Recognizing the Value of Innovation in HIV/AIDS Therapy

Catherine Augustyn, Brigham Walker, and Thomas F. Goss, PharmD
INTRODUCTION

In the last two decades, we have seen remarkable progress against HIV/AIDS (human immunodeficiency virus/acquired immunodeficiency syndrome), transforming the disease from an acute, fatal illness to a chronic condition. In the United States, death rates have fallen 79 percent since 1995 as a result of highly active antiretroviral therapy (HAART, or ART as is more commonly used today) and other new medications. Advances in treatment have increased survival, slowed progression, prevented hospitalizations, and allowed patients to lead full lives. In retrospect, the clinical improvements produced by novel treatment options for HIV/AIDS have been far above what could have been anticipated or achieved at the time of the initial introduction of these individual medicines. Understanding how this progress was achieved — as well as how the evidence supporting it evolved — is important to sustaining an environment for future advances.

This progress has been realized through a complex process of incremental gains that have unfolded over many years. Although not well-characterized or understood, this innovation process has involved the step-wise accumulation of treatment improvements over time, which has taken place as research has continued to accumulate evidence that has driven changes in HIV treatment. Our understanding of how certain novel therapies may be optimally applied to patient care changes and improves as HIV therapies are introduced and evaluated in real-world clinical practice, resulting in new approaches to treatment, which incrementally increased efficacy and tolerability. The key element to ensuring continued, and at times, unexpected innovation that drives improved patient outcomes is to ensure flexible access to therapeutic options. This access supports the step-wise process that has been central to clinical gains made in HIV and many other disease areas, and has enabled patients around the world to live longer and better than ever before.

Since medical progress with individual compounds may be realized gradually over time, the optimal role and full value of a therapy typically cannot be known at the time of Food and Drug Administration (FDA) approval or U.S. market launch. Although one of the distinctive features of new medicines is the rigorous clinical research that must be conducted to secure FDA regulatory approval, these studies are designed for controlled evaluation of safety and efficacy. Therefore, pre-approval trials are limited in their ability to capture the broader and longer-term clinical and quality-of-life benefits that may be associated with a specific therapy as physicians accumulate evidence using the new agents in real-world settings.

We selected HIV/AIDS as a case study for this analysis because significant gains in clinical outcomes have been achieved over the past 15 years, which are clearly documented in scientific literature. This paper evaluates how step-wise progress was achieved over time and the ways in which biopharmaceutical innovations have enabled better disease management and improved quality of life for patients.

This white paper is the second installment in a series of papers focused on recognizing value in biopharmaceutical innovation. The previous white paper, Recognizing Value in Oncology Innovation (June 2012), demonstrated how the full clinical value of a cancer therapy typically evolves significantly after FDA approval. These reports illustrate how this evolution frequently reveals that for many therapies, greater clinical value is realized based on real-world experience than was able to be demonstrated prior to launch. These reports also acknowledge that, at times, real-world experience can prove a medicine to be less valuable than initially expected.

Background on HIV/AIDS

HIV infection is one of the most prevalent infectious diseases in the world, affecting more than 34 million people globally in 2011 and 1.2 million people in the United States as of 2008. In people infected with HIV, the virus gradually compromises the immune system by entering and taking over T-cell lymphocytes. The adoption of antiretroviral therapies to treat HIV/AIDS starting in the 1990s has led to sharp mortality declines and greatly improved quality of life. These medicines have fundamentally changed HIV from an acute fatal illness to a manageable chronic disease.
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The treatment paradigm for HIV/AIDS has evolved dramatically over the last several decades to the point where combination therapy has become the mainstay in HIV/AIDS treatment. Combination therapy has been shown to provide the best opportunity for clinical response and disease remission in HIV/AIDS patients, even beyond initial expectations.

The value of combination therapies in the treatment of HIV/AIDS cannot be overstated. These combinations are critical to preventing the development of viral resistance and successfully treating the primary infection. Highly active antiretroviral therapy describes a type of combination regimen used in HIV/AIDS treatment that typically includes two nucleoside analogue reverse transcriptase inhibitors (NRTI) and either a non-nucleoside analogue reverse transcriptase inhibitor (NNRTI), a protease inhibitor (PI), or an integrase inhibitor (II).

In the current era, all four classes are indicated for use in combination with other antiretroviral agents for the treatment of HIV infection. However, this understanding has evolved significantly over time based on rigorous evaluation of new combinations, as new classes of agents have been discovered and approved. In the early stages of HIV/AIDS therapy, combination therapies were used in combinations, earlier use, and new indications.

FDA approval often marks the “starting point” for a number of additional evaluations of a novel therapy. Following launch, a larger body of evidence is developed through real-world practice and ongoing research. In the case of HIV/AIDS, antiretroviral therapies have proven to be effective in a broader cohort of patients than were represented in the clinical trial data submitted for initial FDA approval. Individual and combination therapies have created new opportunities for improved disease control and remission, particularly when used in patients with earlier disease stages who were not included as part of pre-approval trials, reinforcing that it is important to recognize that the full clinical value and potential of a therapy may only be identified and realized through a “step-wise transformation” over time.

*This may include both new indications approved by the FDA and off-label uses supported by research and deemed clinically appropriate by physicians. The evidence in this paper focuses on new FDA-approved indications.

FIGURE 1. Evolution of the Treatment of HIV Infection: 1980s to Present

- Use in combination with other agents
- Use earlier in treatment line and earlier in disease state
- Use in different disease indications*

NEW DRUG APPROVALS

1980s–1990s
HIV/AIDS
Acute, fatal illness

Today
HIV/AIDS
Chronic, manageable condition

Use in Combinations

Earlier Use

New Indications

• Use in combination with other agents
• Use earlier in treatment line and earlier in disease state
• Use in different disease indications*

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Combination Therapy

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Regimens were not available and viral resistance quickly became a challenge. It has taken time and real-world clinical practice to identify and test a variety of HAART combinations, which today yield improved efficacy and better tolerability and safety profiles than ever before.

Since 1996, HAART combination regimens have significantly reduced the mortality rate of HIV-infected patients. According to 2010 Centers for Disease Control and Prevention (CDC) data, the age-adjusted number of deaths per 100,000 due to HIV in the United States has decreased by 79 percent over the last two decades. The Kaiser Family Foundation attributed this dramatic improvement as “largely due to [the adoption of] highly active antiretroviral therapy.” More than 30 treatment options for HIV have been developed since 1987, arming physicians with increasingly more therapeutic options that support these kinds of improvements in patient survival.

Over time, moving from the pre-HAART era in which no HAART regimens were available, to the early- and then late-HAART eras in which not only have more antiretroviral therapies been developed but also new combinations have been tested, clinical outcomes have improved dramatically. The multitude of antiretroviral agents approved in the past two decades has allowed clinicians to tailor therapy to a patient’s specific needs and viral profile.

One large study by Danish researchers assessed the mortality rates of 3,990 HIV-infected individuals and 379,872 general-population controls from the pre-HAART (1995-96), early-HAART (1997-99), and late-HAART (2000-05) eras. In these distinct phases, new medicines became available and researchers discovered more effective combinations. Researchers reported that the highest mortality rate among HIV-infected patients – 124 per 1,000 person years – was observed in the pre-HAART period, falling to 38 per 1,000 in the early-HAART period, and further to 25 in 1,000 in the late-HAART period. These data support the hypothesis that developing and making available more therapeutic options can provide opportunity for clinical breakthroughs as new combination regimens are tested over time.

An examination of the death rates among HIV-infected individuals over the stages described above (pre-HAART, early-HAART, and late-HAART) reveals a similar change in the United States as these innovative therapies and combinations were introduced. While the death rate does not represent a comprehensive measure of mortality, it can be indicative of a trend, and in this case shows the rapid decline in deaths among individuals infected with HIV when the use of HAART therapies increased through the 1990s (See Figure 2).

Since the 1990s, certain HAART regimens have yielded better outcomes in HIV patients over time as their use has been refined in a real-world population. An analysis presented in 2008 at the 9th International Congress on Drug Therapy in HIV Infection compared the efficacy of first-line HAART regimens in 2006 to those used in 1998. The analysis included 146 patients starting first-line HAART during these years (67 in 1998; 79 in 2006). HIV suppression at 48 weeks was observed in 59.1 percent of patients in 1998 and 88.6 percent in 2006 (P < 0.001). In a multivariate analysis, virologic suppression was independently associated only with two factors: at least 48-week adherence and being treated in 2006 versus 1998. These results support an independent association between better outcomes and the specific year of treatment, suggesting that the availability of new antiretroviral agents allows for more refined and effective combination therapy.

These observations may be explained by a number of potential factors, including earlier diagnosis and treatment, better tolerance of available regimens leading to improved efficacy of, and adherence to, treatments, and adoption of better understood treatment combinations.

In addition, in recent years we also have seen significant advances in antiretroviral therapy dosing that have led to simpler regimens with reduced pill burden on patients. These co-formulations combine two or more antiretroviral medications into one dosage form with the same clinical impact, meaning HIV treatment is more effective today in part due to improved patient adherence.
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In addition to an increased use of combination therapy, the treatment paradigm for HIV/AIDS has evolved to reflect the benefits of initiating therapy earlier to better control disease progression. Real-world clinical practice and recent data support the notion that earlier initiation of treatment in the disease cycle leads to improved long-term outcomes and immunologic response.

The effectiveness of ART therapy to treat HIV patients has driven not only widespread use of combination therapy, but also progressively earlier use in the timeline of disease progression. The 2011 Department of Health and Human Services (HHS) Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents affirm that there is evidence to support the benefits of viral suppression and immunologic response in patients with higher pre-treatment CD4 counts (immune response cells) – in other words, with earlier-phase disease. In HIV-infected individuals who are not treated adequately, CD4 counts generally decrease as HIV progresses. A low CD4 count indicates a weakened immune system and a higher chance of acquiring opportunistic infections. However, today patients previously considered to be in “pre-treatment” phase (with higher CD4 counts) often receive early ART treatment and are able to derive short- and long-term benefits.

Sources:
S.L. Murphy, J. Xu, and K.D. Kochanek, “Deaths: Preliminary Data for 2010,” U.S. HHS, CDC, NCHS, National Vital Statistics Reports 60, no. 4: (2012);
U.S. HHS, CDC, NCHS, “Health, United States, 2008 with Special Feature on the Health of Young Adults,” Table 41, http://www.cdc.gov/nchs/data/hus/hus08.pdf, (2009);
The median CD4 count for newly diagnosed patients is around 200 cells/mm³. Yet the HHS Guideline Panel gave its highest recommendation that antiretroviral therapy be initiated in all patients with a CD4 count as high as 500 cells/mm³. The Guideline Panel based its recommendation on several recent developments:

- A report from the recent NA-ACCORD cohort study demonstrating survival benefit with initiation of antiretroviral therapy at “pre-treatment” CD4 count levels greater than 500 cells/mm³;
- The study observed patients who started treatment at CD4 counts greater than 500 cells/mm³ or after CD4 counts dropped below this threshold.
- The risk of death was 94 percent higher among the 6,935 patients who deferred therapy until CD4 counts fell to less than 500 cells/mm³ compared with rates in the 2,200 patients who started therapy while CD4 count was greater than 500 cells/mm³.
- Growing awareness that untreated HIV infection may be associated with development of many non-AIDS-defining diseases, including cardiovascular disease, kidney disease, liver disease, and malignancy; and
- Availability of antiretroviral regimens that are more effective, more convenient, and better tolerated than antiretroviral combinations no longer in use.

Citing its own evolution over time, the Guideline Panel summarized its findings by stating that prior concerns about long-term toxicity, reduced quality of life, and the potential for drug resistance previously acted as barriers to its recommendation of earlier treatment initiation. But this year, the Guideline Panel concluded that increasing evidence supports earlier initiation of antiretroviral therapy.

Extending the research showing the benefits of early treatment, researchers have found that early use of antiretroviral treatments reduced the chances of transmission to an uninfected partner by 96 percent. This large international study compared an early treatment group, in which the HIV-infected partner initiated ART treatment immediately, with a deferred group, in which patients waited to begin treatment until their CD4 count fell below 250 cells/mm³ or they had an AIDS-related illness. The findings were robust enough that the study was unblinded four years early.

**USE IN ADDITIONAL DISEASE INDICATIONS**

*Improved understanding of disease pathology – in many cases at the molecular level – has had a direct impact on the development of ART and other HIV treatments over the past two decades. With a better understanding of how the disease evolves and progresses, therapies have become more targeted and have proven to be beneficial not only for the treatment of the disease but also for the prevention of transmission, leading to new uses and indications for many treatment regimens.*

In the case of HIV infection, access to multiple treatment options has enabled clinicians and researchers to uncover additional and inherent – but previously unrecognized – secondary values of individual regimens. Although by their nature antiretrovirals do not lend themselves to new indications as much as some other disease areas (e.g., oncology), even in this area, potential for use in new populations has been uncovered.

**Preventing Maternal-Fetal Transmission**

Antiretrovirals were developed and first approved for patients with primary HIV infection. Yet certain antiretrovirals have provided additional specific benefit to infected pregnant women and their unborn children, helping to drive down the rate of maternal-fetal HIV transmission.

The most salient example is zidovudine (ZDV, Retrovir®), which was initially approved by the FDA in 1989 to treat HIV infection, but subsequently was approved for the prevention of maternal-fetal HIV-1 transmission. In February 1994, results from the Pediatric AIDS Clinical Trials Group indicated a 67 percent reduction in perinatal HIV transmission using ZDV. Two months later, the CDC issued provisional guidelines supporting the use of the therapy for this purpose, followed by formal FDA approval, and finally published consensus recommendations jointly issued by the
Antiretroviral use for the purpose of preventing perinatal HIV transmission has increased dramatically in the United States, and transmission rates have diminished. One multi-state study determined that from 1993 – before approval of ZDV for the specific indication – to post-approval in 1996, infected pregnant women were increasingly offered ZDV over other therapies. The authors asserted that “the proportion of HIV-infected pregnant women offered prenatal ZDV increased from 27 percent to 85 percent, the proportion offered intra-partum ZDV increased from 5 percent to 75 percent, and the proportion offered neonatal ZDV increased from 5 percent to 76 percent.” The expanded use of ZDV for this subsequent indication has contributed dramatically to driving maternal HIV transmission rates down from 30 percent to less than two percent. (See Figure 3.)

The updated HHS guidelines specifically encourage the treatment of infected pregnant women to prevent maternal-fetal HIV-1 transmission. The guidelines now recommend that a combination regimen be initiated in all infected pregnant women – even those who would not be candidates based on their own clinical presentation – with the goal of preventing perinatal transmission of HIV to the fetus. This updated recommendation reflects a focus on decreasing maternal-fetal HIV transmission, and therefore an emerging consideration of risk to both a mother and her fetus.

Based on these kinds of clinical observations, physicians and patients can make more informed decisions today about the differential risks and rewards of regimens with similar approved indication profiles. Furthermore, because guidelines now support the use of antiretroviral therapies for the prevention of maternal-fetal HIV-1 transmission, physicians and patients together can consider and select the optimal therapy regimen based on family planning and risk to a woman’s fetus. This is another example of incremental research leading to increased utility and optimized treatment selection that was not proven at the time of approval of certain therapies like ZDV.

Prevention of HIV Infection in High-Risk Populations
Building on the successful use of ART in the prevention of maternal-fetal HIV-1 transmission, researchers have worked to establish the use of these therapies to help prevent HIV infection in high-risk populations. Recent evidence has led to the approval of emtricitabine/tenofovir disoproxil fumarate (Truvada) in July 2012 for the prevention of HIV/AIDS in uninfected people, or pre-exposure prophylaxis (PrEP). This is the first approval of its kind.

Emtricitabine/tenofovir disoproxil fumarate is already approved, in combination with other antiretroviral agents, for treatment of HIV-1 infection in adults and pediatric patients ages 12 and older. It will now be used, in combination with safe sex practices and other prevention strategies, by uninfected individuals who are at high risk of HIV infection and who may engage in sexual activity with HIV-infected partners.

The new indication was approved based on two large clinical trials. The iPrEx trial conducted by the National Institute of Allergy and Infectious Diseases (NIAID) found that a once-daily oral dose of emtricitabine/tenofovir disoproxil fumarate provided protective efficacy of 44 percent among men and transgender women who have sex
with men compared with placebo. Efficacy was strongly connected with adherence; participants who took PrEP medication on 90 percent or more days during the treatment period had an estimated 73 percent HIV risk reduction, while those who took PrEP medication on more than 50 percent of days had an estimated 50 percent HIV risk reduction.18 (See Figure 4.)

A study conducted by the CDC among heterosexual men and women in Botswana showed that emtricitabine/tenofovir disoproxil fumarate reduced the risk of acquiring HIV infection by 62 percent.19 The Partners PrEP study indicated a reduced risk of transmission from one partner to the other of 75 percent when compared to placebo.16 This study, with clinical sites in Kenya and Uganda, was conducted among heterosexual couples where one partner is HIV positive.

CONCLUSION

This paper illustrates the substantial clinical gains that have been made in the treatment of HIV/AIDS, and some of the important factors in these gains, over the past two decades. HIV/AIDS has evolved from a lethal disease to one that is chronic, manageable, and preventable for patients who have access to medicines. Mortality rates related to HIV infection are at an all-time low, and the availability of multiple antiretroviral options allows physicians to select the optimal combination regimen to achieve undetectable viral load and to prevent or delay the development of drug resistance. Even patients who have failed prior treatment regimens or suffer from drug-resistant virus can generally achieve positive outcomes with today’s extensive therapy options.

These gains have been made slowly but steadily through a complex process of “step-wise transformation” that involves introduction of a series of incremental improvements in treatment over time. The introduction of new medicines is clearly fundamental to advancing treatment. However, this paper focuses on another important, but less recognized aspect of medical progress: the evolution of our understanding of value of new medicines over time through continued research and use in real-world clinical practice.

Over the past two decades, a greater understanding has evolved of the optimal clinical role and value of new HIV treatments, both alone and in different combination therapies, as well as the value of their utilization at earlier stages of the disease cycle. Early combination regimens are recognized to offer the best opportunity for disease control and remission. What is more, many of these treatments have been shown to provide previously unrecognized benefit in a variety of new preventative and prophylactic indications. For example, certain antiretrovirals now provide tremendous opportunity for the management of pregnant women who are infected with HIV and some have been shown to prevent infection in adults.

It is important to recognize that these broader benefits are frequently not proven at the time of initial FDA approval. An assessment based on available evidence at the time of launch would have substantially underestimated the full clinical value of these treatments to patients with HIV/AIDS. Over time, real-world practical experience and a growing body of published clinical data documenting this experience have revealed unforeseen elements of value for individual therapies. Because the optimal role
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Policymakers can foster this continued progress, and the evolution of knowledge that supports it. Policy approaches that seek to assess the definitive value of a therapy at the time of introduction will fail to capture its full value over time and will act as a disincentive to long-term research, innovation, and patient care. On the other hand, flexible policies that are sensitive to the way the evidence of value emerges over time will help ensure that new treatments are properly valued and available to patients. Such policies, which are in line with the incremental scientific process, will also promote future advances by properly incentivizing innovation. Continued innovation and evolution with both existing and as-yet undiscovered therapies provide hope for future clinical advances that will benefit individual patients and society as a whole.

ENDNOTES


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White Paper | December 2012