The Value of Innovation in HIV/AIDS Therapy

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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 at the time of initial diagnosis, to a chronic condition. In the United States, death rates from HIV infection have fallen by close to 85 percent since peaking in 1995, including a reduction of 14 percent between 2009 and 2010 alone, as a result of highly active antiretroviral therapy (ART) and other new medications. Advances in treatment options have helped to increase survival, slow progression, prevent hospitalizations, and allow patients to lead full lives. These clinical improvements, credited to the novel treatment options now available for HIV/AIDS treatment, have been far greater than what was anticipated at the time of the initial introduction of these 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 several decades. Although not well-characterized or understood, progress has resulted from the step-wise accumulation of treatment improvements over time, as research has continued to build a substantial body of evidence that has driven changes in HIV treatment over time. Our understanding of how certain novel therapies may be optimally applied to patient care has changed and improved as HIV therapies have been introduced and evaluated in real-world clinical practice. This has resulted in new approaches to treatment, thereby leading to increases in efficacy and tolerability. The key element to ensuring continued, and at times unexpected, innovation that drives improved patient outcomes is to ensure access to a wide range of therapeutic options. This access supports the step-wise process that has been central to clinical gains made in HIV treatment and many other disease areas, and has enabled Americans to live longer and healthier than ever before.

Medical progress with individual compounds or regimens is often realized gradually over time. Therefore, the optimal role and full value of a therapy typically cannot be known at the time of FDA (Food and Drug Administration) approval or at the time of 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.

The rigorous, controlled clinical trials required under FDA’s market review process provide for explicit efficacy and safety data to support approvals of indications. However, this research often fails to capture the broader and longer-term clinical and quality-of-life benefits that may be associated with a specific therapy or regimen as physicians accumulate evidence while using new regimens in real-world settings.

This white paper is part of a series of papers focused on recognizing value in biopharmaceutical innovation. Previous white papers, Recognizing Value in Oncology Innovation (June 2012) and Recognizing the Value of Innovation in the Treatment of Rheumatoid Arthritis (March 2013), demonstrated how the full clinical value of many therapies typically evolves significantly after FDA approval. These reports illustrate how for many therapies additional clinical value is realized based on real-world experience beyond what was 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 35 million people globally; the U.S. Centers for Disease Control and Prevention (CDC) estimates that 1.1 million people in the United States are currently living with HIV. In people infected with HIV, the virus gradually compromises the immune system by entering and taking over T-cell lymphocytes. The adoption of ART to treat HIV/AIDS, which started in the 1990s, has led to sharp mortality declines and a greatly improved quality of life for those affected. These medicines have fundamentally changed HIV from an acute, often advance-stage and fatal illness at the time of initial diagnosis, to a manageable chronic disease.
In this white paper, an update from 2012, we will explore the treatment of HIV/AIDS and highlight the various ways in which additional clinical value — including improved survival and quality of life — has been realized over time. The pathways identified here show some of the ways a medicine’s value changes over time, including a few that are shared in common with cancer treatments, as discussed in the previous white paper:

- Use in combination with other agents
- Use earlier in treatment line and earlier in disease state
- Use in different disease 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, ART regimens have been proven to be effective in a broader cohort of patients than were represented in the clinical trial data submitted for initial FDA approval of individual agents. 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 evaluated 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.

**COMBINATION THERAPY**

*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, by reducing the probability of drug resistant mutations emerging.*

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 (ART) describes a type of combination regimen used in HIV/AIDS treatment that typically includes combinations from four distinct classes of antiretroviral active against HIV:

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*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.*
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 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 number of ART combinations, which today yield improved efficacy and better tolerability and safety profiles than ever before.

Since 1996, ART combination regimens have significantly reduced the mortality rate of HIV-infected patients. According to CDC data from 2013, the age-adjusted number of deaths per 100,000 due to HIV in the United States has decreased by close to 85 percent over the last two decades. Additionally, HIV was the number one cause of death for persons 25-44 years old in 1994 and 1995 and has since decreased to the 7th leading cause of death in 2010, with the last published trend suggesting HIV mortality in this age group may soon drop below nearly equivalent rates associated with stroke, diabetes, and chronic liver disease. The Kaiser Family Foundation stated this dramatic improvement was “largely due to [the adoption of] highly active antiretroviral therapy.” Nearly 40 antiretroviral drugs for HIV have been developed and approved since 1987, arming physicians with increasingly more therapeutic options that result in improvements in patient survival.

Over time, moving from the pre-ART era, in which no ART regimens were available, to the early- and late-ART eras, during which more antiretroviral therapies were developed and new combinations were tested, respectively, 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, a process that continues today.

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-ART (1995-96), early-ART (1997-99), and late-ART (2000-05) eras. In these distinct phases new medicines became available and researchers rapidly discovered and tested 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-ART period, falling to 38 per 1,000 person-years in the early-ART period, and further to 25 per 1,000 person-years in the late-ART period. These data support the hypothesis that developing and making available more therapeutic options provides the necessary environment for clinical breakthroughs as new regimens of combination therapies are tested over time.

An examination of the death-rates among HIV-infected individuals over the stages described above (pre-ART, early-ART, and late-ART) 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 ART therapies increased through the 1990s (See Figure 2).

Since the 1990s, certain ART regimens have yielded better outcomes in HIV patients as their use has been refined to address the needs of real-world patient populations. An analysis presented in 2008 at the 9th International Congress on Drug Therapy in HIV Infection compared the efficacy of first-line ART regimens in 2006 to those used in 1998. The analysis included 146 patients starting first-line ART 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 ART dosing that have led to simpler regimens with reduced pill burden on patients. These treatments combine two or more antiretroviral medications into one dosage form with the same clinical impact, meaning that rather than taking multiple doses of different medicines at different times in a day, a patient only needs to take one dose, resulting in improved adherence.11

**EARLIER USE OF NEW THERAPIES IN DISEASE MANAGEMENT**

*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 other 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 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 2014 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.12 In HIV-infected individuals
who are not treated adequately, CD4 counts generally decrease as HIV progresses and these individuals will eventually develop progressive immunosuppression, ultimately leading to AIDS-defining illnesses and premature death.12 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 proven short- and long-term benefits.

The median CD4 count for newly diagnosed patients is around 200 cells/mm³. However, in their most recent guidelines both the HHS Guideline Panel12 and the World Health Organization (WHO)13 gave their highest recommendations that ART be initiated in all patients with a CD4 count as high as 500 cells/mm³. These guidelines reflect evidence from studies that reveal ART improves survival and delays disease progression in patients with a CD4 count of less than 200 cells/mm³ and/or history of an AIDS-defining condition.12 Early treatment also reduces the risk of sexual transmission of HIV. One study estimated that early treatment with ART prevented 188,000 cases of HIV in the United States from 1996 to 2009, and four-fifths of these cases were prevented due to “very early” treatment (with CD4 counts greater than 500 cells/mm³).14

The HHS Guideline Panel based its recommendation on several recent developments:

- A report from the recent NA-ACCORD cohort study15 demonstrating lower risk of death with initiation of ART at “pre-treatment” CD4 count levels greater than 500 cells/mm³.16
- The study observed patients who started treatment at CD4 counts greater than 500 cells/mm³ compared to patients who started treatment after CD4 counts dropped below 500 cells/mm³.
- The risk of death was 94 percent higher among the 6,935 patients who deferred therapy until CD4 count fell to less than 500 cells/mm³ compared with the mortality rate in the 2,200 patients who started therapy while CD4 count was greater than 500 cells/mm³.16
- 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.
- Availability of antiretroviral regimens that are more effective, more convenient, and better tolerated than antiretroviral combinations no longer in use.
- Public health benefit of earlier initiation of ART in reducing HIV transmission.
  - The HIV Prevention Trials Network (HPTN) 052 trial enrolled nearly 2,000 HIV-1 serodiscordant couples, in which one partner is HIV positive and one is not, across the globe to assess the effect of immediate treatment versus delayed therapy (not started until CD4 count is less than 250 cells/mm³) on HIV transmission.12
  - Twenty-eight linked HIV transmission events were identified during the study period, but only one event occurred in the early therapy arm, thus there was a 96 percent reduction in transmission associated with early ART.12

Furthermore, the WHO Guidelines Development Group cites early evidence that expanding the ART eligibility criteria to initiate treatment at 500 cells/mm³ or less could not only lead to substantial health benefits, but also may be cost-effective. Although earlier ART would mean increased costs initially, they may be offset by reduced costs attributed to decreased hospitalizations, increase productivity, and prevention of new infections.13

Citing its own evolution in perspectives over time, the HHS 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.12 The 2013 WHO Guidelines Development Group13 agreed that longer follow-up is needed to evaluate the potential harms and benefits. Both groups concluded that increasing evidence supports earlier initiation of ART.
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 drug classes in some other disease areas (e.g., oncology), even in this area, the 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 (commonly referred to as “mother-to-child transmission,” or MTCT).

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 U.S. Public Health Service Task Force (USPHSTF) and CDC.

Antiretroviral use for the purpose of preventing MTCT 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 2 percent. The 2013 WHO guidelines as well as the updated HHS guidelines recommend the treatment of all infected pregnant and breastfeeding women to prevent maternal-fetal HIV-1 transmission — even those who would not be candidates based on their own clinical presentation. These updated recommendations reflect a focus on decreasing maternal-fetal HIV transmission, and therefore an emerging consideration of risk to both a mother and her fetus.

The WHO guidelines recommend two specific options for this population:

- Providing lifelong ART to all pregnant and breastfeeding women living with HIV regardless of CD4 count or clinical stage.
• Providing a triple-drug ART drug regimen as prophylaxis for pregnant and breastfeeding women with HIV during the mother-to-child transmission risk period and then continuing lifelong ART for those women eligible for treatment for their own health.13

Based on these kinds of clinical observations, physicians and patients can make more informed decisions today about which particular regimens are most appropriate for a given patient based on the expanded indication profiles. Furthermore, because clinical guidelines now support the use of ART for the prevention of maternal-fetal HIV-1 transmission, physicians and patients together can consider and select the optimal therapy regimen. This is another example of how incremental research has resulted in increased utility and optimized treatment selection that was not anticipated 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. In July 2012, evidence led to the approval of emtricitabine/tenofovir disoproxil fumarate (FTC-TDF/Truvada®) as a measure for the prevention of HIV/AIDS in uninfected people, or pre-exposure prophylaxis (PrEP). FTC-TDF is already approved, in combination with other antiretroviral agents, for treatment of HIV-1 infection in adults and pediatric patients ages 12 and older.21 It will now be used in combination with safer 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.22

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 FTC-TDF 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.23 (See Figure 4.)

Similarly, the TDF2 study conducted by the CDC among heterosexual men and women in Botswana showed that FTC-TDF reduced the risk of acquiring HIV infection by 62 percent.24 The Partners PrEP study indicated a reduced risk of transmission from one partner to the other of 75 percent when compared to placebo.21 This study, with clinical sites in Kenya and Uganda, was conducted among heterosexual couples where one partner is HIV positive.

The recently released 2014 WHO guidelines for key populations recommend that men who have sex with men (MSM) consider PrEP as a part of a comprehensive HIV prevention package.25 This is the first recommendation of its kind and signifies increasing support for PrEP in populations that are disproportionally affected by HIV. The WHO guidelines are in line with those released by the CDC in early 2014 that suggest HIV-negative individuals who are at a “substantial risk for HIV infection” consider the use of PrEP as a prevention option. The CDC defines those populations as men who have sex with men, heterosexual men and women, and injection drug users.26
The recommendations are based on robust safety and efficacy evidence from a series of clinical trials that analyzed PrEP use in high-risk populations which showed that patients with high adherence of daily oral TDF (taking a pill at least 71 percent of days and missing no more than two consecutive doses) had a reduced risk of infection of 74 percent. In addition to use of PrEP, all trial participants (including those in drug treatment group and those in placebo group) were supplied with and regularly encouraged to use condoms, and received sexual risk-reduction counseling, as well as regular testing and treatment of sexually transmitted infection.

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 and manageable 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. Furthermore, these regimens are being simplified into a single oral fixed-dose combination that is easier to take and has fewer side effects, facilitating better adherence to antiviral drugs and reducing costly hospitalizations. Even patients who have failed prior treatments 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”, which involves introduction of a series of cumulative improvements in treatment over time. The introduction of new medicines to expand treatment options for patients is fundamental to achieving progress against diseases like HIV/AIDS. 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 of the optimal clinical role and value of new HIV treatments has evolved, revealing additional value of their use, alone and in different combination regimens, as well as in earlier stages of the disease cycle. Early combination treatments are recognized to offer the best opportunity for disease control and remission. In addition, many of these treatments have been shown to provide previously unrecognized benefit in a variety of new preventive and prophylactic indications. For example, certain antiretrovirals now provide tremendous opportunity for the prevention of fetal transmission in 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 fully recognized 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 previously undocumented value for individual therapies. Because the optimal role and full value of an individual therapy cannot be known at the time of FDA approval — for HIV and other disease areas — it is important that patients, and the clinicians who care for them, have access to a full range of treatment options, and the incentive to continually add to the therapeutic armamentarium. At the conclusion of the 2014 International AIDS conference, researchers expressed optimism when talking about future progress in the search for cures or treatments for HIV disease. The meeting highlighted the continued need for rigorous research targeted at multiple disease targets and endpoints, including vaccines, therapies targeted at inducing remission, and therapies targeted at disease eradication and cure. The consensus remains that there is work to be done.27

Policymakers can foster this continued progress, and the evolution of knowledge that supports it. Policy approaches that seek to limit the defined value of a therapy to data available 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 value emerges over time will help ensure that new treatments are properly valued and available to patients. Such policies, which are in line with continuous scientific progress, 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.

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ENDNOTES

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