ABSTRACT

The growing number of antiretroviral agents makes it possible to design various effective treatment regimens. However, the development of drug resistance weakens the antiviral activity of these regimens or one or more of their components. Therefore, it is important to consider the implications of resistance in long-term therapeutic strategies and sequential regimens when initiating treatment and when making subsequent treatment decisions.

Against this backdrop, the major issues are whether resistance can be prevented in the initial regimen, whether resistance testing should be done before therapy is initiated, how resistance testing is best utilized when choosing an alternative regimen because of virologic failure on the initial regimen, and whether future treatment options can be preserved.

Complicating these issues are the wide variability in resistance testing results, the difficulties associated with the interpretation of genotypic and phenotypic resistance assays, limited data on the use of ritonavir-boosted protease inhibitors in preventing resistance in the initial regimen, the undetermined role of resistance testing in treatment-naive patients, and the lack of uniformity among national health organizations regarding guidelines for resistance testing in drug-naive patients.


CAN FUTURE TREATMENT OPTIONS BE PRESERVED?

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A B S T R A C T

Although the increasing number of antiretroviral agents makes it possible to devise various potent and durable highly active antiretroviral therapy (HAART) regimens, the development of drug resistance resulting from continuous virologic replication weakens the antiviral activity of these regimens or their components. Therefore, despite the many antiretroviral agents from which to choose, it is important to consider the implications of resistance in long-term therapeutic strategies and sequential regimens when initiating treatment and before each treatment decision.

Data have been presented that demonstrate “a favorable resistance profile” for many of the newly approved antiretroviral agents, and there are claims that at least some of these agents will “preserve future treatment options.” However, there are many questions regarding the interpretation of these data and whether these drugs can, in fact, prevent resistance and be used as components in building effective, long-term sequential HAART regimens.

Although there is agreement that resistance testing is an important tool in guiding treatment decisions once treatment failure has occurred, it is not yet known for certain whether resistance testing before therapy is initiated is equally important. In this situation, the role of resistance testing is still undetermined. Because transmission of drug-resistant virus to newly infected patients may be overlooked, what is considered the “best option” in treatment-naive patients may not be the best option at all.

Given the current understanding of resistance and resistance assays, the major issues are whether resistance can be prevented, whether resistance testing should be done before therapy is initiated, and whether future treatment options can be preserved.

RESISTANCE TESTING WHEN CHOOSING AN ALTERNATIVE REGIMEN

Video Commentator: The principal questions that are...
frequently asked are how I use resistance testing in choosing an alternative regimen and how I make the choice between genotypic and phenotypic resistance assays.

Using drug resistance assays in clinical practice involves using the assays to choose an alternative regimen, choosing between genotypic and phenotypic resistance assays, and interpreting the data provided by each type of assay.

At present, genotypic assays are widely available and include 2 kits approved by the US Food and Drug Administration and the European Medical Association as well as numerous “home-brew” methods. By comparison, phenotypic assays are highly sophisticated, restricted to 3 commercial companies, and are very expensive.

Prospective drug resistance trials evaluating whether genotypic or phenotypic assays provide added value to the standard of care in guiding therapy support the use of genotypic assays in clinical practice (Table 1). Only one of these studies supports the use of phenotypic assays in clinical practice. A study evaluating whether phenotypic assays provide added value to genotypic assays concluded that they did not.

A genotypic report typically includes a list of resistance mutations and interpretation (ie, a large number of rule-based algorithms, which are first based on the correlation between mutations and phenotype). The major limitation is that there are difficulties determining phenotypic cutoff values for some drugs, such as didanosine, stavudine, tenofovir, and amprenavir.

Algorithms need to be clinically validated on the basis of correlation studies between mutations at baseline and virologic response to the drug, with multivariate analyses done to account for all confounding variables. In addition, there are discrepancies between algorithms, and few algorithms are clinically derived. Accordingly, there is now an international effort to pool databases and establish standardized analyses.

One study of 3 algorithms (Resistance Collaborative Group, National Agency for AIDS Research, and HIVdb, a database of the structures of HIV protease) and 5 protease inhibitors (PIs), 5 nucleoside reverse transcriptase inhibitors (NRTIs), and 3 nonnucleoside reverse transcriptase inhibitors (NNRTIs) found discordances among the 3 algorithms by drug, along with an 84% concordance in determining whether an isolate was susceptible or resistant. Four of the 14 drugs—amprenavir, stavudine, abacavir, and didanosine—accounted for two thirds of the discordances.

A clinically validated algorithm from NARVAL, however, showed that the abacavir genotype score according to the number of mutations predicted the viral load response to the drug. Patients with fewer than 4 mutations had the highest viral load response and were not resistant, those with 4 mutations had lower viral load response and were possibly resistant, and those with 5 to 6 mutations had the lowest viral load response and were resistant.

Interpreting a genotypic resistance assay depends on the use of clinically validated algorithms, expert opinions, and a team effort that involves the clinician, the virologist, and the pharmacologist. To optimize the choice of new therapy, the team should consider the treatment history, the viral and immune response to the past regimen, intolerance, adherence, pharmacologic data, and the potential for drug interactions in interpreting the resistance results.

**Previous Resistance in the Initial Regimen**

**Video Commentator:** Recent data have shown that using boosted PIs may prevent the occurrence of resistance, at least in the initial treatment regimen.

Several studies have evaluated therapy with PIs that were usually boosted with low-dose ritonavir. Some of these trials have shown that patients failing an initial boosted regimen had rarely selected mutations. However, no data from clinical trials show how to sequence antiretroviral drugs.

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**Table 1. Results of Prospective Trials Evaluating Added Value of Resistance Assays**

<table>
<thead>
<tr>
<th>Genotypic Assays (added value to SOC)</th>
<th>Phenotypic Assays (added value to SOC)</th>
<th>Phenotypic Assays (added value to genotypic assay)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Viradapt (yes)</td>
<td>VIRA 3001 (yes)</td>
<td>ERA (no)</td>
</tr>
<tr>
<td>GART (yes)</td>
<td>Kaiser (no)</td>
<td></td>
</tr>
<tr>
<td>NARVAL (yes, in multivariate analysis)</td>
<td>NARVAL (no)</td>
<td></td>
</tr>
<tr>
<td>HAVANA (yes)</td>
<td>CCTG 575 (no)</td>
<td></td>
</tr>
<tr>
<td>ARGENTA (yes)</td>
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</tbody>
</table>

SOC = standard of care; ERA = Evaluation of Resistance Assays; GART = Genotypic Antiretroviral Resistance Testing.
In Study 863, patients who were naive to antiretroviral therapy were randomized to ritonavir-boosted lopinavir twice daily plus nelfinavir placebo plus stavudine plus lamivudine (n = 326) or nelfinavir 3 times daily plus boosted lopinavir placebo plus stavudine plus lamivudine (n = 327). Samples were sent for genotyping in any patient whose HIV RNA level was above 400 copies/mL at 24, 32, 40, 48, 60, 72, 84, and 96 weeks. At 96 weeks, 79% of patients randomized to boosted lopinavir still had a viral response compared with 58% among those randomized to nelfinavir.

In another report from the same study, the incidence of drug resistance among patients with detectable viral loads and viral genotypes through week 96 was significantly higher in those receiving the nelfinavir regimen compared with those receiving the boosted lopinavir regimen: 48% vs 0% for primary PI mutations (P < .001), 53% vs 14% for secondary PI mutations (P < .001), 82% vs 37% for lamivudine resistance (P < .001), and 9% vs 0% for stavudine resistance (P < .027).

In the SOLO study, which was similar to Study 863 in patient population (therapy-naive) and N RTI backbone regimen (abacavir/lamivudine), with identical criteria for analyses, 322 patients were randomized to 908 boosted with low-dose ritonavir once daily and 327 were randomized to nelfinavir twice daily. Virologic failure defined as greater than 1000 copies/mL plasma HIV RNA at 2 consecutive time points at week 12 or beyond, was seen in 39 patients (12%) receiving boosted 908 and in 62 patients (19%) receiving nelfinavir. None of the failing patients receiving boosted 908 had primary or secondary PI mutations or K65R or L74V mutations to abacavir versus 27 and 3, respectively, in those receiving nelfinavir (P < .001). Four patients receiving boosted 908 had an M184I/V mutation to lamivudine vs 30 in those receiving nelfinavir (P < .001).

It is unclear whether the lower incidence of resistance with the boosted PI in SOLO compared with Study 863 was due to better adherence to therapy, the increased potency of boosted 908 compared with boosted lopinavir, or some other factor. In addition, it is uncertain whether the absence of detectable mutations at virologic failure is a guarantee that more future therapeutic options can be preserved. Clearly, there is a need for a therapeutic trial that specifically addresses preservation of future treatment options, including the possibility of keeping the boosted PI, the possibility that there are resistant minor species that are not detectable in the plasma, and whether there are resistant mutations in proviral DNA.

**Treating Patients with Selected Mutations in the Initial Regimen**

**Video Commentator:** How are you going to treat a patient with a 184 and a 103 mutation?

K103N mutation is selected by NNRTIs, causes cross-resistance to the class, and prevents further use of the current NNRTI in switching regimens. By comparison, M184V mutation is selected by lamivudine and abacavir and does not cause cross-resistance to other NRTIs. In fact, in vitro studies have shown that virus with an M184V mutation has impaired replication fitness, and its presence seems to enhance susceptibility to other NRTIs.

As a rule, if there is a first virologic failure on 2 NRTIs plus 1 NNRTI, all the drugs in the regimen should be changed to 2 other NRTIs plus a PI boosted with low-dose ritonavir. The choice of the 2 alternative NRTIs depends on the backbone of the first regimen and on genotype assay results. However, because the M184V mutation is selected by lamivudine, and because the presence of this mutation seems to enhance susceptibility to other NRTIs, an important question arises: Should lamivudine be kept in the regimen?

Data from a recent report of 4 patients with HIV-1 infection and M184V and multiple thymidine analog mutations show that lamivudine contributes to partial HIV-1 suppression in patients with thymidine analog mutation resistance despite the presence of an M184V mutation. These data suggest that the use of lamivudine may have some virologic benefit in highly experienced patients with M184V and thymidine analog mutations. No data support such consideration in patients experiencing a first virologic failure.

**Resistance Testing in Treatment-Naive Patients**

**Video Commentator:** What is the role of resistance testing in patients who are naive to antiretroviral therapy before initiating therapy?

The role of resistance testing in treatment-naive patients before initiating therapy is not clear-cut because of variations in surveillance methods and reversion following transmission of resistant viruses. Depending on the surveillance methods, which vary with regard to patient recruitment and the definition of genotypic resistance, the prevalence of mutations can range considerably (Table 2).

If the definition is based on mutations, does it include relevant mutations or the V118I mutation? In some cases,
as with 70R and zidovudine, a single mutation may not be responsible for so-called resistance. In contrast, if the definition is based on algorithms, is the algorithm identified? For example, in the French study referred to in Table 2, the prevalence of mutations was 6%, but resistance to at least one antiretroviral drug according to the ANRS algorithm (not shown) was 1.6%.

Echoing the variations in surveillance methods for resistance testing is the lack of uniformity among national health organizations regarding guidelines for resistance testing in drug-naive patients (Table 3).

**CONCLUSION**

It is clear that much work remains regarding resistance testing when choosing the first regimen as well as alternative regimens in cases of virologic failure, preventing resistance in the initial regimen, and treating patients who select mutations in the initial regimen. However, with the aid of resistance testing, it may be possible in the near future to preserve future treatment options in patients who have failed initial therapy. Data regarding resistance testing, prevention of resistance, and preservation of future treatment options should therefore be interpreted carefully.

**REFERENCES**


