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NEW TREATMENT GOALS FOR ADULT HIV INFECTION

Part 3: Managing the Treatment-Experienced Patient

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PREFACE

This monograph is the third in a series entitled, *New Treatment Goals for Adult HIV Infection*. The purpose of this series is to provide HIV specialists with a practical guide to the use of antiretroviral therapy in adult patients.

The first antiretroviral agent was approved for use in the United States in 1987. Twenty years later, the range of options available for treating persons infected with HIV is considerable and continues to expand. The evolution of antiretroviral therapy has translated into an extraordinary improvement in the duration and quality of life for persons living with HIV infection. The improved outcomes reflect not only better antiretroviral agents but also a better understanding of how to use these drugs to maximum effect. Advantages of some of the newer agents include dosing convenience, improved tolerability and safety profiles, greater barriers to resistance generation, and enhanced pharmacokinetics. In addition, the availability of improved tools for assessing and monitoring the effects of treatment, such as viral load measurements and resistance testing, has enabled significant improvements in the clinical management of HIV-infected persons.

One critical factor enhancing success in treating HIV infection is the ability to individualize treatment decisions based on a variety of factors that differ from patient to patient. One size clearly does not fit all. However, general principles that should guide HIV therapy have emerged and reflect the synthesis of clinical trials data and clinical experience. These principles and the general approach to antiretroviral treatment are addressed in published guidelines, including those from the U.S. Department of Health and Human Services as well as from the International AIDS Society–USA, both of which are updated regularly.

New Treatment Goals for Adult HIV Infection addresses major elements of the clinical care of HIV-infected adults, with a focus on current guideline recommendations for optimizing patient outcomes. Each monograph provides a review of the available literature in the context of one or more clinical cases. The case format is used to reinforce the clinical decision-making process and to guide application of research to practice. The first monograph in this series discussed the approach to initiating antiretroviral therapy in patients newly diagnosed with HIV infection, including strategies for maximizing adherence. Unfortunately, HIV treatment is associated with a wide range of medication toxicities that may undermine adherence and impact patient quality of life. Potential short- and long-term adverse effects of antiretroviral therapy as well as strategies for management of medication toxicities were reviewed in the second monograph. This final installment of the series addresses the evaluation and management of antiretroviral-experienced patients with treatment failure and examines the potential role and optimal use of newly available therapies.

This series is the result of a shared concern for improving the quality of care received by patients living with HIV infection. The monographs in the series have been developed with input from each of the contributing editors as well as from external peer reviewers.

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Managing the Treatment-Experienced Patient

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Tremendous progress has been made in the management of HIV-infected individuals over the last 10 years. Since the availability of triple combination antiretroviral (ARV) therapy with protease inhibitors (PIs), along with quantitative plasma HIV RNA assays, it has been the standard of care in treatment-naïve patients to suppress plasma HIV RNA to below the limits of detection in order to prevent the emergence of drug-resistant virus and disease progression. Nevertheless, the high level of viral turnover seen in vivo [1,2] along with the low fidelity of the reverse transcriptase enzyme [3] allows for the emergence of drug-resistant virus if full virologic suppression is not achieved [4,5].


The best way to deal with drug resistance is to prevent it from happening. This requires that decisions surrounding when to start and when to change therapy be made in a careful and deliberate way. In particular, it is crucial that a patient is ready, willing, and able to commit to a treatment regimen prior to initiating it [6]. A special effort must be made to assure that there is no transmitted drug-resistant virus present and that the patient is prepared to deal with the dosing schedule of the regimen as well as any potential toxicities that may develop. An important, preventable reason that virologic rebound may occur on treatment is poor adherence, which may be the result of a complex dosing schedule, poor tolerability, or comorbid conditions such as depression or substance abuse. In fact, in select cases, viral rebound is not associated with the emergence of drug resistance, and suppression can be achieved if adherence is enhanced. However, in other cases, ARV resistance does emerge, leading to treatment failure and ultimately limiting future therapeutic options.

Fortunately, new agents in existing as well as novel classes have recently become available, expanding the ability to suppress plasma HIV RNA in patients with multidrug-resistant virus. In addition, laboratory technology is available to enhance the management of these patients, including genotypic and phenotypic drug resistance testing as well as the recently licensed entry and tropism assays to assess susceptibility to the fusion inhibitor enfuvirtide (ENF) and the likelihood of response to CCR5 antagonists, respectively. With access to new drugs and technology comes the need for enhanced strategies to improve the likelihood of success when modifying a patient's ARV regimen. This monograph summarizes how to use available tests and therapeutic

agents in order to optimize the chances of virologic suppression in treatment-experienced patients.

ASSESSING TREATMENT FAILURE

Case Presentation

 A 43-year-old man presents to a university-affiliated HIV clinic to initiate care with a new provider. The patient recently moved from another state as a result of a job transfer.

The patient reports that he was diagnosed with HIV in 1992, after presenting with cryptococcal meningitis and a CD4 count of 18 cells/mm³. He was successfully treated for his meningitis and was followed in a clinic, where he initially was treated with zidovudine (AZT) for 2 years, followed by AZT plus lamivudine (3TC) for 1 year, and then AZT plus 3TC with indinavir (IDV) through 1998. Since that time, he has had persistently detectable plasma HIV RNA levels, and his therapy has been repeatedly modified, at various times including nelfinavir (NFV), saquinavir (SQV) with ritonavir (RTV), lopinavir/ritonavir (LPV/r), and efavirenz (EFV). Despite the inability to fully suppress his viremia, the patient's CD4 count has remained between 50 and 200 cells/mm³ and he has been clinically stable.

Currently, the patient has no symptoms, denies the use of illicit drugs or alcohol, is not hepatitis B or C infected, and does not have diabetes or hypertension. Physical examination is unremarkable except for mild onychomycosis. He has been on a fixed-dose combination of AZT/3TC/abacavir (ABC) plus tenofovir DF (TDF) and LPV/r for the last 6 months, with no side effects. Testing performed in the last month demonstrated a CD4 count of 134 cells/mm³ and plasma HIV RNA of 33,400 copies/mL, down from 192,000 copies/mL when the patient was previously on a fixed-dose combination of TDF/emtricitabine (FTC) along with atazanavir (ATV) plus RTV. He takes no other medications. During the last several years, the patient has had drug resistance tests that has documented the presence of multiple reverse transcriptase and protease mutations.

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- What are the potential causes of treatment failure that should be investigated in this patient?

Although the definition of “treatment failure” or “virologic failure” vary, if the goal is to achieve virologic suppression to below the limits of detection, this patient certainly would be considered to be experiencing failure. Based on his treatment history, there is little doubt that drug-resistant virus is present and limiting the ability to achieve full virologic suppression. This is supported by the fact that the patient has received sequential nonsuppressive therapy for many years, a sure recipe for the selection of increasingly resistant virus. Moreover, previous resistance testing during the course of his care has documented the presence of multidrug-resistant virus. Nevertheless, poor adherence and intolerance to medications may also be contributing to an inadequate virologic response and must be formally addressed before consideration is given to any further modifications in treatment. This should include an assessment of the patient’s level of treatment adherence as well as potential drug-drug or drug-food interactions.

In all patients experiencing viral rebound on a stable regimen, it is crucial to determine whether they are consistently taking their medications, and if they are not, to define what the obstacles might be. It is vital to assure that a new regimen is not initiated until a patient is committed to taking the specific medications. Increasingly, clinicians realize that the optimal way to deal with ARV resistance is to prevent it from occurring. This includes careful use of ARVs in a first regimen as well as at the time of each switch in therapy. All potential factors that might limit adherence should be dealt with prior to initiating treatment, including a variety of established obstacles to consistently taking medications, such as psychiatric disease, substance abuse, and homelessness [7]. In addition, patients need to be fully informed as to how medications should be taken, potential toxicities, and important drug-drug and drug-food interactions.

For the case patient, once due diligence in these areas has occurred, including making sure that the current regimen has been reasonably well tolerated and that there is a commitment to making a switch, the clinician must determine the level of drug-resistant virus likely to be present in the patient’s body. Importantly, this includes any resistant virus that might have been selected for in the past as well as resistant virus detected while on the current regimen. This determination will require a thorough assessment of the patient’s treatment history along with past and current drug resistance test results. The patient may then be categorized as having many, some, or limited treatment options.

Table 1. Currently Approved Antiretroviral Agents

NRTIs	PIs
Zidovudine (AZT)	Saquinavir (SQV)
Didanosine (ddI)	Ritonavir (RTV)
Zalcitabine (ddC)	Indinavir (IDV)
Stavudine (d4T)	Nelfinavir (NFV)
Lamivudine (3TC)	Fosamprenavir (FPV)
Abacavir (ABC)	Lopinavir/ritonavir (LPV/r)
Emtricitabine (FTC)	Atazanavir (ATV)
Tenofovir DF (TDF)	Tipranavir (TPV)
NNRTIs	Darunavir (DRV)
Efavirenz (EFV)	Entry inhibitors
Nevirapine (NVP)	Enfuvirtide (ENF)
Delavirdine (DLV)	Maraviroc* (MVC)
Etravirine* (ETR)	Integrase inhibitor
	Raltegravir* (RAL)

NNRTIs = nonnucleoside reverse transcriptase inhibitors; NRTIs = nucleoside reverse transcriptase inhibitors; PIs = protease inhibitors.

*Newly approved agents.


- What is the goal of therapy for treatment-experienced patients?

It is important to note that recent guidelines have evolved with regard to the management of ARV-experienced patients. In fact, the availability of new treatment options for patients with multidrug-resistant virus has resulted in recent guidelines recommending that the goal of treatment be similar to that in treatment-naïve patients—to achieve plasma HIV RNA levels below the limits of detection, typically defined as less than 50 copies/mL [6,8]. Although drug resistance is an obstacle to reaching this goal, it nevertheless is achievable in some patients using agents recently approved (Table 1) [9–14]. In other patients, however, full virologic suppression is not achievable, and in this case the goal of therapy shifts to delaying CD4 cell decline and clinical deterioration while awaiting the availability of new treatment options.

Data derived from retrospective analyses of clinical trials of treatment-experienced patients have consistently shown a relationship between the number of phenotypically or genotypically susceptible drugs included in the regimen and the level of viral suppression and likelihood of achieving undetectable levels of plasma HIV RNA [8,15,16]. In general, the addition of a single active drug in the setting of virologic failure typically does not result in durable suppression but rather the emergence of further resistance and cross-resistance. Therefore, current guidelines stress that at least 2,

and ideally 3, fully active agents be included in a new regimen in order to optimize the chance of suppressing plasma HIV RNA to undetectable levels [6,8].

Case Continued

 A detailed discussion with the patient reveals no adherence or medication intolerance problems that could account for his suboptimal treatment response. This, along with the history of extensive drug-resistant virus, suggests that his virologic failure is resulting from resistance mutations. In order to optimize the selection of any new ARV agents, a detailed review of the patient's treatment history and previous resistance testing is performed, and the patient undergoes drug resistance testing.

- **What is the clinical value of drug resistance testing, and what approaches are appropriate for the treatment-experienced patient?**

Drug Resistance Testing

ARV drug resistance testing provides key information regarding which mutations are likely to emerge at the time of virologic failure. Understanding how drug resistance is measured in practice and how it emerges in the context of different regimens is essential to optimize the management of highly ARV-experienced patients.

Current Methods for Resistance Testing

The first tests for resistance used standard sequencing methods of the polymerase gene to detect mutations in the coding regions for reverse transcriptase and protease that have been associated with phenotypic resistance. Genotypic testing is readily available and relatively inexpensive and, when used, has been shown to improve virologic responses in treatment-experienced patients [17–19]. One of the challenges of using this technology is interpreting the results, which can become complex in the presence of multiple mutations. In addition, plasma levels of resistant virus present in less than approximately 20% of the total population will often be missed by genotypic assays [6].

Phenotypic testing is commercially available from select laboratories and detects the fold-change in susceptibility of the patient's virus relative to a wild-type control strain. Like genotypic testing, it will not detect minority species of drug-resistant virus. Moreover, if mixtures of resistant and wild-type virus are present, the test may underestimate the degree of true resistance. Nevertheless, in the face of complex mutation patterns, phenotypic assays can help characterize the level of resistance present to each drug. Interpretation of the results requires defining the clinically relevant cutoffs in fold-change

susceptibility for each drug. This limitation likely accounts for conflicting results from randomized controlled trials designed to determine whether the availability of phenotypic data improves virologic outcomes [20,21]. As clinical cutoffs have been defined, the utility of these assays has improved.

An alternative method, “virtual” phenotypic testing, is performed with genotypic technology followed by a probabilistic estimate of the actual phenotype based on matching against a large proprietary database of genotyped and phenotyped samples [22]. The phenotypic fold-change in resistance relative to wild type is averaged for the measured phenotype of all viruses that have matching genotypes in the database. This allows for estimated phenotypic data to be generated without the additional expense and effort of performing an actual phenotypic test. All of the limitations of genotypic and phenotypic testing apply to results from this form of analysis. It also has limited value with new drugs for which there are few matching genotypes and phenotypes in the database [23]. Although results vary, both genotypic and phenotypic results do have the potential to enhance the selection of a new regimen in ARV-experienced patients.

Drug Resistance Testing in Practice

Groups in the United States and Europe have proposed guidelines for the use of ARV drug resistance testing in clinical practice [6,24,25]; current recommendations from the U.S. Department of Health and Human Services are summarized in **Table 2**. Based on prospective trials, there is agreement that susceptibility testing should be performed in persons experiencing virologic failure on a stable ARV regimen [17–19]. Guidelines have increasingly suggested that resistance testing also be performed on patients who are newly infected [26] as well as those who are chronically infected and treatment naive because of the documented prevalence of drug-resistant virus detected in these individuals [27–29]. A consensus also exists for using susceptibility testing in pregnant women, based on the urgent need to achieve very low levels of plasma HIV RNA in order to minimize the risk of transmission to the child [26,30,31]. Clinicians should interpret the results of resistance testing using all available resources, including information from the clinical laboratory and susceptibility databases such as those maintained by the International AIDS Society–USA Drug Resistance Mutations Group (www.iasusa.org) [32] and Stanford University (<http://hivdb.stanford.edu>).

The selection of which test to use in a given situation is not well defined, but guidelines generally recommend genotypic testing for patients who are treatment naive or experiencing virologic failure on one of their first regimens. In contrast, those with more advanced failure may have complex mutation patterns that may benefit from

phenotypic testing, possibly combined with genotypic testing. The CERT (Centers for Education and Research on Therapeutics) study randomized patients experiencing virologic failure to phenotypic testing, genotypic testing, or no resistance testing (control). Although overall the use of resistance testing did not affect the endpoint, outcomes were better among those who had a history of treatment with 4 different regimens or with nonnucleoside reverse transcriptase inhibitor (NNRTI) therapy and who underwent phenotypic testing [33].

Predicting Drug Resistance in Practice

Many patients with multidrug-resistant virus have had extensive treatment prior to the availability of resistance testing. In this situation, the patient’s treatment history is invaluable in fully assessing the likelihood that drug-resistant virus exists. In fact, it is the availability of resistance testing used during the course of clinical trials that has made it increasingly possible to define which viral mutations might have been—or may be—selected for during the course of a patient’s therapy. Moreover, clinical trials show that resistance to some drugs will develop much quicker than resistance to others (Figure).

Resistance to nucleoside reverse transcriptase inhibitors (NRTIs). Resistance to NRTIs differs depending on which drugs are used and whether mutations preexist. For example, AZT and stavudine (d4T) typically select for mutations at codons 41, 67, 70, 210, 215, and 219, the so-called thymidine analogue mutations (TAMs). An increasing number of these mutations is associated with phenotypic resistance to all NRTIs [32,34]. Although the level of resistance varies, even a moderate change in susceptibility influences the response to didanosine (ddI), d4T, and TDF [35–38]. Multinucleoside resistance can also occur with the development of a mutation in reverse transcriptase at codon 151, often with secondary mutations at codons 62, 75, 77, and 116 or in association with the insertion of 3 amino acids between codons 69 and 70, often with secondary mutations at codon 62 with a background of TAMs [24,32]. The use of nonthymidine analogues in NRTI-naive patients is associated with mutations at codon 74 (with use of ddI and ABC) and at codon 65 (with use of TDF, ABC, and to a lesser extent d4T) [39–42]. Finally, the use of the cytosine analogue 3TC or FTC as part of a less than fully suppressive regimen is associated with the rapid selection of a single mutation at codon 184. Since any single mutation can be rapidly selected for, this mutation is often present at the time of viral rebound in a patient treated with any 3TC- or FTC-containing regimen [42–47]. The mutation at codon 184 has been associated with delayed development of other NRTI mutations and decreased, or partially reversed, phenotypic resistance to AZT, TDF, and d4T [34]. In contrast,

Table 2. Recommendations for Use of Resistance Testing in Practice

Clinical Setting	Recommendations
Acute infection	Genotypic testing at time of diagnosis, regardless of whether treatment is to be started
Chronic infection	Genotypic testing at time of diagnosis, regardless of whether treatment is to be started
Virologic failure	Testing performed while on therapy; use of genotypic testing, phenotypic testing, or both dependent upon clinical situation
Suboptimal virologic response	Testing performed while on therapy; use of genotypic testing, phenotypic testing, or both dependent upon clinical situation
Pregnancy	Testing performed prior to initiation of therapy or if on therapy with detectable plasma HIV RNA; use of genotypic testing if not on therapy, otherwise genotypic testing, phenotypic testing, or both might be used dependent upon clinical situation

NOTE: Resistance testing is not routinely recommended for patients off therapy for more than 4 weeks or if plasma HIV RNA level is less than 1000 copies/mL. (Adapted from Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services; January 29, 2008:59. Available at www.aidsinfo.nih.gov. Accessed 11 Feb 2008.)

a mutation at codon 184 can increase the level of phenotypic resistance to ddI, ABC, and zalcitabine (ddC) [34].

Resistance to NNRTIs. Resistance to the NNRTI class also occurs rapidly with the emergence of a single mutation, typically at codon 181 or 103, either one of which can reduce the likelihood of response to first-generation NNRTIs [24,32]. Analogous to what is seen with 3TC and FTC, this low genetic barrier to resistance makes NNRTIs a “fragile” part of any regimen, with these signature mutations frequently emerging when plasma HIV RNA is not suppressed below the limits of detection [48]. When combination therapy includes both NNRTIs and 3TC or FTC, viral rebound is often associated with selection of virus with resistance to the cytosine analogues, the NNRTIs, or both [41,42,49]. When the third drug in a regimen is a thymidine analogue, the development of TAMs usually occurs after months of persistent viremia. However, when used in combination with a nonthymidine analogue such as TDF, mutations at codon 65 are observed with increasing frequency, albeit in relatively low numbers relative to the total study population [42,49].

Resistance to PIs. Resistance to PIs emerges in various ways depending on which agent is used. The first approved PIs—SQV, RTV, and IDV—selected for a variety of overlapping mutations that with time often resulted in cross-resistance

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	ddl		
3TC	TDF	AZT	
FTC	ABC	d4T	
NNRTIs	ENF	PIs	PIs + RTV
Days–weeks	Weeks–months		Months–years

Figure. Time to developing resistance to different drugs when given to treatment-naive patients who experience ongoing viremia. 3TC = lamivudine; ABC = abacavir; AZT = zidovudine; d4T = stavudine; ddl = didanosine; ENF = enfuvirtide; FTC = emtricitabine; NNRTIs = first-generation non-nucleoside reverse transcriptase inhibitors (efavirenz, nevirapine, delavirdine); PIs = non-ritonavir-boosted protease inhibitors (saquinavir, indinavir, nelfinavir, fosamprenavir, atazanavir); PIs + RTV = ritonavir-boosted PIs (saquinavir, fosamprenavir, lopinavir, atazanavir, darunavir); TDF = tenofovir DF.

to the class. NFV, the fourth PI approved by the U.S. Food and Drug Administration (FDA), has a lower genetic barrier to resistance than the others. In a study in PI-naive patients, NFV typically selected for a single mutation at codon 30, and less frequently at codon 90, either of which alone is associated with resistance to this drug [50]. Nevertheless, with time and ongoing viremia, additional mutations and cross-resistance to other PIs evolve [51–53]. Another PI, amprenavir (APV), now available as fosamprenavir (FPV), has activity against many viruses resistant to earlier agents in the class. When used as a first PI, APV selected for a unique mutation at codon 50 (I50V) that confers limited resistance to other drugs in the class. Finally, ATV is a PI that can be used once daily with minimal effects on lipids [54,55]. In patients without underlying PI resistance, ATV selects for a mutation at codon 50, in this case I50L, which is not associated with resistance to other PIs [32,56,57]. In patients who are PI-experienced prior to starting any of these agents, the existence of multiple primary and secondary protease mutations can be associated with decreased susceptibility to many of the agents in the class.

It is well known that most PIs are substrates for cytochrome P450, and their metabolism is inhibited by coadministration with even low doses of RTV. In fact, LPV is coformulated with RTV, resulting in LPV levels that far exceed the inhibitory concentration of wild-type HIV and that of many PI-resistant strains. Data from Abbott study M98-863 demonstrated reliable virologic response to LPV/r and showed that the genetic barrier to resistance to LPV was very high [58]. In fact, an unprecedented observation at the time was the very rare detection of primary PI mutations in patients experiencing virologic failure. This has now been seen in treatment-naive patients treated with RTV-boosted FPV, ATV, and darunavir (DRV)—the most recently approved PI [46,59–61]. In addition, as previously seen with LPV/r, the use of other RTV-boosted PIs seem to be associated with a lower risk of developing NRTI resistance as well [46,59–61]. These findings demonstrate that enhanced pharmacokinetics likely

change the genetic barrier to resistance of a given drug and alter the patterns in which drug-resistant mutations emerge, substantially enhancing the availability of future options.

Resistance to fusion inhibitors. The fusion inhibitor ENF has now been widely used in ARV-experienced patients. This 36 amino acid peptide binds to the first heptad repeat region of envelope glycoprotein 41 (gp41) of HIV, which is critical for viral fusion to the CD4 T cell. ENF is administered as a subcutaneous injection twice daily and significantly reduces viral load in patients with multidrug-resistant HIV [9,10]. Not surprisingly, mutations within the N helix of gp41 have been selected for both in vitro and in vivo, conferring resistance to this compound. In particular, substitutions at positions 36 through 38 of gp41, and in others between codons 36 and 46, have been identified in most patients experiencing virologic failure while taking ENF [62,63]. Moreover, it has been shown that resistance occurs fairly rapidly if a patient has ongoing viremia while on ENF treatment [64,65].

Summary. Understanding the patterns as well as the time line for the development of drug-resistant mutations with different combinations allows clinicians to optimize the use of ARV therapy (Figure). It is increasingly clear that careful follow-up of treated individuals, along with strategic use of drugs, may enhance the likelihood of achieving full virologic suppression and preserving future treatment options. Similar data have recently begun to emerge from clinical trials with newer drugs in novel classes, such as CCR5 antagonists and integrase inhibitors, the details of which are summarized in the next section (*see page 9*).

CHANGING THERAPY

Case Continued


 The patient undergoes genotypic resistance testing, the results of which are summarized in **Table 3**. Drug resistance phenotypic testing is also performed by a

Table 3. Case Patient's Resistance Genotype

NRTI mutations	PI mutations
D67N	L33L/F
T69D	F53L
K70K/R	I54I/V
V118I	A71V
M184V	G73S
K219Q	I84V
NNRTI mutations	L90M
K103N	

NNRTI = nonnucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; PI = protease inhibitor.

commercial laboratory, with the changes in drug susceptibility summarized in **Table 4**.

- What are the implications of these test results?
- What is the next step in this patient's management?

It is clear that this patient has considerable resistance to protease and reverse transcriptase inhibitors. An important consideration is how this patient developed such a highly drug-resistant virus. Although a thorough assessment did not reveal an adherence problem in the case patient, certainly, in all such patients, consideration must be given to the potential role of nonadherence in the emergence of resistance. In the case patient, resistance likely occurred as a result of starting treatment prior to the availability of highly active combination ARV therapy. Many such patients received sequential nonsuppressive treatment and consequently were allowed to accumulate multiple reverse transcriptase and protease mutations. In this patient, sequential NRTI therapy with the subsequent addition of multiple PIs and an NNRTI resulted in the high-level resistance to NRTIs, NNRTIs, and PIs. Assuming good adherence with therapy, patients starting treatment in the current era would be at much lower risk of accumulating extensive resistance to NRTIs and would not be expected to develop any significant PI resistance when starting with RTV-boosted PIs [66]. Yet, a considerable number of patients remain a significant challenge to manage, like the case patient.

Based on this patient's resistance data and treatment history, the objective now is to identify potentially active agents that could be incorporated into a new ARV regimen. While data from clinical trials of treatment-experienced patients can help inform this decision, the key factor that will predict the likelihood of response is the number of active drugs that can be included in the next regimen. Fortunately, the availability of several new agents in both existing and novel

Table 4. Case Patient's Resistance Phenotype

NRTI		NNRTI		PI	
Drug	FC	Drug	FC	Drug	FC
TDF	1.1	DLV	98	IDV*	7.3
ABC	5.1	EFV	19	TPV	1.8
ddl	1.5	NVP	51	FPV*	4.9
FTC	> 100			LPV	12.0
3TC	> 100			SQV*	10.7
d4T	1.8			ATV*	6.0
AZT	6.4			NFV	7.0
				RTV	17.0

NOTE: Based on current cutoffs used by Monogram Biosciences phenotypic assays. Normal font denotes fully resistant; italics and bold denote intermediate susceptibility; bold denotes fully susceptible. 3TC = lamivudine; ABC = abacavir; ATV = atazanavir; AZT = zidovudine; d4T = stavudine; ddl = didanosine; DLV = delavirdine; EFV = efavirenz; FC = fold-change in susceptibility compared with wild-type reference strain; FPV = fosamprenavir; FTC = emtricitabine; IDV = indinavir; LPV = lopinavir; NFV = nelfinavir; NNRTI = nonnucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; NVP = nevirapine; PI = protease inhibitor; RTV = ritonavir; SQV = saquinavir; TDF = tenofovir DF; TPV = tipranavir.

*Cutoffs for when used with RTV-boosting.

classes increases the potential to achieve full virologic suppression even in a highly ARV-experienced patient.

- How can available study data help to guide treatment decisions in the ARV-experienced patient?

Important Considerations in Choosing a New Regimen

Just as there are numerous potential drug combinations for the management of treatment-naïve patients, there are many options for those with drug-resistant virus. In light of the diversity of patients and treatment options, there never will be studies to formally compare all potential regimens for this patient population. In fact, in those with drug-resistant virus, it is more important that therapy be designed to treat the patient's specific virus than to randomly assign the patient to one regimen over another. Nevertheless, comparative trials of several drugs have been done in treatment-experienced patients and do provide some insight into the optimal way to manage these patients.

In the more treatment-experienced patient, the decision as to which drugs to use is first and foremost based upon susceptibility. Selection of a new regimen should incorporate the identified potential active agents, always keeping

MANAGING THE TREATMENT-EXPERIENCED PATIENT

Table 5. Protease Mutations Associated with Reduced Response to Tipranavir and Darunavir

Mutation	Tipranavir	Darunavir
10V		
11I		
13V		
20M/R/V		
32I		
33F	X	X
35G		
36I		
43T		
46L		
47V		
50V		
54A/M/V	X	
54L/M		
58E		
69K		
73S		X
74P		
76V		
82L/T		
83D		
84V	X	X
89V		

NOTE: Shaded box denotes mutation associated with reduced virologic response for the drug listed. X denotes a mutation present in the case patient's virus.

in mind that if full suppression is not achieved, resistance will develop and may limit treatment options for the future. When several options exist, other factors require additional consideration, such as convenience of dosing and tolerability. Although the focus of this discussion is how to strategically select an active regimen for a given patient, the clinician must also be aware of the potential toxicities and drug-drug interactions that might influence treatment choices.

PI Trials

The Context Study included 315 PI-experienced patients with documented treatment failure who were randomized to 1 of 3 regimens that included 2 active NRTIs: once-daily FPV (1400 mg) with RTV (200 mg), FPV (700 mg) with RTV (100 mg) both given twice daily, or twice-daily LPV/r (400/100 mg) [67]. At 48 weeks, similar reductions in plasma HIV RNA were found in the twice-daily FPV plus RTV and LPV/r groups, and a similar percentage of patients in each of these 2 groups achieved plasma HIV RNA levels less than

50 copies/mL (46% in the twice-daily FPV plus RTV arm vs. 50% in the LPV/r arm). Of note, the once-daily FPV with RTV group had lower FPV trough concentrations than the twice-daily FPV with RTV group and resultant reduced rates of viral suppression; therefore, once-daily FPV with RTV is not recommended for treatment-experienced patients.

This experience is analogous to that observed in studies with ATV. The BMS 043 study compared regimens that included unboosted ATV or LPV/r in 290 PI-experienced patients with prior treatment failure who were also taking 2 NRTIs [68]; 48-week efficacy results revealed greater viral suppression in the LPV/r than the ATV groups ($P < 0.001$). Based on these data, unboosted ATV is not recommended in ARV-experienced patients. In contrast, RTV-boosted ATV was shown to be active in PI-experienced patients within BMS 045, a randomized, open-label study performed in patients who had failed at least 2 prior ARV regimens that included an NRTI, an NNRTI, and a PI [69,70]. Patients were divided into 3 arms and given NRTIs that included TDF with either once-daily ATV (300 mg) pharmacologically boosted with RTV (100 mg), ATV (400 mg) plus SQV (1200 mg) both given once daily, or LPV/r (400/100 mg) twice daily. At 48 and 96 weeks, ATV plus RTV and LPV/r were found to be equivalent with regard to reduction in plasma HIV RNA and increase in CD4 cells [69,70]. However, the ATV plus SQV arm showed inferior responses, which may in part reflect the fact that TDF lowers ATV levels and emphasizes why it is recommended that ATV always be used with RTV in patients who are also taking TDF. Subanalyses of BMS 045 showed that patients with higher levels of protease resistance had better virologic response to LPV/r than to ATV with RTV [71].

Two novel nonpeptidic PIs—tipranavir (TPV) and DRV, both given twice daily with RTV—were recently approved for ARV-experienced patients. Both drugs were initially investigated as part of combination therapy in patients with multidrug-resistant virus. Based on treatment history and resistance data, patients were given an investigator-selected optimized background regimen (OBR) and randomized to the selected available PI or the new PI being studied. The pivotal trials with TPV, RESIST 1 and RESIST 2, were open-label phase 3 studies that included more than 1500 patients, the results of which favored TPV at weeks 24 and 48 for both reduction in viral load and proportion of patients achieving undetectable levels of plasma HIV RNA [11]. Treatment responses were even better in the subset that used ENF for the first time, illustrating the incremental improvement in response seen with increasing numbers of active drugs included in the OBR. More detailed investigation of TPV has defined key protease mutations and phenotypic cutoffs associated with attenuated response, the results of which are of value in defining the optimal patient for this therapy (Table 5) [72].

DRV received FDA approval based on the results of 2 ongoing randomized phase 2B dose-finding studies (POWER 1 and POWER 2) and an open-label, single-arm study (POWER 3) [12–14]. POWER 1 and 2 enrolled treatment-experienced patients to investigator-selected OBR with comparator PI or DRV with RTV. Although these were relatively small studies, with limited numbers receiving the currently approved dose of DRV (600 mg) with RTV (100 mg) twice daily, the results clearly favored DRV over the comparator PI. Consistent with the results of the RESIST studies and emerging principles of ARV therapy, inclusion of more active drugs (eg, first-time use of ENF as part of the OBR) improved virologic responses. Although POWER 3 was not randomized, this study provided additional safety data and confirmed efficacy with the approved dose of DRV in this patient population [14]. Post hoc analyses of the POWER studies were performed to define genotypic and phenotypic predictors of virologic response to DRV (Table 5). Additional safety and efficacy data for DRV come from the TITAN study, which demonstrated noninferiority to LPV/r in PI-experienced but LPV/r-naive patients [73]. In fact, the study showed superior responses to DRV plus RTV-containing regimens, with some of this enhanced response related to the fact that there was a larger proportion of patients at baseline with resistance to LPV/r than resistance to DRV [73].

NNRTI Trials

NNRTIs have been an important part of therapy for both treatment-naive and treatment-experienced patients. However, once resistance to NNRTIs develops, it is associated with cross-class resistance, with limited data suggesting that there is any benefit associated with recycling drugs from this class [74].

A second-generation NNRTI, etravirine (ETR), is newly approved and appears to have a higher genetic barrier to resistance and *in vitro* activity against NNRTI-resistant HIV strains [75]. DUET-1 and DUET-2 are 2 ongoing, large multinational phase 3 trials evaluating ETR in patients with NNRTI-resistant virus [76,77]. These tandem studies differ only in the countries in which they are being conducted. Study subjects had at least 3 PI resistance mutations and at least 1 NNRTI mutation either at time of enrollment or confirmed by historical genotypic test results. Patients were randomized in a double-blind fashion to receive ETR or placebo along with OBR, which included DRV with RTV and other drugs at the discretion of the investigator. Results at 24 weeks were nearly identical for both studies, with plasma HIV RNA levels less than 50 copies/mL in 56% to 62% of patients in the ETR group compared with 39% to 44% in the control group ($P \leq 0.005$). Since ETR is from an existing class, as with newer PIs, it is anticipated that some patients will have variable levels of cross-resistance. Recent analyses

from the DUET studies have attempted to use genotypic markers to define the patients most likely to benefit from the addition of ETR to an OBR. Preliminary analyses have identified 13 reverse transcriptase mutations associated with a reduced response to ETR, including V90I, A98G, L100I, K101E/P, V106I, V179D/F, Y181C/I/V, and G190A/S. Of note, the K103N mutation is not included in this group. The most apparent drop off in response was seen in patients with 3 or more of these mutations, which was the case in only 14% of the study subjects [78,79]. It is important to note that there are significant drug-drug interactions with ETR and other ARV agents and that ETR cannot be used with TPV.

Studies of Novel Agents

Entry inhibitors. Agents in 2 classes of entry inhibitors are now approved for the treatment of ARV-experienced patients—the fusion inhibitor ENF and the CCR5 antagonist maraviroc (MVC). Both of these drugs are first in class; therefore, unlike newer PIs or NNRTIs, their use should not be limited by cross-resistance to existing agents. Importantly, ENF has been shown to enhance virologic response when used with an OBR and other new agents such as DRV, TPV, MVC, and integrase inhibitors [9–14,80–83].

Before fusion between HIV and the cell membrane can be mediated by gp41, 2 binding steps must occur. First, the HIV envelope binds the CD4 molecule, resulting in a conformational change that allows the viral envelope to interact with a chemokine coreceptor, either CXCR4 or CCR5. HIV that uses the CXCR4 coreceptor is often labeled as an X4 virus, while HIV that uses the CCR5 coreceptor is often referred to as an R5 virus. Some patients have only R5 virus, others have only X4 virus, and some have viruses that can use both coreceptors (dual tropic) or that exist as mixtures of R5 and X4 viruses. Several assays can assess viral tropism, with the most commonly used method validated during the course of the studies of these drugs being a phenotypic assay that reports the virus as being either R5, X4, or dual/mixed (D/M) [84]. While these assays are associated with additional costs and delays in modifying therapy, they define the patients most likely to benefit from CCR5 antagonist therapy. This is particularly true in light of the fact that the frequency of CXCR4-utilizing virus varies from patient to patient, with R5 virus tending to be detected alone in approximately 80% of individuals in the earlier stages of disease, and the emergence of X4 or D/M virus occurring in approximately 40% to 50% of those with more extensive treatment histories and in the advanced stages of disease [85–87].

Although there is interest in developing ARV agents that block both coreceptors, CCR5 antagonists are furthest along in development, with MVC recently approved for treatment-experienced patients who do not have detectable CXCR4-utilizing plasma virus. Approval was based on results of

the ongoing MOTIVATE 1 and 2 studies [80,81]. These double-blind, phase 2b/3 studies compared the efficacy and safety of MVC given once or twice daily to triple-class-experienced patients without detectable CXCR4-utilizing virus. MVC is a cytochrome P450 substrate and was given either once or twice daily in the clinical trials; the drug is currently approved for twice-daily use. The 300-mg dose was used in those who were not taking RTV or delavirdine (DLV), or in those receiving TPV. At 24 weeks, approximately twice as many patients in the MVC arms of both trials had plasma HIV RNA levels less than 50 copies/mL, compared with the OBR controls. In addition, the CD4 cell increase was significantly greater in those receiving MVC than placebo [80,81].

Since CCR5 antagonists are novel drugs that target the cell rather than the virus, there have been unique concerns. These include the implications of selecting for D/M or X4 viruses, the presence of which has previously been shown to be associated with accelerated disease progression in natural history studies [85]. Reassurance has come from several studies, including one that administered MVC to patients who had D/M, X4, or nonphenotypable virus [88]. Although there was little ARV activity, illustrating why the target population for this drug will be those who are R5-only, there also were no deleterious effects on CD4 cell counts. Furthermore, the MOTIVATE studies showed that patients experiencing virologic failure with D/M or X4 virus did not demonstrate significant CD4 cell decline. In fact, approximately 65% of those with virologic failure had evidence of the emergence of D/M or X4 virus [80,81]. In contrast to the high frequency of emerging D/M or X4 virus in those with virologic failure, preliminary data suggest that only a minority of these individuals actually developed true MVC resistance [89]. While all CCR5 antagonist-naïve patients are likely to have CCR5-utilizing virus that is susceptible to the drug, no antiviral effect has been demonstrated in those with detectable CXCR4-utilizing virus [88]. Consequently, an assay for tropism needs to be performed in order to determine whether MVC will be an active drug in any given patient.

Integrase inhibitors. Integrase allows free, double-stranded viral DNA to be incorporated into the host chromosomal DNA. Raltegravir (RAL) was designed to inhibit this enzyme and prevent strand transfer and was recently evaluated in 2 similar phase 3 trials known as BENCHMRK-1 and BENCHMRK-2 [82,83]. These studies randomized triple-class (NRTI, NNRTI, and PI)-experienced patients to OBR alone or with RAL 400 mg twice daily. Combined week 24 data showed significant promise for this drug, with 75.5% of patients in the RAL arm compared with 39.3% of those given OBR alone achieving plasma HIV RNA levels less than 400 copies/mL ($P < 0.001$ at 16 weeks, with a partial

analysis at 24 weeks). When RAL was combined with other novel active agents such as ENF and/or DRV, viral suppression was achieved in a higher percentage of individuals.

Like all ARV agents, resistance will occur to integrase inhibitors if full suppression is not achieved. A preliminary cross-sectional analysis of integrase resistance from the BENCHMRK studies showed that 32 of the 41 patients with virologic failure who were studied had new mutations in integrase. These mutations tended to be at either N155H or Q148K/R/H and to exist along with other mutations [82,83]. Additional cross-sectional and longitudinal data have been reported from Protocol 005, a phase 2 dose-ranging study of RAL in treatment-experienced patients [90,91]. In this study, 35 of the 38 patients with virologic failure were found to have mutations in integrase, primarily at Q148H/R/K or N155H, as well as other compensatory mutations. It is important to note that some cross-resistance has already been reported between raltegravir and elvitegravir, the latter being another integrase inhibitor in clinical development [92].

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- **In view of current data for available ARV agents and the drug resistance test results for the case patient, what drugs are appropriate choices for a new treatment regimen for this patient?**
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In evaluating the available active drugs for this patient, it is clear that while NRTIs may contribute to the OBR, they will not constitute “fully active” agents. Similarly, the newer PIs such as TPV or DRV may contribute some antiviral activity to the next regimen, but they too would not be expected to be highly active based on available genotypic and phenotypic data. Although the patient’s phenotype showed a fold-change of 1.8 in susceptibility for TPV, which would predict susceptibility [72], the genotype shows mixtures at 2 positions that influence TPV susceptibility, L33L/F and I54I/V. Consequently, while TPV might be an option, it probably cannot be assumed to be one of the fully active agents in the next regimen. Because the phenotypic report did not include DRV, since this drug was not available at the time the test was performed, an estimate as to the potential utility of this drug in a new regimen would need to rely on the genotypic score (Table 5), which shows that 3 DRV mutations are present at codon 33, 73, and 84. These results suggest that while DRV may be an option for this patient, it probably could not be relied upon to be a fully active drug in the next regimen. Since the patient is NNRTI-experienced, it is expected—and in this case confirmed by resistance testing—that he would have resistance to NVP, EFV, and DLV.

Based on this initial assessment of the case patient’s treatment options, it is fairly clear that the next regimen will

include select NRTIs and a PI but will also require at least 2 if not 3 other drugs for which there is full susceptibility. Fully active drugs could include RAL, ENF, and—depending upon the results of a tropism assay—possibly MVC. ETR may be another option for this patient since he has no ETR-associated mutations at this time.


Since this patient may have 3 or even 4 potential fully active drugs to include in the next regimen, careful consideration must be given as to how many need to be used now versus saved for the future. Unfortunately, data are somewhat limited as to how many such drugs are truly needed at this time to optimize the chance of achieving an HIV RNA level less than 50 copies/mL. Post hoc analyses of recent trials vary as to whether the addition of a third fully active drug enhances the likelihood of viral suppression over 2 such agents [9,10,80–83]. The reason for the observed variability between these studies likely reflects the different criteria used to define a fully active agent and the type of new drug added, such as one from a new class versus new drugs from existing classes for which there may be only partial susceptibility. Nevertheless, the choice of the next regimen must be made with caution because if full suppression is not achieved, resistance to the newer agents may develop quickly and limit options for the future.

• **What is the goal of treatment when full virologic suppression is not achievable?**

In patients with multidrug-resistant virus, therapeutic options may be limited, making it unlikely that a regimen with at least 2 or 3 fully active drugs can be identified. For these individuals, the goal of treatment may be to prevent CD4 cell decline and disease progression. There is growing evidence and consensus that stopping treatment can be associated with worse immunologic and clinical outcomes in patients similar to the one in this case study and, therefore, should not be recommended [93–95]. Alternatively, there is considerable evidence that stability can be maintained in some patients by simply continuing a partially suppressive regimen [93,94]. In particular, continuing a regimen with NRTIs such as 3TC or FTC may be of some benefit [93,96]. This may be due in part to a negative effect of resistance mutations on viral “fitness” and/or some residual antiviral activity despite the presence of resistance. It is important to note that the benefit of a partially suppressive regimen must be weighed against the risk of developing further resistance and losing future therapeutic options. In fact, an observational study of ARV-experienced patients on a partially suppressive regimen showed that approximately 30% lost susceptibility to 1 drug by 1 year [97].

In patients with low CD4 cell counts and at high risk for clinical deterioration if 2 active agents are not available, guidelines suggest that adding a single, novel active agent to help prevent immediate clinical decline may be considered [6]. However, this strategy is suboptimal, and the risk of developing resistance to the new drug and losing this option for the future is high. If this situation exists, the provider must have a detailed discussion with the patient regarding the potential benefits and risks of such a strategy. Fortunately, given the breadth of new agents currently available, this situation should be much less common now than it was in the past.

Case Conclusion

 After a detailed discussion with the patient about options for viable regimens, including newly approved drugs, the patient and his physician agree that the OBR will include TDF and FTC along with DRV plus RTV. Although it is acknowledged that none of these drugs is likely to be fully active, it is anticipated that they may contribute some antiviral activity and would be reasonably well tolerated. DRV is selected over TPV because of the desire to use ETR as one of the fully active drugs and an understanding that TPV markedly reduces the levels of ETR and therefore can not be coadministered [98]. Additionally, drugs that are included in the regimen and felt to be fully active are RAL and MVC, the latter selected after a tropism test demonstrates no detectable CXCR4-utilizing virus. The patient tolerates the regimen well and his plasma HIV RNA declines to undetectable levels within 8 weeks, remaining there during the subsequent course of follow-up.

SUMMARY

A tremendous amount of clinical trial data and experience have enhanced our ability to minimize the development of drug-resistant virus in patients infected with HIV. Furthermore, this experience, along with the availability of new drugs in existing and novel classes, has resulted in improved outcomes even in patients with multidrug-resistant virus. While the case patient illustrates the many challenges facing clinicians as we embark upon using multiple new drugs in the clinic, it also demonstrates the new hope offered to patients in the current era of ARV treatment.

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