

Treatment ISSUES

Redefining EAPs for Patients With MDR-HIV

By Nelson Vergel and Dan Tietz

Introduction

We have repeatedly heard the following statements about multi-drug resistant HIV (MDR-HIV) patients in a host of meetings on treatment access and HIV research: “These patients no longer exist – they’re either dead or have responded to the latest ARVs”; “Only patients who do not adhere to their HIV regimens have MDR-HIV”; and “Our clinic cannot provide expanded access programs (EAPs) due to cost and staff restraints.” However, after surveying physicians around the country, we have found that although these patients are in a minority, they do exist and are anxiously waiting for access to viable regimens that could save their lives.

No one can deny that many patients can now suppress their HIV with effective regimens that cause fewer side effects. However, a vulnerable and often forgotten minority of people are still struggling with MDR-HIV while they anxiously await for access to life-saving regimens that would finally control their virus replication. Although some of these patients may have developed resistant HIV due to lack of adherence or other issues, many of them have been strictly following their doctor’s orders for years. They’re often veterans of drug development research who have accumulated HIV resistance as they repeatedly joined antiretroviral (ARV) studies or traditional EAPs of a single new drug out of desperation to control their HIV viral load. As they signed up for studies that helped companies get their drugs approved by the FDA, many of these patients were exposed to suboptimal HIV regimens (namely, functional monotherapy or the addition of a single new active ARV to a failing HIV regimen). It is time to create a new paradigm to break the vicious cycle of single drug access that has failed these patients.

A complicating factor for these patients’ fate is the fact that the current HIV investigational drug pipeline has very few ARVs in similar phases of development to enable multiple drug access to help them. Continuing with traditional EAPs that provide access to a single investigational ARV will only ensure the demise of these patients by repeating past mistakes of functional monotherapy.

Although most clinicians would agree that MDR-HIV patients are a minority, there is no way to quantify this vulnerable population since no patient registry exists for them.

Due to several factors to be reviewed in this article, it is imperative that a new type of smaller expanded access program of multiple concurrent investigational ARVs is created to help patients that could fall through the cracks due to geographical and/or clinic cost and staff limitations. Fortunately, some physicians treating patients that have run out of treatment options have started campaigning along with activists to have pharmaceutical companies collaborate in providing early access to multiple investigational ARVs. This article will describe a new approach to addressing the urgent treatment needs of this easily forgotten minority in the era of successful ARV treatment.

It is time to create a new paradigm to break the vicious cycle of single drug access that has failed these patients.

Background

The management of drug resistant HIV has improved dramatically in recent years with the approval of a number of highly effective ARVs, including raltegravir, maraviroc, darunavir, and etravirine. Among this recent generation of FDA approved HIV drugs, perhaps the most promising is raltegravir, the first inhibitor of HIV integrase to become available. When used in combination with other active drugs, raltegravir has proven to be very potent, well-tolerated, and highly effective. In phase II and phase III clinical trials, the vast majority of patients who were able to combine raltegravir with at least one other active drug achieved durable viral suppression.

Despite the impressive efficacy of these drugs in clinical trials, a subset of patients has exhibited virologic failure. Most failures likely occurred because of the inability to construct a regimen that contained two to three fully effective agents. Adverse events, drug-drug interactions and non-adherence also likely contributed to the inability of these drugs to result in durable viral suppression. As a consequence of these factors, the failure rates in recent phase III studies such as DUET (etravirine+darunavir), MOTIVATE (maraviroc), and BENCHMRK (raltegravir) were in the 27-40 % range. The picture gets even less encouraging when

looking at longer term data. Patients using raltegravir for 144 weeks show failure rates of 40-56%, even in those patients with one or more active agents in their background therapy. This is reflected by their HIV's genotypic sensitivity score (GSS), a score reflective of how many active ARVs they have left to fight their HIV. A GSS of zero means no ready options for suppressing HIV replication.

It is assumed that many of the patients who failed these recent studies were subsequently unable to construct a suppressive regimen, although the long-term outcome of those failing these clinical trials is unknown. Most dropped out of these studies in search of something that may save their lives. And others have died in that search.

The prevalence of multi-regimen failure in clinical practice is unknown. Dr. Steven Deeks and his colleagues at the University of California, San Francisco, in partnership with San Francisco General Hospital, have an ongoing observational cohort of patients who have developed drug resistant HIV (known as the SCOPE cohort). Most of these patients have been able to construct a fully suppressive regimen and are currently doing well. But of the original 300 patients, approximately 40 now have evidence of having failed all six therapeutic drug classes currently available. These 40 patients have a GSS of zero, and have no ready options for suppressing HIV replication. Many have advanced disease (CD4 < 100) and, hence, may not be able to wait for the development and approval of multiple new options. Some clinicians refer to them as patients in "deep salvage."

There is no registry in the U. S. that includes patients with HIV who have developed resistance to all commercially available ARVs. In an effort to gather data about this vulnerable population, an informal online survey was prepared with the help of a team of investigators and activists that was presented in a meeting with the Food and Drug Administration (FDA) and clinicians, sponsored by the Forum for Collaborative HIV Research in November 2009. It is important to note that this survey was done two years after raltegravir's approval, so results reflect patients who had already been exposed to that drug.

The survey obtained replies from 83 physicians around the U.S. Two thirds of them reported having at least one patient with MDR-HIV, with a total of 252 patients with a GSS of zero or one (zero or one active commercial ARV left in their HIV treatment options).

Possibly the most surprising finding is the wide geographical distribution of the patients, with physicians from 47 cities. Although the largest cities had the most patients, many lived in small towns that are far from research sites or large medical practices that maybe better equipped to handle EAPs.

Expanded Access Programs

Expanded access programs (EAP's) were developed in order to make promising treatments available to patients who need them as early in the drug evaluation process

as possible. The goal is to make HIV drugs under review and not yet FDA approved available to patients who have exhausted all currently approved therapies. Early in the HIV epidemic, HIV activist organizations challenged the existing drug approval process as too cautious, particularly in the face of a deadly epidemic that was claiming thousands of lives for lack of effective therapies. Their efforts shifted the balance from the strictly protective model, with an emphasis on preventing harm to patients, toward increasing access to potentially effective therapies for patients who are in need.

The emergence of the HIV epidemic and the advocacy of HIV activists increased public awareness of the consequences of delaying drug approval. HIV activists argued that they were willing to accept the risks associated with early access in exchange for the potential life-saving benefits the drugs could provide. The FDA responded to the demands of HIV patients and clinicians by streamlining the approval process for drugs for serious and life-threatening conditions, and by codifying mechanisms for providing access to drug therapies prior to FDA approval. As a result, in the late 1980s and early 1990s, thousands of patients accessed the nucleoside agents that were progressing through clinical development. For example,

the EAPs for zidovudine (AZT) and didanosine (DDI) occurred via the treatment investigational new drug (IND) pathway, which allows access to drugs that have demonstrated some level of efficacy and safety. The clinical experience in these large trials

provided useful clinical information that was subsequently published in the literature.

The FDA also responded to the demand for ARVs by revising and updating the approval process. Beginning in 1987, the review of HIV medications received the highest priority at all stages of the approval process. The agency also developed an expedited review process for HIV medications, which has improved to the point that the FDA now frequently approves HIV medications for use in the U.S. before virtually any other country.

There are a number of mechanisms through which patients may obtain access to unapproved therapies. Clinical trials constitute the most common way that patients receive drugs before they are approved. Given the controlled nature of clinical trials, which are designed to look at very specific efficacy and safety outcomes of one new drug at a time, enrollment qualifications are generally highly selective. This limits enrollment only to those patients who meet strict entry criteria. In addition to clinical trials, there are a number of expanded access mechanisms by which drug companies can make unapproved drugs available to patients in need, but most have not included two investigational medications from different manufacturers taken at the same time. The FDA also allows for a physician to apply to a pharmaceutical company for access of a research drug for a patient in dire need (Single Patient Treatment IND). However, most physicians

The emergence of the HIV epidemic and the advocacy of HIV activists increased public awareness of the consequences of delaying drug approval.

are not familiar with this process or may not have the necessary staff to handle its requirements. And in most cases, access to more than one drug is needed, which means applying to a concurrent EAP or clinical study for access to the second active ARV. Furthermore, the FDA does not require that pharmaceutical companies agree to provide access to a patient in need. It is important to note that drug safety and dosing (phase II clinical trials) data are needed before providing any potential access. Finally, the company can deny the physician's request without any penalties or actions from the FDA or activists.

The number of patients enrolled in EAPs in the U.S. has slowly declined as more therapies in different treatment classes became available and more people were able to control viral replication with increasingly effective and newer treatments.

EAPs usually start after full enrollment of the drug's phase III studies is completed, with an average of 6 to 18 months prior to the approval of the drug. Due to activist pressure, pharmaceutical companies have allowed access to other companies' research drugs in some recent EAPs (darunavir-Prezista, raltegravir-Isentress and maraviroc-Selzentry) to enable patients to construct a viable HIV regimen. For instance, Merck allowed the use of Prezista, a protease inhibitor then available via EAP, in their phase III studies of Isentress. This meant that a physician had to apply for an EAP and a phase III study to provide access for patients in need, an approach that is time and resource consuming.

Unfortunately, most EAP documentation and related nurse/physician staff time are not reimbursable or covered by study resources. Physicians who have traditionally provided EAP access did so out of generosity and a commitment to help the considerable number of salvage patients in the past. But as salvage patient numbers decreased, it became difficult for many teaching hospitals and clinics to justify the additional staff time to complete the EAP documentation, particularly given many clinics' financial, administrative and other limitations.

Given that patients who are unable to construct a viable regimen often fail therapy, the FDA and others have advocated that future clinical trials only enroll patients able to construct background treatment regimens with a GSS greater or equal to one. In other words, the patient is rejected from a clinical trial for a new drug unless the patient's HIV is still susceptible to at least one other drug currently on the market. Although this is an ethically sound recommendation, an unfortunate consequence is that those who have now progressed to multi-drug resistant deep salvage are no longer able to access experimental drugs via clinical trials.

Making matters worse, the HIV drug pipeline has fewer new agents with new modes of action in development due to the relatively competitive U.S. market, high drug development costs, and the difficulty of finding treatment experienced patients with one or more active ARVs with which

to combine an investigational drug. As a result, pharmaceutical companies have abandoned further development of some promising new treatments that could help people with MDR-HIV.

Luckily, the FDA has proposed a new trial design that may facilitate the development of medications for treatment experienced patients, which may encourage pharmaceutical companies to continue HIV drug development. However, even this new proposal does not address the needs of deep salvage patients with a GSS of zero.

For the moment, however, it will remain virtually impossible to construct an effective treatment regimen (at least two active agents plus background therapy) for those who have MDR-HIV. In the meantime, many patients with low CD4 cell counts are not likely to survive. Only collaboration among pharmaceutical companies can shift the current access paradigm by providing an innovative early EAP which makes available a combination of at least two new investigational agents that have progressed beyond phase II trials (for which safety and dosing data are known).

A Proposed Solution

A multi-drug expanded access program (MDEAP) has been proposed by a coalition of leading medical providers and advocacy organizations. Leading investigators championing this effort include Dr. Steven Deeks and Dr. Jay Lalezari from San Francisco and Dr. Jerry Ernst from ACRIA in New York. Two pharmaceutical companies with new

ARVs in development also support this initiative, at least in principle. One of the companies is ViiV Healthcare, makers of the new integrase inhibitor dolutegravir that has completed phase III studies and which seems to be active against many raltegravir-resistant HIV. The other is TaiMed Biologics, the maker of ibalizumab, an entry inhibitor (monoclonal antibody), which has gone through two phase II studies. Dosing and safety data are available for both drugs. Used together, these drugs may help to suppress MDR-HIV, as long as they are combined with another active ARV to which the patient's HIV has not developed resistance.

This proposal consists of a pilot phase in New York and San Francisco with 40 patients, then an expansion phase to the rest of the country. It is also proposed that a centralized Institutional Review Board (IRB) be used nationally to provide access to patients in small cities from clinics that do not have access to IRB's. A non-profit clinical organization could handle the administrative burden of documenting potential significant adverse events and managing report forms for physicians around the country, especially for those who lack the resources to do so. Since the deep salvage population is relatively small and spread out geographically, a centralized administrative organization would facilitate access that otherwise would not be available to these patients due to limitations in their clinics.

Only collaboration among pharmaceutical companies can shift the current access paradigm by providing an innovative early EAP.

EDITOR: ROBERT VALADÉZ
ASSISTANT EDITOR: ELIZABETH LOVINGER
ART DIRECTOR: ADAM FREDERICKS
GMHC *Treatment Issues* is published by GMHC, Inc.
All rights reserved.
Noncommercial reproduction is encouraged.

GMHC Treatment Issues
446 West 33 Street, New York, NY 10001
gmhc.org
© 2012 Gay Men's Health Crisis, Inc.



ViiV Healthcare recently initiated an expanded access program for dolutegravir, an integrase inhibitor, which completed phase III studies in patients with raltegravir resistance. For the reasons described above, however, patients with a GSS of zero cannot construct an effective treatment regimen with this drug alone even if accessing it through ViiV's new EAP. Dolutegravir may be FDA approved in the coming months.

TaiMed's ibalizumab recently ended phase II studies. It is a genetically-engineered monoclonal antibody that could be administered intravenously once every two weeks and the company is also developing an injectable, subcutaneous formulation of this drug. Because ibalizumab has a completely new mode of action, most patients could be expected to respond to it when used with at least one other active agent. It is different from the CCR5 receptor entry inhibitor maraviroc (Selzentry) in that it blocks the CD4 receptor on T-cells rather than blocking a co-receptor. This means it could be effective against a virus that uses either the CCR5 or CRX4 co-receptor. Unfortunately, due to its small size and limited funding, TaiMed cannot proceed with phase III studies to get ibalizumab approved until a development partner is found.

Neither TaiMed nor ViiV expect any negative interactions if dolutegravir and ibalizumab were to be combined.

While ViiV and TaiMed have expressed interest in helping patients in deep salvage and will provide their unapproved drugs free of charge for patients with declining health and at high risk of death, TaiMed's need for a new development partner means that ibalizumab cannot presently be provided as part of a MDEAP. As a result, the project is on hold and patients in great need continue to wait.

Luckily, ViiV is also developing a non-nucleoside reverse transcriptase inhibitor (NNRTI) that shows promising activity against NNRTI-resistant virus. In addition, Bristol-Myers Squibb (BMS) is developing a new entry inhibitor that holds promise for people who have MDR-HIV. Although BMS has not been a part of discussions regarding this MDEAP, it is our hope that the company will consider joining the conversation as the new drug's safety and dosing data become available.

Conclusion

HIV treatment has made great strides in the past few years. But multidrug resistance is here to stay until a cure is found. Although the number of patients with MDR-HIV

may be decreasing as more people are able to sustain viral suppression with newer and more tolerable ARVs, there is still a need to find effective ARV combinations for those who have not fared as well due to accumulated resistance. Smaller and innovative EAPs that include several investigational agents will not only potentially save lives by preventing functional monotherapy, but also gather safety data on new ARV combinations before they are widely used in the field. We can only hope that pharmaceutical companies cooperate to make this a reality with the support of the community, the FDA, and clinicians around the country.

Help for Patients Who Are Running Out of Time

How to apply for Emergency Treatment IND (Single Patient) access of a single investigational drug. While it may seem intimidating at first to a primary care provider, the process for a single patient emergency IND is rather straightforward. The patient must have evidence of resistance to all commercially available ARVs and a viral load that suggests that their HIV disease is not responding to a current drug regimen. The usual laboratory tests include a phenotypic resistance test and an HIV tropism assay. It is important to also know if phenotypic resistance to T-20 (Fuzeon) is present. Additionally, genotypic integrase mutations need to be characterized to assess the patient's potential response to dolutegravir.

If the patient's health is at risk, i.e. a CD4 cell count under 100 cells/ml and a declining clinical outlook, and the patient's HIV has developed resistance to all commercially available or expanded access ARVs, then the treating provider should:

Contact the pharmaceutical companies with the investigational ARVs to obtain free drugs in advance of FDA approval for the commercial market.

Upon each manufacturer's agreement, the provider should follow the procedure described in this FDA link (<http://1.usa.gov/ODDgPk>), to complete the required forms and obtain institutional review board (IRB) approval.

Admittedly, this single-patient IND procedure is seldom used by physicians due either to a lack of information or concerns about its complexity. While it may be a bit time consuming the first time, it is not particularly complex. And the FDA will permit its use for small groups of similarly situated patients.

Moreover, many local IRBs will expedite approval in urgent circumstances and the FDA will orally approve a single patient IND if the patient has an expected survival of less than 30 days (called an emergency IND). Indeed, the drug company will ship the drug in an expedited manner while the provider completes the forms. For a sample consent form and cover letter for IRB submission go to www.salvagetherapies.org.

For more information on the content provided by the authors, please contact NelsonVergel@yahoo.com.

Nelson Vergel has lived with MDR-HIV for many years and knows first-hand the issues surrounding salvage therapy. He created www.salvagetherapies.org to help people like him who have run out of HIV treatment options.

Daniel Tietz is the Executive Director of the AIDS Community Research Initiative of America (ACRIA).