Evidence-Based Health Benefits Management: Strategies to Optimize Antiretroviral Medication Adherence and Outcomes in HIV/AIDS

RICHARD A. ZABINSKI, PharmD

ABSTRACT

OBJECTIVE: To review how evidence-based principles can be applied to benefit design, specialty network management, and medication therapy management to successfully manage pharmaceutical benefits for patients infected with human immunodeficiency virus (HIV).

SUMMARY: The most critical barrier to successfully managing HIV disease is suboptimal patient adherence to antiretroviral therapy. Managing HIV infection is unique in that the risk of treatment failure increases remarkably with even relatively minor lapses in patient adherence. The incremental cost of HIV treatment failure has been approximated at \$26,000 per patient per year. Treatment failure, of course, also drives mortality related to HIV and acquired immunodeficiency syndrome (AIDS). Benefit design, specialty medication management strategies, and care management programs can be integrated to deliver high-quality, efficient care that optimizes clinical outcomes for populations of HIV-infected individuals.

CONCLUSION: Managed care programs can be structured to provide HIV care that allows optimal patient adherence and clinical outcomes.

KEYWORDS: HIV/AIDS, Antiretroviral therapy, Medication adherence, Benefits management

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Author

RICHARD A. ZABINSKI, PharmD, is vice president, Pharmaceutical Solutions, Health Solutions Group, UnitedHealthcare Corporation, Golden Valley, Minnesota. He is also president-elect of the Academy of Managed Care Pharmacy.

AUTHOR CORRESPONDENCE: Richard A. Zabinski, PharmD, Vice President, Pharmaceutical Solutions, Health Solutions Group, UnitedHealthcare Corporation, 6300 Olson Memorial Hwy. MN010-E133, Golden Valley, MN 55427. Tel: (763) 797-2642; Fax: (763) 797-2532; E-mail: richard_a_zabinski@uhc.com

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An integrated approach to health benefits management is essential to optimizing the quality and efficiency of pharmaceutical care. Such an approach is particularly important when managing care for patients infected with human immunodeficiency virus (HIV) and acquired immunodeficiency syndrome (AIDS). Since the introduction of multidrug, highly active antiretroviral therapy (HAART), the mortality rate for persons with HIV/AIDS has declined. Effective antiretroviral drug regimens have changed the consequences of HIV infection from an inevitable death sentence to a manageable chronic illness.

However, in order for long-term treatment of HIV infection to be effective, a high degree of patient adherence to antiretroviral drug regimens must be achieved. Unfortunately, the complexity and tolerability of HAART therapy have challenged patients' ability to maintain optimal adherence. As shown in Figure 1, even relatively small declines of 25% in patient adherence to antiretroviral treatment increase the rate of treatment failure.¹ High but suboptimal levels of adherence can expose HIV to subinhibitory drug concentrations and thereby open the door to viral mutations and antiretroviral drug resistance. As a result, suboptimal patient adherence to treatment increases the economic burden of managing HIV/AIDS.

FIGURE 1 Relation Between Adherence and Treatment Failure

Relationship between patient adherence and antiretroviral treatment failure. In a study investigating the relationship between patient adherence and treatment failure, regardless of the regimen used, even relatively small declines in patient adherence to antiretroviral treatment increase rate of treatment failure. Adapted from Maggiolo et al. *Clin Infect Dis.* 2005;40:158-63. NNRTI=nonnucleoside reverse transcriptase inhibitor; PI=protease inhibitor.

Benefit design, specialty network management, and pharmaceutical care programs play pivotal roles in addressing the issue of patient adherence to treatment and in optimizing HIV-related outcomes. Evidence-based principles form the foundation of each of these components in the delivery of a total health care benefit solution. Prescription drug list (PDL) tier placement should represent a drug's total health care value, which is driven by pharmacoeconomic evidence, clinical effectiveness, and net acquisition cost. Specialty medication networks should be formed around evidence-based metrics that integrate clinical, economic, and humanistic outcomes. In addition, care management, disease management, and medication therapy management programs need to be driven by the very same evidence-based criteria and case assessments. The purpose of this report is to describe how these principles can be applied to successfully managing pharmaceutical benefits for HIV-infected patients.

Economic Burden of Antiretroviral Nonadherence

Antiretroviral medications are a prime example of drugs that provide a good return on investment. According to Bozzette et al.,² HIV-associated drug costs have steadily increased as a percentage of total HIV-related health care spending (Figure 2). While the cost of drug therapy has increased in this population, the total cost of managing HIV has declined—from about \$1,800 per patient per month (PPPM) in 1996 to just more than \$1,500 PPPM in 1999. Viewed from a managed care perspective, such data show that antiretroviral medications represent a sound return on investment and an excellent example of pharmaceutical value.

Suboptimal adherence to treatment has serious consequences for the HIV-infected patient. The resultant decline in immune status, as indicated by a fall in the CD4+ cell count, signals disease progression, and as the rate of treatment failure increases, the overall costs of treatment subsequently increase. Another finding in the study by Bozzette et al.² showed that the cost of managing HIV-infected patients increases from \$500 PPPM to approximately \$2,500 PPPM when the CD4+ count drops from 500 cells/mm³ to less than 50 cells/mm³. That cost—the incremental cost of treatment failure—is approximately \$26,700 per year (adjusted to 2006 U.S. health care dollars).

Claims data can be used to identify patients who are non-adherent to medication. At any one time, 3% of HIV-treated enrollees are nonadherent (defined as a mean possession ratio of less than 0.85) to therapy (unpublished data; UnitedHealthcare, Edina, Minnesota; 2006). Applying this prevalence figure of 3% to the costs derived from the Bozzette study reveals that the estimated direct health care costs of antiretroviral medication nonadherence is \$0.03 PPPM. Moreover, applying this nonadherence rate to the estimated life expectancy after an HIV diagnosis (20 years) and to the yearly earnings of HIV-infected workers (\$32,400) correlates to an estimated humanistic burden of 31.4 quality-adjusted life-years per 100,000 covered lives and an associated annual loss in productivity of \$1.02 million.

FIGURE 2 Average Monthly Expenditures for Care of HIV-Infected Adults

Average monthly expenditures for the care of human immunodeficiency virus (HIV)-infected adults. Cost of care data from approximately 231,000 HIV-infected adults receiving care in the contiguous United States during the first 2 months of 1996 and followed until October 1998 (approximately 181,000 patients still alive at that point). Reprinted from Bozzette SA et al. *N Engl J Med.* 2001;344:817-23, with permission from Massachusetts Medical Society, Copyright© 2001.

FIGURE 3 What Drives HIV Medication Maladherence?

What drives patient nonadherence to antiretroviral therapy? In a survey of 299 HIV-infected patients, the main drivers of antiretroviral resistance was total pills per day, followed by dosing frequency and adverse effect. Copay was ranked seventh. Adapted from Stone et al., 2004.³

FIGURE 4 Formulary Design Needs to Be Based on Total Health Value

Flowchart for developing formulary design based on total health value.
 ER=emergency room; FDA=U.S. Food and Drug Administration;
 P&T=pharmacy and therapeutics; Rx=prescription.

Predictors of Nonadherence

To establish the determinants of patient adherence to antiretroviral therapy, Stone et al.³ surveyed 299 patients infected with HIV on their opinions regarding 7 diverse HAART regimens, with each regimen rated according to 10 different attributes: number of pills (i.e., tablets and capsules) per day; tablet and capsule size; adverse effects; dietary restrictions; dosing frequency; need for dosing at bedtime; and the number of prescriptions, refills, medicine bottles, and required copayments. The survey results suggested that the main driver of antiretroviral adherence was “total pills per day,” followed by “dosing frequency” and “adverse effects” (Figure 3). Respondents most preferred the regimen choice that included 2 pills twice daily with no food restrictions, 1 prescription, 1 refill, 1 medication bottle, and 1 copayment. (A fully once-daily regimen was not available at the time of the survey and thus was not an option.)

Although copayments ranked seventh in importance in the survey by Stone et al., a more recent study by Shrank et al.⁴ found that formulary tier status was the leading predictor of adherence in a general population of health plan enrollees (i.e., the study was not specific to HIV-infected patients). Generic drugs were most strongly correlated with adherence (odds ratio [OR] 1.62; 95% confidence interval [CI], 1.39-1.89), followed by preferred brands (OR 1.3; 95% CI, 1.15-1.47). Other drivers of adherence were annual income and male gender; that is, higher rates of adherence are more likely in men and in those who have higher incomes. Differences in the findings from this study with those of Stone et al. may indicate that, relative to a general population of health

plan enrollees, medication adherence among HIV-infected enrollees is less sensitive to formulary tier status and the associated member cost share.

Benefit Designs for Optimizing Outcomes

Designing simplified, easy-to-understand benefit plans for the HIV-infected patient is another way to optimize treatment outcomes. Benefit design needs to be based on total health value (Figure 4). Formulary (or PDL) tier placement should represent a drug's total health care value based on pharmacoeconomic evidence, clinical effectiveness, and net acquisition cost. If coordinated with effective consumer communication strategies, PDL placement can drive consumer decision making. In cases where a class of drugs is known to have great value (e.g., insulin and insulin test strips), and copayments could be a barrier to adherence, managed care organizations may even position branded products as first tier. This strategy drives total health care value when applied to therapeutic categories associated with both medication adherence issues and relatively large offsets in direct and indirect health care costs.

HIV Treatment: Progress and Continued Challenges

Treatment for HIV infection has advanced rapidly in the past decade. In 1996, 10 tablets or capsules 3 times daily was a typical regimen. Today, once-daily antiretroviral regimens with as few as 1 pill a day represent the standard of care. This evolution in the treatment of HIV infection has ameliorated the 2 biggest drivers of antiretroviral medication nonadherence: pill burden and dosing frequency.

Progress has also been made in reducing the adverse effects of antiretroviral therapies that have been associated with suboptimal adherence and treatment discontinuation. However, toxicity issues with many antiretroviral therapies remain an important consideration in the design of highly effective drug regimens. In 1998, Munk⁵ showed that the common side effects associated with antiretroviral drugs—vomiting, nausea, diarrhea, headache, and fatigue—are all causes of missed doses, which subsequently lead to treatment failure and drug resistance.

Clinical research has shown that different combinations of antiretroviral drugs can have substantially different short- and long-term side-effect profiles. With more persons surviving HIV infection because of newer and more effective treatments, the long-term drug toxicities, such as those that impact cardiovascular risk, have become an important focus of HIV clinicians.⁶ In an efficacy and safety randomized controlled trial by Gallant et al.,⁷ 600 treatment-naïve patients received either tenofovir disoproxil fumarate (DF) (n=299) or stavudine (n=301) in combination with 2 other antiretroviral drugs. In an analysis of treatment effect on serum lipid levels, which was a secondary study end point, marked differences were noted between the tenofovir DF and stavudine treatment arms with respect to increases in triglyceride and cholesterol

levels. After 3 years of follow-up, 3 times as many patients treated with the stavudine-containing regimen experienced lipid abnormalities requiring treatment with lipid-lowering agents (Figure 5).⁸ Further, the results of a 48-week extension of this study reported by Madruga et al. demonstrated that stavudine-induced serum lipid abnormalities could be reversed by switching patients to a tenofovir-containing regimen.⁹ The 85 patients evaluated in this extension study by Madruga et al. had received the stavudine-containing regimen for a median duration of 152 weeks prior to being switched over into the tenofovir DF treatment arm.

The research published by Gallant and Madruga have major implications for managed care. Claims analyses of UnitedHealthcare databases revealed that 22% of 355 patients on antiretroviral treatment were also being prescribed lipid-lowering drugs, which not only directly increases the cost of care but also indirectly increases the cost because of the potential for unwanted drug-drug interactions (unpublished data; UnitedHealthcare, Edina, Minnesota; 2006). Of these, 74% of patients were being treated with antiretroviral agents most associated with lipid abnormalities (i.e., zalcitabine, didanosine, stavudine, or zidovudine). Such claims data analyses can help to identify treatment gaps and can be used as opportunities to provide information to patients and physicians to improve outcomes.

Anemia is another side effect of certain antiretroviral agents, particularly zidovudine. A recently reported study of treatment-related anemia showed that hemoglobin and hematocrit levels dropped significantly following treatment initiation with regimens that contained zidovudine.¹⁰ Claims analyses have shown that 2% of HIV-infected patients are prescribed recombinant erythropoietin (EPO) to treat their anemia. Twenty-eight percent of these EPO users concomitantly received a zidovudine-containing regimen (unpublished data; UnitedHealthcare, Edina, Minnesota; 2006).

■ Evidence-Based Clinical Programs

Total health benefit management involves integrating evidence-based decision making into both clinical programs and benefit design to optimize the quality and efficiency of pharmaceutical care. Evidence-based medicine (EBM) criteria applied to claims databases can form the basis for integrating care coordination, disease management, and medication therapy management programs. EBM criteria may be used to identify cases of antiretroviral medication nonadherence, missing laboratory values (e.g., CD4+ count and viral load measurements), and lapsed clinic visits.

■ An Example of Clinical Care Integration

The following case demonstrates how evidence-based clinical programs can be integrated to optimize the quality and efficiency of pharmaceutical care for an HIV-infected enrollee.

EJ is a 43-year-old man with a diagnostic history of HIV/AIDS, depression, *Pneumocystis carinii* pneumonia (PCP), and oropharyngeal candidiasis. A query of his prescription drug claims history revealed that EJ was being treated with a HAART regimen,

FIGURE 5 Time to First Lipid-Lowering Drug

Comparison of antiretroviral drug regimens for time from start of treatment to use of first lipid-lowering agent. Adapted from Gallant et al., 2004.⁸

comprising zidovudine and lamivudine (Epivir) plus efavirenz (Sustiva), along with recombinant erythropoietin (Procrit), escitalopram (Lexapro), clarithromycin, lansoprazole (Prevacid), trimethoprim-sulfamethoxazole, and fenofibrate (Tricor). A proprietary EBM-rules engine identified 2 treatment gaps: the patient appeared to be nonadherent to efavirenz and to be concomitantly receiving zidovudine and erythropoietin. In addition to these treatment gaps, the rules engine revealed 2 opportunities on which EJ could act to reduce his out-of-pocket prescription drug expenses. If deemed appropriate by EJ and his physician, EJ could save money by using omeprazole (Prilosec OTC) rather than Prevacid and by participating in his health plan's Lexapro tablet-splitting program. Medication therapy management letters were sent to EJ and each of his prescribing physicians to inform them of the treatment gaps and savings opportunities identified by the EBM-rules engine.

In addition to the information mailed to EJ and his physicians, EJ also received a customer service call from his health plan representative, during which EJ participated in an interactive voice response (IVR)-based assessment of his medication utilization patterns. The IVR-based assessment revealed 2 causes of EJ's problems with medication adherence: (1) taking medications more than once a day is inconvenient for EJ and (2) sometimes he just forgets to take his medications as prescribed. Based on this assessment, the IVR system delivered customized advice that EJ could use to stay more adherent with his antiretroviral therapy. As a follow-up to the phone call, EJ's health plan mailed to him the results of the IVR-based assessment, along with customized medication adherence "helpful hints."

On receiving the results of his IVR-based assessment, EJ called his plan's health information support line. The health information nurse confirmed EJ's HIV diagnosis and provided him with coaching related to his health conditions, particularly stressing

the importance of adhering to his HAART regimen. The nurse also advised EJ to visit his HIV physician every 6 months and reinforced the money-saving advice that EJ received in the medication therapy management letters (i.e., the advice to use an over-the-counter alternative to Prevacid and to use tablet-splitting with Lexapro). Finally, the nurse guided EJ to his health plan's Web site where he could access other information about the health conditions and services available to health plan enrollees.

Conclusions

Recent advancements in the treatment of HIV infection have dramatically improved survival rates among those infected with the virus. HIV has been transformed from a death sentence to a chronic condition that can be effectively managed through treatment. Today, the most critical barrier to successfully managing HIV disease is suboptimal patient adherence to antiretroviral therapy. Managing HIV infection is unique in that the risk of treatment failure increases remarkably with even relatively minor lapses in patient adherence. Treatment failure has been shown to increase by 13% when patient adherence falls to 75%.¹ This drop-off in adherence also drives HIV drug resistance, which, in turn, further increases the total cost of managing this disease.

The incremental cost of HIV treatment failure has been approximated at \$26,000 per patient per year. Treatment failure, of course, also drives HIV/AIDS-related mortality. Benefit design, specialty medication management strategies, and care management programs can be integrated to deliver high-quality, efficient care to HIV-infected patients that reduces the risk of treatment failure.

DISCLOSURES

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