EDITORIAL REVIEW

Antiretroviral therapies for treatment-experienced patients: current status and research challenges

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Introduction

Despite the success of combination antiretroviral therapy, a significant proportion of patients experience a loss of virologic, immunologic, or clinical benefit from their current regimens. Frequently, these patients have limited options for alternative treatment regimens. Developing safe and effective therapies for treatment-experienced patients, particularly for those with documented three- or four-class antiretroviral drug resistance is a public health priority [1] that poses significant challenges. Causes of treatment failure are diverse as are target patient populations with respect to the type and duration of treatment experience. These aspects of patient care necessitate individualized treatment plans and make standardization of objectives and study designs for development of new therapies difficult. Issues in study design include the choice of adequate control arms, appropriate endpoints, and reasonable expectations for duration of response and safety considerations.

The Salvage Therapy II workshop was held 16–17 April 2004, to discuss these issues with HIV-treating clinicians, clinical research investigators, pharmaceutical industry representatives, regulatory authorities and interested HIV-community leaders. The workshop focused on issues concerning heavily treatment-experienced patients, specifically patients who are three- or four-drug classes experienced with limited or no options for suppressive antiviral regimens. This review summarizes the proceedings from this meeting and represents both a consensus of the views expressed during the workshop as determined by the authors as well as the views of the authors themselves. The review also highlights the discussions on challenges that surround new therapy development and clinical management of treatment-experienced patients [2].

Drug development issues for treatment-experienced patients

Historical perspective

The introduction of suppressive (triple-combination) antiretroviral therapy led to dramatic decreases in morbidity and mortality of HIV-infected individuals during the 1990s [3–6]. Unfortunately, limitations accompanied these therapies, especially for patients with previous exposure to antiretroviral therapy. Issues of drug resistance, cross-resistance to multiple drugs from a single class, regimen complexity, frequency of dosing, variable plasma concentrations and drug toxicities all contributed

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to poor antiviral responses or failure of initially successful regimens.

By the late 1990s, an increasing number of patients receiving triple combination therapy experienced treatment failure, leaving them with few or no new therapeutic options. Virologic failure rates over 60% after 1 year on treatment were observed in some cohort studies [7,8]. 'Salvage therapy' was now required for those who not only failed earlier mono and dual combination therapies, but also later suppressive triple combination regimens. Limited treatment guidance was available to help physicians and patients select an optimal regimen as few post-triple combination 'salvage therapy' trials were being conducted and most of these included small sample sizes. Furthermore, unknown drug–drug interactions resulting in reduced drug exposure also contributed to poor virologic responses seen in studies and in the clinic [9]. Nevertheless, several expert groups formulated treatment guidelines and provided initial guidance for the selection of regimens with optimal activity in treatment-experienced patients. In the absence of evidence from clinical trials, the recommended regimens for treatment-experienced patients were based on the expert opinion of the Department of Health and Human Services Treatment Guidelines Committee [10]. The recommendation that 'Optimally and when possible, the regimen should be changed entirely to drugs that have not been taken previously . . . at least two and preferably three new drugs should be selected that are not anticipated to be cross-resistant to drugs given previously . . .' was difficult to implement in the absence of available new drugs. The guidelines stressed the need for high-level expertise and recommended assistance through consultation with more experienced clinicians [10]. To further illustrate the state of uncertainty regarding clinical management of treatment failure, the guideline committee noted that these recommendations were a 'work in progress' and that more clinical trials were urgently needed [10].

Early studies investigating potential regimens in treatment-experienced patients were designed simply by selecting drugs that the patient had not previously taken. These studies yielded disappointing results, probably due to high degrees of cross-resistance between drugs. Studies of protease inhibitor (PI)-experienced patients showed poor virologic response rates; only 20 to 50% achieved HIV RNA levels below 400 copies/ml at 24 weeks [11–13] Investigators pursued alternate strategies, including multiple-drug rescue therapy (regimens containing up to nine drugs), and structured treatment interruptions (STIs). Results from the multiple-drug rescue studies were variable. Most studies reported virologic suppression rates of only 30 to 50% and participants commonly experienced moderate to severe toxicities resulting in suboptimal adherence, frequent changes in regimens or discontinuation of certain drugs [14,15]. Through retrospective studies, several groups documented shifts from multiple-drug-resistant virus to wild-type virus populations in treatment-experienced patients undergoing an interruption of antiretroviral treatment and suggested investigating STIs as a treatment strategy for this patient population [16,17]. Subsequently, prospective controlled studies of STIs showed more rapid CD4 cell declines, HIV RNA rebounds and clinical events in comparison with continuous treatment [18,19].

Recognizing the lack of treatment options and guidance for heavily treated patients, advocates and researchers focused their efforts by organizing a series of meetings on this issue. A meeting was co-sponsored by The Forum for Collaborative HIV Research in 1999 to discuss the design and implementation of studies in the treatment-experienced population; to present needs, priorities and challenges faced by industry, researchers, regulators and patients; to define treatment failure and success; and to discuss what was necessary and feasible when designing studies of new drugs in this setting [20]. This meeting led to an FDA Antiviral Drugs Advisory Committee Meeting in 2001 to discuss clinical trial design issues in heavily treatment-experienced patients and an FDA letter to pharmaceutical companies urging collaboration to allow testing of multiple investigational agents in one study [1,21]. Improvements in the management of treatment-experienced patients resulted from these meetings, including incorporation of novel strategies (e.g., drug-resistance testing) and development of new antiretroviral agents. However, despite some advances, treatment for antiretroviral-experienced patients remains the greatest challenge in the clinical management of HIV-infected individuals.

Current standard of care for the treatment-experienced patient

Clinical management of treatment-experienced patients has evolved over the years. More than 20 different antiretroviral agents and formulations spanning four drug classes are available for the treatment of HIV infection. Prior to the year 2000, controlled trials were largely conducted in treatment-naive or nucleoside-experienced patients and data regarding dosing, safety and efficacy in treatment-experienced patients were lacking. Today, data exist for several antiretroviral agents in the setting of three-drug class experience. In addition, we have a better understanding of how to use technologies such as resistance testing.

Current treatment guidelines suggest several approaches to the management of treatment-experienced HIV-infected patients [22,23]. Strategies for assessment and management of patients with limited, intermediate or extensive prior treatment and/or drug resistance are different [22] and reflect the recognition that different treatment goals may be appropriate for these populations.

Although a number of reasons for treatment failure can be identified, medication intolerance and suboptimal adherence are probably the most common, and drug resistance is the final common pathway [24,25].

Patients experiencing failure of their first treatment regimen generally have several treatment options and the goal of therapy remains complete suppression of HIV RNA. In contrast, a patient with failure of multiple prior regimens and significant drug resistance has limited, if any, treatment options; for this patient the goal of therapy is to preserve immune function and prevent clinical progression while waiting for newer strategies or treatments.

The evaluation of patients with treatment failure includes assessment of virologic, immunologic and clinical status; determination of the cause of treatment failure; and review of pharmacokinetic parameters. In addition, resistance testing is performed while patients are still taking their failing regimen [21,26] to identify active antiretroviral drugs for subsequent treatment regimen [27–29].

The inclusion of a drug class that is new to each patient, such as a non-nucleoside reverse transcriptase inhibitor (NNRTI) [12,13,30] or HIV entry inhibitor [31,32] provides virologic benefit for many patients. Not surprisingly, the more active drugs (ideally three or more) in a regimen the greater the likelihood of viral suppression [26,27]. However, selection of subsequent regimens can be problematic; studies show expert advice combined with resistance testing provides greater benefit than selection of an antiretroviral regimen based on resistance testing alone [33].

Other strategies to maximize antiviral activity include the use of dual PIs and pharmacokinetic enhancement. Ritonavir, a potent inhibitor of the cytochrome P450 3A hepatic enzyme, increases concentrations of most other PIs resulting in improved antiretroviral activity against partially resistant viral strains [13,34]. In patients experiencing virologic failure on a PI, the use of dual PIs is also associated with improved virologic responses [12,13]. Ritonavir-boosted dual PI regimens have been explored [35] but unexpected drug–drug interactions may occur [36] and this approach has not been shown to be better than unboosted dual PI regimens. Further research is needed before this approach can be integrated into treatment guidelines.

Older strategies such as empiric multiple drug selection of regimens have largely been abandoned. More recently, a strategy of partial treatment interruption (i.e. continuing some drugs in a regimen) suggested sustained virologic control and reduced toxicity [37,38] but this strategy awaits further evaluation. In the US, routine use of therapeutic drug monitoring (TDM) is not currently recommended; however, in Europe TDM is frequently used [2]. The clinical utility and optimal use of TDM in treatment-experienced patients is under investigation.
In summary, the current standard of care for patients not responding to their present antiretroviral regimen includes the following:

(1) identify and address the reason for treatment failure;
(2) perform drug-resistance testing; and
(3) use drug-resistance testing results to design a new regimen with at least two active antiretroviral drugs (including consideration of investigational agents, if available).

The major challenge facing patients and physicians today is the availability of at least two active antiretroviral drugs to construct a new regimen. Addition of one active drug to a failing regimen typically is not recommended because of the risk of developing resistance to that drug. However, in patients at high risk for clinical progression, this strategy may provide some benefit, at least temporarily, while waiting for availability of newer active therapies.

Challenges to developing new therapies

In 2003, a fourth therapeutic drug class, entry inhibitors, was added to the armamentarium of HIV treatment. Today, development of new molecular drug targets such as HIV entry and viral integration continues along with development of new agents in existing drug classes [39]. General and class-specific challenges in trial design and data interpretation in treatment-experienced patient populations include:

(1) heterogeneity of study participants;
(2) identification of acceptable comparator regimens;
(3) complex efficacy and safety assessments due to cross-over options for participants who experience virologic failure; and
(4) definitions of clinically relevant and achievable end-points.

The heterogeneity of study participants contributes to challenges in designing trials that are acceptable to patients and investigators and reflect the population likely to use the new therapy in clinical practice [2]. Addressing these challenges is imperative, and to achieve this goal, study treatments consistent with standard of care, including the use of genotypic and/or phenotypic resistance data to construct an optimized antiretroviral background regimen (OBR) are critical. As stated previously, regimens with at least two active antiretroviral drugs are preferred; therefore, studies should ideally allow the use of approved and investigational agents.

Drug interactions and heterogeneity of the baseline resistance profile also add to the complexity in designing trials. Heavily treatment-experienced patients often take drugs for prophylaxis of opportunistic infections or

require complicated regimens that involve ritonavir 'boosting' or dual PI therapy [40]. The potential for multiple drug interactions is increased and can pose safety risks or loss of efficacy. Some patients are willing to accept the risk of combining new investigational agents before all necessary drug interactions studies are completed. These risks are not necessarily acceptable for all treatment-experienced patients and must be carefully weighed with any perceived benefits for patients with few or no treatment options.

Heterogeneity of the patient population can also be viewed as a positive aspect of trials enrolling heavily treatment-experienced patients. Diverse resistance profiles allow evaluation of a spectrum of responses according to baseline parameters. Similar to dose-response, differential responses by baseline resistance profiles provide evidence of activity and useful information for clinicians.

Heterogeneity of the viral population within individual patients also presents unique class-specific challenges for the development of new agents such as CCR5 (R5) co-receptor antagonists. The utility of these drugs may depend on viral populations and viral tropism. Patients may harbor viral strains with R5 co-receptor tropism, CXCR4 (X4) receptor tropism, dual tropism or mixtures of viruses with different tropisms (R5/X4). The antiviral activity of several R5 co-receptor antagonists in patients with R5 virus was shown in early clinical studies [41–43] however, *in vitro*, these drugs were not active against X4-tropic virus. Therefore, at this stage of development, the activity of R5 co-receptor antagonists against mixed or dual tropic viruses is unknown. In addition, disease progression may potentially accelerate when a patient's predominant virus changes from R5 coreceptor use to X4 co-receptor use [44–46]. As a result, a patient's predominant viral population (R5, X4 or R5/X4) must be assessed before initiating treatment with a CCR5 co-receptor; however, this assessment requires use of an investigational tropism assay. Current co-receptor assays are not quantitative, do not provide a relative ratio of R5 or X4-tropic viruses, and are not able to differentiate between mixed and dual tropic viruses.

Another challenge of antiretroviral drug development in general is identification and blinding of acceptable comparator regimens. In treatment-experienced patients with few or no remaining treatment options, an individualized OBR is an acceptable treatment comparison. Blinded comparisons are preferred because blinding reduces bias due to differences in management, treatment, or assessment of patients arising from investigator or patient knowledge of the randomized treatment [21]. Unfortunately, blinding is not always possible, particularly for OBR or drugs with unique and identifiable toxicities or formulations such as injectables. When blinding is not possible, studies must include detailed procedures to minimize bias and interpretability of study results. Study procedures designed to minimize bias include choice of OBR prior to randomization, identical rules for changes to OBR in all study arms, and clearly specified switching criteria for active and control groups [31,32].

A standardized comparator regimen may be an alternative; however, this option is not feasible for all treatment-experienced patients because of cross-resistance issues. Selective randomization can be used to minimize the possibility that patients are assigned drugs they have already received [13].

Another design challenge is the need for a trial to be responsive to patients clinical care needs. Options include 2 : 1 randomization (new drug: control) and cross-over designs that provide access to the investigational agent for all patients at some point during the study. Crossover designs have been used in past trials [31,32,47,48]; however, this design presents unique challenges for efficacy and safety evaluations. Cross-over options lead to a declining number of subjects in the control arm and create challenges in comparative safety assessments. This design also requires careful correction of the incidence of adverse events for the duration of exposure as described below.

Choice of clinically relevant and achievable endpoints is another challenge. Achieving and maintaining HIV RNA levels below the limit of assay detection may not be feasible for certain treatment-experienced patients [21]. Alternatives include assessing mean change from baseline HIV RNA levels or proportion of subjects with 1 log or greater reduction in HIV RNA. Results from the enfuvirtide trials, TORO 1 and 2, and the tipranavir trials, RESIST I and II, demonstrated that achieving a 1 $\log_{10}$ decrease in HIV RNA levels from baseline and HIV RNA < 400 copies/ml or even < 50 copies/ml is possible for many patients [31,32,47–49]. Knowledge of achievable response rates from the TORO and RESIST studies and other studies is useful for designing future trials in similar patient populations.

Yet another challenge is the ability to predict the future needs of an evolving treatment-experienced population. As a result, physicians and patients face difficult decisions on whether to delay or to immediately use new therapies. Should patients enroll into a clinical trial with one new investigational agent or wait for the availability of two or more new drugs? How might new therapies affect future treatment options? The sequence and timing of the initiation of new drugs may be important factors in the long-term management of such patients.

Furthermore, challenges continue to exist for the development of new investigational agents in existing drug classes, and each class of antiretroviral drugs has unique issues. Although several investigational agents

with activity against drug-resistant HIV strains are in development, benefit from these drugs for heavily treatment-experienced patients may be limited. For example, resistance can develop rapidly (e.g. with as little as one dose) to existing and potentially new NNRTI drugs, clearly demonstrating the importance of having additional active drugs available for combination therapy to delay the development of resistance. Short-term activity has been observed with new investigational NNRTIs [48,50]; however, the long-term utility of these agents may be limited in treatment-experienced patients with no viable OBR options.

For certain drugs, such as nucleoside reverse transcriptase inhibitors (NRTIs) or PIs, with activity against drug-resistant virus, the number and/or type of NRTI and PI-associated mutations may affect virologic response rates [51]. As seen with tenofovir, patients with three or more zidovudine-associated mutations that included mutations at reverse transcriptase positions 41 or 210 had reduced response rates compared to patients who did not have the 41 or 210 mutations present at baseline [52]. Some phase II studies with tipranavir, an investigational PI, showed reduced response rates when more than two baseline PI mutations were present at positions 33, 82, 84 and 90 [53]. As a result, this information was used to develop exclusion criteria in phase III trials. [54]. In addition, early determination of the effect of baseline genotype and phenotype for new investigational agents is important for patient selection into clinical trials. Within existing drug classes, new agents that are not adversely affected by primary NRTI or PI mutations are needed.

Despite these challenges progress in HIV drug development continues. Table 1 provides a summary of new HIV agents in development. The need to develop new drugs from existing drug classes and new antiretroviral drug targets is important and collaboration between pharmaceutical companies, government agencies, clinical researchers and the HIV community is vital to the success of new therapies.

Table 1. Investigational agents – 2005.

Drug name	Phase of development
Nucleoside reverse transcriptase inhibitors	
D-d4FC; Reverset; Pharmasset	I/II
Racivir (PSI 5004); Pharmasett	I/II
SPD 754; Shire BioChem	I/II
Non-nucleoside reverse transcriptase inhibitors	
Capravirine; Pfizer	II
GW678248; GlaxoSmithKline	I/II
TMC125; Tibotec	II
TMC278; Tibotec	I/II
Protease inhibitors	
Tipranavir; Boeringer Ingelheim	III
TMC114; Tibotec	II
Entry inhibitors	
CD4 attachment inhibitors	
PRO 542; Progenics	I/II
TNX-355; Tanox	I/II
CCR5 co-receptor antagonists	
UK 427, 857; Pfizer	II/III
GW873140; GlaxoSmithKline	II
SCH 417690; Schering-Plough	II
CXCR4 co-receptor antagonists	
AMD 070; Anormed	I/II
Maturation inhibitors	
PA-457; Panacos	I/II

Regulatory issues in the development of new therapies for treatment-experienced patients

Developing new therapies for treatment-experienced patients must balance access issues and ethical concerns with the need to obtain useful scientific data and prescribing information. Rapid access to new therapies, improved study designs and useful prescribing information are critically needed for treatment-experienced patients. Addressing these competing concerns may allow the field to move forward in a rational manner.

Providing access

Patients who have exhausted available therapies need new treatment options to reduce their risk of disease progression and/or death. For these patients, participation in randomized controlled trials is not always desirable and participation in open-label, compassionate-use safety studies or expanded access studies is more appropriate. Providing easy and rapid access to investigational antiretroviral drugs without imposing undue burdens for patients, clinicians and investigators is an important goal. However, at times, expanded access programs compete with enrollment of phase III trials or compete with investigators' time for conducting other studies. In fact, it has been pointed out that the most rapid access to investigational agents may result from timely enrollment and completion of phase III studies. Burdensome paperwork and/or data collection interferes with the goal of easy and rapid access. Lack of compensation for physicians and their staff also add to the difficulties of carrying out these programs. Additional challenges for expanded access studies include the often limited availability of sufficient information on active doses and drug–drug interaction data.

There are many regulatory routes for providing access to investigational agents in all phases of drug development. In the United States, these routes range from access via parallel track regulations in early drug development to use of more traditional expanded access programs later in development. Barriers to expanded access programs in the clinic lie with implementation of these programs. In larger expanded access programs, the challenge is providing access with the least amount of regulatory burden and paperwork; therefore, collection of detailed information or use of these protocols to answer important questions regarding efficacy and safety is not realistic. At

best, new serious adverse events might be identified and serve as a signal for further investigation, similar to investigation of post-marketing reports after initial approval. For detailed collection of data in heavily pretreated patients, smaller studies designed to evaluate specific pharmacokinetic, safety or virologic endpoints are preferred.

Regardless of the type of study, the FDA allows the use of more than one investigational agent in clinical studies; however, the ability to use investigational agents safely with other antiretrovirals, including other investigational agents, should be evaluated in smaller studies prior to expanded access, which typically provides access to thousands of patients. Collaboration between several pharmaceutical companies in the development of expanded access protocols can be critical for making more than one investigational agent available at the same time to patients who need them. One recent example of successful collaboration was the creation of concurrent expanded access programs for abacavir, amprenavir, and efavirenz. Co-enrollment in these protocols allowed patients to receive active therapies without formal direct comparison of the drugs, alleviating each sponsor's concerns of a competitor's drug outperforming its own drug.

Meeting regulatory standards

Balancing regulatory standards for drug approval and access to investigational agents is a challenge. Access to new therapies and the need to know how best to use a new drug in combination with other antiretroviral drugs, are both important. Information on dosing, drug interactions and resistance is crucial for effective clinical management of treatment-experienced patients. Clinicians also need information regarding the impact of resistance on treatment response.

For regulatory approval, substantial evidence of safety and efficacy must be established in adequate and well-controlled clinical trials; however, pivotal studies in every patient subgroup are not required. The European Union Committee for Proprietary Medicinal Products [55] and FDA make a distinction between treatment-experienced patients with remaining approved options and those with no available options except investigational therapies. Both regulatory authorities state in guidance documents that the salvage population may not be appropriate for registrational type studies typically used to support approval. As previously stated, these patients may be better suited for single arm or dose comparison studies in which everyone receives one or more new investigational agents. Endpoints such as pharmacokinetic parameters, virologic response according to baseline genotype or phenotype, and frequency of adverse events could be investigated in these studies. These data are not essential for approval but are supportive and could translate into useful prescribing information for heavily treatment-experienced patients. As a result, the focus of these trials changes from traditional regulatory studies to study designs that provide important prescribing information for the heavily pretreated subgroup.

Developing acceptable study designs

When designing future studies, using the lessons learned from past studies is imperative. Previously, many patients developed multiple drug resistance after receiving sequential monotherapy (i.e. the introduction of new agents one by one over time). Therefore, study designs that avoid jeopardizing future treatment options are desirable. In studies evaluating a new investigational agent plus OBR or OBR alone, patients are at risk of developing resistance to the one new drug, their remaining therapeutic options (OBR) or both. The risk of resistance often depends on the activity derived from the remaining options. Some have criticized trial designs where one investigational agent added to OBR is compared to OBR alone. Patients who *can* afford to wait for new drugs to become available often do not enroll into clinical trials for fear of rapidly developing viral resistance to the investigational agent and potentially to a new class of drug. Patients who cannot afford to wait (e.g., those with very low CD4 cell counts and extensive drug resistance) are often referred to trials out of desperation; however, these patients may have a poor response to therapy or a limited response due to the development of resistance to the investigational agent.

Lessons learned from past studies and practices illustrate options for trial designs for the heavily treated-experienced population. Several possible alternatives exist to the traditional trial designs in which participants are randomized to an investigational agent plus OBR or placebo plus OBR. Three options (described below) are suitable for answering scientific questions while a fourth option is more suitable for expanded access protocols, but may also address important clinical issues.:

(1) Traditional study designs comparing an investigational agent to placebo when added to OBR is an option for certain treatment-experienced patients. Included in these studies are provisions for early treatment switches to the investigational agent for not achieving or maintaining a specified virologic response. As noted with the enfuvirtide development program [31,32], a disadvantage with this cross-over design is the potential for systematic bias, specifically the lower mean exposure of the control arm in comparison with the new drug arm. Patients who switch from the control group to the investigational arm may be those who are more advanced and not responding to therapy. Given that adverse events often occur with increased frequency in patients with lower CD4 cell counts [31,32,56], imbalances in treatment switches may cause bias. To

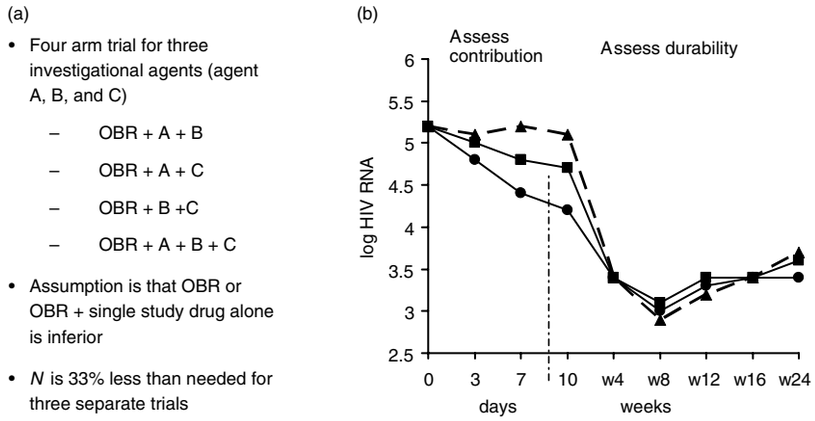

Fig. 1. Study design options. (a) Modified factorial design; OBR, optimized background regimen; (b) Two-part hybrid design. Closed triangles, current regimen; closed squares, OBR; closed circles, agent X + current regimen. Dotted line indicates time-point at which agent X and OBR are added to all treatment arms.

adjust for imbalances in the duration of treatment regimen exposure, one approach is to assess adverse event rates per 100 patient-years.

(2) Modified factorial designs (see Fig. 1a), including trials with multiple investigational agents is another alternative. However, these designs require the availability of several study drugs at the same stage of development. Pharmaceutical company collaboration, particularly for drug interaction and dosing information, is essential to the success of these trials. In the absence of complete information, smaller lead-in cohorts are an option in which real-time pharmacokinetic or TDM data are assessed and dose adjustments made in a limited number of patients before enrollment of the entire cohort.

(3) Two-part hybrid studies (see Fig. 1b) are designed to assess the contribution and durability of a new drug. The study is controlled (investigational agent versus placebo) for a brief period (e.g. 2 weeks), then all participants receive the investigational agent plus OBR for the duration of the study. The controlled portion of the study allows for the evaluation of activity while decreasing the risk of resistance to the new drug or OBR. This design is a good option when only one new drug is available. The appropriate duration for these studies with regard to efficacy and safety assessments is still an open question; however, for safety considerations the longest feasible duration is preferred. Virologic response may diminish after 4 to 6 months; therefore, the long-term demonstration of response may not be feasible. Control arms, even for short durations are helpful in discerning causality of adverse events.

(4) Open label, non-comparative 'compassionate use' studies, including the use of multiple investigational agents are particularly suitable designs for patients who are not candidates for controlled clinical trials. As already mentioned, if the primary goal is to provide access to an investigational agent for a larger group, then answering scientific questions is burdensome to this process. Smaller compassionate use trials with more intensive monitoring or study endpoints could run in parallel with larger compassionate use studies or comprise one tier of the protocol.

A recurring theme is the need for access to several new active drugs simultaneously. For this, collaboration from several different pharmaceutical companies and/or government-sponsored investigators is imperative. In the past this has been problematic. Examples exist where studies of multiple investigational agents were no longer feasible due to safety concerns or manufacturing problems with one of the new drugs. Others examples include completed protocols in which unexpected drug interactions reduced efficacy.

No good solutions to this challenge exist other than persistence. The failure of one collaborative endeavor should not discourage future attempts. Government-sponsored research is uniquely able to work with multiple pharmaceutical companies and such studies should be encouraged [13,57].

Conclusion

Currently, many patients in the triple drug-class experienced group are those who initiated antiretroviral therapy at a time when suboptimal treatment regimens (mono or dual therapy) were the only option. The future needs of patients initiating therapy today are unknown and no systematic mechanisms are available to make these predictions. Initiating triple combination therapy according to current treatment guidelines will hopefully diminish the numbers of patients who have exhausted available treatment options. Nevertheless, long-term toxicities, drug resistance, and adherence issues lead to frequent changes in antiretroviral therapies. As a result, the heavily treatment-experienced population will continue to grow unless more durable, convenient

regimens with minimal toxicities become available for naive or less-treatment experienced patients. In the meantime, the development of effective strategies for the management of HIV-infected antiretroviral treatment-experienced patients is a public health priority.

The population of treatment-experienced individuals is heterogeneous and the management of these patients is necessarily individualized and complex. Fortunately, a number of antiretroviral agents with activity against drug-resistant virus are in development. However, challenges remain in making investigational agents accessible and in designing optimal clinical studies. The current goal of therapy is to provide treatment-experienced patients with at least two and preferably three active agents, but this is not always feasible. Some patients can participate in clinical studies with novel designs such as two-part hybrid or modified factorial designs which address specific clinical questions and support clinical development and regulatory approval of newer antiretroviral drugs. However, not all patients are candidates for clinical trials, and open-label expanded access programs, allowing for the simultaneous use of multiple new drugs, are acceptable options for certain patients.

The lessons learned from past studies help to optimize future study designs for patients most in need of new therapies. Challenges in the design and conduct of trials in treatment-experienced patients remain and collaboration between pharmaceutical companies, clinicians, clinical researchers, government agencies and the HIV-infected community are paramount for the successful development of new therapies and effective treatment strategies.

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