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Antiretroviral Therapy in Patients with Suboptimal Virologic Suppression

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Abstract

The advances in our understanding of the pathogenesis of infection by human immunodeficiency virus type (HIV-1) during the past 3 years has led to antiretroviral therapeutic strategies capable of maximally suppressing plasma HIV-1 for prolonged periods of time, immunologic reconstitution, and clinical benefits including an overall decrease in HIV-related mortality. Despite these advances, up to half of patients who initiate therapy with an appropriate antiretroviral regimen either do not achieve or maintain a durable antiviral response. The reasons for suboptimal antiviral treatment responses are complex and include: acute and chronic drug intolerance, non-adherence, adverse drug interactions, pharmacokinetic variability, and drug resistance. Treatment strategies for individuals experiencing a significant increase in plasma levels of HIV-1 RNA have been recommended based on the concept of replacing the current antiretroviral treatment regimen with drugs previously not used and likely to be active. The limited number of such options has forced clinicians and researchers to search for alternative approaches including reexamination of the definition for treatment failure. Approaches such as strategic sequencing, treatment intensification, the recycling of multiple previously used drugs (i.e. mega-HAART), and scheduled treatment interruption have been attempted. Much of the success of these approaches has been dependent on the timing of such treatments and the use of either genotypic and phenotypic resistance testing. The questions remain as to when to make any change, when to add a drug, when to replace an entire regimen, and what to do if these approaches are unsuccessful. It is obvious to everyone managing the antiretroviral therapy in patients that with the currently available drugs, subsequent treatment following virologic rebound is more difficult than initiating therapy. Novel drug-sparing and recycling strategies, resistance testing and development of newer agents that target different stages in the viral life cycle and which are not cross-resistant with the current drugs will improve the ability to treat patients whose therapy is failing them.

Key words

Antiretroviral therapy. Drug failure. Treatment strategies.

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Despite our best efforts, the likelihood of achieving a sustained antiretroviral response in patients treated with any of the triple therapy regimens presumed to be effective approximates 50%[1]. While antiviral rebound or failure does not necessarily translate to immediate clinical failure, it certainly predicts a poorer outcome than when the virus is optimally controlled. Immunologic failure, crudely defined as a decrease in the absolute CD4 count to levels associated with high clinical risk (i.e. CD4 < 200 cells/mm^3), rarely occurs without concomitant loss of optimal viral suppression. The development of clinical disease while receiving antiretroviral therapy would constitute as a clinical failure, however, this may not necessitate a change in antiretroviral therapy if the virus is optimally suppressed.

The reasons for antiretroviral treatment failure are multiple and include acute drug intolerance, non-adherence to the prescribed treatment regimen, drug-drug interactions resulting in subtherapeutic levels of the antiretroviral agents, variable pharmacokinetic properties of the different therapies, resistance to one or more of the chosen antiviral drugs, and advanced stage of disease at the time of treatment initiation (Table 1). Therefore, the reasons for a suboptimal therapeutic response and the subsequent treatment choice must be individualized.

Table 1. *Reasons for antiretroviral treatment failure or suboptimal suppression of HIV-1.*

Acute drug intolerance
Chronic drug intolerance
Non-adherence
Drug-drug interaction
Variable pharmacokinetic properties
Resistance
Advanced stage of HIV disease

Long before clinical disease progresses, the plasma HIV-1 RNA, or viral load, typically increases, indicating that viral replication is taking place in the presence of the therapy prescribed. Persistent viral replication in the presence of drug for a significant period of time places the patient at great risk for the development of resistance to the exposed treatment regimen. This should be avoided if at all possible, as many of the currently available drugs are cross resistant to other members of their class[2]. For example, the non-nucleoside class (efavirenz, nevirapine, and delavirdine) all select for the single K103N reverse transcriptase mutation and are completely cross resistant. While the protease resistance profile shows some variability and specificity, there is general cross resistance following the development of 3 or more codon mutations[3]. The nucleoside reverse transcriptase inhibitors have different resistance profiles, however, following treatment failure, subsequent response to supposedly susceptible nucleosides may be significantly blunted. It has been postulated that this may be due to an alteration in intracellular kinetics of nucleoside phosphorylation[4]. Resistance testing, either by genotype of phenotype, is commercially available, but its exact utility has yet to be fully characterized. It is likely that resistance testing will become a helpful management tool when treatment changes based on these type of test results are proven beneficial and the assays receive formal regulatory approval.

Defining treatment failure

The term "treatment failure" has been used to describe a variety of clinical, immunologic and virologic situations including: the development of an HIV-related clinical event; the reduction in CD4 cell count to less than 50% of the baseline level; the inability to have a sustained treatment-induced reduction in plasma HIV-1 RNA to below the level of assay detection within 12-16 weeks of initiating therapy; once achieving an optimal antiretroviral response, to then have an increase in plasma HIV-1 RNA to near baseline levels, > 200-500 copies/mL or to > 50 copies/mL (Fig. 1). Current guidelines focus on the antiviral responses associated with therapy[5,6].

An important distinction needs to be made in regard to defining "treatment failure" with "suboptimal virologic suppression". Most would agree that an increase in plasma HIV-1 RNA levels to within 0.5 $\log_{10}$ copies/mL of the pre-therapy values with subsequent decreases in the absolute CD4 cell count and development of clinical events means treatment failure[7]. In this definition of treatment failure, the antiviral drugs are all likely to be resistant. A complete change in therapy to a regimen that included drugs of different classes or those likely or proven to be sensitive would be the preferred choice. All other virologic responses that do not result in maximal reductions of HIV-1 RNA are better termed "suboptimal virologic suppression". In these instances, resistance to all the antiviral agents may not be complete, offering the potential for selective drug substitutions.

The numeric threshold for further defining suboptimal virologic suppression has not been determined. A rise in viral load of at least 0.5 $\log_{10}$ copies/mL (3 fold) is known to be significant. A rise to greater than or equal to the pre-therapy level is generally agreed to be considered failing. However, the significance in viral load levels less than 500, 1000, 5000 or 10,000 copies/mL is not completely understood. This observation was illustrated in the preliminary results from two studies which compared triple nucleoside regimens to the standard protease inhibitor-based therapy. In the Atlantic Study, the cohorts receiving stavudine/didanosine/lamivudine overall did as well as the cohorts receiving either the non-nucleoside nevirapine or the protease inhibitor indinavir with stavudine/didanosine. However, in subjects with baseline HIV-1 RNA > 4.36 $\log_{10}$ copies/mL (the median), while a similar number were < 500 copies/mL after 48 weeks, fewer achieved suppression to < 50 copies/mL ($p = 0.023$) in the triple nucleoside group[8]. A similar finding was

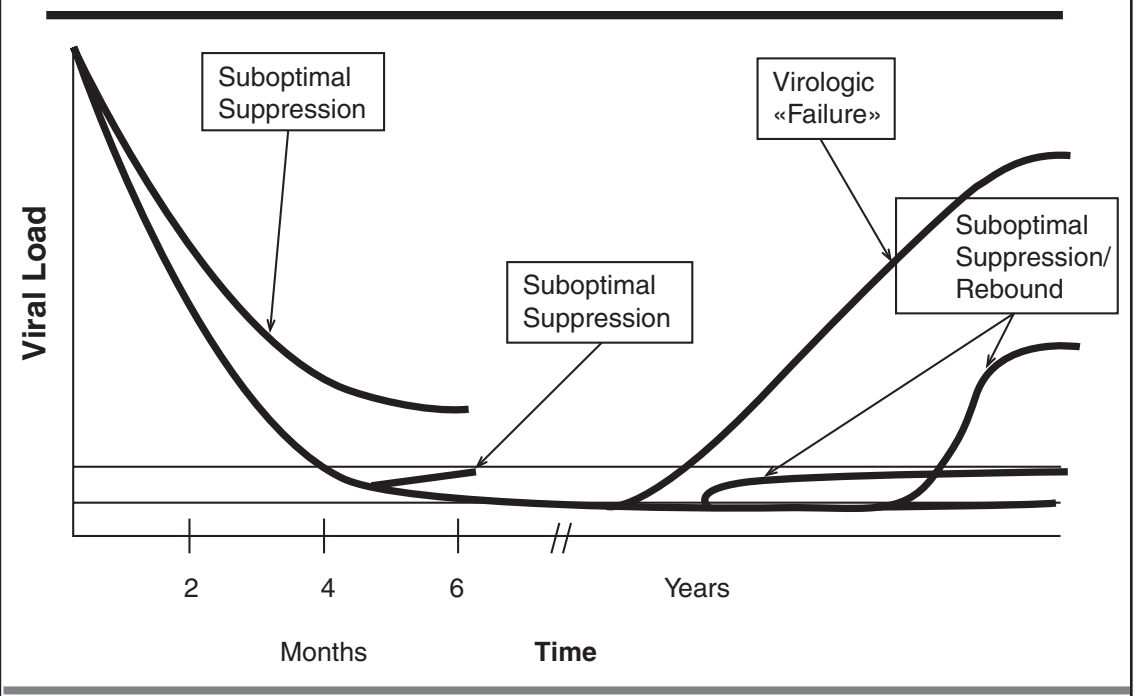

Fig. 1. *Suboptimal virologic suppression and failure*

observed in the CNA3005 Study, which compared abacavir/zidovudine/lamivudine with indinavir/zidovudine/lamivudine, where the subjects with the higher viral loads in the triple nucleoside arm were as likely to suppress viral load to < 500 copies/mL but less likely to suppress HIV-1 RNA to < 50 copies/mL[9]. The significance of these findings are uncertain but suggest that for some individuals, the threshold for changing therapy because of suboptimal virologic suppression may be greater than 50 copies/mL, the lowest level we can reliably measure at the present time.

Current guidelines for treatment of virologic failure or suboptimal suppression

Current guidelines recommend that when a treatment change is considered, two new nucleosides be chosen plus a different protease inhibitor likely to be sensitive[5,6]. These guidelines are based on expert opinion using theoretical possible alternative regimens without the aid of resistance testing. For purely virologic reasons, this makes sense, however, if a patient has trouble with adherence; changing medications, often to an even more complicated regimen, is unlikely to be very helpful. There have been no controlled studies comparing different strategies in patients who have failed an active three drug antiretroviral regimen, although there have been multiple studies describing results in patients who have failed dual nucleoside regimens. In practice, what commonly occurs following loss of maximal virologic suppression is the double protease inhibitor approach with or without a non-nucleoside in addition to new nucleosides, if possible. Response rates in these situations vary and are dependent upon how long the patient was receiving the failing regimen, how many prior drugs have already been administered, and genotypic and/or phenotypic resistance to the various drugs. Virologic success rates with subsequent therapy range from 28-80%. The cohorts of patients that have done the best are those where therapy was changed very quickly after the viral load rebounded to greater than 500 copies/mL[10] and in those where combination protease inhibitor therapy was employed[11-13]. In one study, 264 patients treated with nelfinavir for at least 48 weeks and having detectable viral load (median viral load, 46674 copies/mL) were treated with a ritonavir/saquinavir-based regimen. In 22/24, viral load decreased to < 500 copies/mL on at least one occasion, and 14/24 (58.3%) had sustained antiviral suppression. In this trial, a higher baseline viral load predicted subsequent treatment failure. Interestingly, the D30N mutation, unique to nelfinavir, did not predict the treatment response, suggestion that subsequent protease inhibitor-based approaches may be successful[11].

Weidle *et al* calculated the odds ratios for a successful treatment option following modification of an initial failing regimen consisting of at least 2 drugs (Table 2). The data showed that the addition of a new

Table 2. *Factors associated with successful modification of antiretroviral therapy.*

Treatment Change	Odds Ratio
Add a new class of drug	7.3
Add a non-nucleoside as a new drug	5.5
Addition of > 2 new drugs	2.7
Change to a new protease inhibitor	1.1
Change to a new nucleoside	1.0
Change to nelfinavir as a new drug	0.5

(Adapted from ref. 14.)

class of drugs in the rescue regimen had the highest correlation with a successful outcome, followed by having a non-nucleoside as a new drug, and adding at least 2 new drugs. Change to a new protease inhibitor or nucleoside analogue were not associated with a successful modification of therapy[14].

Recently, several prospective studies have reported results of specific rescue strategies, including: AIDS Clinical Trials Group (ACTG) 359, ACTG 372b, ACTG 373, and CNA2007. The results from these trials are reviewed below:

ACTG 359 was a 277 person study in indinavir-experienced, but non-nucleoside-naïve subjects with plasma HIV-1 RNA between 2000-200,000 copies/mL. Subjects were randomized to receive saquinavir soft-gel capsules with either ritonavir or nelfinavir, together with the non-nucleoside delavirdine, the nucleotide adefovir, or both. Overall, 30% of patients had plasma HIV-1 RNA ≤ 500 copies/mL at week 16. In a factorial analysis, there was no difference between the ritonavir or nelfinavir groups; however, the pooled delavirdine groups had a better response that the adefovir groups including those assigned delavirdine plus adefovir (40% *vs.* 18%). The overall results of this study were disappointing. This may have been due to the choice of delavirdine and adefovir as part of the new regimen and a potential unexpected interaction may have occurred in the group receiving the combination adefovir plus delavirdine[15].

ACTG 372b was a 94 person study in indinavir-experienced, but non-nucleoside-naïve subjects who were treated in with zidovudine/lamivudine plus indinavir as part of ACTG 320 and had virologic rebound or failure. All subjects received open-label efavirenz and adefovir and were randomized to also take abacavir or 1-2 new nucleoside reverse transcriptase inhibitors with or without the blinded protease inhibitor, nelfinavir. Overall, 35% of patients had plasma HIV-1 RNA < 500 copies/mL by week 16. The pooled nelfinavir groups did better than the groups that did not receive nelfinavir (45% *vs.* 24%). There was no difference in response between the abacavir group compared to the group that added 1-2 new nucleosides[16]. The overall results of this study were somewhat disappointing and may have been improved by the addition of a double protease inhibitor-based regimen.

ACTG 373 is a 54 person study in amprenavir-experienced subjects who had been enrolled in the ACTG 347 trial which compared amprenavir alone to amprenavir, zidovudine, lamivudine[17]. All subjects received open-label indinavir, the non-nucleoside nevirapine and the nucleosides stavudine plus lamivudine. Approximately 60% of subjects had plasma HIV-1 RNA < 500 copies/mL after 48 weeks. Subjects with HIV-1 RNA < 500 copies/mL at baseline were more likely to remain suppressed following change to the new regimen as were subjects with lower levels of virologic rebound suggesting that earlier switches to a single protease inhibitor based regimen are more likely to be successful[10].

CNA2007 was a 90 person study who had received extensive prior antiretroviral therapy. All subjects received open-label abacavir, efavirenz, and amprenavir. Overall, 26% of subjects had plasma HIV-1 RNA < 400 copies/mL at week 16. Individuals who were non-nucleoside-naïve and had HIV-1 RNA < 40,000 copies/mL at study entry did better.

Efavirenz was shown to lower amprenavir levels by approximately 36%, which may have affected the results of the study[18]. These patients may have done better if an additional protease inhibitor was included in the regimen.

Treatment of virologic failure or suboptimal suppression with newer agents

Two investigational antiretroviral agents have been studied in patients with suboptimal viral suppression and/or failure. The results, although preliminary in nature, are encouraging.

Lopinavir, formerly referred to as ABT-378, is a new protease inhibitor that is characterized by its exquisite pharmacokinetic enhancement to low doses of ritonavir. When given in combination with 100 or 200 mg ritonavir, plasma trough levels of lopinavir are 25-100 fold higher than the expected EC_{50} of wild type virus. Lopinavir has been studied in both treatment-naïve and experienced subjects. In the treatment experienced trial, 70 subjects who were single-protease inhibitor experienced, but non-nucleoside-naïve and had plasma HIV-1 RNA levels between 10,000-100,000 copies/mL, had their protease inhibitor switched to lopinavir while continuing with the other drugs in their regimen. After 2 weeks, the non-nucleoside nevirapine was added and the background nucleosides were adjusted with at least one new one added. After 48 weeks, 78% of subjects had plasma HIV-1 RNA < 400 copies/mL; only 2 patients stopped therapy because of side effects related to study drugs[19].

These results are some of the most encouraging reported among subjects with suboptimal viral suppression and are likely due to the favorable pharmacokinetic and side effect profile of lopinavir, the addition of a non-nucleoside into the rescue regimen, and relatively early change in therapy for the cohort. Lopinavir is expected to be available in the later part of 2000.

T-20 is a synthetic 36 amino acid peptide that is unlike any of the currently available antiretroviral agents in that it inhibits HIV fusion. This drug is not as far along in clinical development as lopinavir, however it has been studied in mulitple phase I and II trials including 55 extensively pre-treated subjects enrolled in study T20-205. At baseline into this trial, patients had experienced a mean of 11 prior antiretroviral agents and 93% had experienced all three classes of drugs (protease inhibitors, non-nucleoside and nucleoside reverse transcriptase inhibitors); almost all patients had genotypic resistance to drugs they had received in the past; median plasma HIV-1 RNA was 4.9 $\log_{10}$ copies/mL and CD4 was 70 cell/mm^3. At 16 weeks, 60% of subjects had a decrease in plasma HIV-1 RNA of at least 1.0 $\log_{10}$ copies/mL from baseline or were < 400 copies/mL; 36% were < 400 copies/mL. No

subjects discontinued therapy because of drug-related toxicities[20]. Although early in development, T-20 looks important for subjects with true virlogic failure or suboptimal suppression. T-20 suppresses HIV-1 by a completely different mechanism of action compared to currently available drugs. If combined with active drugs or used earlier before frank virologic failure occurs, results are likely to be even more encouraging.

Treatment intensification

While not formally recommended, one experimental approach that has been taken in a limited number of clinical studies is the addition of a single active agent, or "treatment intensification", to a patient experiencing a rebound in plasma viremia. The potential advantage of such an approach is patients would preserve more aggressive treatment strategies for a later time. The results from one of the first treatment intensification strategies were first reported in a group of heavily nucleoside pretreated patients who were then switched to ritonavir/saquinavir therapy. In several patients who experienced virologic rebound following many months of optimal suppression with ritonavir/saquinavir, the addition of lamivudine and stavudine, two nucleosides that the patients had never before received, resulted in a renewed and sustained antiretroviral suppression[21].

Treatment intensification has also been successfully observed when the antimetabolite hydroxyurea was added to patients with measurable viremia following therapy with didanosine and stavudine. In this study, patients naïve to therapy were treated with didanosine/stavudine plus hydroxyurea or placebo. After 12 weeks, the virologic "non-responders" assigned to placebo were given open-label hydroxyurea. By 24 weeks, the antiviral response in the patients originally treated with hydroxyurea and in those who added it after 12 weeks was equivalent, with approximately 79% achieving optimal suppression[22].

A placebo-controlled trial of treatment intensification was reported with the nucleoside abacavir. In this study, patients receiving their first active antiretroviral therapy with plasma HIV RNA levels up to 50,000 copies/mL had their regimen "intensified" with abacavir or placebo. After 24 weeks, 39% in the abacavir group versus 8% receiving placebo had plasma HIV RNA < 400 copies/mL, demonstrating that a significant proportion of those treated were able to achieve an effective antiretroviral response by intensifying their regimen. However, these results were not sustained. After 48 weeks, 25% in the abacavir group compared to 6% in the placebo group continued to have HIV-1 RNA < 400 copies/mL ($p = 0.001$)[23]. It is possible that subjects in this study would have had better antiviral responses if their treatment had been intensified earlier.

Preliminary but encouraging results have been reported in a treatment intensification study with tenofovir, the nucleotide reverse transcriptase inhibitor formerly known as oral PMPA. In a phase II study, 189 subjects with HIV-1 RNA between 400-100,000 copies/mL receiving ≤4 stable antiretroviral drugs for at least 8 weeks received tenofovir 75, 150, 300 mg or placebo once daily to their background regimen. Baseline viral load ranged from 3.68-3.88 $\log_{10}$ copies/mL. A dose response was observed with the greatest reduction in plasma HIV-1 RNA shown in the tenofovir 300 mg group of 0.83 $\log_{10}$ copies/mL. No change in CD4 counts were noted between the groups. No significant toxicities were observed during this 24 weeks of observation[24]. These results are very significant in light of the fact that 94% of these subjects had resistance to zidovudine and/or lamivudine, but were tenofovir sensitive.

While treatment intensification is an attractive alternative to the standard approach of changing the entire therapeutic regimen, it must be approached with caution. In patients with extensive treatment histories, this approach is likely to fail due to significant baseline resistance at the time of intensification. Drugs with low thresholds for the development of resistance, such as the non-nucleosides and lamivudine, should be avoided because of the likelihood of the development of further resistance. Patients with relatively high plasma viral loads should also not be considered candidates for intensification, as the power of any single available agent may not be enough. Clinicians considering this approach should consider utilizing a commercial resistance assay prior to making the switch. Blood samples for resistance testing should be drawn while patients are receiving their treatment regimens.

Multi-drug rescue therapy, "mega-HAART"

A novel treatment approach has more recently received serious attention in a very advanced group of patients who have failed multiple drug treatments. In one such cohort, the administration of 6 or more drugs, many of them having been used in the past, has been attempted and has been termed "mega-HAART". In one such group of 37 patients treated with at least 6 antiretroviral drugs, 10/24 who were followed for at least 8 months, were shown to have decreased their viral load to < 500 copies/mL. Prior drug "holidays" and sensitive virus, based on the Antivirogram® resistance assay, were associated with a successful antiviral response. Long term therapy with this many drugs was not feasible for the majority of the patients because of intolerance[25]. In another cohort of 163 patients with virologic failure now treated with up to 9 drugs, between 30-60% were able to suppress HIV-1 RNA to < 400 copies/mL. Adverse drug effects were a frequent problem for the cohort[26].

These studies, among others, illustrate important points, such as recycling of drugs and multi-drug rescue strategies. Despite high drug intolerance rates, many patients were able to tolerate these complicated regimens and achieve significant virologic and clinical benefit.

Table 3. *Examples of common treatment strategies.*

Treatment Course	Protease Inhibitor-Based	Non-nucleoside-Based	Double Protease Inhibitor-Based	Triple Nucleoside-Based
Initial	indinavir or nelfinavir + NRTI-1/NRTI-2	Efavirenz or nevirapine + NRTI-1/NRTI-2	ritonavir (400 mg q12 h) plus saquinavir (400 mg q12 h) or NRTI-1/NRTI-2	stavudine/ didanosine/ lamivudine or abacavir/ zidovudine/ lamivudine
2nd line	double protease inhibitors (see above) + NRTI-3/NRTI-4 (optional to add efavirenz or nevirapine)	Indinavir or nelfinavir + NRTI-3/NRTI-4	efavirenz or nevirapine + NRTI-3/NRTI-4 (optional to add a 5th NRTI and/or hydroxyurea)	indinavir or nelfinavir + NRTI-4 + nevirapine or efavirenz
3rd line	no recommendation	Double protease inhibitor (see above) + NRTI-5/NRTI-6	no recommendation	double protease inhibitor (see above) + NRTI-5/NRTI-6

NRTI: nucleoside reverse transcriptase inhibitor

Scheduled treatment interruption

A novel approach to treatment of patients failing multiple drug therapies is withholding all therapy for a period of time and then reinstituting ≥3 drugs after a period of time. This strategy, termed "scheduled treatment interruption" or "drug holiday", was first reported by Miller *et al*[27] in early 1999. Resistance analyses are available for 39 patients, with a shift to wild type virus occurring in 26/39 (67%). Subsequent treatment with 3-8 drug regimens resulted in a reduction in plasma HIV-1 RNA of 2.9 $\log_{10}$ copies/mL for patients with wild type virus, versus 0.78 $\log_{10}$ copies/mL for those without a shift to wild type. For patients with the shift to wild type virus, 19/24 reached to < 500 copies/mL at 24 weeks compared to only 1/9 without the shift to wild type. During the actual scheduled treatment interruption, HIV-1 RNA inceased by 0.71 $\log_{10}$ copies/mL and CD4 counts decreased by a median 89 cells/mm^3. These pilot results suggest that scheduled treatment interruption associated with return to wild type virus may be of significant benefit for patients who have failed multiple regimens. Caution must be exercised however for patients who are likely to experience significant decreases in CD4 cell counts putting them at risk for clinical disease progression[28].

Utilization of resistance testing

The use of both genotypic and phenotypic resistance testing to assist in the choice of subsequent antiretroviral therapy has been used with a favorable response in several clinical trials. While not universally available at this time, these assays should become more available within the next year. Resistance testing is helpful to clinicians and patients because it allows for two things: 1) the exclusion of drugs and drug classes unlikely to provide any significant activity, and 2) the selection of drugs that *may* be of benefit. The second point is important as there are limitations on the value of these tests, including the inability to adequately characterize the extent and significance of circulating minority quasispecies that may carry resistance-associated mutations.

Two studies have demonstrated the benefit that genotyping may provide. In the GART Study, 153 subjects who experienced virologic rebound following at least 16 weeks of protease inhibitor-based therapy, were randomized to receive either genotyping with expert interpretation or no genotyping, with decisions left to the primary clinicians. All patients had individually selected salvage regimens prescribed. The virology results at 4-8 weeks showed that the GART group had a significantly greater mean decrease of 1.19 $\log_{10}$ copies/mL compared to only 0.61 $\log_{10}$ copies/mL in the no genotyping group[29]. Similar results were reported in the VIRADAPT study. In this trial, 108 subjects who had taken at least 6 months of antiretroviral therapy and plasma HIV-1 RNA > 10,000 copies/mL were randomized to receive treatment selected based on genotyping results or best available therapy without genotyping. After 24 weeks, 32% in the genotyping group compared to 14% in the no genotyping group had HIV-1 RNA < 200 copies/mL ($p = 0.67$); changes in viral load from baseline were -1.15 and -0.67 $\log_{10}$ copies/mL respectively ($p = 0.05$)[30]. In addition to the resistance testing results, drug concentrations were also found to independently predict the virologic response. Subjects with trough protease inhibitor concentrations above the IC_{50} were more likely to have an effect on viral load ($p = 0.013$)[31].

Phenotypic susceptibility testing has also been shown to be predictive of improved antiviral responses. In one study, 71 treatment-experienced subjects with a median plasma HIV-1 RNA of 70,644 copies/mL and CD4 count of 142 cells/mm^3 were retrospectively studied with the ViroLogic Phenosense® assay. A multivariate analysis revealed that the number of sensitive drugs, using either a susceptibility cut off of either $\leq$ 2.5 or $\leq$ 4.0, was the best independent factor associated with time to virologic failure (RR 0.59 per susceptible drug; 0.46, 0.77). Antiretroviral history did not provide additional predictive value when added to this model[32]. These studies all support the use of resistance testing when devising a rescue treatment regimen. Not only will they likely aid in the selection of active drugs, but they will save costs and potential toxicities of therapies unlikely to be of benefit.

Formulating a strategy

Initiating therapy and following published guidelines superficially appears quite easy. However, if a miscalculation is made, the results can be quite unfavorable for the patient, as subsequent options are limited. It is necessary to strategize a sequence of therapeutic interventions. A realistic goal for the year 2000 is to suppress the virus as much as possible. Utilization of sequencing strategies, resistance testing, intensification, "mega-HAART" therapy, and scheduled treatment interruptions are all options currently available to clinicians and patients requiring more suppressive therapy. The antiretroviral drugs currently in development coupled with the potential for immune interventions look promising and are likely to provide further significant benefit to our patients. Table 3 outlines several of the strategic approaches available to patients at the present time.

Table 4. *Treatment options for patients with suboptimal viral suppression and/or rebound*.

Change entire regimen
Change definition or threshold for viral rebound/failure
Treatment intensification
Recycling and use of multiple drugs (i.e. "Mega-HAART")
Scheduled treatment interruption
Resistant-testing based treatment changes
New antiviral agents and classes of drugs

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