Is It Time to Rethink the Expanded-Access Programs for HIV Infection?

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The purpose of expanded-access programs (EAPs) for antiretroviral therapy has been to allow patients without alternative treatment options to obtain drugs before formal Food and Drug Administration approval. Given the dramatic changes that have occurred in antiretroviral therapeutic approaches during the past 2 decades, we wish to review the history of antiretroviral EAPs and to propose an updated model for expanded access that would achieve maximal patient benefit and add useful knowledge that could guide treatment decisions in patients infected with multidrug-resistant human immunodeficiency virus.

The original purpose of expanded-access programs (EAPs) for HIV medications was to make promising drugs available to patients without other therapeutic options as early as possible in the drug-evaluation process [1]. In the 20 years since the zidovudine EAP began, HIV drug therapy in the United States has evolved dramatically. It is time that all of us who are interested in the welfare of those living with HIV, from community activists to HIV clinicians to policy makers, reexamine these EAPs to ensure that patient health and safety are placed as top priorities. Almost 30 drugs and drug formulations are Food and Drug Administration (FDA) approved for the treatment of HIV. Because of these agents, a diagnosis of HIV infection is no longer a death sentence in the developed world. Nonetheless, many people infected with multidrug-resistant HIV who have limited treatment options and advanced disease rely on newly developed drugs as soon as they are available, often through clinical trials and EAPs. As advances in HIV therapeutics have occurred, the role of the EAPs has also evolved. At a time when multiple new antiretroviral drugs are in development, it is essential to question who is benefiting most from the current EAP model.

We believe it is valuable to examine and critique the evolution of EAPs for antiretrovirals. As novel approaches are being proposed for clinical trials involving patients infected with HIV resistant to multiple drug classes [2], there is an opportunity to link a restructured model for expanded access to antiretrovirals with these approaches to ensure access and measurable patient benefit.

STRUGGLE FOR ACCESS

The thoughtful caution exhibited by Frances Kelsey in withholding approval for thalidomide in the early 1960s was a defining event for the FDA, and well into the 1980s the FDA’s core mission remained protection of the public health by ensuring the safety, efficacy, and security of human drugs. The emergence of the HIV epidemic challenged this mission fundamentally. HIV activists succeeded in putting a face on the abstract consequence of delaying drug approval [3]. HIV activists, organized in groups that included the Gay Men’s Health Crisis, ACT UP (AIDS Coalition to Unleash Power), and others, protested the existing drug-approval structure that made caution paramount and led the FDA to streamline the drug-development processes for serious and life-threatening conditions—and for AIDS in particular. In the process, they altered the paradigm for clinical research, drug approval, and early drug access in the United States. Their example of advocacy and activism led the way for the cancer and autism research movements and for other medical advocacy groups of today.

Against this backdrop, in the late 1980s and early 1990s, as each new nucleoside analogue progressed through clinical trials, thousands of patients accessed the drugs before approval. On the basis of experience gained from the zidovudine EAP [4], mechanisms for access to medications for serious conditions before their FDA approval were formally codified [1, 5, 6].
The EAPs for zidovudine and didanosine occurred through the treatment investigational new drug (T-IND) pathway, a mechanism for allowing access to drugs with some proven efficacy and safety data [5]. The didanosine program involved >20,000 patients who had clinically progressed while receiving zidovudine or were zidovudine intolerant and who had highly advanced disease (with 60% having CD4 cell counts <50 cells/mL) [7]. The lamivudine EAP involved nearly 30,000 patients. The stavudine program, which was administered through a slightly different mechanism than expanded access (termed a “parallel track protocol”), demonstrated that a lower dose of stavudine was associated with a lower incidence of peripheral neuropathy [8]—an example of the helpful clinical information these programs could provide. Experience with the drugs in these large trials was published and gave helpful clinical information [4, 7].

VIRTUAL MONOTHERAPY

Little outcome data on safety and efficacy from EAPs have been published in the past 10 years, and the presented safety data have often been incomplete, making it difficult to draw conclusions on the basis of these data. For example, in the 2006 presentation of the >10,000 patients receiving tenofovir internationally through expanded access, data on baseline and follow-up renal function were present for <10% of enrolled patients [9]. Given that entry criteria have become generally less restrictive, it is unclear that participating in these programs is the most beneficial course for all of those enrolled. One concern is that patients may be exposed to “virtual monotherapy” through these programs. In 1997, the efavirenz EAP was given a new eligibility criterion based on the investigators’ recognition that the addition of a nonnucleoside reverse-transcriptase inhibitor to a failing regimen was unlikely to produce a durable virological response. They required the use of at least 1 other active agent in conjunction with the investigational drug [10]. Subsequent programs have not, however, generally incorporated this restriction. Today, our ability to treat HIV infection and our understanding of the optimal treatment for patients with unsuppressed HIV replication—that is, virological treatment failure—continues to progress. It is now clear that when a person with HIV infection experiences significant drug resistance and requires new medications, it is best, if possible, to begin multiple active agents at once, because the likelihood of successful viral suppression is greater. Although this concept has been applied in the design of recent phase 3 trials that allow the use of other investigational drugs obtained through EAPs, it is unclear whether this is what is occurring in today’s EAPs. For HIV-infected individuals with virus resistant to all available drugs or with treatment-limiting intolerance, participation in today’s EAPs now may mean exposure to a single new agent, which in some situations can be the equivalent of virtual monotherapy. This scenario can lead to further resistance and the need for still-newer agents. Some patients have disease that is so clinically advanced that there is not time to wait for access to multiple new agents, and virtual monotherapy may be acceptable. However, for many others, the soundest clinical option might be to maintain therapy with a failing regimen.

EARLY ACCESS TO DRUGS—UNPREDICTABLE INTERACTIONS

Although early EAPs included patients with low CD4 cell counts and no viable therapeutic options, today these programs typically do not have CD4 cell count criteria for entry, although participants are generally 3-class-experienced patients, as evidenced by treatment failure or intolerance. Recent programs produced objective harm to some participants by exposing them to unforeseen and unknown drug interactions or adverse effects. We cite 3 examples where this is likely to have occurred. The atazanavir EAP occurring in 2002–2003 allowed access for hyperlipidemia, which was in many cases severe, although not immediately life threatening [11]. In a subset of patients presented at the 2004 International AIDS Society Conference, the mean CD4 cell count was >450 cells/mL. Information that tenofovir lowered atazanavir drug levels and should be used with the boosted combination atazanavir/ritonavir only became widely available in the months after atazanavir’s approval. During the program, 75% of trial participants received tenofovir and 90% received unboosted atazanavir—what is now known to be suboptimal therapy. Although not reported, it is likely that this situation led to the unnecessary development of resistance in a significant proportion of participants. Another treatment regimen now known to be inadequate, the triple-nucleoside combination of tenofovir, abacavir, and lamivudine [12], was also used in an EAP, as was the combination of full-dose didanosine and tenofovir, now known to be associated with high-grade toxicity [13]. These examples highlight our concern that the current EAP model can produce a detrimental treatment strategy for HIV-infected individuals with reasonably preserved CD4 cell counts who are receiving single new drugs via an EAP, generally only several months before drug approval. Although physicians also used the regimens that are now known to be inferior immediately after approval, the preapproval interval was an opportunity to critically examine these interactions rather than to allow unrestricted access.

PHARMACEUTICAL ROLE

In the past, pharmaceutical companies launched EAPs in response to community calls. Although this is still the case in part, current large EAPs may be of financial benefit to pharmaceutical companies and can serve as an “early launch” for their new products [14]. In addition to circulating advertised announcements of the EAP for their drug in national journals, pharmaceutical companies gain both a cohort of patients ready to purchase the drug
once FDA approval is granted and cohorts of physicians familiar with prescribing the drug in advance of its approval. Having a large number of patients already receiving a particular drug on the day of its approval may also exert pressure on states to include the drug in the state formularies immediately. Although this pressure is arguably beneficial in facilitating access to the new drug, it may create an environment that does not allow states to even consider bargaining down the drug’s price and, thus, might be a contributing factor to the spiraling costs of antiretrovirals, which now comprise >60% of the total cost of HIV care in the United States [15]. Although it is difficult to document the contributing factors to the rising costs in the United States, it is noteworthy that the prices of antiretrovirals are thousands of dollars per year lower in Europe, where the pricing of drugs is heavily bargained before approval. If pharmaceutical companies potentially benefit financially from the current EAPs, this does not inherently imply that patients do not; however, we feel that these programs could be further optimized to the greater benefit of HIV-infected individuals.

There is other potential for inequity of true access in today’s EAPs on several fronts that could be lessened by pharmaceutical, regulatory, and clinical researcher initiatives. Insufficient funding and commitment exists in certain clinical settings and academic institutions for the nursing, clerical, and regulatory support necessary to initiate and participate in an EAP in a timely fashion. Lack of compensation for the paperwork involved in administering a program may contribute to this. Mechanisms to streamline and modernize the processes involved would lessen this inequity. Initiatives between involved parties and local review boards might also prove beneficial in these regards.

A PLAN FOR THE FUTURE

Today, HIV care providers are happily faced with a new responsibility to protect HIV-infected individuals from the long-term consequences of our therapeutic decisions. Providers must tread cautiously and question critically how and why patients are exposed to new drugs and must examine more carefully who are the most appropriate people to receive new drugs through EAPs. When an HIV-infected person is clinically stable but not achieving virological control with his current therapy, he or she may be best served either by accessing experimental therapies in the context of rigorous trials that elucidate the unforeseen interactions and toxicities of new agents or by continued monitoring until multiple elements of an optimized new regimen are available. In this situation, starting a single novel agent through an EAP may neither constitute the best possible treatment strategy for the individual nor be consistent with the spirit of the original expanded-access mechanism for patients with imminently life-threatening conditions. Because it is not always possible or practical for a patient to enroll in a clinical trial as a result of geographical, social, or other barriers, any restructuring of EAPs must not generate unrealistic barriers to patient access. Although the bureaucratic labor involved in obtaining a drug through an EAP for a patient may be a natural selective force in ensuring that only appropriate patients are involved, no objective data are available to demonstrate that this is, in fact, the case.

Because the goal of EAPs is to allow early access, not to rigorously study specific scientific questions or the long-term consequences of this access, we unsurprisingly could find no studies addressing long-term outcomes in participating patients through a review of all articles obtained via MEDLINE searches using the search terms “expanded access” and “HIV” or “compassionate use” and “HIV” and a search of all abstracts from the Conference on Retroviruses and Opportunistic Infections and International AIDS Society meetings from 1996 through 2007 for “expanded access” and “compassionate use.” With growing emphasis on making therapeutic decisions guided by evidence-based medicine, HIV care providers and clinical researchers should assess whether more harm than good is achieved by enrolling certain individuals in unstudied programs and should question to what extent virtual monotherapy is genuinely occurring in EAPs. Physicians should caution and educate patients on the unknown possibilities of these programs. Pharmaceutical companies launching a new antiretroviral and analyzing what place it will eventually have in therapeutic sequencing in clinical practice should question whether the drug’s role in an unstudied salvage expanded-access regimen is appropriate.

What is a preferable strategy to today’s EAPs? Non-placebo-controlled cohort trials allowing multiple experimental agents are focused studies designed to collect specific pharmacokinetic, drug interaction, activity, and/or toxicity data that can lead to important prescribing information [16] and would add scientific rigor to the current preapproval access mechanisms. Because multiple new drugs in existing and new classes are in development, there are unique opportunities to initiate new approaches today. Although taken alone the data generated might not be able to definitively distinguish the effects of individual drugs, the drug-combination information could complement clinical trial data. Traditionally, the pharmaceutical industry has not embraced this type of collaboration; however, such cooperation may be beginning, and continued encouragement for collaboration from the HIV advocacy community, the FDA, and clinical researchers may be important in promoting such cooperation. As pharmaceutical companies begin to collaborate, streamlined approaches to regulatory hurdles, perhaps relying more heavily on technology, will be needed. To reduce costs, industry could collaborate with the Division of AIDS at the National Institutes of Health or with other neutral organizations and conduct these small trials in one of the existing HIV-related clinical research networks. These studies could also collect baseline genotypic information and the antiretroviral histories of enrolled pa-
patients and link these data to clinical and virological outcomes in the patients receiving the initiated regimens. The data could be made publicly available in several currently existing genotype-interpretation databases [17] so that therapeutic decisions for subsequent patients could be based on actual clinical information rather than “guesses” by clinicians, thus leading to improved care for the HIV-infected population as a whole. Although allowing compassionate use and clinically relevant early information about a drug need not be mutually exclusive, a concern regarding this approach would be that patients who could not participate in this expanded-access design would be excluded. To address this concern, expanded access through a T-IND could be reserved for patients with truly advanced disease who are unable to participate in these trials or for patients with geographical limitations to this type of participation. This approach is summarized in the appendix.

Perhaps through novel approaches such as these we can achieve greater benefit for HIV-infected individuals—for the long term.

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APPENDIX

PROPOSED MODEL FOR EXPANDED ANTIRETROVIRAL ACCESS

Current approach

- New drug added to optimized background regimen through EAP
- Potential problems: untested combinations leading to treatment failure, drug resistance, and unpredictable overlapping toxicities

Proposed approach

- Maintain expanded access and streamline bureaucratic processing through the T-IND pathway for
  — Those too ill to access experimental therapy through the study
  — Those with geographical limitations to participation
  — Those with other limitations to participation

- Expand noncomparative small combination trials of experimental agents before approval
  — Goals: evaluation of pharmacokinetic interactions and efficacy and toxicity data
  — Facilitate and limit costs through pharmaceutical and clinical research network cooperation

- Make data publicly available through existing databases to give objective guidance to clinicians

References