

## Special Contribution

# Questions to and Answers from the International AIDS Society–USA Resistance Testing Guidelines Panel

*In 1996 the International AIDS Society–USA convened an international panel of experts in HIV drug resistance and clinical management to develop guidelines for the clinical use and limitations of resistance testing. Since then the International AIDS Society–USA Resistance Testing Guidelines Panel has developed and regularly published its recommendations. The latest panel recommendations appear in the July 1 issue of Clinical Infectious Diseases.*

*We periodically pose questions to the panel relating to clinical elements of resistance testing that have been collected from HIV practitioners across the nation. We are happy to feature the latest edition in this issue of Topics in HIV Medicine. It is our hope that addressing these issues will help guide your treatment strategy decisions regarding resistance testing.*

*The International AIDS Society–USA Resistance Testing Guidelines Panel consists of Martin S. Hirsch, MD; Françoise Brun-Vézinet, MD, PhD; Bonaventura Clotet, MD, PhD; Brian Conway, MD; Daniel R. Kuritzkes, MD; Richard T. D’Aquila, MD; Lisa M. Demeter, MD; Scott M. Hammer, MD; Victoria A. Johnson, MD; Clive Loveday, MD, PhD; John W. Mellors, MD; and Douglas D. Richman, MD.*

*On a related note, the International AIDS Society–USA Drug Resistance Mutations Group will publish its update later this year in Topics in HIV Medicine. The current version is available at [www.iasusa.org](http://www.iasusa.org).*

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### **Question 1: Are there some patient populations for whom you would not perform resistance testing (eg, substance users, nonadherent patients) and rely only on clinical indicator as a screening measure?**

**Dr D’Aquila:** No. Resistance testing is an adjunct that can help to choose which antiretroviral drugs to use. The decision to start or change therapy must be based on other factors (CD4+ cell count, viral load, or clinical manifestations). In any situation when antiretroviral therapy is going to be changed, and in many situations when therapy is to be started, I would order a resistance test. There is no other way in which to know whether a patient has a fully wild-type drug-susceptible virus or to gauge the magnitude and type of drug-resistant virus predominating in that patient at that time. We no longer prescribe what should work best for most patients who are in certain circumstances. We can now prescribe the best choices for each individual patient at any point in the course of his or her disease. Resistance testing is one of the tools that can help us to do that, and I use it whenever a patient has access to it.

### **Question 2: In the setting of genotypic testing showing only minor mutations, would you change the drug regimen?**

**Dr Conway:** No, if the level of viremia and CD4+ cell count suggests continuing therapy, I would not change only on the basis of minor mutations being present. I would follow the level of virologic suppression that is being maintained, ensure adherence to the regimen is optimal, and have a low threshold for repeating resistance testing if progressive virologic breakthrough is observed. If changes in viral load or CD4+ cell count suggest a change in the regimen is indicated, I would select the most effective combination that would also favor patient adherence, taking all the resistance mutations into consideration (even the minor ones) that are present at that time.

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### **Question 3: A patient’s 3-drug regimen is starting to fail. Resistance testing results show mutations associated with resistance to only 1 of the 3 drugs. Would you replace just the 1 drug?**

**Dr Mellors:** I would not change just one drug in a failing regimen as the only

alteration in patient management. I would try to determine why the regimen failed. Without this understanding, the next regimen might fail also. Was the reason inadequate regimen potency, advanced disease (low CD4+ cell count and high HIV-1 RNA levels), incomplete regimen adherence, drug intolerance, pre-existing resistance, or inadequate drug exposure from malabsorption or negative drug-drug interactions? I would probably increase the potency of the regimen as well as its convenience. There is no set formula for managing drug failure, and therapy changes must be individualized.

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### **Question 4: Is there a point in time after which resistance testing in drug-naive patients may not be useful (ie, time after seroconversion)?**

**Dr Conway:** Probably after 18 to 24 months. After this time, it is likely that resistance mutations that may have been present initially have been out-competed by wild-type isolates in the absence of drug pressure. In such patients, I would favor performing a resistance test if appropriate virologic suppression is not achieved in the first 4 to 6 weeks of therapy. This is enough

time to allow for the selection of a minority species of resistant viruses that could have been present in the baseline viral swarm.

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**Question 5: Can therapeutic drug monitoring combined with genotypic and phenotypic testing improve care outcomes? If so, why is it taking so long to incorporate therapeutic drug monitoring (TDM) into practice in the United States, compared with in Europe?**

**Dr Demeter:** TDM has been proposed as potentially useful, primarily to optimize levels of protease inhibitors (PIs). Retrospective data suggest that having higher trough levels of PIs is associated with improved virologic outcome. In addition, retrospective data correlating inhibitory quotient (IQ = trough level/IC<sub>50</sub>) with plasma HIV-1 RNA suppression indicate that IQ may be a better predictor of outcome than trough level or IC<sub>50</sub> alone. However, it is still not clear whether TDM to increase PI dose and optimize IQ is a useful prospective strategy for managing treatment-experienced patients. One problem is the variable quality of current TDM laboratories and insufficiently rigorous standards to evaluate their performance in measuring antiretroviral drug levels. The second problem is that the VIRADAPT trial, the one prospective study that has evaluated TDM in treatment-experienced patients, showed no benefit of TDM. A weakness of this trial is that PI drug levels, rather than IQs, were used to adjust dosing (ie, the targeted drug levels were not chosen to exceed the IC<sub>50</sub>). TDM strategies are being evaluated in a number of clinical trials currently, but cannot be recommended at this time for routine clinical use.

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**Question 6: Should lamivudine be used even if the M184V mutation is present, based on the assumption that this mutation makes the virus less "fit"?**

**Dr Kuritzkes:** To date this remains a hypothetical rationale for maintaining lamivudine in a failing regimen. There are, as yet, no compelling data for or against this strategy.

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**Question 7: What is the current practice in antiretroviral cycling to decrease the emergence of drug resistance?**

**Dr Clotet:** Cycling of drugs is not currently used as a strategy outside of clinical trials. However, many patients on highly active antiretroviral therapy (HAART) who undergo a simplification or switch for intolerance or side effects while having plasma HIV-1 RNA levels below detection limits are in fact experiencing preemptive switching. This antiretroviral cycling might decrease the risk of emergence of resistance. The SWATCH study<sup>1</sup> showed that the virologic outcome was better with preemptive switching and drug alternating than with the current standard of care. In addition, this approach had similar adverse events and adherence to that observed with currently prescribed fixed HAART. Preemptive switching and alternating of antiretroviral regimens with different drug-resistance profiles theoretically might extend the overall long-term effectiveness of the first- and second-line drug options without adversely affecting either patients' adherence or quality of life, assuming tolerance and toxicity do not adversely affect outcome.

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**Question 8: For a pregnant woman who emigrated from Africa to the United States and is infected with HIV-2, which resistance and HIV-2 quantitative tests should be used and what is the availability of such tests in the United States?**

**Dr Loveday:** HIV-2 originated in West Africa and is found predominantly in patients in this region and in countries that have colonial links to it. Clinically, HIV-2 appears to be less pathogenic than HIV-1, with slower progression to symptomatic disease and death; overall its numerical contribution to the AIDS pandemic is minor. Nevertheless, it does contribute to morbidity and mortality. At present there are approximately 100 reported cases of HIV-2 in the United States. Genetically, HIV-2 has approximately 40% homology with HIV-1, and this can lead to difficulties in interpretation of laboratory diagnostic tests. This is further confounded by the

increasing prevalence of dual HIV-1/HIV-2 infections in patients originating from West Africa.

In the case described, the clinical diagnosis of HIV-2 should first be reviewed, as the local diagnostic tools may not be reliable. This is best carried out using a commercial dual-screening enzyme immunoassay (EIA) to assess reactivity and confirmed using an HIV-2-specific EIA or HIV-2 Western blot assay and polymerase chain reaction (PCR). The goal is not only to confirm the diagnosis but also to confirm the exclusion of dual infection with HIV-1 and HIV-2. The confirmation of dual infection has major implications for future management of the patient and her offspring. For example, dual infection requires a more aggressive strategy, selective use of nonnucleoside reverse transcriptase inhibitors (NNRTIs, which are not effective against HIV-2), and cautious diagnosis of mother-to-child transmission that may theoretically include both or either virus. HIV-1 is more readily transmitted from mother to child than is HIV-2.

I know of no US Food and Drug Administration-approved assays for PCR-based diagnosis, or for quantification of HIV-2 viral load and resistance determination. In the United Kingdom, the Public Health Laboratory Service (soon to be renamed the Health Protection Agency: [www.phls.co.uk](http://www.phls.co.uk)) can furnish advice and some "home brew" PCR assays for diagnosis, quantification, and genotypic analysis of reverse transcriptase and protease genes on an ad hoc basis. However, these are not clinically routine tests.

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**Question 9: Is there any research being conducted into ways to "reverse" drug resistance (eg, the association between the M184V mutation and enhanced sensitivity to zidovudine, and "hypersensitive" viral strains)? Are there any novel molecules that may be able to cause similar results?**

**Dr Kuritzkes:** Although some drugs select resistance mutations that sensitize HIV to other drugs, when confronted with both drugs simultaneously the virus inevitably finds an alternative pathway, leading to evolution of dual- (or

multi-) drug resistance.

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**Question 10: When the M184V mutation is present in a patient who is receiving lamivudine and zidovudine, are both drugs effective? Does zidovudine reverse resistance to lamivudine caused by M184V? In addition, given the rapid emergence of resistance to lamivudine, should lamivudine be reserved as a “booster” for other nucleoside reverse transcriptase inhibitors (NRTIs) for which the M184V mutation increases viral sensitivity?**

**Dr Kuritzkes:** Zidovudine resistance does not reverse lamivudine resistance. When zidovudine and lamivudine are used together in the setting of treatment failure, eventually dually resistant viruses are selected by emergence of additional nRTI-associated mutations (NAMs). The goal of therapy is complete virus suppression, not selection of particular mutations. There are no data at present to favor a strategy that defers use of lamivudine for later regimens.

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**Question 11: For patients who discontinue antiretroviral therapy independently, is there any advantage in reinstating therapy before sampling for genotypic resistance?**

**Dr Brun-Vézinet:** The question of whether treatment interruptions, either in patients with controlled viremia or in patients in whom therapy is failing, lead to virologic or immunologic benefit remains controversial. The optimized use of resistance assays during treatment interruptions, either structured or self-directed, is unknown. In patients interrupting treatment when HIV-1 RNA level is below detection, it could be appropriate to reintroduce the same antiretroviral treatment without performing resistance testing. If this regimen contained NNRTIs (nucleoside reverse transcriptase inhibitors), it is recommended to temporarily replace NNRTIs with other agents prior to complete discontinuation of the therapy, as drug resistance could emerge when NNRTI levels are subtherapeutic.

In highly experienced patients in whom antiretroviral therapy is failing, the treatment interruption may lead to

reversion from resistant viruses to a dominant plasma drug-sensitive wild-type virus population with an improved response to the subsequent reinstatement of salvage therapy. This concept of improving outcomes with treatment interruption before salvage therapy is controversial.<sup>2,3</sup> In patients interrupting therapy while in virologic failure, the resistance profile should be evaluated just before stopping treatment. In a small number of patients, a durable response to salvage therapy was observed among those who initiated a subsequent regimen containing at least a single agent to which their virus was fully susceptible before interruption.<sup>4</sup>

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**Question 12: It has been suggested that resistance testing is useful in primary infection. What is the prevalence cutoff to make this prediction? The studies by Richman<sup>5</sup> and Little<sup>6</sup> show the cutoff as greater than 20%, but one study showed 11% in 10 US cities. Is 11% high enough? If prevalence decreases in later years, do you stop conducting resistance tests in primary infection?**

**Dr Richman:** There is no precise criterion to define what prevalence of transmitted drug resistance is an indication for testing of recently infected patients. Little et al<sup>6</sup> documented the adverse impact of transmitted drug resistance on treatment efficacy. Various studies in Europe and North America have reported rates between 5% and 20% over the past several years. Although the rates vary by location and year, the recent IAS–USA Resistance Guidelines Panel<sup>7</sup> concluded that any rate in this range indicated resistance testing for recently infected patients. If treatment is selected, then the components of the regimen can be optimized. If treatment is deferred, then documentation of whether resistant virus was transmitted is available for future use. Accumulating data suggest that transmitted drug resistance persists for months to years. Thus the rapid reversion of resistant virus is not likely to provide misleading information; however, drug-resistant virus could be archived but no longer circulating in the blood of a patient who defers treatment for years. A significant

decline in transmitted drug resistance might diminish the indications for obtaining drug-resistance testing in the future, but unfortunately this is an unlikely prospect.

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**Question 13: In a drug-naïve patient diagnosed last year, resistance testing showed M41L and L210W without other mutations and with no evidence of phenotypic resistance. Could these mutations indicate that the patient was actually infected with a strain fully resistant to zidovudine or stavudine, but that additional mutations are in the “archived” strain and cannot be detected? Should this possibility be taken into account in choosing the first regimen?**

**Dr Demeter:** It is certainly possible that more highly resistant minority variants are present and not detectable by the resistance test. It is reasonable to take this consideration into account when designing an initial regimen for this patient.

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**Question 14: With more reports on the persistence of NNRTI mutations, should resistance testing be done for chronically infected patients?**

**Dr Johnson:** The IAS–USA panel has recommended resistance testing be done on patients with established HIV infection of up to 2 years’ duration and perhaps longer, as some mutations conferring resistance may persist for prolonged periods of time (ie, more than 12 months).<sup>7</sup> We also recommend resistance testing in subjects initiating therapy who have chronic HIV infection of more than 2 years if regional data are available showing genotypic or phenotypic drug-resistance prevalence is greater than 5%. My own clinical experience (and that of other practitioners) is that some patients can indeed harbor NNRTI resistance mutations in their blood while not on any therapy, based on both genotypic and phenotypic assay results. In some instances, the patients are reportedly drug-naïve, suggesting that they were infected with drug-resis-

tant viral variants. In other cases, NNRTI-resistant viral variants have been found in chronically infected patients who have been off NNRTI therapy for many months to years, suggesting that persistence of these mutant viruses can occur and may impact the success of subsequent therapeutic regimens. This suggests that HIV drug-resistance testing may be increasingly important to consider in subjects with chronic HIV infection who are either drug-naive or drug-experienced, particularly in regions where patient populations are heavily exposed to antiretroviral agents (including NNRTIs) and when planning HAART therapy that includes a drug from the NNRTI class.

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**Question 15: Can replication capacity be helpful in judging when to start HIV therapy?**

**Dr Richman:** The measurement of replication capacity has been shown to be a predictor of the benefits conferred by drug-resistant virus on the discordant response.<sup>8</sup> Discordance is defined as a sustained CD4+ cell count elevation despite incomplete suppression of HIV-1 RNA levels with chemotherapy. It is likely that changes in replication capacity may impact pathogenesis and natural history in other settings; however, the utility of the measurement of this parameter for clinical management at present requires further investigation.

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**Question 16: If virus in a patient is resistant to all currently available antiretroviral drugs, is it better to stay on a suboptimal regimen or to discontinue drug therapy completely until a better treatment comes along?**

**Dr Hammer:** It is difficult to provide an answer to this question that fits all patient circumstances. The data available suggest that ongoing benefit may be provided by regimens to which multidrug resistance has developed. The drop in CD4+ cell count and rise in plasma HIV-1 RNA levels that occur after drug discontinuation in this setting reflect the fact that antiviral activity may still be present or that a viral replicative defect may be conferred by some of the drug-

resistance mutations. Conflicting data were presented at the recent 10th Conference on Retroviruses and Opportunistic Infections in Boston concerning the efficacy of drug interruptions in the setting of multidrug resistance. The CPCRA 064<sup>2</sup> study did not demonstrate a benefit but the ANRS GIGHAART<sup>3</sup> study did. These contrasting results may be explained by the patient populations studied and the lengths of treatment interruptions, which differed in the 2 studies. Although there might not be a consensus in the field, in general, treatment interruptions should not be a routine clinical strategy in the management of the treatment-experienced patient with multidrug resistance at the present time.

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**Question 17: Given the increasing transmission of resistant virus as reported by Little and colleagues<sup>6</sup>, which regimen would you recommend for initial treatment in the setting of very limited resources and the inability to genotype newly diagnosed patients?**

**Dr Clotet:** The most frequently transmitted drug-resistant viruses are those resistant to NNRTIs. Thus recently infected patients should not be started on a regimen including that class of drugs without a drug-resistance test. Since the most common mutations to the other drug classes found in recently infected patients are at codons 118, 184, 215, and 103 of the reverse transcriptase gene and codons 82 and 90 of the protease gene<sup>6</sup>, I might recommend starting with lopinavir/ritonavir plus tenofovir plus abacavir. This approach may be active enough to control viral replication even if the patient's virus harbors all the above-mentioned mutations.

**Dr D'Aquila:** This might not be a feasible strategy over a long term. Today, viruses resistant to a relatively new drug might be less common among recently infected subjects. However, this may change over an unpredictable time span as resistant virus emerges after wider use of that new drug. Resistance testing may also prove less costly than frequent viral load/CD4+ cell count monitoring that might be an alternative strategy to

ensure an adequate response. My first line choices, however, if resistance testing is not available for technical reasons (for example, the laboratory fails to get a result) or due to unavoidable lack of access would be based on ease of adherence and tolerability. Options that I would suggest include lamivudine along with either stavudine, zidovudine, or tenofovir and either efavirenz, nevirapine, nelfinavir, or lopinavir/ritonavir. I would monitor viral load at least monthly over the first 6 months.

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**Question 18: How useful is resistance testing in a patient almost certainly infected more than 6 to 12 months previously who is treatment-naive? Is it possible to reliably detect archived virus or is testing in this case a waste of money?**

**Dr Loveday:** The initiation of antiretroviral therapy is a crucial decision made between patient and physician, as it currently involves a life-long commitment by the patient to daily drug therapy. Failure of such treatment due to viral resistance to the drug(s) can have disastrous effects on the patient, both physically in terms of limiting future treatment options and psychologically in terms of the patient's future confidence in his or her clinical management. Resistance tests have a limited sensitivity, and because resistance prevalence in specific communities remained very low, the benefits (in terms of cost-effectiveness) were limited.

Evidence now exists that drug resistance is increasing in patients who are naive to therapy. For example, in 2002 in our United Kingdom (UK) group (undertaking the clinical molecular virology care for 7000 UK patients), of 91 drug-naive patients tested, 24 (26.4%) had 2 or more mutations (according to the IAS-USA Drug Resistance Mutations in HIV-1 summary, available at [www.iasusa.org](http://www.iasusa.org)) associated with resistance, a marked increase in number and distribution from our survey in 2000.<sup>9</sup> Further, 48% had major mutations including all drug classes. These data have since been confirmed (but not yet published) by the Medical Research Council UK Collaborative Group in HIV Resistance, which describes an overall prevalence

of 17% (n=2000 patients) with no differences between acute or recent and nonacute naive infections. In other geographic areas where antiretroviral therapy is in use, similar results have been reported.

These data provide evidence that resistance testing will benefit a significant proportion of the population and should be part of our standard of care for management of patients infected with HIV-1 prior to initiating therapy. In circumstances in which this testing cannot be performed, a sample should be stored as soon as possible after infection for later review and support of patient care.

Data regarding the persistence of transmitted drug-resistant virus are sketchy; however, several cases describing the detectability of drug-resistant virus to both NNRTIs and PIs as long as 2 to 3 years after infection without treatment have recently been reported.<sup>10</sup>

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**Question 19: Resistance testing is indicated in primary HIV infection, but what is the recommendation for patients who had a negative resistance test 3 months, 6 months, or 1 year ago? If you are not going to treat such patients now, do you order the resistance test anyway and use the results years later when treatment is started?**

**Dr Demeter:** Resistance testing is currently indicated for use in guiding initiation of therapy in the setting of primary HIV infection. Resistance testing could be ordered for a patient who has been infected for up to 2 years, or even longer, even if treatment is not planned immediately, so as to have a history of prior possible resistance. Resistance testing of this patient population in the absence of planned therapy may also be appropriate as part of a larger surveillance effort.

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**Question 20: How large an impact does “ideal” use of resistance test results have on outcome (ie, plasma HIV-1 RNA levels in the short term, percent below detection levels, and patient survival)? Is there a measurable benefit in the fine-tuning of antiretroviral regimens now becoming standard?**

**Dr D’Aquila:** This is difficult to quantify, and clinicians need to consider this issue for an individual patient, not an idealized population of research subjects. It is the help provided by a resistance test result in choosing more active drugs and minimizing toxicity from ineffective drugs that benefits the patient. In clinical trials in which subjects are randomized to receive resistance testing or not, there was about a one-half to 1 log copies/mL greater drop in HIV-1 RNA level for the group randomized to testing. However, in our practices, there will be a large difference in response with testing in a patient with a very resistant virus (or one with an unexpected resistance pattern), but testing may make little difference in others who have an anticipated, fully wild-type virus. The clinical reality is that we cannot differentiate which individual will benefit greatly or not from resistance testing. In my opinion, the lesser benefit in some is balanced by the great benefit in a few and warrants testing for all.

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## References

1. Martinez-Picado J, Negredo E, Shintani A, et al and the SWATCH Study Team. Alteration of antiretroviral drug regimens for HIV infection: a randomized controlled trial. *Ann Intern Med*. 2003. In press.
2. Lawrence J, Mayers D, Huppler Hullsiek K, et al. CPCRA 064: a randomized trial examining structured treatment interruption for patients failing therapy with multi-drug resistant HIV. [Abstract 67.] 10th Conference on Retroviruses and Opportunistic Infections. February 10-14,

2003; Boston, Mass.

3. Katlama C, Dominguez S, Duvivier C, et al. Long-term benefit of treatment interruption in salvage therapy (GIGHAART ANRS 097). [Abstract 68.] 10th Conference on Retroviruses and Opportunistic Infections. February 10-14, 2003; Boston, Mass.

4. Deeks SG, Grant RM, Wrin T, et al. Persistence of drug-resistant HIV-1 after a structured treatment interruption and its impact on treatment response. *AIDS*. 2003;17:361-370.

5. Richman DD, Bozzette S, Morton S, et al. The prevalence of antiretroviral drug resistance in the US. [Abstract LB-17.] 41st Interscience Conference on Antimicrobial Agents and Chemotherapy. December 16-19, 2001; Chicago, Ill.

6. Little SJ, Holte S, Routy JP, et al. Antiretroviral-drug resistance among patients recently infected with HIV. *N Engl J Med*. 2002;347:385-394.

7. Hirsch M, Brun-Vézinet F, Clotet B, et al. Antiretroviral drug resistance testing in adults infected with human immunodeficiency virus type 1: 2003 recommendations of an International AIDS Society–USA panel. *Clin Infect Dis*. 2003;37:113-128.

8. Deeks SG, Wrin T, Liegler T, et al. Virologic and immunologic consequences of discontinuing combination antiretroviral-drug therapy in HIV-infected patients with detectable viremia. *N Engl J Med*. 2001;344:472-480.

9. Loveday C, MacRae E, Johnson M. A marked increase in prevalence of ART mutations in naive patients with HIV-AIDS in the UK in 2002—time to recommend resistance testing prior to therapy. [Abstract 632.] 10th Conference on Retroviruses and Opportunistic Infections. February 10-14, 2003; Boston, Mass.

10. Little SJ, Dawson K, Hellmann NS, Richman DD, and Frost SDW. Persistence of transmitted drug-resistant virus among subjects with primary HIV infection deferring antiretroviral therapy. [Abstract 115.] XII International HIV Drug Resistance Workshop. July 10-14, 2003; Los Cabos, Mexico.

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