State-of-the-Art HIV Management: An Update

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Within the past 3 years, dramatic changes have taken place in the standard of care for HIV patients. Despite improvements in care (with decreased mortality), the rate of new infections remains unchanged if not increased within most at-risk groups. This general overview is intended for the physician who, while not providing ongoing HIV care, desires an update on the major treatment issues. Current demographic trends, new methods available for testing, and the use of the viral load test for both staging and gauging response to the new combination antiretroviral treatment regimens are detailed. It is suggested that physicians consult with an experienced HIV clinician before starting a treatment regimen in the newly diagnosed patient.

The primary HIV syndrome is reviewed in detail since this diagnosis is often missed and an opportunity for early intervention is lost. Physicians not providing ongoing HIV care must be comfortable making this diagnosis and doing an initial work-up. Focused prevention especially tailored to younger high-risk patients is reviewed. Treatment protocols (with an emphasis on new antiretrovirals), gauging success of treatment, and the management of treatment failures are reviewed in detail. Common antiretroviral drugs are listed with side effects, drug interactions, and average monthly costs. Care of pregnant patients and exposed healthcare workers is also briefly discussed. The need for more primary care-based prevention is also discussed.

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Within the past 3 years, the course usually followed by someone who is infected with HIV has changed dramatically. Developments in testing, staging, and treatment have revolutionized the state-of-the-art management of this disease. It is important that physicians familiarize themselves with the basics of many of these changes.

In 1996, the incidence of AIDS dropped (6%) for the first time since the beginning of the epidemic (1). Deaths from AIDS were also reduced (25%) for the first time. Dramatic reductions in vertical transmission have reduced new cases of perinatally acquired AIDS to an all time low. As new treatments have extended the healthy lifespan of people with AIDS, overall AIDS prevalence has continued to grow. As of December 31,1998, it was estimated that close to 300,000 people in the United States were living with AIDS (1).

Unfortunately, HIV incidence continues to increase despite preventative efforts. An estimated 650,000 to 900,000 Americans are now living with HIV, and at least 40,000 new infections occur each year. These new cases also reflect a changing demographic trend in the cross section view of who is becoming infected. Women, the majority African American or Hispanic, make up an increasing number of the newly infected. Fifteen percent of the new cases are in young people 13-24 years old (1), and half of these new cases are in women, indicating an increase in heterosexually transmitted infection.

Although older gay and bisexual men have generally heeded prevention messages, an alarming trend among young men who have sex with men is emerging. Rates of sexually transmitted disease and new HIV infection range from 8-33% among young men treated at urban public health clinics in the past year (1). Syphilis, felt to be under control only a few years ago, has reoccurred in epidemic fashion among some high-risk urban groups.

This article summarizes the major developments in testing, staging, antiretroviral treatment, prophylaxis of major opportunistic infections (OIs), and primary care-based prevention. This is intended as a general overview for those physicians who are not intimately involved in HIV patient care

but wish to keep abreast of developments in the field. It is recommended that those physicians beginning to treat newly diagnosed HIV positive patients consult with an expert clinician to devise an initial treatment and monitoring plan.

Testing

Testing protocols for the general at-risk population remain mostly unchanged. Informed written consent should be obtained before sera is drawn for the test. Positive enzyme-linked immunoadsorbent assay (ELISA) tests are repeated and confirmed with a Western Blot before the test is reported as positive. Physicians should be aware of local regulations for reporting positive results as well as community support services prior to testing. It is useful to discuss reporting responsibilities with patients before they agree to the testing.

New rapid HIV tests have been developed to test high-risk populations who are unlikely to return to receive their test results. Youth at sexually transmitted disease clinics and pregnant women presenting in labor without any prenatal care are two targeted groups for these new tests (2). Blood, oral mucosa, and urine can now all be used for testing.

Protocols have also been developed which use older, less sensitive HIV antibody tests and then follow up with the newer more sensitive tests. In high-risk HIV-negative patients who are being followed with serial HIV testing, these protocols are most useful to pinpoint more accurately the time of actual seroconversion.

Primary HIV Syndrome

Of the 40,000 patients with new HIV infections each year, 30% to 80% will develop some aspects of the primary HIV syndrome, also known as acute retroviral syndrome (3). Within 1-3 weeks of infection, most patients experience a burst of viremia. The patient mounts an immune response 1-3 months later, which is evident by antibody production and other T cell-mediated responses.

The most common non-specific symptoms of this syndrome are fever, adenopathy, and sore throat, which occur in about two thirds of patients with the syndrome. A nonpruritic rash, most commonly macular and occurring on the trunk, is a more specific finding. The rash is often confused with that present in secondary syphilis.

Although the majority of these patients present to a health care provider for symptom control, very few are diagnosed correctly as having the acute retroviral syndrome (4). Either patients do not feel they are at risk or do not disclose risk factors to the physician. Often, providers do not ask risk assessment questions or misdiagnose the symptom complex.

If the physician suspects acute retroviral syndrome, an HIV viral load (either polymerase chain reaction [PCR] or branched DNA) should be ordered. This test would likely be positive well before the antibody test becomes reactive and will be read out as a quantitative number of copies of the HIV virus–the higher the number, the more likely the patient will progress to AIDS in a more rapid fashion (5). Patients who experience more symptoms during this syndrome also experience a more rapid progression. These facts should guide the physician in determining the aggressiveness of treatment for patients at this stage of illness.

One should also not forget common laboratory abnormalities that may indicate asymptomatic HIV infection such as leukopenia, anemia, thrombocytopenia, elevated transaminases, and atypical lymphocytosis. A high protein/low albumin ratio or abnormally low cholesterol level may also be subtle signs of HIV infection.

Staging

Staging protocols remain relatively unchanged except for the addition of the HIV viral load test. As of December 1999, only the Roche(Palo Alto, CA) PCR technique is FDA approved for staging, but many different methods are now in widespread clinical practice. Conformity of method is important when comparing serial testing. Results are read out in a quantitative fashion noting the number of copies of the HIV virus that are present. The larger the number, the poorer the result since large quantities denote high viral activity present.

A complete blood count with differential and platelets, comprehensive metabolic panels, liver function, tests for syphilis, hepatitis (A, B, and C), cytomegalovirus (CMV), toxoplasmosis exposure, and a purified protein derivative test (with candida and/or mumps for control) for tuberculosis exposure are part of the initial baseline assessment. Pap smears, ophthalmological and gynecological examinations, chest x-rays, and urinalysis should be performed when clinically appropriate. CD4/CD8 lymphocyte profiles denoting the absolute number of CD4 cells are a crucial parameter along with the viral load for staging. In the newly diagnosed patient, these two tests should be repeated at least once before treatment is begun.

Recently, more sensitive HIV viral load tests have been developed that can detect virus down to 25 copies. Most available tests read the presence of less than 200-500 copies as undetectable. Since the goal is to reduce virus to the lowest level possible, the new ultrasensitive tests allow you to fine-tune your treatment. It remains unproven, though, whether a viral load of 50 versus 250 truly offers a long-term benefit for the HIV patient.

Table 1. Nucleoside Reverse Transcriptase Inhibitors (NRTIs).

Drug-Manufacturer	Dosage	Special instructions	Cost*
Retrovir (AZT, zidovudine) Glaxo Wellcome	300 mg BID	Take with light meal	100 mg-$176.95/100
Videx (DDI, didanosine) Bristol-Myers Squibb) (<60kg 150 mg BID)	200 mg BID	1 hr before meals or 2 hrs after	25 mg-$27.10/60 50 mg-$54.19/60 100 mg-$113.23/60 150 mg-$162.54/60
Zerit (D4T, stavudine) Bristol-Myers Squibb	40 mg BID (<60 kg 30 mg BID)		15 mg-$242.28/60 20 mg-$251.97/60 30 mg-$262.88/60 40 mg-$284.84/60
Epivir (3TC, lamivudine) Glaxo Wellcome [for Hepatitis B virus]	150 mg BID		100 mg-$272.59/60
Combivir (AZT/3TC, lamivudine/zidovudine) Glaxo Wellcome (300 mg AZT, 150 mg 3TC)	1 tab BID		150/300 mg-$591.07/60
Ziagen (abacavir) Glaxo Wellcome	300 mg BID		300 mg-$366.31/60

Table 2. Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs).

Drug-Manufacturer	Dosage	Special instructions	Cost
Viramune (nevirapine) Roxane	200 mg/day x 14 days then BID		200 mg-$278.64/60
Rescriptor (delaviridine mesylate) PharmaciaUpjohn	4 - 100 mg tabs TID	Make slurry of pills and 4 oz H_2O	100 mg-$282.96/360
Sustiva (efavirenz) DuPont	3- 200 mg tabs	Take at night for first 2 weeks to reduce effects on the central nervous system	50 mg-$32.88/30 100 mg-$65.70/30 200 mg-$394.20/90

*drug prices as of January 2000, subject to change
BID = twice daily
TID = three time daily

Table 3. Protease Inhibitors (PIs).

Drug-Manufacturer	Dosage	Special instructions	Cost
Crixivan (indinavir) Merck	2- 400 mg tabs TID	1 hr before meals or 2 hrs after meal	200 mg-$463.50/360 333 mg-$289.40/135 400 mg-$463.50/180
Norvir (ritonavir) Abbott	6- 100 mg tabs TID		100 mg-$311.65/168 100 mg-$222.60/100
Fortovase (saquinavir) Roche	6- 200 mg soft gel capsules TID	Take with high fat meal	200 mg-$207.71/180
Invirase (saquinavir) Roche	3- 200 mg hard capsules TID	Take with high fat meal	200 mg-$603.95/270
Viracept (nelfinavir mesylate) Agouron	3- 250 mg tabs TID	Take with light snack	250 mg-$609.12/270
Agenerase (amprenavir) Glaxo Wellcome	8 –150 mg tabs BID	Can take on empty stomach	50 mg-$211.48/480 150 mg-$317.22/240

*drug prices as of January 2000, subject to change; BID = twice daily; TID = three time daily

Table 4. Common Side Effects/Drug Interactions for new HIV/AIDS Drug Treatments.

Nucleoside Reverse Transcriptase Inhibitors (NRTIs)	
AZT, zidovudine Glaxo Wellcome (Retrovir)	anemia, neutropenia
DDI, didanosine Bristol-Myers Squibb (Videx)	pancreatitis, peripheral neuropathy
D4T, stavudine Bristol-Myers Squibb (Zerit)	peripheral neuropathy
3TC, lamivudine HBV, Glaxo Wellcome (Epivir)	minimal toxicity
abacavir sulfate Glaxo Wellcome (Ziagen)	hypersensitivity reaction (can be fatal)
Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)	
nevirapine Roxane (Viramune)	rash, increased transaminases
delaviridine mesylate PharmaciaUpjohn (Rescriptor)	rash, increased transaminases
efavirenz DuPont (Sustiva)	rash, CNS effects (usually transitory), false cannabinoid test
Protease Inhibitors (PIs) All of these drugs have significant drug interactions due to inhibition of pathways within the P450 cytochrome mechanism. The majority exercises this through the 3A pathway, but recently, significant lipid abnormalities with body fat distribution have also been demonstrated.	
PI Agent-Specific Side Effects	
indinavir Merck (Crixivan)	nephrolithiasis
ritonavir Abbott (Norvir)	GI intolerance
saquinavir Roche (Fortovase)	GI intolerance
nelfinavir mesylate Agouron (Viracept)	diarrhea

GI = gastrointestinal

Treatment

Nowhere has there been a more dramatic change in HIV care than in the availability of new antiretroviral medications. These new medicines have allowed the development of multiple combination therapy regimens, which have been called Highly Active Anti Retroviral Therapy (HAART). These new drugs have helped usher in a new age where people living with HIV/AIDS are suffering less opportunistic infections and living longer, healthier lives. (Patients are still encouraged to maximize nutritional and vitamin intake and take steps to reduce stressful and unhealthy lifestyle practices.) Unfortunately, these new medications bring with them a new level of complexity for both the patient and the provider that can appear daunting at times.

In May 1999, the Department of Health and Human Services (DHHS) convened an expert panel and issued guidelines to address the many treatment issues concerning HIV infected adults and adolescents (6). The 50-page guidelines can be summarized as follows:

Whom to Treat

- Those with acute retroviral syndrome
- Anyone thought to have seroconverted in the past 6 months
- Anyone symptomatic (thrush, unexplained fever, weight loss, or diarrhea)
- Asymptomatic patients who have CD4 counts < 500 or a viral load (via PCR) of 20,000 or greater

It remains controversial as to when asymptomatic individuals with unknown seroconversion dates, CD4 > 500, and viral loads < 20,000 should be treated. One group of experts advocates early, aggressive therapy as soon as seroconversion is documented. Another equally large group suggests a more conservative "wait and see" approach while monitoring for signs of immune compromise.

The decision to treat in all these cases, of course, rests with the patient after consultation with the provider. It is important to assess the likelihood of the patient adhering to the prescribed therapy before starting. Lack of adherence, with frequent missed dosages, is a setup for developing viral resistance and treatment failure. As in other treatment decisions, a patient-specific risk benefit analysis should take place before starting therapy.

What to Treat With

(See Tables 1-3 for available antitretroviral agents.)

First-line therapy should include two nucleoside reverse transcriptase inhibitors (NRTIs) plus either one non-NRTI or protease inhibitor (PI). An alternative treatment can be two PIs such as ritonavir (Norvir) or saquinavir (Fortovase or Invirase).

Common side effects and drug interactions of these therapies are shown in Table 4. While these medications are covered by most health plans, physicians must usually acquire pre-authorization before prescribing them. State and federal programs exist to assist patients who experience financial difficulty in maintaining these drug regimens. Despite the significant cost, several studies indicate a cost effectiveness for these therapies due to their dramatic reduction in hospitalization for opportunistic infections (7).

Drugs to Generally Avoid in a Patient with HIV

Due to considerable drug/drug interactions, several drugs should be avoided in HIV-positive patients. The most common drugs include simvastatin (Zocor), lovastatin (Mevacor), rifampin, astemizole (Hismanal), cisapride (Propulsid), midazolam (Versed), triazolam (Halcion) and ergot alkaloids (DHE 45). It is important that patients realize that despite their concerns about confidentiality, they need to reveal what HIV medications they are taking regardless of clinical situation.

How to Gauge Treatment Success

The use of HIV viral load quantitative levels is the cornerstone of treatment monitoring. In general, this test should be repeated 2 months after treatment is begun and every 3 months thereafter. For successful treatment, expect a 1-log (10-fold) drop in viral load at 8 weeks and < 500 copies at 4-6 months.

How to Manage Treatment Failure

Persistently elevated HIV viral load levels suggest resistance to the antiretrovirals being used and indicate that at least two of the three medications in the combination should be changed based on what the physician suspects is the most likely resistance pattern. The use of genotyping and phenotyping to determine resistance has become more accepted and may play a role in patients who have experienced persistent failure with multiple medication regimens or in patients beginning therapy who are suspected to be infected with resistant viral strains.

Once the regimen is changed, HIV viral loads should be followed serially to determine a fall in viral activity. Determination of subsequent treatment failure should be deferred for at least 6 months unless the clinical status of the patient deteriorates. Expect that at least 50% of the patients treated with these regimens will experience failure sometime in the course of treatment. Nonetheless, providers should not give the message to patients that THEY have failed, rather that the regimen needs to be changed.

Treatment of Pregnant Women

In general, guidelines for the treatment of pregnant and nonpregnant women are the same, but HIV-positive women not currently on antiretrovirals who find themselves pregnant may wish to postpone treatment until after their first trimester. Most organogenesis is completed by week 12, and deferral of medication may reduce neonatal toxicity. Treatment of women with advanced disease should be based on their clinical status and not the potential toxicity to the infant.

Use of antiretrovirals in pregnant women and infants in the immediate newborn period have dramatically reduced the incidence of HIV in infants born in the United States. Some optimistic estimates predict a virtual eradication of this phenomenon within the next 5 years. Recent studies (8) have shown that even a single dose of the NNRTI viramune given to pregnant women and to the newborn child significantly reduces transmission. Of course, this is based on vigilant monitoring of all pregnant women at risk and the availability and acceptance of treatment. Elective C-sections at 38 weeks may also dramatically reduce vertical transmission.

Treatment of Exposed Healthcare Workers

In 1998, the Centers for Disease Control and Prevention changed their treatment recommendations to state that all health workers with a high-risk exposure should be treated. This stronger recommendation reflects the dramatic reduction in transmission in workers who are treated immediately after exposure. Clinics that treat HIV-infected patients, or those at high risk, should have antiviral medication on site for instituting treatment rapidly. Side effects for short-term therapy are limited, and no long-term deleterious effects are expected. Some clinicians have also begun post-high-risk sexual exposure prophylaxis in some selected patients, although the efficacy remains unproven at this point.

Prophylaxis for Opportunistic Infections

DHHS guidelines released in August 1999 (9) revised the protocols for prophylaxis of OIs. This reevaluation was prompted by the dramatic reduction in OIs seen since the advent of HAART. As patients' CD4 counts began to rise on this therapy, clinicians questioned whether prophylaxis was still needed and if it was safe to remove therapy.

Several recently released studies appear to validate the safety of discontinuing primary prophylaxis for *Pneumocystis carinii* pneumonia (PCP) and mycobacterium avium complex (MAC) disease when there is evidence of immune reconstitution (10). Guidelines suggest that the CD4 count should be above 200 and that the viral load has remained in an undetectable level for at least 6 months. The dramatic drop in OI rates is further confirmation to the efficacy of HAART in most patients.

Recently, some smaller studies have indicated that it also appears safe to stop secondary prophylaxis for PCP, MAC, and CMV disease once these immune parameters are met (11). Given the large number of pills many patients have to take, any reductions in the number of medications and their potential side effects are welcomed. Of course, the patient must feel comfortable with discontinuing these medications and be aware of the small, but real, chance of developing an OI off the medication.

Primary Care-Based Prevention

Although much progress has been made in the treatment of HIV-positive patients, it is disheartening that the rates of new infection remain steady if not increasing. Compounding this fact is the increase in new cases among young people between the ages of 13 and 24. It is crucial that physicians step up and play more of a role in primary prevention of HIV disease. Unfortunately, attempts to develop a safe and efficacious vaccine for widespread use has been much slower and less successful than anticipated. With respect to youth, it is important that physicians encourage open communication about risk factors and present a prevention message in nonjudgmental terms. Abstinence, the safest option, should be encouraged but with the understanding that most young people will choose eventually to become sexually active. Where possible, physicians should support and play a role in school-based and community programs that foster peer support to maintain low-risk behavior.

When treating adults, risk assessment for sexually transmitted diseases including HIV must become a routine part of the general examination. Multiple studies have shown patient acceptance of these questions but persistent nonparticipation in this risk assessment by physicians. For patients determined to be at increased risk, two important activities must take place:

- Testing should be offered to determine serostatus and
- Risk reduction activities should take place regardless of the patient's HIV status.

Physicians also can play a role in secondary prevention by reinforcing the fact to HIV-positive patients that they remain capable of transmitting the virus regardless of whether their HIV viral load is reported as undetectable. As people live longer and healthier, the tendency to resume unsafe practices needs to be acknowledged and dealt with. It is crucial that patients do not resume unsafe sex or needle sharing activity.

Conclusion

The last 3 years have been a time of tremendous progress in the treatment of HIV-positive patients, resulting in many more people living longer, more healthy lives. As these treatments continue, though, we can expect to witness more cases of treatment failure. There is an obvious need for more medications, hopefully with fewer side effects, which also can attack other areas of the HIV virus's life cycle.

At the same time, increasing numbers of young people are being infected. Disproportionate numbers of African Americans and Hispanics are being affected by this epidemic. Despite having dealt with this disease for over 15 years, prevention efforts have not become commonplace or accepted by most of populations at increased risk.

Physicians must recognize the important role they can play in helping to prevent new cases of HIV. As well, they should remain up to date on the general treatment of HIV-positive patients and should familiarize themselves with the local medical and support services available for consultation. Given the trend of more patients living longer with this disease, it will be the unusual physician who does not experience some aspects of the clinical care of this population.

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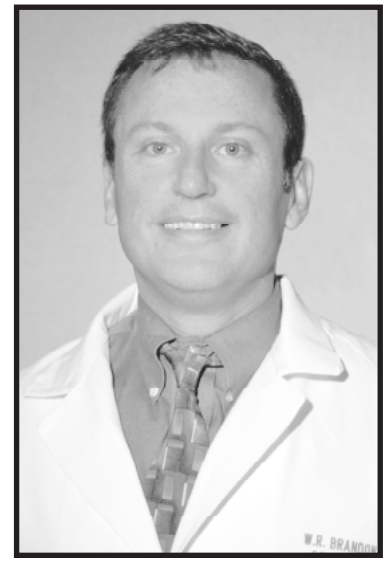

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