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Cost Prevention of HIV

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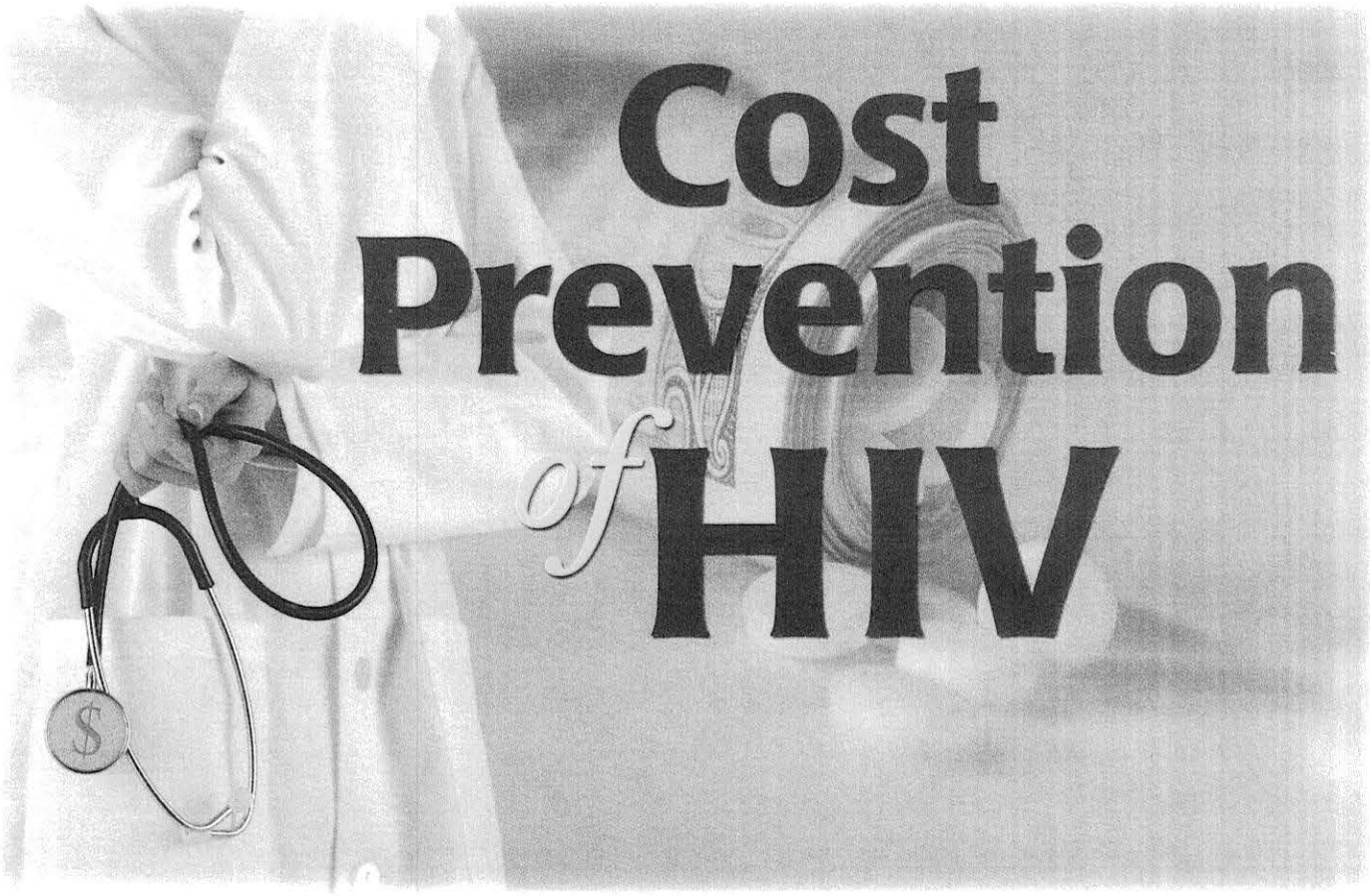


by Jerika T. Lam, PharmD

Introduction

Since the introduction of highly active antiretroviral therapy (HAART) in the late 1990s, management of patients with human immunodeficiency virus (HIV) infection has improved where they are living longer and with fewer incidences of opportunistic illnesses. Furthermore, significant progress has been made in the understanding of the disease, the ability to quantify viral load and correlate with clinical outcomes, genotypic and phenotypic resistance assays designed to assess viral susceptibility, and a heightened awareness and appreciation of the importance of treatment adherence to ensure virologic suppression.[1] In spite of the benefits that HIV-infected patients may have acquired in terms of more antiretroviral agents to select from and with more antiviral potency, the newer HAART regimens should not be overlooked as simple and tolerable medications. In fact, HAART regimens are ever more complex and challenging because of the high pill burden, drug-drug or drug-food interactions, formulation characteristics, and long-term drug class-associated side effects. While the goal of HIV therapy is to achieve maximal viral load suppression to undetectable levels (<50 copies/ml) and to improve and stabilize the immune system (CD4 cell count >250 cells/mm^3), successful pharmacologic management has become difficult due to a continued high rate of treatment non-adherence. Consequently, viral resistance to several HAART regimens inevitably develops, which ultimately leads to drug failure.

High Costs Associated with HIV Therapy

Drug therapy, hospitalizations, and other comorbidities or coinfections (e.g. hepatitis C) all affect the cost and health care utilization. Published guidelines from the Department of Health and Human Services (DHHS) presently recommend at least a three-drug antiretroviral regimen as the standard of care for the treatment of HIV-infected patients. HIV medications can be expensive, where prices for nucleosides range from approximately $2,500 per person, per year compared to $8,000 per person, per year for those receiving a protease inhibitor agent. Therefore, one could imagine the high costs associated with combination HIV therapy.

Several clinical trials have looked at the cost-effectiveness of combination HIV therapy, cost associated with life expectancy, life expectancy adjusted for the quality of life, lifetime direct medical costs, and cost effectiveness per quality-adjusted year of life gained. For instance, data from the AIDS Clinical Trial Group (ACTG) 320 delineate the cost differences between those HIV-infected patients who were treated on a three-drug regimen versus those who were untreated. The ACTG 320 trial showed that HIV-infected patients who had received zidovudine (AZT, ZDV), lamivudine (3TC), and indinavir (IDV) had an estimated per-person lifetime cost of $77,300 compared to $45,460 for those infected patients not receiving therapy. However, the life expectancy adjusted for the quality of life in those receiving therapy was 2.91 years versus 1.53 years in the untreated

group. The incremental cost per quality-adjusted year of life gained was $23,000 for the treated group versus untreated group.[2] In comparison, the Johns Hopkins HIV Clinic cohort trial demonstrated that the life expectancy adjusted for the quality of life increased from 2.92 to 4.43 years, and per person lifetime costs increased from $54,150 to $80,460 for those receiving the 3-drug regimen (AZT + 3TC + IDV) as compared to the untreated group. The incremental cost per quality-adjusted year of life gained, as compared with the untreated group, was $17,000.[3] On a similar note, Freedberg et al. reported that, even though, combination HIV therapy is costly, it is more cost effective than many other therapies such as the treatment of hypercholesterolemia ($47,000 per year of life gained), radiation therapy for early stage breast cancer ($30,000 per quality-adjusted year of life gained), and dialysis in patients expected to live for less than six months ($150,000 per quality-adjusted year of life gained).[4] These large, randomized clinical trials help to shed light into the costs and benefits of drug expenditures for HIV-infected patients. However, they do not incorporate the costs of other external, but very important variables such as long-term antiretroviral drug side effects and toxicities, routine care (e.g. genotypic and phenotypic resistance tests, viral loads, and CD4 cell counts), effects of interventions and tools designed to improve medication adherence and to reduce the rate of treatment failure.[4] These costs continue to require further elucidation.

Benefits of HIV therapy

Presently, several investigators have reported improved virologic and clinical outcomes for those who were HIV-infected and were initiated on combination HIV regimens. From these trials, enrolled patients who were appropriately treated benefited from decreased incidences of opportunistic infections, hospitalizations, and mortality.[1] Interestingly, though, one must remember that clinical trials represent a more ideal setting than what actually occurs in clinical practice. For instance, in a clinical trial, there are several factors that buttress the study design from failing such as the enrollment of motivated patients, consistent counseling of the study medications, and regulated monitoring and follow-up from various health disciplines.

Challenges in the Management of HIV

Patient adherence to HIV drugs continues to remain the ultimate challenge towards successful management of HIV. At the present, the complexity of HIV regimens, including their intolerable side effects (e.g. gastrointestinal, CNS, and neuromuscular) challenge health care providers to successfully help HIV-infected patients attain undetectable viral loads and an increased CD4 cell count. Evidence reports that poor adherence to HIV regimens results in an increased likelihood for developing viral resistance, clinical complications, and increased mortality.[5-7] Several studies have reported that HIV drug side effects pose as an infrequent reason for poor adherence. Gifford et al showed that organizational difficulties (e.g. too busy, forgetfulness, away from home, change in routine) and emotional issues were the most common reasons for missed doses among their patients, which comprised primarily of men (86%).[8] In studies that had looked at barriers to HIV regimen adherence among women, depressive symptoms, adverse life events, HIV-related stress, and care-giving commitments were significant factors.[9-10] Wilson et al. reported that among 895 women enrolled in their study, poor adherence was more associated to intravenous drug use, smoking, and having a lower quality of life.[11] Laine et al. found that among the 682 pregnant HIV-infected women evaluated for adherence, the adjusted odds ratio (AOR) for adherence was 70% lower than for older women (AOR, 0.34; 95% CI, 0.12-0.90) and 50% lower (P value = 0.01) for black or Hispanic women versus

Table 1. FDA-Approved Antiretroviral Agents

Generic Name	Brand Name	Usual Adult Dosages	Number of Pills/Capsules Daily
Nucleoside Reverse Transcriptase Inhibitors (NRTIs)			
Abacavir (ABC)	Ziagen®	300 mg BID or 600 mg daily	1-2
Didanosine (ddI)	Videx®, Videx® EC	>60 kg: 200 mg BID or 400 mg daily <60 kg: 125 mg BID or 250 mg daily	1-2
Emtricitabine (FTC)	Emtriva™	200 mg daily	1
Lamivudine (3TC)	Epivir®	150 mg BID or 300 mg daily	1-2
Stavudine (d4T)	Zerit®	>60 kg: 40 mg BID<60 kg: 30 mg BID	2
Tenofovir (TDF)	Viread®	300 mg daily	1
Zalcitabine (ddC)	Hivid®	0.75 mg TID	3
Zidovudine (AZT, ZDV)	Retrovir®	200 mg TID or 300 mg BID	2-6
Fixed-Dose Combination NRTIs			
AZT + 3TC	Combivir®	1 tab BID	2
AZT + 3TC + ABC	Trizivir®	1 tab BID	2
ABC + 3TC	Epzicom®	1 tablet daily	1
TDF + FTC	Truvada™	1 tablet daily	1
Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)			
Delavirdine (DLV)	Rescriptor®	400 mg TID or 600 mg BID	6
Efavirenz (EFV)	Sustiva®	600 mg QHS	1-3
Nevirapine (NVP)	Viramune®	200 mg BID	2
Protease Inhibitors (PIs)			
Amprenavir (APV)	Agenerase®	1200 mg BID	16
Atazanavir (ATV)	Reyataz®	400 mg daily	2
Fosamprenavir (FPV)	Lexiva™	1400 mg BID	4
Indinavir (IDV)	Crixivan®	800 mg Q8H	6-12
Lopinavir/Ritonavir (LPV/RTV)	Kaletra®	3 capsules BID	6
Nelfinavir (NFV)	Viracept®	1250 mg BID	4
Ritonavir (RTV)	Norvir®	600 mg BID	12
Saquinavir-HGC (hard gel capsule)	Invirase®	2000 mg daily + RTV 100 mg daily	5
Tipranavir	Aptivus®	500 mg BID + RTV 200 mg BID	8
Entry Fusion Inhibitor			
Enfuvirtide (T-20)	Fuzeon™	90 mg SQ BID	2

Table 2. DHHS Guidelines for Initiation of Therapy[32]

Clinical Category	CD4+ Cell Count and Plasma HIV-1 RNA	Recommendation
Symptomatic*	Any value	Treat
Asymptomatic	CD4+ <200 cells/mm^3	Treat
Asymptomatic	CD4+ >200 cells/mm^3 but <350 cells/mm^3	Treatment should be offered
Asymptomatic	CD4+ >350 cells/mm^3 & plasma HIV-1 RNA >100,000 copies/mL	Some clinicians defer therapy and monitor frequently
Asymptomatic	CD4+ >350 cells/mm^3 and HIV-1 RNA <100,000 copies/mL	Defer treatment

*AIDS-defining illnesses or malignancies and AIDS wasting
DHHS = Department of Health and Human Services

white women.[12-13] Of note, younger individuals, women, persons of minority ethnic backgrounds, and patients without health or Medicaid insurance were less likely to report good treatment adherence.[14] Similarly, other studies reported that female sex, younger age, African-American descent, alcohol abuse, and intravenous drug use were associated with poor treatment adherence.[6, 15-17]

While the goals of HIV therapy are to achieve maximum viral suppression and to maintain a robust immune system, factors such as viral mutations, poor drug absorption, sub-optimal drug exposures, drug-drug interactions, and non-adherence pose significant challenges for HIV pharmacotherapy specialists such as pharmacists.[18] It has been reported that greater than 95% treatment adherence is crucial for achieving satisfactory virologic suppression.[19] In order to ensure that HIV-infected patients are adherent to their treatments, pharmacists should employ tools, such as medication counseling, pill counts, appropriate dosing frequencies, monitoring for side effects and drug-drug or drug-food interactions, therapeutic monitoring of drug levels, and phone follow-ups for naïve-treated patients or those on complex regimens. Reiterating the reasons reported from several of the clinical trials discussed earlier in this article, factors that have been suggested to lead to treatment non-adherence include psychosocial factors (e.g. depression, alcohol abuse, and illicit or intravenous drug use), education factors (e.g. comprehension of the HIV disease, its progression if poorly treated, opportunistic infections, and the importance of HIV therapy), provider and healthcare-related factors (e.g. patient trust in the clinicians and medical staff), and clinical factors (e.g. pill burden, administration frequency, and drug toxicities).[18]

Antiretrovirals and Adverse Effects

There are certain toxicities that persist and become more evident with prolonged use (over years). These drug-associated toxicities are frequently class-related. Table 1 illustrates FDA-approved antiretroviral agents that are presently available. Adverse side effects may occur early in therapy and become transient. Many of the antiretroviral agents' side effects are common and are manageable with patient counseling, adjunctive treatments, and careful dose adjustment.[18] For instance, nausea and/or vomiting could be managed by taking the antiretroviral agent with food or at bedtime. Similarly, frequent diarrheal episodes could be managed with ingestion of over-the-counter calcium containing supplements (e.g. Tums) or Immodium®. Severe diarrhea could be further managed with prescription Lomotil®.

Nucleoside Reverse Transcriptase Inhibitors

As a class, nucleoside reverse transcriptase inhibitors (NRTIs) have been associated with mitochondrial toxicities, which could manifest as mild peripheral neuropathy to life-threatening lactic acidosis. Didanosine (ddI), stavudine (d4T), and zalcitabine (ddC), otherwise termed the "d" drugs, have been reported with increased rates of mild to moderate peripheral neuropathy. The incidence of mild to moderate peripheral neuropathy could occur anytime during HIV treatment, and may become ameliorated with low-dose tricyclic antidepressants (e.g. amitriptyline), anticonvulsants (e.g. gabapentin or lamotrigine), or with topical agents (e.g. capsaicin cream) if it persists. Abacavir (ABC) has been associated with a potentially fatal skin rash, also termed "abacavir hypersensitivity reaction," with manifestations such as severe nausea, fatigue, fever, and/or a blistering rash. Occurrence of these symptoms necessitates immediate discontinuation of abacavir. Re-challenge of patients who have experienced or suspected to have had an "abacavir hypersensitivity reaction" is contraindicated.[20]

Non-nucleoside Reverse Transcriptase Inhibitors

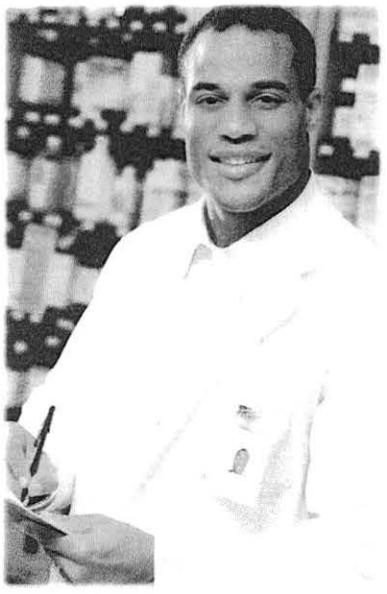
Non-nucleoside reverse transcriptase inhibitors (NNRTIs) have been associated with dermatologic manifestations such as skin rash. The rashes are usually mild and could often be treated with an antihistamine agent (e.g. Benadryl®). However, life-threatening and fatal rashes have been reported, where their manifestations closely resemble Stevens-Johnson Syndrome.[21] When these severe rashes occur, discontinuation of the suspected agent is imperative. Efavirenz is unlike delavirdine and nevirapine, where it has been reported to cause transient CNS effects that include vivid dreams or nightmares, somnolence, dizziness, and/or difficulty concentrating. Most of these side effects usually resolve between one to three weeks.[22]

Protease Inhibitors

Class adverse effects to the protease inhibitors (PIs) may be associated with long-term metabolic complications, which may manifest as lipodystrophy (abnormal fat redistribution), glucose intolerance, and hyperlipidemia.[23-24] Adverse effects of PIs include primarily the gastrointestinal system, where nausea, vomiting, bad taste, bloating, and diarrhea occur frequently in the initial weeks of drug therapy. Hepatitis, hyperbilirubinemia, nephrolithiasis, and paresthesias have been reported, however, their occurrences are not common.[25-27]

Fusion Inhibitor

Enfuvirtide (T-20, Fuzeon™) is currently the only agent available for the entry fusion inhibitor class. Furthermore, it is the only injectable antiretroviral agent that is administered subcutaneously. Common adverse effects from this agent include myalgias, fatigue, nausea, and injection site reactions (redness, itching, pain, swelling or tenderness). Hardened skin or bumps do occur, but not as frequent as the other side effects.



DHHS Guidelines for HIV Regimens

Currently, the DHHS guidelines recommend at least a three-drug regimen for stan-

Table 3. DHHS Recommendations for ARV Regimens in Treatment Naïve Patients[32]

Preferred Regimens	Regimens	Comments
NNRTI-Based	EFV + (3TC or FTC) + (AZT or TDF)	EFV is not recommended in 1st trimester of pregnancy or in women with high pregnancy potential
PI-Based	Kaletra® + (3TC or FTC) + AZT	
Alternative Regimens	**Regimens**	**Comments**
NNRTI-Based	•EFV + (3TC or FTC) + (ABC or ddI or d4T)	EFV is not recommended in 1st trimester of pregnancy or in women with high pregnancy potential
	•NVP + (3TC or FTC) + (AZT or ABC or ddI or d4T or TDF)	
PI-Based	•ATV + (3TC or FTC) + (AZT or ABC or ddI or d4T) or (TDF + RTV 100 mg/day) •FPV + (3TC or FTC) + (AZT or ABC or ddI or d4T or TDF) •FPV/RTV + (3TC or FTC) + (AZT or ABC or ddI or d4T or TDF) •IDV/RTV + (3TC or FTC) + (ABC or ddI or d4T or TDF) •NFV + (3TC or FTC) + (AZT or ABC or ddI or d4T or TDF) •SQV/RTV + (3TC or FTC) + (AZT or ABC or ddI or d4T or TDF)	
3 NRTI-Based	ABC + AZT + 3TC (Trizivir®)	Recommended only when a preferred or an alternative NNRTI- or PI-based regimen cannot or should not be used

dard HIV care (Table 3). Individualized HIV regimens should be considered so to tailor to each patient's specific needs such as ability to swallow large sized capsules, tolerability of common side effects, drug interactions with concomitant medications, convenience and adherence potential. Initial antiretroviral regimens should include a nucleoside reverse transcriptase inhibitor (NRTI) agent combined with agents from either a non-nucleoside reverse transcriptase inhibitor (NNRTI) class or protease inhibitor (PI) class.

The Role of the Pharmacist

Pharmacists have been providing pharmaceutical care since the AIDS epidemic.[18] They have been documenting activities to enhance adherence; providing written, individualized medication calendars, organizing pill boxes, giving out beepers,[28] performing telephone follow-up.[29] In addition, they could assess treatment adherence, evaluate potential drug-drug or drug-food interactions, monitor and manage potential drug-associated toxicities with adjunctive treatments, recommend appropriate dosages, and engage in educational patient counseling. More importantly, the intensive training that pharmacists receive in pharmacokinetics and pharmacodynamics allow them to help clinicians optimize patient HIV regimens. Since therapeutic efficacy is associated with the plasma levels of several antiretroviral agents, primarily the NNRTI and PI agents, interpretation of these concentrations remains essential, but challenging towards optimizing HIV therapy.[18]

Evidence suggests that interventions by HIV pharmacists have improved virologic outcomes in HIV-infected patients. One study had evaluated the impact of pharmacists' interventions on improving patients' adherence to their HIV regimens. Among those experienced-treated patients on salvage therapy, 36% showed a clinical significant viral response. These patients have reported receiving adherence counseling sessions with an HIV pharmacist.[30] HIV clinics that implement therapeutic drug monitoring (TDM) programs have been designed to integrate the pharmaceutical care from HIV pharmacists so to ensure improved adherence and successful virologic suppression.[31]

Conclusion

Since the development of HAART in 1996, the AIDS community has witnessed improvements in the quality of life and a significant decrease in morbidity and mortality from AIDS-related illnesses. Improvements in the development of antiretroviral therapy have become ever more complex, and have made pharmacologic assessment of the patient vital in HIV management. HIV pharmacists are poised to significantly impact virologic outcomes in HIV therapy by evaluating the patients' complex drug regimens, practice appropriate adherence interventions, and monitor and manage drug interactions and drug toxicities. In doing so, HIV pharmacists could help ensure the fundamental goals of HIV therapy: virologic suppression and an improved immune system.

About the Author

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