Salvage therapy is an approach taken when previous anti-HIV treatments fail to achieve desired goals, which include undetectable viral load, CD4 cell levels above 200 cells/mm³, and the prevention of HIV disease progression. It is one of the most difficult situations to face as a patient, and one of the most problematic challenges for health-care providers. Though sometimes euphemistically referred to as “management of treatment-experienced patients,” many HIV positive people, having already exhausted the benefits of at least a couple of drug combinations, think of their next regimen as salvage or “rescue” therapy.

A few physicians argue that due to cross-resistance among different drugs within the same class, people with HIV infection have only one good shot at treating it, and that any treatment regimen beyond the first is therefore salvage therapy. Others see salvage therapy as literally the end of the line—when an individual’s HIV has developed extensive resistance to all currently available treatments. But most providers consider salvage therapy to be somewhere in between these extremes. Understanding that the term can refer to different treatment situations is important. Nevertheless, most of the information in this article will be relevant for anyone changing a drug regimen, no matter where that person is on the treatment path.
Individualized Care

Salvage therapy is one of the most difficult topics to write about because every statement must be qualified in relation to an individual’s personal treatment history. Although this should be the case with any medical decision, choices about HIV treatment should be tailored for each person. As therapeutic options become more limited, the stakes are arguably higher. More than at any other time in a person’s treatment history, salvage therapy requires highly individualized care.

It is important for people to keep their own treatment history file that includes CD4 cell count, viral load, and resistance test results, together with a list of drugs previously used, medication allergies, past side effects, and adherence levels (frequency of taking doses as prescribed). As antiretroviral therapies become more effective, it is clear that we now need to plan for 30 years or more of treatment. Keeping complete treatment records is especially important when changing providers or hospitals.

Whether an individual has failed an initial regimen, has been HIV positive for many years and has used all the available drugs, or has been recently infected with a multidrug-resistant HIV strain, the approach will be similar. It involves looking at five or six key areas, each of which must be addressed to optimize the chances of success with a subsequent regimen. This highly individualized approach is not based on new science, and in fact has changed very little over the past three or four years.

Why Treatments Fail

Although the range of antiretroviral therapies has expanded, the basic principles of HIV treatment have been understood for some time and remain fairly constant. Apart from a few exceptions, such as recent research on viral fitness (replication capacity), most of the approaches discussed in this article are not new or recently discovered.

John Mellors, MD, of the University of Pittsburgh outlined the foundations of HIV therapy in a keynote speech opening the 1999 Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC) in San Francisco. The multidisciplinary approach he described was also stressed at the Workshop on Management of Treatment Experienced Patients held in San Diego, California, this past September.

Both lectures emphasized that there are only a limited number of known reasons why treatment might fail: drug resistance, inadequate drug potency, suboptimal drug levels, poor adherence, and drug toxicity. At least one—and possibly a combination—of these factors are responsible for the failure of each treatment regimen used in the past, whether it was the first or the fifth combination. To avoid repeating the same mistakes with salvage therapy, it is important to understand why each previous treatment attempt failed.

Resistance

Drug resistance is recognized as the reason most combination regimens fail, but how resistance develops is still often misunderstood.

The medical explanation for the development of resistance is that ongoing viral replication occurs in the presence of a drug regimen that does not adequately suppress the virus. This means that if a person has a detectable viral load (over 50 copies/mL) while on treatment, enough new virus is produced each day for resistance to develop by chance due to random viral mutations (genetic changes). Once resistance develops by chance, however, if a person continues to take the drugs to which HIV is no longer susceptible, the resistant virus will continue to replicate until it becomes established as the majority strain.

Resistance, therefore, does not cause a treatment to fail, but rather develops if one or more of the other key factors related to treatment failure are present. If a combination regimen is not potent enough, if drugs are poorly absorbed, if adherence is not perfect, or if the drugs are not effective due to pre-existing resistance, a person may not achieve or maintain a viral load under 50 copies/mL. Then, as a result of continuing treatment with a detectable viral load, viral mutations may develop and resistance can follow.

However, studies show that if viral load is reduced to an undetectable level (usually below 50 or 25 copies/mL, depending on the assay) and all other factors related to treatment success are taken into account, then a combination regimen will continue to work and the virus is much less likely to develop further resistance. Individuals who achieve and maintain undetectable viral load levels with any drug combination, first-line or salvage, are in the best position to see their viral load remain this low for many years. The magnitude of the drop in viral load—even if it is reduced by hundreds of thousands of copies—is not as important as getting viral load as low as possible. Some studies suggest that it may be beneficial to aim for a viral load below 5 copies/mL; ongoing research should clarify whether this is important for long-term health.

Another important concept is that resistance rarely acts like an on-off switch. Think of resistance more as being on a continuum, with completely sensitive or even hypersensitive virus at one end and completely resistant virus at the other. The medical explanation for the development of resistance is that ongoing viral replication occurs in the presence of a drug regimen that does not adequately suppress the virus.

Reasons for Treatment Failure

- drug resistance
- inadequate drug potency
- suboptimal drug levels
- poor adherence
- drug toxicity
Considerations When Changing Antiretroviral Therapy

If viral load starts to rise above 50 copies/mL, don’t panic—but do take it seriously.

Have a new viral load test done on the same day you get the results of the first test to determine whether the first result was accurate. Viral load levels often fluctuate, and a single high result may not indicate that treatment is failing. Collect the new test results as soon as they are available (usually within two weeks).

If the new test results show that viral load is continuing to rise, changing drug regimens quickly will give the next combination the best chance of success. Be careful to change medications only when treatment failure—and the reasons for it—have been confirmed to avoid prematurely discarding viable treatment options.

Find out why the current drug combination failed. Was it due to resistance, lack of potency, poor adherence, suboptimal drug absorption, or a combination of these factors?

Choose the most potent combination available for salvage treatment. Dose reductions or drug substitutions can always be considered later.

Use as many drugs as possible that are not cross-resistant to previously used drugs. Ask for genotypic and phenotypic drug resistance tests.

Monitor the effectiveness of the new regimen carefully, preferably with a viral load test 4–12 weeks after the treatment change, then every three months. Discuss any problems with adherence or side effects with a health-care provider.

Find out what new treatments will become available and when, including through expanded access programs or clinical trials. Taking new drugs may not be necessary, however. If your CD4 cell count is stable, it may be better to save new drugs until they are most needed.

Keep up to date on the latest research areas such as mega-HAART, structured treatment interruption, and new drugs in development.

Even if viral load is detectable and new treatments are not available, staying on a regimen that partially suppresses HIV is much safer than stopping all drugs.

virus at the other. In between these two extremes, other factors come into play. For example, HIV generally slowly accumulates mutations that gradually limit how effective protease inhibitors (PIs) are against the virus. But even with extensive resistance, the drugs still can have some clinical benefit. If a person with drug-resistant HIV discontinues treatment and viral load increases further, this is evidence that the drugs were providing some anti-HIV activity. Since resistance is on a continuum, increasing the dose or concentration of a drug often can overcome resistance—although doing so may also increase drug toxicity.

Resistance Testing

Resistance tests are used to identify drugs that are not effective against an individual’s specific strains of HIV. There are two main types of resistance tests. Genotypic tests look for genetic changes in a person’s virus and match these mutations against a database of known mutations that in clinical trials have been associated with resistance to different drugs. Phenotypic tests look at how viral replication is affected when increasing concentrations of different drugs are added to an individual’s HIV in a test tube. A third variation called a “virtual phenotype” compares genotypic results with a large database of phenotypic results.
Both genotypic and phenotypic tests only detect resistance once it is relatively extensive. The tests are less sensitive to minority drug-resistant strains of HIV that are present in the body at low levels. For the most reliable results, the viral load should be above 1,000 copies/mL and the individual should currently be taking anti-HIV therapy. While several studies have shown that resistance tests can help physicians select an optimal drug regimen, other studies have not shown a dramatic benefit in terms of clinical outcome. This is likely because as a person’s HIV becomes more resistant, there are fewer effective treatment options available. Resistance tests can tell which drugs are no longer active, but someone whose virus is no longer sensitive to any drugs will not be able to construct an effectively suppressive regimen.

Experts have begun to recognize the value of resistance tests at every important change in a person’s HIV disease progression. Julio Montaner, MD, of the University of British Columbia in Vancouver has referred to the combined history of all of an individual’s worst resistance profiles over time as “virtual resistance.” Compiling such a profile involves blood tests when HIV is originally diagnosed and before starting treatment, a complete history of all drugs a person has taken, and viral load test results for the periods during which those drugs were used. It also requires knowing the exact timing of previous resistance tests and what drugs were being taken at the time of these tests.

Short-term treatment benefit has been observed when resistance testing is used in conjunction with therapeutic drug monitoring (TDM) to ensure optimal drug levels (discussed below). Long-term TDM data for anti-HIV medications are not yet available.

**Drug Potency**

Potency refers to the strength of drugs in a combination regimen—how effective they are at reducing viral replication and maintaining a response. On a basic level, drug potency refers to how much of a viral load reduction a drug generates by itself. The greater the potency of each drug in a combination, the greater the magnitude and durability of viral load reduction.

Anti-HIV drugs are approved only when they show a clear antiretroviral effect; even the newest drugs that have been studied for use in salvage therapy must show this effect. For example, results from a recent study of the fusion inhibitor T-20 (enfuvirtide, Fuzeon) showed that T-20 added to the best available existing choice of therapy produced a 1.7 log reduction in viral load, while the best existing regimen alone produced only a 0.7 log reduction. The European/Australian segment of this study (TORO 2) showed slightly less of an effect (1.4 log and 0.6 log reductions with and without T-20, respectively) in people who had more resistance to existing drugs before they started the study. From this, it appears that T-20 can produce an approximate 1 log reduction in viral load, although this will of course vary among individuals.

The reason combination antiretroviral therapy includes three or more drugs is largely linked to the issue of potency. The potency of a regimen is determined not only by the activity of each drug, but also by the combined activity of the regimen as a whole. The overall potency of a combination regimen must be strong enough to reduce viral load from baseline to an undetectable level and to maintain this response for months and, ideally, years.

If a single drug could produce a 5 log or 6 log reduction in viral load on its own, it could theoretically be used without other drugs in a combination (although resistance is more likely when a drug is used alone). However, existing drugs produce viral load reductions only of about 0.4 to about 2.5 logs. Therefore, at least three highly suppressive drugs are generally required to reduce viral load from baseline to an undetectable level. By definition, people who require salvage therapy do not have three potent drugs available, so regimens with larger numbers of drugs—sometimes up to nine—may be needed to achieve adequate potency. Even drugs that are not very potent by themselves can still contribute some antiretroviral activity to a combination.

Potency depends not only on the effectiveness of a drug itself and the other drugs it is used with, but also on the specific virus it is used against. A few drugs can be more effective against drug-resistant virus than against wild-type (nonmutated) HIV, but in general, resistance and previous treatment experience render new drugs less potent. For example, studies have shown that the recently approved nucleotide reverse transcriptase inhibitor (NtRTI) tenofovir DF (TDF, Viread) produces an average 0.6 log viral load reduction in treatment-experienced people compared with a 1.1 log drop in those who are treatment-naive. Tenofovir may therefore contribute more potency as part of a first-line regimen than as part of a salvage regimen.

**Suboptimal Drug Levels**

A third important reason for treatment failure is suboptimal drug levels in the body. Suboptimal drug levels may be due to inadequate dosing, but may also be related to individual differences in pharmacokinetics (drug absorption, metabolism, and excretion). How drugs are absorbed in the body is highly individual, and blood drug levels are subject to significant variation among different people taking exactly the same dose. For some drugs used for conditions other than HIV this
is not a problem, because their generally low toxicity means the drugs can be given in sufficiently high doses to allow for this variability. But this is not the case for most anti-HIV medications. Due to the toxicity of antiretroviral drugs, the highest tolerable dose may be only just above the minimum dose required to avoid resistance.

Many antiretroviral drugs are metabolized in the liver by the cytochrome P450 (CYP450) enzyme system. Some people naturally metabolize drugs more slowly or more rapidly than others. For example, those with existing liver damage often have impaired drug metabolism. People who metabolize drugs faster than average run the risk of developing resistance due to suboptimal drug levels. Those who metabolize drugs more slowly than average may experience increased side effects due to high drug levels. Among people who metabolize drugs quickly or do not achieve adequate concentrations in the body for other pharmacokinetic reasons, even perfect adherence will not ensure safe levels.

In addition, drugs that are metabolized by the CYP450 pathway can interact. When multiple drugs that use the same pathway are present, metabolism may be slowed, leading to higher drug levels. In other cases, certain drugs can stimulate CYP450 metabolism, leading to more rapid drug processing and lower levels. Every recent medical conference on AIDS has included reports about drug interactions, often involving medications that have been licensed for many years. Some foods and herbal remedies (for example, grapefruit juice and St. John’s wort) can also affect drug metabolism.

Peak and trough levels and area under the curve (AUC) are important concepts in understanding drug levels. The peak level is the highest drug level in the body after taking a dose. The trough level is the lowest drug level between doses, usually reached right before the next scheduled dose is taken. On a graph, the line that joins peak and trough levels is a curve; therefore, the amount of drug exposure over a dosing interval is represented by the “area under the peak/trough curve,” or AUC.

It is best to have a constant therapeutic drug level in the body over time, since high levels can cause increased side effects and low levels can promote resistance. Several new antiretroviral drug formulations are designed to last longer in the body and achieve steady drug levels with a single daily dose.

Sometimes low drug levels and resulting drug resistance can be overcome with higher doses. Increasing drug dosages can produce a stronger antiviral effect, but also heighten the risk of side effects. For example, it is well known that the first studies of AZT (zidovudine, Retrovir)—which used three or four times the current accepted dose—led to side effects that were very difficult to tolerate. What is less well known is that AZT monotherapy at these high doses produced about a 4 log reduction in viral load. Using such high doses as part of salvage therapy is not common, but may be useful on an individual basis (though only in consultation with a physician).

With regard to T-20, it should be noted that maximum dose cut-offs for efficacy or tolerability were not reached in the registrational studies due to supply problems and the difficulty of asking subjects to inject the drug more than twice per day. There may therefore be a subgroup of people using T-20 in the context of salvage therapy who could benefit from the potentially greater antiviral activity of higher doses.

**Drug Boosting**

One way to increase the antiretroviral activity of a drug is to add another medication that “boosts” the blood level of the first drug. As discussed above, this works because certain medications inhibit drug metabolism in the liver.

Ritonavir (Norvir) is used most often to boost the levels of other PIs. Numerous studies have shown that using ritonavir to boost indinavir (Crixivan) can overcome indinavir resistance; however, as blood levels of indinavir increase, so too does the incidence of side effects. The new PI Kaletra includes a small amount of ritonavir in the pill to increase levels of lopinavir. The added ritonavir boosts lopinavir well above the minimum concentration needed to inhibit 50% or 95% of viral replication (called the IC50 or IC95, respectively; IC refers to the “inhibitory concentration” as determined in laboratory tests). This is one of the reasons Kaletra has proven to be so effective against HIV that is resistant to older PIs. Lopinavir itself has a resistance profile similar to that of other PIs, but boosting with ritonavir can overcome this resistance.

As another example, a recent study suggested that using a low dose (300 mg) of hydroxyurea (Hydrea) twice daily could enhance the activity of ddI (didanosine, Videx) while reducing ddI toxicity. It has also been suggested that mycophenolate (mycophenolic acid, CellCept; used in organ transplantation) can similarly increase the potency of abacavir (Ziagen) and a few other nucleoside reverse transcriptase inhibitor (NRTI) drugs, although clinical benefit from this approach has not been clearly shown in recent studies.

**Therapeutic Drug Monitoring**

Therapeutic drug monitoring (TDM) refers to measuring the levels of medications in the body. The goal of TDM is to help achieve optimal drug levels on an individualized basis. The technique can provide protection against...
excessively low or high drug levels, and thereby improve virological outcomes and reduce toxicity. TDM is most useful with PIs and may also be used with non-nucleoside reverse transcriptase inhibitors (NNRTIs); however, it is not recommended for NRTIs due to current technological limitations. Results from a large European trial (named ATHENA) of subjects taking their first antiretroviral regimen showed that TDM led to lower rates of treatment discontinuation and higher rates of virological response. Some clinicians believe TDM may be beneficial for people taking salvage regimens as well.

By helping to optimize treatment, TDM can lead to the use of very different dosing regimens in different individuals. For example, indinavir/ritonavir is often dosed at 400 mg/100 mg twice daily in France, where TDM is widely used. (The typical dose in the U.S. is 800 mg indinavir with 100 or 200 mg ritonavir twice daily.) People in the Netherlands using the original formulation of saquinavir (Invirase) with the benefit of TDM received “double dosing” and avoided the early failures seen in the U.S. due to suboptimal drug levels. And in the UK, a patient whose damaged liver allowed only extremely slow metabolism of efavirenz (Sustiva) was given a low dose of 200 mg twice weekly prior to a liver transplant.

Such individualized dosing is possible only when drug levels can be monitored and adjusted on a person-by-person basis; it is not possible simply to guess drug levels. Further research needs to be done in this area, however, as optimal drug levels are not precisely understood and drug level tests have not been standardized.

Scientific opinions about TDM differ considerably between Europe and the U.S., as does access to it. Countries in Europe with leading research programs on drug metabolism already have laboratories that can analyze blood drug levels in people receiving antiretroviral therapy. In the Netherlands TDM is part of the standard of care; all people starting anti-HIV regimens that include a PI or an NNRTI have their levels of these drugs measured. In France TDM is not universal, but it is widely used, especially for people receiving salvage therapy. In the UK TDM is available to a wide range of people, mainly those using PIs. Use varies by clinic, and some offer TDM to all patients; due to the efforts of treatment advocates in the UK, the additional cost of the tests is covered by drug manufacturers.

Availability of TDM in the U.S. has increased over the past few years, although it is still uncommon. U.S. clinicians generally are ambivalent about the benefits of TDM for anti-HIV therapy due to the wide variability of drug levels within a single individual (especially due to timing of doses, food requirements, and varying adherence levels over time), uncertain therapeutic ranges of anti-HIV medications, lack of standardization of drug level measurements, variability in laboratory accuracy, and difficulties in interpreting TDM results. Some providers also question the value of measuring boosted PI combinations (that is, regimens with minimized peak/trough variability).

Yet clinicians such as Steve Miles, MD, of the University of California at Los Angeles (UCLA) nevertheless believe that TDM can help individualize HIV treatment, including in people whose previous regimens have failed and in those with few therapeutic options, for whom “a mistake in drug levels could doom a regimen.” (Dr. Miles also noted that TDM is reimbursed by Medicare and Medi-Cal at approximately $40 per assay.)

In a position paper published in the August 10, 2002 issue of AIDS Research and Human Retroviruses, the Adult Pharmacology Committee of the U.S. Adult AIDS Clinical Trials Group (AACTG) stated that “data generally support the use of TDM.” While acknowledging difficulties in this rapidly changing area of treatment, the committee also provided guidelines to assist clinicians, particularly when using TDM in conjunction with phenotypic testing for people receiving salvage therapy. Encouragingly, Edward Acosta, PharmD, from the AACTG committee, in a lecture on TDM use in the U.S. at the September 2002 ICAAC, concluded that “TDM will likely be incorporated into treatment, especially in salvage therapy…and especially if the rate of new drug development is unable to keep pace with the development of resistance.” (See also “Therapeutic Drug Monitoring,” BET A, Autumn 2000, page 22. For information on a currently enrolling trial studying TDM, see page 47 in this issue.)

Combining TDM and Resistance Testing

While the benefits of resistance testing and TDM on clinical outcome have been evaluated separately, two important resistance studies showed that both drug sensitivity and optimal drug levels are necessary to achieve a sustained virological benefit from treatment.

In the GART study, Douglas Mayers, MD, of Henry Ford Hospital in Detroit, Michigan, and colleagues studied 153 subjects who experienced a greater than three-fold rise in HIV viral load while using a regimen containing a PI and two NRTIs for over 16 weeks. Subjects were randomized to receive either treatment recommendations based on genotypic testing or else no genotypic test results. In a pharmacokinetic substudy, blood levels of all drugs (including NRTIs) from random (untimed) samples from 147 participants were measured using the VircoPK assay at baseline and at weeks 4, 8, and 12. The week 12 results were used to determine whether individual subjects
had drug levels above or below the median. Genotypic and phenotypic test results were also used to determine the number of more active and less active drugs for each participant. Researchers calculated viral load changes from baseline to week 12 and their relation to drug levels. Inhibitory quotients (IQs, see sidebar on this page) were calculated as drug level at week 12 divided by fold change of IC_{50} at baseline, and were also classified as being above or below the median for the group.

Suboptimal levels of more active drugs led to a reduced antiviral effect compared with higher concentrations of less active drugs, reaching statistical significance for the genotypic analysis. A clear relationship was also found between the average change in viral load at week 12 and the number of drugs with mean IQ above the group median. For the cohort as a whole, the additional viral load reduction was 0.2 logs for each drug with an IQ above the median. Even though the differences in this study may appear small, they can be significant in a salvage setting in which any added viral suppression is likely to contribute to a longer duration of response to treatment.

The VIRADAPT study showed a virological benefit when using genotypic resistance test results to guide treatment choices for second-line and salvage therapy combinations. Results were presented by Rodolphe Garraffo, PharmD, and colleagues from Nice, France, at the September 1999 ICAAC and published in the July 7, 2000 issue of AIDS. Drug level monitoring for PIs was also done in this study to determine the impact of medication levels on therapeutic success or failure.

Eighty-five participants (49 in the genotypic testing arm and 36 in the control arm) received 575 PI drug level measurements. Participants were considered to have optimal drug concentrations if two or more measurements were greater than the IC_{50} for the specific PI they were receiving. Subjects who had two or more measurements below the IC_{50} were considered to have suboptimal drug concentrations. Participants with suboptimal drug concentrations achieved a 0.3 log reduction in viral load at week 48, compared with a 1.2 log decrease in those with optimal drug concentrations. In a multivariate analysis, drug concentrations above the IC_{50}, the use of genotypic testing, and the presence of primary resistance mutations for PIs were independently associated with virological response.

**Adherence**

Some providers believe that adherence is often the likeliest cause of treatment failure; drugs cannot be effective if people are unable to take them as prescribed. As discussed above, due to toxicity the highest tolerable dose of an antiretroviral drug may be only just above the amount needed to avoid resistance. Missing even an occasional dose can cause drug levels between doses to fall so low that the drug no longer suppresses the virus. This is a particular concern with once-daily medications, since more time passes between doses and the virus

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**The inhibitory quotient (IQ)** is a measure of drug exposure and susceptibility in an individual. It is typically calculated as the minimum drug concentration (C_{min}) divided by viral susceptibility to that drug in an individual (IC\textsubscript{50} or fold change as measured by a phenotypic assay). In the case of virtual phenotyping, the virtual IC\textsubscript{50} (the fold change reported in this test) is used and the IQ is referred to as the virtual inhibitory quotient (VIQ).

The IQ or VIQ may prove to be a more practical measure of resistance than genotyping or phenotyping alone because it combines drug susceptibility and drug exposure. Several studies have shown that increasing drug doses can sometimes overcome reduced susceptibility. By relating individual drug exposure to the level of viral resistance in that same person, a more accurate prediction of virological response to that drug may be achieved.

For example, a person may have perfect adherence—allowing adequate drug levels—but moderately resistant virus, and therefore therapy may fail despite the good drug levels. The IQ or VIQ provides additional information along with phenotypic testing and therapeutic drug monitoring, and serves as a guide for dosage adjustment in order to achieve the drug levels needed to overcome resistant virus.

Although IQ and VIQ measurements are a relatively new concept, their integration into clinical care for salvage therapy could provide another opportunity for individualization. Yet until these measurements are standardized to define therapeutic and toxic IQ levels, their use in clinical practice will remain limited.
Viral fitness refers to HIV's ability to replicate and infect new cells. Strains of HIV often become less fit and presumably less harmful as they mutate to resist drugs; nonmutated virus is known as wild-type virus.

Researchers from the Royal Free Centre for HIV Medicine in London have developed a model for rotating drugs as monotherapy, dual therapy, or triple therapy on a daily or weekly basis. Using a model allowing for 128 different subpopulations of virus and combinations of seven anti-HIV drugs, Andrew Phillips, PhD, and colleagues calculated that sequential daily or weekly monotherapy with the seven different drugs was as likely to produce sustained 3 log viral load reductions over three years as continuous use of a seven-drug combination regimen. According to the model, in some circumstances dual or triple therapy may be more likely to work than monotherapy, and it would probably be best to start with such combinations. The only advantages of monotherapy are reduced toxicity and cost.

Although viral resistance would be present on each day of treatment, the sequential regimen would remain effective because any given subpopulation would not have time to grow sufficiently during the short period in which a specific drug was used. One caution with this approach is that it may require more classes of drugs than are currently available. However, if the rationale is plausible, this strategy would work best for people who have already developed the most resistance, who arguably have therefore more time to replicate in the absence of an adequate concentration of the drug in the event of a missed dose. Following the dietary requirements for a medication is also important.

While some people can be 100% adherent and still experience treatment failure due to pre-existing resistance, suboptimal drug levels, or an insufficiently potent regimen, many others will not have been as adherent as they wanted or needed to be.

Adherence rates among people taking anti-HIV therapy are probably higher than for practically any other condition—including other life-threatening infections—yet even this high adherence rate is not high enough. Although the importance of adherence may be widely recognized, it remains problematic in day-to-day practice. For many people, the need for salvage therapy may provide an opportunity to take treatment more seriously than ever before.

If adherence has been very poor, a person may have avoided resistance because of insufficient continuous drug levels. That is, the concentration of a medication may have been too low to pressure the virus to develop drug-resistant mutations. This possibility should be taken seriously. Before choosing new drugs, people who are considering changing their treatment regimens due to viral load rebound should tell their health-care providers how they were actually taking their medications. Resistance testing may be another way to confirm whether drug resistance has developed.

Getting adherence right should be the primary focus for people on any therapy until they develop good habits. Support programs and adherence teams (i.e., peer advocates, social workers, pharmacists, and nurses) can be more helpful than many doctors, and often are more trusted by patients. These adherence experts can provide tips and tools such as timers, phone reminders, and beeping pillboxes. Support for adherence should be included as part of every treatment plan. Designing a strategy for near-perfect adherence when taking salvage therapy can be as beneficial as having access to a new drug.

Drug Toxicity

Drug toxicity leading to discontinuation is another possible cause of treatment failure. For a minority of people, severe or life-threatening reactions to anti-HIV medications can eliminate these drugs as options, and therefore can be seen as medically responsible for treatment failure.

Hypersensitivity reactions to abacavir and nevirapine (Viramune), hepatotoxicity (liver toxicity), seriously elevated lipid levels, and manifestations of mitochondrial toxicity (for example, muscle aches and weakness) can all lead to drug discontinuation.

Less serious toxicities may also lead to treatment failure if they are not managed properly. For example, diarrhea and vomiting can prevent adequate drug absorption. Any side effects that have a negative impact on quality of life may lead to problems with adherence. Close monitoring and effective management of side effects can only increase the chances of successful treatment. In some cases, switching drugs to improve tolerability may also be important.

A session at the Workshop on Management of Treatment-Experienced Patients this past September highlighted the importance of drawing upon specialized expertise to prevent and manage both side effects and opportunistic illnesses (OIs). This may become increasingly important in the case of side effects that are outside the realm of expertise of most clinicians trained in infectious disease management, such as elevated blood lipid levels and loss of bone mineral density.

Salvage Therapy Strategies

Addressing the various factors that contribute to treatment failure can improve the likelihood of successful salvage therapy. Two management approaches will be discussed below: whether or not to interrupt therapy before starting a new salvage regimen,
and whether there is a benefit to using multiple drugs in salvage therapy. Both approaches have been used in salvage therapy settings in well-publicized cohort studies from London, Frankfurt, Montreal, and Paris. They are being further studied in a large, randomized international trial called OPTIMA. (The future of this study is currently unclear due to slow enrollment; many researchers and participants are reluctant to accept randomization in the context of salvage therapy.) For more information about OPTIMA and other salvage therapy trials, see page 46.

**To Interrupt or Not to Interrupt?**

There are several reasons underlying the strategy of interrupting therapy before starting a new salvage regimen. These include allowing a reversion from resistant to wild-type virus, a break from side effects, and a short period to psychologically prepare to cope with a subsequent mega-HAART combination (a regimen containing five or more drugs).

The French GIGHAART study showed that a treatment break of eight weeks prior to optimized salvage therapy could dramatically increase the chances of subsequently achieving virological benefit. Results were presented by Christine Katlama, MD, of Hôpital Pitié-Salpêtrière in Paris and colleagues at the 8th European Conference on Clinical Aspects and Treatment of HIV Infection in October 2001, and again at more recent conferences. In this randomized study, the arm that took a break before resuming treatment and the arm that immediately started salvage therapy both experienced a viral load decrease greater than 1 log over the first two weeks. However, viral load gradually rebounded in the immediate treatment arm, leaving only a 0.4 log drop from baseline at week 12. The deferred treatment arm experienced continued viral load decline to 1.9 logs below baseline. The greater benefit seen in the deferred therapy arm led to the early termination of the study.

Taking these results back to individualized care, the prospect of better results with deferred therapy is exciting, but the potential risks are also very real. Treatment-experienced people who interrupt therapy will need more frequent monitoring and possibly prophylaxis drugs to protect them from developing OIs if their CD4 cell counts are at risk for dropping below 200 or even 100 cells/mm³. However, the cost savings from not using antiretroviral drugs during this period should easily cover the expense of additional monitoring.

Other studies of treatment interruption have shown that a CD4 cell decrease of more than 100 cells/mm³ may be expected, and that the optimum time to defer therapy appears to be 8–12 weeks. These results are from averaged data and, as always, treatment decisions should be individualized. Some people may need to start salvage therapy earlier, while others may be able to delay resuming treatment for longer periods.

**Mega-HAART**

The second main salvage therapy strategy is to increase the number of drugs in an antiretroviral regimen. Some studies have used combinations of up to nine drugs. Such studies looked at multidisciplinary approaches to salvage therapy in people who had run out of other treatment options and were happy to try a new strategy. Participants in the French GIGHAART study, for example, had CD4 cell counts under 200 cells/mm³, resistance to three classes of antiretroviral drugs, and a median viral load of over 50,000 copies/mL. It is notable that major studies of mega-HAART have used TDM to confirm the levels of each PI and NNRTI, and have adjusted doses appropriately on an individualized basis.

Combinations used in the GIGHAART study included three to five NRTIs (ddI, d4T [stavudine, Zerit], AZT, 3TC [lamivudine, Epivir], and/or abacavir) plus one NNRTI (nevirapine, delavirdine [Rescriptor], or efavirenz) plus three PIs (either 400 mg ritonavir/600 mg amprenavir [Agenerase] twice daily or 300 mg ritonavir/400 mg lopinavir twice daily, plus either 400 mg few other alternatives and who therefore would be most likely to want to try this option.

At the 2002 International AIDS conference in Barcelona, Franco Maggiolo, MD, of Ospedali Riuniti in Bergamo, Italy, and colleagues presented very interesting results from a pilot study of a similar approach: cycling drug combinations to allow for constant selective pressure on the virus. They reported continued low levels of viral replication in a group of 34 subjects with HIV resistant to three drug classes; baseline viral load was about 25,000 copies/mL. Anti-HIV drug combinations were selected on the basis of genotypic resistance test results; no regimen included more than four drugs. Viral load was monitored every two months, and treatment was changed if viral load rose above 10,000 copies/mL. Throughout the two-year study period participants maintained viral loads between 3,500 and 10,700 copies/mL. Therapy cycles lasted a mean of about six months. Importantly, CD4 cell counts increased steadily from a baseline mean of 239 cells/mm³ to a mean of 323 cells/mm³ at 24 months. Only two participants experienced HIV disease progression.

While this strategy is still theoretical, attempts to define and harness reduced viral fitness for clinical benefit, and proof-of-concept case studies, will be followed with great interest. ViroLogic launched its Replication Capacity (RC) assay to measure viral fitness in June 2002, which may make such studies more feasible.
Participants achieved adequate drug levels in the immediate arm compared with the deferred arm (74% vs 80%). When results from resistance testing were correlated with either adequate or low drug levels, a better virological response was associated with reversal of resistance mutations when adequate drug levels were achieved.

Safety and tolerability are always a concern when dealing with regimens containing numerous drugs. Participants in this study generally experienced a low level of toxicity for a group with such advanced disease. Rates of grade 3 (severe) toxicities and HIV-related OIs were similar in the immediate and deferred arms, with slightly more events reported in the immediate treatment arm (although numbers were small).

Data from Dr. Montaner’s mega-HAART cohort were presented at the XIV International AIDS Conference in Barcelona this past July. The results showed that this multidrug approach may produce a durable response with tolerable side effects. In this study 248 participants with multidrug-resistant HIV received regimens containing up to nine drugs (median of six). TDM was used to ensure adequate drug levels.

Using an intent-to-treat (ITT) analysis in which all participants were analyzed whether or not they continued in the study, 69% achieved viral loads below 400 copies/mL on at least two consecutive measurements and about 40% achieved viral load levels below 50 copies/mL by week 48. This response was sustained out to 24 months in 80% of those who achieved undetectable viral loads.

Dr. Montaner concluded that aiming for undetectable viral load in treatment-experienced people is both realistic and sustainable. Even more optimistically, he showed that using this aggressive, multidrug approach in individuals with highly drug-resistant HIV produced a survival benefit similar to that seen in treatment-naive people using normal HAART regimens.

Strategies for Using New Drugs

Access to new drugs may provide the best hope for many people with HIV, especially those who continue to experience rising viral load levels after trying a mega-HAART combination. But the use of new medications requires careful consideration. In particular, it is important to avoid simply adding new drugs sequentially to an existing regimen as they become available. Adding a new drug to a regimen in which the existing medications are no longer effective is similar to using the new drug as monotherapy—a recipe for resistance. Some drugs in the development pipeline hold great promise, but they will produce better results if they are supported by other effective drugs in a combination regimen. (See “The HIV/AIDS Drug Pipeline,” BETA, Summer/Autumn 2002, page 29.)

For each individual, weighing how long one can delay treatment with a new drug compared with how urgently one needs the medication can be very difficult. For people who have no other options and whose clinical health is at risk, any new drug may...
provide an important benefit—even if it is only for the short term.

Study results presented by Steven Deeks, MD, of the University of California at San Francisco (UCSF) and colleagues at the February 2002 Conference on Retroviruses and Opportunistic Infections (CROI) support the argument against changing treatment in the face of high-level resistance. Instead, people with high CD4 cell counts who are clinically well may stay on a “failing” PI combination, perhaps for several years. After 2–3 years on PI-based regimens, a subset of subjects who retained high CD4 cell counts who are clinically well may, instead of changing treatment, continue for a while on salvage therapy by stating, “There are lots of bad doctors, bad nurses, bad drugs, and bad patients,” and that if each of these problems were addressed, there would be little demand for salvage therapy. Dr. Youle clarified that lack of experience on the part of health-care providers, or an unwillingness to keep completely up-to-date on HIV treatment advances, directly affects the health and care of patients, an observation that has been supported by several studies.

People receiving HIV therapy—especially those with extensive treatment experience—should be treated by a physician who is aware of the most current research and is willing and able to develop individualized approaches to treatment. People with HIV should also keep up with the latest advances in treatment strategy and the availability of new drugs, so that decisions will be based on the best research available. Successful outcomes are often the result of collaboration and teamwork between informed patients and their physicians.

Experience Counts

The experience of physicians is an important factor in the success of salvage therapy. This past summer Mike Youle, MD, of the Royal Free and University College Hospital in London, who has been at the forefront of many new strategies to individualize patient care in the UK, began a presentation to the UK Community Advisory Board on salvage therapy by stating, “There are lots of bad doctors, bad nurses, bad drugs, and bad patients,” and that if each of these problems were addressed, there would be little demand for salvage therapy. Dr. Youle clarified that lack of experience on the part of health-care providers, or an unwillingness to keep completely up-to-date on HIV treatment advances, directly affects the health and care of patients, an observation that has been supported by several studies.

People receiving HIV therapy—especially those with extensive treatment experience—should be treated by a physician who is aware of the most current research and is willing and able to develop individualized approaches to treatment. People with HIV should also keep up with the latest advances in treatment strategy and the availability of new drugs, so that decisions will be based on the best research available. Successful outcomes are often the result of collaboration and teamwork between informed patients and their physicians.

Summary

Look at lifetime resistance—keep a history of drugs used in the past and previous resistance test results. These can be used to develop a worst-case “virtual resistance” profile.

Maximize potency—even if each drug only works a little, a mega-HAART combination can provide the combined potency many people need to reduce their viral load to an undetectable level.

Consider TDM—suboptimal drug levels may explain why a past treatment regimen failed despite perfect adherence. Therapeutic drug monitoring may help determine optimal doses to overcome resistance or safely allow for drug interactions when using mega-HAART combinations.

Focus on adherence—starting salvage therapy can be a good opportunity to devote attention to improved adherence. Count pills each day and keep a strict pill diary. Think about nothing else until you get it right!

Try to improve tolerability—when using multiple drugs, careful management of side effects such as nausea, diarrhea, and interrupted sleep becomes more important than ever. Report all adverse events to a health-care provider. Such symptoms can often be reduced using adjunct therapies such as antiinfluenza or antiinfluenza medications or sleep aids.

Consider viral fitness—new research shows that reduced viral fitness may be an important aspect of PI-resistant mutations. The possibility of frequently rotating drugs to maintain reduced viral fitness may be an option for the future.

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This article has been adapted from a revised version of “Changing Treatment: A Guide to Second-line and Salvage Therapy,” a patient guide first produced in 1998 by HIV i-Base and updated every 4–6 months as new information becomes available. The guide is available at www.i-Base.org.uk.

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