, et al.; PharmAccess African Studies to Evaluate Treatment Resistance. HIV-1 drug resistance in antiretroviral-naive individuals in sub-Saharan Africa after rollout of antiretroviral therapy: a multicentre observational study. Lancet Infect Dis 2011; 11:750–9.

8. Hirsch MS, Günthard HF, Schapiro JM, et al. Antiretroviral drug resistance testing in adult HIV-1 infection: 2008 recommendations of an International AIDS Society–USA panel. Clin Infect Dis 2008; 47:266–85.

9. Wensing AM, Culvee V, Günthard HF, et al. 2017 Update of the drug resistance mutations in HIV-1. Top Antivir Med 2017; 24:132–3.

10. Hofstra LM, Sauvageot N, Albert J, et al.; SPREAD Program. Transmission of HIV drug resistance and the predicted effect on current first-line regimens in Europe. Clin Infect Dis 2016; 62:655–63.

11. Hauser A, Hofmann A, Hanke K, et al. National molecular surveillance of recently acquired HIV infections in Germany, 2013 to 2014. Euro Surveill 2017; 22:30546.

12. Tostevin A, White E, Dunn DT, et al.; UK HIV Drug Resistance Database. Recent trends and patterns in HIV-1 transmitted drug resistance in the United Kingdom. HIV Med 2017; 18:204–13.

13. Frange P, Assoumou L, Descamps D, et al.; French ANRS CO 6 PRIMO Cohort, the ANRS 147 OPTIPRIM Clinical Trial and the AC11 Resistance Study Groups; French ANRS CO 6 PRIMO Cohort the ANRS 147 OPTIPRIM Clinical Trial and the AC11 Resistance Study Groups. HIV-1 subtype B-infected MSM may have driven the spread of transmitted resistant strains in France in 2007-12: impact on susceptibility to first-line strategies. J Antimicrob Chemother 2015; 70:2084–9.

14. Baxter JD, Dunn D, White E, et al.; International Network for Strategic Initiatives in Global HIV Trials (INSIGHT) START Study Group. Global HIV-1 transmitted drug resistance in the INSIGHT Stratified Strategic Timing of AntiRetroviral Treatment (START) trial. HIV Med 2015; 16(Suppl 1):77–87.

15. Olson A, Bannert N, Sönnerborg A, et al.; for CASCADE Collaboration in EuroCoord. Temporal trends of transmitted HIV drug resistance in a multinational serocohort. AIDS 2018; 32:161–9.

16. Schererrer A, Yang WL, Kouyouos RD, et al.; Swiss HIV Cohort Study. Successful prevention of transmission of integrase resistance in the Swiss HIV Cohort Study. J Infect Dis 2016; 214:399–402.

17. Stekler JD, McKernan J, Milne R, et al. Lack of resistance to integrase inhibitors among antiretroviral-naive subjects with primary HIV-1 infection. 2007–2013. Antivir Ther 2015; 20:77–80.

18. Mourad R, Chevennet F, Dunn DT, et al.; UK HIV Drug Resistance Database & the Collaborative HIV, Anti-HIV Drug Resistance Network. A phylo-type-based analysis highlights the role of drug-naive HIV-positive individuals in the transmission of antiretroviral resistance in the UK. AIDS 2015; 29:1917–25.

19. Dolling D, Sabin C, Delpech V, et al. Time trends in drug resistant HIV-1 infections in the United Kingdom up to 2009: multicentre observational study. BJM 2012; 345:e5253.

20. Yang WL, Kouyouos R, Schererrer AU, et al.; Swiss HIV Cohort Study. Assessing the paradox between transmitted and acquired HIV-1 drug resistance mutations in the Swiss HIV Cohort Study from 1998 to 2012. J Infect Dis 2015; 212:28–38.

21. Boyd SD, Maldarelli F, Sereti I, et al. Transmitted raltegravir resistance in an HIV-1 CRF_06 AG-infected patient. Antivir Ther 2011; 16:257–61.

22. Hernandez AL, Ocfemia MCB, Saduvala N, et al. HIV integrate genotypic testing and resistance in the United States—9 jurisdictions (abstract 478). In: Program and Abstracts of the Conference on Retroviruses and Opportunistic Infections (2017). Seattle, Washington.

23. World Health Organization. Guidelines on the public health response to pretreatment HIV drug resistance: supplement to the 2016 consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection. 2nd ed. 2016. Available at: http://apps.who.int/iris/bitstream/10665/235580/1/9789241550055-eng.pdf?ua=1. Accessed 6 September 2017.

24. Boerma RS, Sigaloff KC, Akanmu AS, et al. Alarming increase in pretreatment HIV drug resistance in children living in sub-Saharan Africa: a systematic review and meta-analysis. J Antimicrob Chemother 2017; 72:365–71.

25. Drescher SM, von Wyl V, Yang WL, et al.; Swiss HIV Cohort Study. Treatment-naive individuals are the major source of transmitted HIV-1 drug resistance in men who have sex with men in the Swiss HIV Cohort Study. Clin Infect Dis 2014; 58:285–94.

26. Yang WL, Kouyouos RD, Bondi I, et al.; Swiss HIV Cohort Study. Persistence of transmitted HIV-1 drug resistance mutations associated with fitness costs and viral genetic backgrounds. PLoS Pathog 2015; 11:e1004722.

27. Marzel A, Shilaih M, Yang WL, et al.; Swiss HIV Cohort Study. HIV-1 transmission in drug-resistant patients. J Infect Dis 2016; 214:399–403.

28. Brenner BG, Roger M, Routy JP, et al.; Quebec Primary HIV Infection Study Group. High rates of forward transmission events after acute/early HIV-1 infection. J Infect Dis 2007; 195:951–9.

29. Hollingsworth TD, Anderson RM, Fraser C. HIV-1 transmission, by stage of infection. J Infect Dis 2008; 198:687–93.

30. Thompson MA, Aberg JA, Cahn P, et al.; International AIDS Society–USA. Antiretroviral treatment of adult HIV infection: 2010 recommendations of the International AIDS Society–USA panel. JAMA 2010; 304:321–33.

31. Thompson MA, Aberg JA, Hoy JF, et al. Antiretroviral treatment of adult HIV infection: 2012 recommendations of the International Antiviral Society–USA panel. JAMA 2012; 308:387–402.

32. Günthard HF, Abegh JA, Eron JJ, et al.; International Antiviral Society–USA Panel. Antiretroviral treatment of adult HIV infection: 2014 recommendations of the International Antiviral Society–USA Panel. JAMA 2014; 312:410–25.

33. Günthard HF, Saag MS, Benson CA, et al. Antiretroviral drugs for treatment and prevention of HIV infection in adults: 2016 recommendations of the International Antiviral Society–USA panel. JAMA 2016; 316:191–210.

34. Ryom L, Boesecke C, GSlev V, et al.; EACS Governing Board. Essentials from the 2015 European AIDS Clinical Society (EACS) guidelines for the treatment of adult HIV-positive persons. HIV Med 2016; 17:83–8.

35. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services. Available at: http://aidsinfo.nih.gov/contentfiles/ bvguidelines/adultandadolescentgpl.pdf. Accessed 20 February 2018.

36. Abrahams MR, Anderson JA, Giorgi EE, et al.; CAPRISA Acute Infection Study Team; Center for HIV-AIDS Vaccine Immunology Consortium. Quantitating the multiplicity of infection with human immunodeficiency virus type 1 subtype C reveals a non-poison distribution of transmitted variants. J Virol 2009; 83:5556–67.

37. Keefe BE, Giorgi EJ, Salazar-Gonzalez JE, et al. Identification and characterization of transmitted and early founder virus envelopes in primary HIV-1 infection. Proc Natl Acad Sci USA 2008; 105:7552–7.
38. Rieder P, Joos B, Scherrer AU, et al. Characterization of human immunodefici
cy virus type 1 (HIV-1) diversity and tropism in 145 patients with primary HIV-1 infection. Clin Infect Dis 2011; 53:1271–9.

39. Cozzi-Lepri A, Noguera-Julian M, Di Giannonno F, et al.; CHAIN Minority HIV-1 Variants Working Group. Low-frequency drug-resistant HIV-1 and risk of virological failure to first-line NNRTI-based ART: a multicohort European case-control study using centralized ultraresensive 454 pyrosequencing. J Infect Dis 2015; 13:7030–40.

40. Giansella S, Delport W, Pacold ME, et al. Detection of minority resistance during early HIV-1 infection: natural variation and spurious detection rather than transmission and evolution of multiple viral variants. J Virol 2011; 85:8359–67.

41. Metzner KJ, Rauch P, von Wyl V, et al. Efficient suppression of minority drug-resistant HIV-1 variants present at primary HIV-1 infection by ritonavir-boosted protease inhibitor-containing antiretroviral therapy. J Infect Dis 2010; 201:11063–71.

42. Metzner KJ, Scherrer AU, von Wyl V, et al; Swiss HIV Cohort Study. Limited clinical benefit of minority K103N and Y181C-variant detection in addition to routine genotypic resistance testing in antiretroviral-therapy-naive patients. AIDS 2014; 28:2231–9.

43. Li JZ, Paredes R, Ribaudo HJ, et al. Low-frequency HIV-1 drug resistance mutations and risk of NNRTI-based antiretroviral treatment failure: a systematic review and pooled analysis. JAMA 2011; 305:1327–35.

44. Ryscavage P, Kelly S, Li JZ, Harrigan PR, Taibo B. Significance and clinical management of persistent low-level viremia and very-low-level viremia in HIV-1-infected patients. Antimicrob Agents Chemother 2014; 58:3585–98.

45. Wynn HE, Brundage RC, Fletcher CV. Clinical implications of CNS penetration of antiretroviral drugs. CNS Drugs 2002; 16:595–609.

46. Baheti G, Riser JJ, Havens PL, Fletcher CV. Plasma and intracellular population pharmacokinetic analysis of tenofovir in HIV-1-infected patients. Antimicrob Agents Chemother 2011; 55:5294–9.

47. Trezza CR, Kashuba AD. Pharmacokinetics of antiretrovirals in genital secretions and anatomic sites of HIV transmission: implications for HIV prevention. Clin Pharmacokinet 2014; 53:611–24.

48. Maggiofio D, Di Filippo E, Comi L, et al. Reduced adherence to antiretroviral therapy is associated with residual low-level viremia. Pragmat GOb Res 2017; 8:91–7.

49. Leirer G, Grabmeier-Pistlshammer K, Steuer A, et al. A single quantifiable viral load is predictive of virological failure in human immunodeficiency virus (HIV)-infected patients on combination antiretroviral therapy: the Austrian HIV Cohort Study. Open Forum Infect Dis 2016; 3:ofi089.

50. González-Serna A, Swenson LC, Watson B, et al. A single unimpaired plasma drug concentration measurement during low-level HIV viremia predicts virologic failure. Clin Microbiol Infect 2016; 22:10049–16.

51. Swenson LC, Min JE, Woods CK, et al. HIV drug resistance detected during low-level viremia is associated with subsequent virologic failure. AIDS 2014; 28:1125–34.

52. Tang MW, Liu TF, Shafer RW. The HIVdb system for HIV-1 genotypic resistance interpretation. Interimvirology 2012; 55:98–101.

53. González-Serna A, Min JE, Woods C, et al. Performance of HIV-1 drug resistance testing at low-level viremia and its ability to predict future virological outcomes and viral evolution in treatment-naive individuals. Clin Infect Dis 2014; 58:1165–73.

54. Assoumou L, Charpentier C, Recordon-Pinson P, et al.; ANRS AC-11 Resistance Study Group. Prevalence of HIV-1 drug resistance in treated patients with viral load >50 copies/ml: a 2014 French nationwide study. J Antimicrob Chemother 2017; 72:1769–73.

55. Taiwo B, Gallien S, Aga E, et al. Antiretroviral drug resistance in HIV-1-infected patients experiencing persistent low-level viremia during first-line therapy. J Infect Dis 2011; 204:515–20.

56. White E, Smit E, Churchill D, et al.; UK HIV Drug Resistance Database and UK Collaborative HIV Cohort Study. No evidence that HIV-1 subtype C infection compromises the efficacy of tenofovir-containing regimens: cohort study in the United Kingdom. J Infect Dis 2016; 214:1302–8.

57. Bannister WP, Ruiz L, Loveday C, et al.; EuroSIDA Study Group. HIV-1 subtypes and response to combination antiretroviral therapy in Europe. Antivir Ther 2006; 11:707–15.

58. Chaux ML, Seng R, Frange P, et al.; ANRS PRIMO Cohort Study Group. Increasing HIV-1 non-B subtype primary infections in patients in France and effect of HIV subtype on virological and immunological responses to combined antiretroviral therapy. Clin Infect Dis 2013; 56:880–7.

59. Antiretroviral Therapy Cohort Collaboration, Canadian Observational Cohort Collaboration, UK Collaboration HIV Cohort Study, Collaboration of Observational HIV Epidemiological Research in Europe. Mortality of treated HIV-1 positive individuals according to viral subtype in Europe and Canada: collaborative cohort analysis. AIDS 2016; 30:503–13.
86. Vingerhoets J, Tambuyser L, Azijn H, et al. Resistance profile of etravirine: combined analysis of baseline genotypic and phenotypic data from the randomized, controlled Phase III clinical studies. AIDS 2010; 24:503–14.
87. Eron JJ, Clotet B, Durant J, et al.; VIKING Study Group. Safety and efficacy of doravirine in treatment-experienced subjects with raltegravir-resistant HIV type 1 infection: 24-week results of the VIKING Study. J Infect Dis 2013; 207:740–8.
88. Rhee SY, Fessel WJ, Liu TIE, et al. Predictive value of HIV-1 genotypic resistance test interpretation algorithms. J Infect Dis 2009; 200:453–63.
89. Frentz D, Boucher CA, Assel M, et al. Comparison of HIV-1 genotypic resistance test interpretation systems in predicting virological outcomes over time. PLoS One 2010; 5:e11505.
90. Vercauteren J, Beheydt G, Prosperi M, et al. Clinical evaluation of Rega 8: an updated genotypic interpretation system that significantly predicts HIV-therapy response. PLoS One 2013; 8:e61436.
91. Eberle J, Gürtler L. The evolution of drug resistance interpretation algorithms: ANRS, REGA and extension of resistance analysis to HIV-1 group O and HIV-2. Intervirology 2012; 55:128–33.
92. Obermeier M, Piontti A, Berg T, et al. HIV-GRADE: a publicly available, rules-based drug resistance interpretation algorithm integrating bioinformatic knowledge. Intervirology 2012; 55:102–7.
93. Fox ZV, Geretti AM, Kjaer J, et al. The ability of four genotypic interpretation systems to predict virological response to ritonavir-boosted protease inhibitors. AIDS 2007; 21:2033–42.
94. Charpentier C, Camacho R, Ruell J, et al. HIV-2EU: supporting standardized HIV-2 drug resistance interpretation in Europe. Clin Infect Dis 2013; 56:1654–8.
95. Vermeiren H, Van Craenenbroeck E, Alen P, Bacheler L, Picchio G, Lecocq P; Virco Clinical Response Collaborative Team. Prediction of HIV-1 drug susceptibility phenotype from the viral genotype using linear regression modeling. J Virol Methods 2007; 145:47–55.
96. Altmann A, Dämmer G, Beerwinkel N, et al. Predicting the response to combination antiretroviral therapy: retrospective validation of geno2pheno-THEO on a large clinical database. J Infect Dis 2009; 199:999–1006.
97. Beerwinkel N, Montazer H, Schulmacher H, et al.; Swiss HIV Cohort Study. The individualized genetic barrier predicts treatment response in a large cohort of HIV-1 infected patients. PLoS Comput Biol 2013; 9:e1003203.
98. Winters B, Montaner J, Harrigan PR, et al. Determination of clinically relevant cutoffs for HIV-1 phenotypic resistance estimates through a combined analysis of clinical trial and cohort data. J Acquir Immune Defic Syndr 2008; 48:26–34.
99. Revell AD, Wang D, Wood R, et al.; RDI Data and Study Group. An update to the HIV-TRePS system: the development and evaluation of new global and local computational models to predict HIV treatment outcomes, with or without a genotype. J Antimicrob Chemother 2016; 71:2928–37.
100. Parkin NT, Hellmann NS, Whitcomb JM, Kiss L, Chappell C, Petropoulos CJ. Natural variation of drug susceptibility in wild-type human immunodeficiency virus type 1. Antimicrob Agents Chemother 2004; 48:437–43.
101. Petropoulos CJ, Parkin NT, Limoli KL, et al. A novel phenotypic drug susceptibility assay for human immunodeficiency virus type 1. Antimicrob Agents Chemother 2000; 44:920–8.
102. Santoro MM, Fabeni I, Armenia D, et al. Reliability and clinical relevance of the HIV-1 drug resistance test in patients with low viremia levels. Clin Infect Dis 2014; 58:1156–64.
103. Hirsch MS, Conway B, D’Aquila RT, et al. Antiretroviral drug resistance testing in adults with HIV infection: implications for clinical management. International AIDS Society–USA Panel. JAMA 1998; 279:1984–91.
104. UK Collaborative Group on HIV Drug Resistance. The increasing genetic diversity of HIV-1 in the UK, 2002–2010. AIDS 2014; 28:773–80.
105. Rambaut A, Posada D, Crandall KA, Holmes EC. The causes and consequences of HIV evolution. Nat Rev Genet 2004; 5:52–61.
106. World Health Organization. Global action plan on HIV drug resistance 2017–2021. Available at: http://www.who.int/hiv/pub/drugresistance/hivdr-action-plan-2017–2021/en/. Accessed 19 December 2017.
107. Cohen MS, Chen YQ, McCauley M, et al.; HPTN 052 Study Team. Prevention of HIV-1 infection with early antiretroviral therapy. N Engl J Med 2011; 365:493–505.
108. Rodger AJ, Cambiano V, Braun T, et al.; PARTNER Study Group. Sexual activity without condoms and risk of HIV transmission in serodifferent couples when the HIV-positive partner is using suppressive antiretroviral therapy. JAMA 2016; 316:171–81.
109. Lundgren JD, Babiker AG, Gordin F, et al. Initiation of antiretroviral therapy in early asymptomatic HIV Infection. N Engl J Med 2015; 373:795–807.
110. Danel C, Moh R, Gabillard D, et al. A trial of early antiretrovirals and isoniazid preventive therapy in Africa. N Engl J Med 2015; 373:808–22.
111. European AIDS Clinical Society. European AIDS Clinical Society guidelines 9.0. Available at: http://www.eacsociety.org/guidelines/eacs-guidelines/eacs-guidelines.html. Accessed 20 November 2017.
112. Richman DD. Editorial commentary: HIV is putting up less resistance. Clin Infect Dis 2016; 62:1318–9.
113. Lodi S, Günthard HF, Dunn D, et al.; HIV-CAUSAL Collaboration. Effect of immediate initiation of antiretroviral treatment on the risk of acquired HIV drug resistance. AIDS 2018; 32:327–35.

APPENDIX

**Box 1. Recommendations for Prevalence of Transmitted or Pretreatment Drug Resistance in Resource-rich and -limited Settings (As Available Resources Allow)**

- Resistance testing in drug-naive individuals is recommended at the time of diagnosis to detect potential transmitted drug resistance (TDR; evidence rating A1a).
- TDR and pretreatment drug resistance should be monitored on a country level, accounting for different transmission groups (evidence rating A1a).
- Resistance testing is recommended for perinatally-infected children, particularly those whose mothers received prevention of mother-to-child transmission treatment (evidence rating A1a).

**Box 2. Recommendations for Transmission of Minority Variants Harboring Drug-resistant Mutations**

- Drug resistance testing to detect minority variants is not currently recommended outside of research settings, but may be considered for nonnucleoside analogue reverse transcriptase inhibitors (NNRTIs; evidence rating A1a).
Box 3. Recommendations for detection of Resistance With Low-level Viremia

- Samples with a blip exceeding 200 human immunodeficiency virus (HIV)-1 ribonucleic acid (RNA) copies/mL should be considered for resistance testing, if available (evidence rating CIII).
- Resistance testing is recommended in patients experiencing low-level viremia above 200 copies/mL (evidence rating AIIa).
- To avoid biases during polymerase chain reaction amplification, more plasma can be used to increase the amount of HIV RNA extracted (evidence rating BIII).

Box 4. Recommendations for Effect of Subtype on HIV-1 Drug Resistance

- HIV-1 subtype need not be a consideration regarding HIV drug resistance in selecting antiretroviral therapy (ART) regimens with nucleoside analogue reverse transcriptase inhibitors (nRTIs), NNRTIs, protease inhibitors (PIs), and integrase strand transfer inhibitors (InSTIs; evidence rating AIII).
- For HIV-2, NNRTIs should be avoided regardless of resistance testing, whereas PIs should be used only under the supervision of a physician experienced at using this drug class for treating HIV-2 (evidence rating AIIa).

Box 5. Recommendations for Methods for HIV-1 Resistance Testing

- As a first choice, genotypic resistance testing is recommended (evidence rating AIIa).
- Phenotypic resistance testing is recommended, in certain situations:
  1. to evaluate HIV susceptibility to new and investigational drugs when drug-resistant mutation patterns have not been fully established (evidence rating AIIa);
  2. when genotypic test results are too complex to interpret (evidence rating CIII); or
  3. when ART options are highly limited and, as a result, salvage ART must rely on residual susceptibilities to different drugs that are difficult to predict from genotypic data (evidence rating CIII).
- The recommended compartment for drug resistance testing is plasma (evidence rating AII).
- Inclusion of the protease and first half of the reverse transcriptase (up to at least nucleotide 215) is recommended for all genotypic testing (evidence rating BIII).
- Routine InSTI resistance testing in drug-naive individuals is currently not recommended (BIII).
- Baseline InSTI resistance testing is recommended in select patients with evidence of TDR, such as those with nRTI- or multi-class resistance (evidence rating AIII).
- Monitoring of TDR/pretreatment drug resistance to InSTI in selected sites in resource-rich settings and low- and middle-income countries is recommended (evidence rating AIII).
- Sequencing of other regions (C-terminus of reverse transcriptase, gag) or even a near full-length of HIV-1 is not recommended for routine clinical management (evidence rating AIIa).
- Genotypic tropism testing is recommended if a CCR5 antagonist is considered for treatment (evidence rating BIIa).
- Peripheral blood mononuclear cell genotypic resistance testing is recommended in patients with low-level viremia or in patients who are virologically suppressed (evidence rating AIII).