Clinical and laboratory guidelines for the use of HIV-1 drug resistance testing as part of treatment management: recommendations for the European setting

The EuroGuidelines Group for HIV Resistance*

Viral drug susceptibility is associated with virologic response to new treatments. Standardized drug resistance tests are now available, and data from some clinical trials suggest that the use of drug resistance testing may be associated with improved virologic outcome. However, drug resistance testing is complex in terms of performance, interpretation and clinical application.

HIV-1 drug resistance testing is used across Europe in patient management, but not in a consistent manner. This is due to differences in the national approaches to treatment, treatment management and reimbursement, as well as availability of tests. National guidelines only exist in some countries. In addition, the laboratory quality assurance and quality control standards are not applied uniformly. The EuroGuidelines Group was established to formulate clinical as well as laboratory guidelines for the use of HIV-1 drug resistance testing that are specific for the European setting. The group is comprised of academic clinicians and virologists, scientist from the industry and representatives of the patient community.

The panel of experts will review these guidelines and update them on a yearly basis as new scientific evidence becomes available.

AIDS 2001, 15:309–320

Keywords: HIV-1 drug susceptibility, drug resistance, antiretroviral therapy, protease inhibitors, reverse transcriptase inhibitors, genotype, phenotype

Introduction

HIV-1 drug resistance has been documented in vitro, and associations between resistance and clinical outcomes were established from the earliest days of antiretroviral treatment [1–4]. These associations have been confirmed for multi-drug combination treatment in retrospective studies [5–15]. Prospective studies have documented that testing for HIV-1 drug resistance may improve virological outcome [16–19].

In order for HIV-1 resistance testing to be clinically applicable and of practical use, standardized techniques suitable for high-throughput must be available. In addition, in individual cases, understanding the contribution of resistance to treatment failure and availability of drugs that are active against resistant viruses are crucial.

Progress in technology and an increased understanding of the complexity of HIV-1 drug resistance have increased the feasibility of resistance testing in routine clinical care. In this context, resistance testing for HIV-1 may soon occupy a status of equal importance to antimicrobial resistance testing [20,21]. It should be realized, however, that treatment failure may have a multi-factorial nature, and that, apart from viral susceptibility, factors such as adherence and pharmacokinetics may contribute to a greater or lesser extent.

Recently an International AIDS Society–USA panel consensus statement on antiretroviral drug resistance
testing in adult HIV-1 infection was published [22]. However, there are issues that are particular to Europe. In comparison with the USA there is a greater diversity of HIV-1 subtypes, including recombinants [23–26], which can affect polymerase chain reaction (PCR) efficiency and drug susceptibility [27–31]. Access to HIV-1 drug resistance testing is not uniform amongst, nor within individual European countries and guidelines exist in only some countries [32–34]. Furthermore, there are no standards for the technology, reporting, or reimbursement of resistance tests. Nevertheless, resistance testing is currently already being used by many European physicians independently to guide treatment management.

It is the aim of the EuroGuidelines group to provide a framework for state-of-the-art patient management for Europe. The group consists of representative academic experts from European countries (clinicians and virologists), representatives from industry and the patient community.

We describe here guidelines for the use of resistance testing for the management of HIV-1-infected patients in the European setting. We define indications for resistance testing based on evidence (where available) or opinion of an expert panel. In addition to the clinical indications, we consider aspects relating to the performance and reporting of resistance tests. The recommendations are summarized in Tables 1 and 2.

**Patient populations and clinical indications**

**Treatment-naive patients**

*Recommendation:* HIV-1-resistance testing in patients initiating treatment should always be considered. It is recommended if suspicion of transmission of a resistant virus is high.

The rationale for drug susceptibility testing in patients prior to first treatment rests on: (1) evidence of regular transmission of drug-resistant variants, and (2) negative impact of resistance on first line treatment response. Reduced susceptibility in viruses from untreated patients has been well documented [35–48] and associated with various modes of HIV-1 transmission [49–54]. Systematic monitoring of resistance testing in newly infected patients is required to evaluate the trend of transmission of resistant viruses in the individual European countries.

The reliability of negative findings (absence of resistance) in this patient population may be a function of time since infection. Resistance-associated mutations that lead to decreases in replicative fitness (also referred to as replicative capacity) may be selected against in the absence of drug pressure [55–62]. The timing of the disappearance from the majority population has not been established, and may vary for each mutation. In viruses with multiple resistance-associated mutations, resistance detectability may decline rapidly at the population level [63–65]. Some mutations, may persist in the absence of drug pressure [66] and reversion to non-wild-type genotypes with fully susceptible phenotypes has also been described (e.g. position 215 of reverse transcriptase) [67,68]. The resultant virus population is in all likelihood not 100% wild-type and the proportion of resistant viruses in the population may influence virologic response [69]. Overall this means that after several years of infection without treatment the major circulating viral population does not necessarily reflect the pool of archived viruses. Archived resistant viruses can rapidly reappear under drug pressure. Thus, it is advised to store plasma samples in the early phase of the infection for subsequent resistance testing (Table 1).

In the setting of single-drug first treatment studies, it has been shown that the presence of mutations associated with resistance to zidovudine or nevirapine diminishes the response to these drugs [70,71]. The impact of resistance to individual drugs on the combination regimen will depend on the composition of the regimen and the drug to which reduced susceptibility has been documented. For example, resistance to zidovudine may or may not affect treatment outcome, depending on the regimen [72–75]. Thus, if choices in regimen are available, knowledge of susceptibility status will provide useful information.

A major part of the reported incidence of resistance in untreated patient populations is based on low-level resistance, viral polymorphisms and/or secondary resistance-associated mutations. The clinical implications of these have not yet been clearly established [43,76]. Current data indicate that low-level resistance to non-nucleoside reverse transcriptase inhibitors (NNRTI) does not affect treatment outcome [77,78], whereas secondary protease mutations may or may not influence response to protease inhibitor (PI)-based treatments [43,76]. Some of the secondary mutations are represented within the polymorphisms of the reverse transcriptase and protease genes at varying prevalences in the different subtypes. However, high-level resistance (presence of primary mutations) does occur and has been associated with a suboptimal treatment response [50].

We discuss the recommendations for treatment-naive patients according to whether they are in primary, recent or in chronic stages of infection. The demarcation of these categories is arbitrary and they may rather be considered as a continuum than clearly demarcated time periods.
Table 1. Summarized guidelines and recommendations.

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Strength of evidence (A–C), A = strongest</th>
<th>Level of recommendation (1–3), 1 = strongest</th>
<th>Comments/secondary recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment-naïve patients Primary infection/recent infection</td>
<td>B</td>
<td>1</td>
<td>• If treatment is not initiated, store plasma sample if possible for future reference</td>
</tr>
<tr>
<td>• Test for resistance if transmission rate is high or grounds to suspect transmission from treated individual exist and treatment is to be initiated</td>
<td>C</td>
<td>2</td>
<td>• If resistance test not performed, store plasma if possible</td>
</tr>
<tr>
<td>• Consider resistance testing in other situations prior to initiation of treatment</td>
<td></td>
<td></td>
<td>If resistance test is not performed, store plasma sample from as close to infection date as possible</td>
</tr>
<tr>
<td>Chronic infection Consider testing for resistance if transmission rate is high or grounds to suspect transmission from treated individual exist</td>
<td>B</td>
<td>2</td>
<td>If resistance test is not performed, store plasma sample from as close to infection date as possible</td>
</tr>
<tr>
<td>PEP Treatment should not be delayed due to resistance testing, but if a sample from the index case is available, test and modify treatment of recipient accordingly</td>
<td>B</td>
<td>1</td>
<td>Test results need to be available within the prophylaxis treatment time</td>
</tr>
<tr>
<td>Treated patients Test for resistance in all cases where changes in therapy are considered due to virologic failure</td>
<td>A</td>
<td>1</td>
<td>Resistance testing is only useful/valid within the context of complete history of antiviral treatment and assessment of other reasons for virologic failure</td>
</tr>
<tr>
<td>Pregnancy Test for resistance if the mother has a detectable virus load</td>
<td>B</td>
<td>1</td>
<td>Treatment should not be delayed in mothers presenting late; all treatment adjustments should follow local guidelines</td>
</tr>
<tr>
<td>Pediatrics Test for resistance in HIV-1 infected children born to mothers with detectable viremia while on treatment Considered testing in children with virologic treatment failure</td>
<td>B</td>
<td>1–2</td>
<td>Resistance testing is only useful/valid within the context of complete history of antiviral treatment and assessment of other reasons for virologic failure</td>
</tr>
<tr>
<td></td>
<td>C</td>
<td>2–3</td>
<td></td>
</tr>
</tbody>
</table>

PEP, Post exposure prophylaxis.
In summary, evidence for viral drug resistance has been reported in all published studies assessing drug susceptibility in treatment-naive patients and response to therapy may be affected depending on the extent of reduction of susceptibility. Detectability of resistance may be a function of time since infection, thus this parameter will affect the decision whether or not to use resistance testing in this patient population.

**Primary (and recent) HIV-1 infection**

The presence of reduced drug susceptibility in virus populations from patients with primary and recent infection has been well documented [36,37,44,50,79]. Reported incidences range from 2 to 33% and include viruses with multi-class resistance.

If treatment is initiated during primary HIV-1 infection, resistance testing should be considered strongly. The decision to use resistance testing would be further supported if the transmission rate in the area and/or risk group was shown to be high (e.g. >10%), or if it is known that the index case was treated with anti-retroviral drugs.

The rationale for treating during primary HIV-1 infection is based on preserving HIV-1-specific immune responses [80]. Thus treatment should not be delayed by waiting for the results of a resistance test, but the treatment may be modified when they become available. For patients presenting during primary HIV-1 infection who elect not to begin treatment during this phase, a plasma sample should be stored for future reference. More definitive recommendations for this patient population await more complete information on the rate of transmission of drug-resistant viruses in different demographic populations in Europe.

**Chronic HIV-1 infection**

HIV-1 drug resistance in chronically infected, drug-naive patients has been reported at a lower frequency than in patients with primary HIV-1 infection [35,42,43,81,82], and the prevalence has been inversely associated with time since infection [42]. Thus the recommendation to use resistance testing in this population is less strong than in primary or recent HIV-1 infection. The implications in cases where resistance is detected are clear; however, the absence of detection of resistance may not provide complete information. As for patients in primary stages of infection, testing may be more appropriate if the likelihood for transmission of resistance is high (see above). Detection of 'reversal mutations' [67,68; see above] is indicative of transmission of a resistant virus and may be associated with a reduced virologic response to therapy [83]. Furthermore, preliminary evidence for super-infection years after initial infection has been presented [84]; future guidelines for this patient population may change if this possibility is confirmed.
Guidelines for this patient population may become clearer upon availability of efficient, routinely applicable methods to reliably detect minority populations. Proviral DNA sequencing (from peripheral blood mononuclear cells) has been proposed as an alternative to assess the presence of virus-bearing resistance mutation(s) in archival virus populations [85], but systematic studies are needed to address this issue. As for patients in primary or recent stages of infection, storage of plasma samples prior to treatment initiation preferably collected as close as possible to the date of infection is recommended.

Post-exposure prophylaxis
The rationale for post-exposure prophylaxis is based on immediate intervention [86,87]; treatment should not be delayed while waiting for a resistance test. Transmission of a resistant virus has been implicated in this setting, with accompanying failure of post-exposure prophylactic treatment [49]. Access to treatment history of the index case when available helps to guide treatment selection. In addition, if index case samples can be accessed, treatment of the recipient should be subsequently modified according to the results of the index case resistance test, assuming it is feasible to obtain results early within the prophylaxis treatment time.

Patients exposed to antiretroviral therapy
Recommendation: resistance testing, as an adjunct to antiretroviral treatment and response history, is recommended for all patients experiencing treatment failure for whom treatment change is being considered.

The recommendation to use resistance testing in the management of pre-treated patients presupposes treatment failure with the accompanying need to change treatment. The complex interactions between viral resistance, pharmacokinetics, adherence, cellular resistance and their role in treatment failure are currently under evaluation [16,88–92]. On the one hand, resistance may result in virologic failure, but non-resistance-mediated viral rebound is permissive for the development of resistance. Thus, for patients experiencing treatment failure, resistance testing may be performed for assessing its cause and for optimizing a follow-up regimen.

Recent data from France indicate a decline in the percentage of patients with severe virologic failure (>50,000 copies/ml and CD4 cell count <200 × 10^6 cells/l) over time; nevertheless the potential for HIV-1 drug resistance among treated patients is high, as indicated by the number of patients with virologic failure across Europe [93,94].

Baseline resistance and treatment outcome
The most compelling demonstration of an independent association of baseline resistance and virologic outcome was provided by the re-analysis of eight retrospective studies and presented to the US Food and Drug Administration Advisory Committee in November of last year [15]. The re-analysis provided a uniform statistical data analysis plan. Resistance, treatment response and description of previous treatment histories were clearly defined. Although all studies were carried out in antiretroviral-experienced patients, the patient populations varied with respect to the extent of their previous drug exposure. After adjusting for baseline plasma HIV-1 RNA load and treatment history, susceptibility of HIV-1 to the drugs used and absence of resistance mutations were consistently associated with virologic response. This suggests that resistance testing provides information over and above that acquired by careful history taking. Other studies have also documented the association of resistance and virologic outcome, although the sample sizes were frequently small and evaluation methods not standardized [5,6,8–14,95].

The rationale for routine use of resistance testing (genotypic or phenotypic) in clinical practice is upheld by studies demonstrating direct clinical benefit attributed to the knowledge of baseline susceptibility status in pre-treated patients switching to a new regimen [16–18]. These studies, two using genotyping and one using phenotyping, demonstrated benefits in terms of virologic outcome at week 12 [16,17]) and months 3 and 6 [16] and up to 12 months [16]. They also demonstrated the contribution of expert interpretation [17] and plasma levels of PIs [18] to optimal treatment outcome. In contrast to the above studies, two additional studies, wherein options for follow-up treatment may have been more restricted, did not demonstrate improved virologic response in the arm receiving resistance testing [96,19]. These data indicate that the outcome benefit of resistance testing is highly dependent on the availability of new treatment options.

Considerations for patients with limited previous antiretroviral treatment
Evolution of resistance while on treatment
Virologic rebound in patients experiencing first line failure (or failure after very limited antiretroviral exposure) is not necessarily associated with reduced viral susceptibility to all drugs in combination regimen. Studies have demonstrated that the first mutations to appear are those associated with resistance to drugs with a ‘low genetic barrier’ to resistance. Thus, in triple-drug regimen including lamivudine, the M184V substitution was the most frequent and often the only substitution detected in PI combination regimen [88,89,97], as well as in triple nucleoside regimen [83]; in failures of NNRTI/PI combinations, the characteristic K103N substitution was detected in rebounding viral populations in the absence of PI resistance-associated mutations [98]. Mutations associated with
Virologic failure of PI-based regimen in the absence of viral resistance serves to illustrate the multi-factorial nature of treatment failure. Two studies that have contributed substantially to this topic looked at simplified maintenance regimen in comparison with standard triple combination (indinavir + zidovudine + lamivudine) [88,89]. Thus, although many of the virologic rebounds did occur while patients were not on ‘full highly active antiretroviral therapy (HAART)’, these investigators were able to demonstrate that factors other than viral resistance, such as adherence and plasma drug levels, play important roles in maintaining durable virologic suppression in PI-based regimen. It should be noted, however, that continued viral replication in the presence of antiviral compounds provides the conditions for evolution of drug resistance and cross-resistance within each drug class.

Impact of viral resistance on first HAART regimen

Reduced drug susceptibility to one or more components of a combination may decrease the total activity of the regimen sufficiently to allow virologic breakthrough. Thus previous exposure to mono or dual nucleoside reverse transcriptase inhibitors (NRTIs) was associated with virologic failure of non-PI-based regimen [99] and zidovudine-associated mutations with failure of nevirapine + zidovudine + didanosine [73]. On the other hand, the presence of zidovudine resistance-associated mutations did not predict failure to zidovudine + lamivudine + PI combination regimen for the duration of study follow-up [72,74,75]. Resistance to lamivudine (M184V) was not predictive for virologic failure of abacavir-containing triple nucleoside regimen [100] confirming previous reports that lamivudine resistance did not appear to impact on response to lamivudine-containing triple drug regimen [101].

Pre-existing viral resistance to one or more component of a combination regimen may also ‘endanger’ the other components of the regimen. In a study of amprenavir- or indinavir-based treatment of NRTI pre-treated patients, the presence of reverse transcriptase mutations was an independent factor for virologic failure of the PI combination regimen and was significantly associated with the development of resistance to either amprenavir or indinavir [102].

Resistance testing for this patient population will be useful in elucidating the cause of treatment failure and in designing a second line treatment that is optimized to the parameters and requirements of the individual patient.

Virologic rebound in patients with more extensive previous experience (having experienced at least one HAART failure) is more often associated with viral drug resistance to more than one component of the regimen [103]. The more treatment that a patient’s virus population has been exposed to, the more likely it is that drug-resistant viral variants may be found, either as actively replicating major species, minority variants or archived in non-replicating cells.

Although the association between baseline resistance and virologic outcome has been clearly demonstrated, the challenge lies in translating this into clinical utility. For patients with extensive prior treatment, interpretation of resistance test results may be more difficult, and results must be viewed within the context of other relevant parameters (treatment history, adherence, etc). The research challenge is the elucidation of what constitutes ‘clinically relevant’ resistance for each drug (or drug class), especially in view of the potential to boost PI plasma levels by taking advantage of the pharmacokinetic effects of ritonavir [108,109]. Whether there is any advantage to coupling resistance testing to therapeutic drug monitoring, and if so, for which drug classes, remains to be established.

Other clinical settings

Paediatrics

Recommendation: resistance testing is recommended for HIV-1 infected children born to mothers with detectable viraemia while on treatment.

As in adults, the development of resistance to one or more of the drugs in a treatment regimen is likely to play an important role in virologic failure, but few data are available on development of viral drug resistance in children. In comparison with adults, HAART appears to be less successful at reducing HIV RNA to below the limit of detection. Reasons for this are likely to include the fact that HIV-RNA in children is very high following infection around the time of birth, and does not appear to reach a ‘set point’ until 5–6 years later [110,111] and that adherence may be more...
HIV drug resistance testing

In a clinical trial of lamivudine added to other NRTI therapy [112], the M184V mutation appeared to develop more slowly in children despite high HIV RNA loads [113] and a nested case-control study of resistance testing in children participating in the PACTG 152 trial (zidovudine versus zidovudine + didanosine versus didanosine) found no relationship between development of resistance and disease progression [114]. Thus, non-resistance-associated mechanisms may account for more treatment failure in children. However, the immature immune status, the high viral loads relative to adults and the limited number of drug options within paediatrics (currently eight registered drugs) are indications for recommending testing in infected babies born to mothers with resistant virus. The usefulness of resistance testing in children with virologic failure is currently being evaluated in an ongoing controlled trial (PENTA 8). The results of this trial will inform clearer guidelines for this patient population.

**Pregnancy**

A number of factors influence decision making in this clinical setting. Heterosexual transmission of resistant viruses before and during pregnancy has been documented (see above). Development of resistance may of course also occur due to present or past suboptimal treatment of the mother [115]. Vertical transmission of resistant viruses from infected mother to developing infant has been described [51], and guidelines are currently in place in a number of European countries for the use of antiretroviral drugs during late pregnancy and for the baby to reduce vertical transmission of infection. Thus, resistance testing should be part of HIV-1 treatment and management during pregnancy, and the resulting treatment choice be made in the context of existing guidelines for the prevention of mother-to-child transmission.

We make recommendations according to specific groups:

1. Mothers with detectable viraemia on existing antiretroviral therapy and presenting early for antenatal care should be screened for resistant viruses and therapy should be adjusted according to the results and the developmental state of the foetus.
2. Therapy-naive mothers presenting early for antenatal care should be screened for resistant viruses and therapy selected for maternal care and infant prophylaxis according to local guidelines, taking into account viral drug susceptibility.
3. Mothers presenting late for care and delivery should have a rapid screen for resistant viruses to guide prophylaxis in late pregnancy and in the new-born baby. As in the case of post exposure prophylaxis, therapy is initiated without delay and adjusted on the basis of the resistance results.

In all cases frequent monitoring of virological response to therapy should be carried out and any suboptimal response should provoke further investigation to check adherence and optimize treatment.

**Recommendations pertaining to laboratory and practical application issues in resistance testing**

**Choice of method**

*Recommendation:* no specific type of assay is recommended at this time.

Genotypic- and phenotypic-based assays are fundamentally different but yield complementary information. Phenotypic tests measure virus drug susceptibility, resulting from known or unknown resistance-related mutations and their interactions. Genotypic tests detect mutations in the viral genome that may be associated with decreased drug susceptibility. Of genotypic tests, sequencing of the gene regions of interest has the advantage of detecting all possible resistance-related mutations, whereas point mutation assays detect the presence of particular pre-selected key mutations. Point mutation assays may have greater sensitivity for the detection of resistant variants present as minority populations, but this needs to be weighed against the restricted information that they yield.

All assays used to assess drug susceptibility are PCR-dependent, and, as such, are vulnerable to variations in primer-binding due to HIV-1 subtype differences. More detailed information on the relative merits of different assays is given elsewhere [116].

**Sample source**

*Recommendation:* the recommended sample source is plasma, obtained from individuals before starting, stopping or changing therapy and who have a plasma HIV-1 load above the performance limit of the resistance test.

HIV-1 in plasma is more representative of actively replicating viruses than is virus in circulating infected cells, such as peripheral blood mononuclear cells. As many resistant viruses are less fit in the absence of drugs, the drug-sensitive, or wild-type viruses can become predominant in the population over time in the absence of drug pressure; thus to capture resistance associated with a failing regimen, it is important to collect samples during periods of drug exposure. The initial steps of resistance assays, viral RNA extraction and PCR amplification are similar for all clinically used genotypic and phenotypic assays. The lower limit of viral load for reliability is thus similar for genotypic and phenotypic assays and currently around 1000 RNA co-

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pies/ml plasma. Test results from samples with lower viral load levels may be subject to bias. The volume of plasma used, correct sample preparation (e.g. avoiding heparine as anticoagulant), proper transport and storage conditions are similar as for viral load testing [116].

**Choice of laboratory**

*Recommendation*: genotypic and phenotypic HIV-1 drug resistance testing for clinical purposes should be performed in a certified laboratory under strict quality control and quality assurance standards.

Both genotypic and phenotypic approaches for monitoring HIV-1 drug resistance are complex techniques that require rigorous adherence to testing procedure and intensive quality control [116]. All clinical and research laboratories that perform genotypic and/or phenotypic testing for clinical use should adhere to current accepted laboratory standards and be externally accredited, thus providing assurance that sources of inaccuracies have been minimized. In Europe, appropriate accreditations can be provided nationally or at the European level according to the EN45001 guidelines. Currently marketed genotyping assay kits should undergo appropriate regulatory approval to assure optimal manufacturing of the kit components as well as proper performance. The laboratory performing the assay should include appropriate blank controls and reference strains and should participate in proficiency panel testing provided by an outside agency to ensure the quality of the generated results. An adequate listing of suitable techniques should be available to the clinicians; this can be provided through a web-site. Such a web-site where service providers and clinical laboratories may list their available services and qualifications/accreditations is currently being designed by this panel.

Storage of plasma samples has been recommended numerous times throughout this document. Consideration will need to be given to quality assurance issues relating to storage, documentation and retrieval of samples.

**Interpretation of results**

*Recommendation*: resistance testing reports should include a list of drug-related resistance mutations (genotype) and/or a list of drug-related fold changes in susceptibility (phenotype), with adequate expert interpretations.

Genotypic test results should list the resistance-related mutations found, and their relevance for particular drugs with expert interpretation [117]. Phenotypic test results should list the observed fold changes in susceptibility towards the tested drugs. Although phenotypic data may be more accessible than genotypic data, expert interpretation may nevertheless be necessary to discriminate between clinically relevant resistance and ‘resistance’ where the clinical relevance is not as clear [109].

The interpretation of genotypic and phenotypic analysis is a complex and developing science. Currently, resistance testing is most useful to identify the drugs least likely to have activity. Expert virologists, pharmacologists and clinicians are encouraged to discuss the interpretation of resistance test results to better understand their clinical significance and to decide on treatment changes taking into account all relevant aspects (clinical, virological, immunological and pharmacokinetic parameters as well as compliance issues and treatment history).

**Discussion/comments**

HIV-1 drug resistance, its assessment and incorporation into clinical management is a rapidly growing field. These guidelines as well as supporting documentation will be updated on a regular basis.

At this point in time, the following policy recommendations may be made:

(1) It is recommended that a European-wide tracking system be developed, in order to monitor transmission of HIV-1 drug-resistance in different geographical regions and/or risk groups.

Although transmission of resistance has been frequently documented, to date only two European states have state-funded public health measures in place to track the epidemiology of transmission of resistance. Infection with HIV-1-resistant variants may become a serious public health issue [118], and needs to be monitored at the European level. Models for tracking resistance to other infectious agents exist [119].

(2) To realize the goal of equal standard of care, resistance testing guidelines and educational material need to be disseminated at the local, regional and European level, in an integrated manner.

**Acknowledgements**

We are grateful for the expert assistance provided by Ton Wortman and Brenda Dauer in the preparation of the manuscript and the coordination of the project.
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HIV drug resistance testing EuroGuidelines
Appendix

The EuroGuidelines Group for HIV Drug Resistance Testing

Writing committee: Veronica Miller (Zentrum der Inneren Medizin, J W Goethe University, Frankfurt); Anne-Mieke Vandamme (Rega Institute and University Hospital, AIDS Reference Laboratory, University of Leuven); Clive Loveday (Department of Retrovirology, Royal Free & University College Medical School, University College London); Schlomo Staszewski (Zentrum der Inneren Medizin, J W Goethe University); Jens Lundgren (Department of Infectious Diseases, Hvidovre University Hospital, Hvidovre); Mike Youle (Royal Free Hospital, London); Mounir Ait-Khaled (Glaxo Wellcome R & D, Stevenage); Charles Boucher (Department of Virology, University Medical Center Utrecht); Françoise Brun-Vézinet (Department of Virology, Bichat Hospital, Paris); Nikos Dedes (European AIDS Treatment Group (EATG), Athens); Carlo Giaquinto (Department of Paediatrics, University of Padua, Padua); Kurt Hertogs (Virco Group NV, Mechelen); François Houyez (European AIDS Treatment Group (EATG), Paris); Luc Perrin (Laboratory of Virology, Hôpital Cantonal Universitaire, Geneva); Deenan Pillay (PHLS Antiviral Susceptibility Reference Unit, University of Birmingham Medical School, Birmingham); Jean-Claude Schmit (Retrovirology Laboratory and National Service of Infectious Diseases, Centre Hospitalier de Luxembourg); Robert Schuurman (Department of Virology, University Medical Center Utrecht); Joep Lange (National AIDS Therapy Evaluation Centre, Department of Virology and Department of Internal Medicine, Academic Medical Centre, University of Amsterdam).

Panel members: Dènes Bânhegyi (Department of Immunology and Tropical Medicine, Saint Lazlo Hospital, Budapest); Giuseppe Biondi (Virco Group NV, Mechelen); Arjen Broekhuizen (European AIDS Treatment Group (EATG), Netherlands); Charlene Bush-Donovan (Bayer Diagnostics, USA); Ricardo Camacho (Laboratório de Virologia, Servico de Imuno-Hematologia, Lisbon); Hilde Carlier (Boehringer Ingelheim, Brussels); François Clavel (Bichat Hospital, Paris); Bonaventura Clotet (Fundacio irisCaixa, Hospital Universitari Germans Trias I Pujol, Barcelona); Nathan Clumeck (Saint-Pierre University Hospital, Brussels); Robert Colebunders (Department of Clinical Sciences, Institute of Tropical Medicine, Antwerp); Katy De Clercq (HIV Association Flanders, Antwerp); Jean-Jacques De Jaegher (Abbott Diagnostics Division, USA); Guido De Schrijver (Virco Group NV, Mechelen); Koen De Smet (Innogenetics NV, Gent); William Hall (Department of Medical Microbiology, University College Dublin, Dublin); Richard Harrigan (Research Laboratories, BC Center for Excellence in HIV/AIDS, Canada); Angelos Hatzakis (National Retrovirus Reference Center, Department of Hygiene and Epidemiology, Athens University Medical School, Athens); Nicholas Hellmann (ViroLogic, USA); Richard Hoevelmans (Department of Pharmacy and Pharmacology, Slotervaart Hospital, Amsterdam); Christopher Holtzer (Visible Genetics Europe SA, Evry, France & University of San Francisco, USA); Christine Katlama (Hôpital de la Pitié-Salpêtrière, Paris); Brendan Larder (Virco, Cambridge); Evelyne Loriaux (Virology Networks BV, Utrecht); Bruce McCreedy (Intelligent Therapeutic Solutions Inc, USA); Fiona Mulcahy (Department of Genito-Urinary Medicine, St. James’s Hospital, Dublin); Milos Opravil (Department of Medicine, University Hospital Zürich, Zürich); Andrew Phillips (Royal Free Centre for HIV Medicine and Department Care & Population Sciences, Royal Free and University College Medical School, London); Nancy Ruiz (Virology DuPont Pharmaceuticals, USA); Eric Shulie (Applied Biosystems, USA); Anders Sönnerborg (Department of Immunology, Microbiology, Pathology and Infectious Diseases, Huddinge University Hospital, Huddinge); Vincente Soriano (Service of Infectious Diseases, Instituto de Salud Carlos III, Madrid); Helen Steel (Glaxo Wellcome R & D, Greenford); Stefano Vella (Instituto Superiore Di Sanità, Rome); Astrid Williams (GPC Germany – ipse Communication, Berlin).