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10 changes in HIV care that are revolutionizing the field

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<http://www.medscape.com/viewarticle/814712>

The challenge of HIV management seemed impossible up to 1996, but since then, it has been an incredible journey that no one saw coming. We now have 28 antiretroviral drugs, huge databases to assiduously track the incredible progress, an army of specialists to provide state-of-the-art care, and near-normal longevity for most who take standard treatment.



Many opine that the war on HIV/AIDS is largely over. But wait. The field of HIV science, patients, and providers never stops.

This review tabulates 10 key changes in HIV testing, clinical care, and healthcare delivery that will probably have a significant impact on where we go from here.

New Tests for Earlier Detection and Better Control of HIV

(1) Fourth Generation HIV Test: The new test adds p24 antigen to the HIV antibody test to permit detection of the disease before seroconversion, which is when the Western blot (WB) becomes positive. This test is approved

(See *HIV Care*, page 6)

Statewide Disease Facts & Comparisons

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Winter Survivalist Stories of Medically Important Arthropods

In North America, mosquitoes enter diapause during seasonal cold weather. Diapause is a delay in development in response to regularly and recurring adverse environmental conditions. Environmental stimuli initiate and terminate diapause. The dormant life stage depends on the mosquito species. Species of *Aedes*, *Ochlerotatus*, and *Psorophora* overwinter as eggs. Overwintering adult mosquitoes, in the *Culex* and *Anopheles* genera, seek shelter in protected, secluded sites. And some species will enter diapause as immature larvae if the water breeding sites are protected from extreme cold and drying.

Winter does influence mosquito abundance, mosquito infection rate, and human incidence of mosquito-borne disease. Cold temperatures have prevented the invasive yellow fever mosquito, *Aedes aegypti*, from establishing in the northern United States (Hawley et al. 1989). In 2004, cold temperatures were responsible for the low vector abundance, late primary transmission season, and low West Nile virus infection rate in the mosquito population in the Central Red River Valley (Bell et al. 2006). And the early seasonal occurrence of West Nile virus positive mosquitoes in Dallas in 2012 (and 2006) was attributed to a warm winter (Chung et al. 2013).

Although mosquitoes can suffer extensive winter mortality from extremely frigid winter weather, many other

significant climatic events can transpire between the middle of winter and early summer. Walsh et al. (2008) is one of the few studies to examine mosquito abundance as a function of both off-season meteorological conditions and environmental conditions immediately preceding (days to weeks before) mosquito activity. One mosquito studied, *Culex salinarius*, overwinters as an adult. A cold January did reduce *Cx. salinarius* survivorship; however, a warmer March and April encouraged population resurgence. Other climatic effects were not as easy to explain, such as the positive effect of the number of cool days in November and the negative impact of relative humidity in October on the summer *Cx. salinarius* population. Since *Aedes sollicitans* survives winter as an egg, different climatic variables influence its survivorship. Unlike *Cx. salinarius*, warm conditions in late December actually had an adverse effect on the population of *Ae. sollicitans* in the following summer. And there was a positive relationship between number of days with subzero temperatures in late March through early April and summer *Ae. sollicitans* populations. The negative effects of high rainfall in late April to early May could be due to inappropriate timing of egg hatch or flooding of egg sites (Walsh et al. 2008).

(See **Cold Insects**, page 3)

West Virginia ticks discussed in this article and the human diseases they transmit

Common Name	Species Name	Human Diseases Transmitted
Blacklegged tick	<i>Ixodes scapularis</i>	Lyme disease (<i>Borrelia burgdorferi</i>) Human anaplasmosis (<i>Anaplasma phagocytophilum</i>) Human babesiosis (<i>Babesia microti</i>) Powassan encephalitis (Powassan virus)
Lone star tick	<i>Amblyomma americanum</i>	Human ehrlichiosis (<i>Ehrlichia chaffeensis</i>) Human ehrlichiosis (<i>Ehrlichia ewingii</i>) Spotted fever rickettsioses (<i>Rickettsia</i> spp.) Tularemia (<i>Franciscella tularensis</i>)
American dog tick	<i>Dermacentor variabilis</i>	Spotted fever rickettsioses (<i>Rickettsia</i> spp.) Tularemia (<i>Franciscella tularensis</i>)
Winter tick	<i>Dermacentor albipictus</i>	None

(*Cold Insects*, continued from page 2)

Unlike mosquitoes from colder climates, which spend winter in a predetermined state of arrested development and hibernation, many temperate climate tick species are actually active during winter. The blacklegged tick (*Ixodes scapularis*) shows high survivorship at subzero temperatures (-11°C through -20°C) under laboratory (Burks et al. 1996) and field conditions (Brunner, Killilea & Ostfeld 2012). In Maryland, Carrol & Kramer (2003) collected blacklegged ticks from snow-covered ground during subzero weather conditions in January and February. In West Virginia, blacklegged ticks have also been found on people during winter time. The lone star tick (*Amblyomma americanum*) and the American dog tick (*Dermacentor variabilis*) are also capable of surviving extremely low temperatures. The lower lethal temperature for lone star tick is -12°C and -14°C for the American dog tick (Burks et al. 1996). Both lone star tick and American dog tick will attach to hosts, feed on blood and deposit eggs during winter (Stewart et al. 1998). And some ticks, such as the 'winter tick' (*Dermacentor albipictus*), are actively engorging on their hosts from late fall through early spring. With so many tick species still remaining active during the 'less active' season in West Virginia, occurrence of human tickborne disease during winter should not be surprising (West Virginia Tickborne Disease Surveillance Summary, 2000-2010, 2011).

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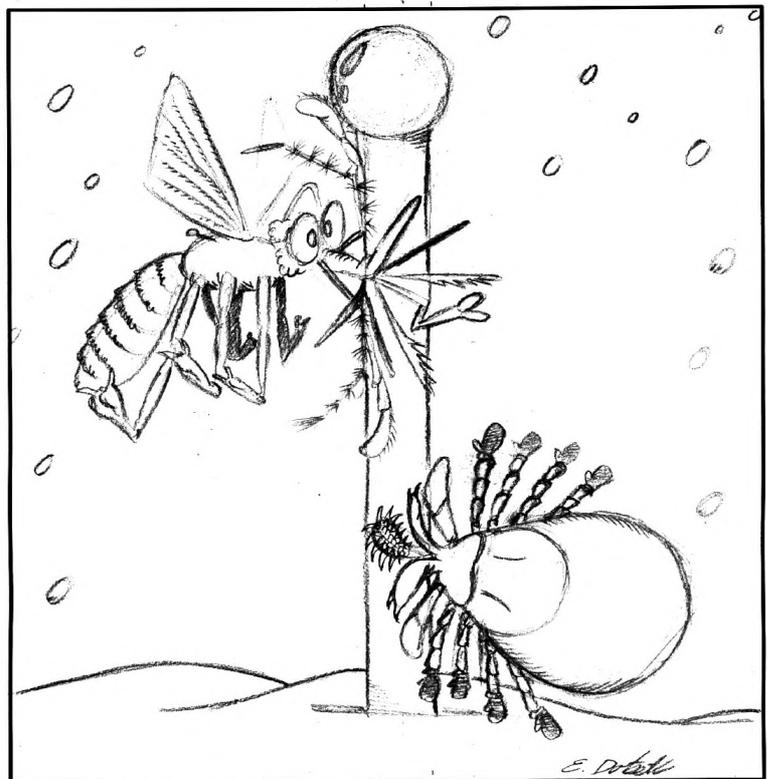
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Do insects "Triple-Dog-Dare" each other when it's really cold?

**West Virginia AIDS and HIV Infection Cases Diagnosed by
Age Group, Gender, Race and Exposure Category
Cumulative through December 31, 2013**

Characteristic	HIV/AIDS †		HIV-NA †		AIDS †	
	No.	%	No.	%	No.	%
Age at Diagnosis §						
< 13 years	23	1	12	1	11	1
13 - 24 years	335	12	217	23	118	6
25 - 44 years	1,804	65	573	61	1,231	67
45 - 64 years	571	21	129	14	442	24
65 + years	40	1	7	1	33	2
Gender						
Males	2,247	81	705	75	1,542	84
Females	528	19	235	25	293	16
Race/Ethnicity						
White	2,025	73	611	65	1,414	77
Black	638	23	281	30	357	19
Other/Unknown*	112	4	48	5	64	3
Exposure Category						
Male-to-male sex (MSM)	1,464	53	454	48	1,010	55
Injection drug use (IDU)	407	15	141	15	266	14
MSM/IDU	125	5	30	3	95	5
Heterosexual contact	387	14	156	17	231	13
Perinatal	25	1	13	1	12	1
Other/Unknown**	367	13	146	16	221	12
Total	2,775	100	940	100	1,835	100

Notes. These are actual numbers of cases of HIV/AIDS that were reported to the WV Department of Health and Human Resources as of December 31, 2013. No adjustments were made for reporting delays. AIDS data includes reports from April 1984 through December 31, 2012; HIV data includes reports from January 1989 through December 31, 2013.

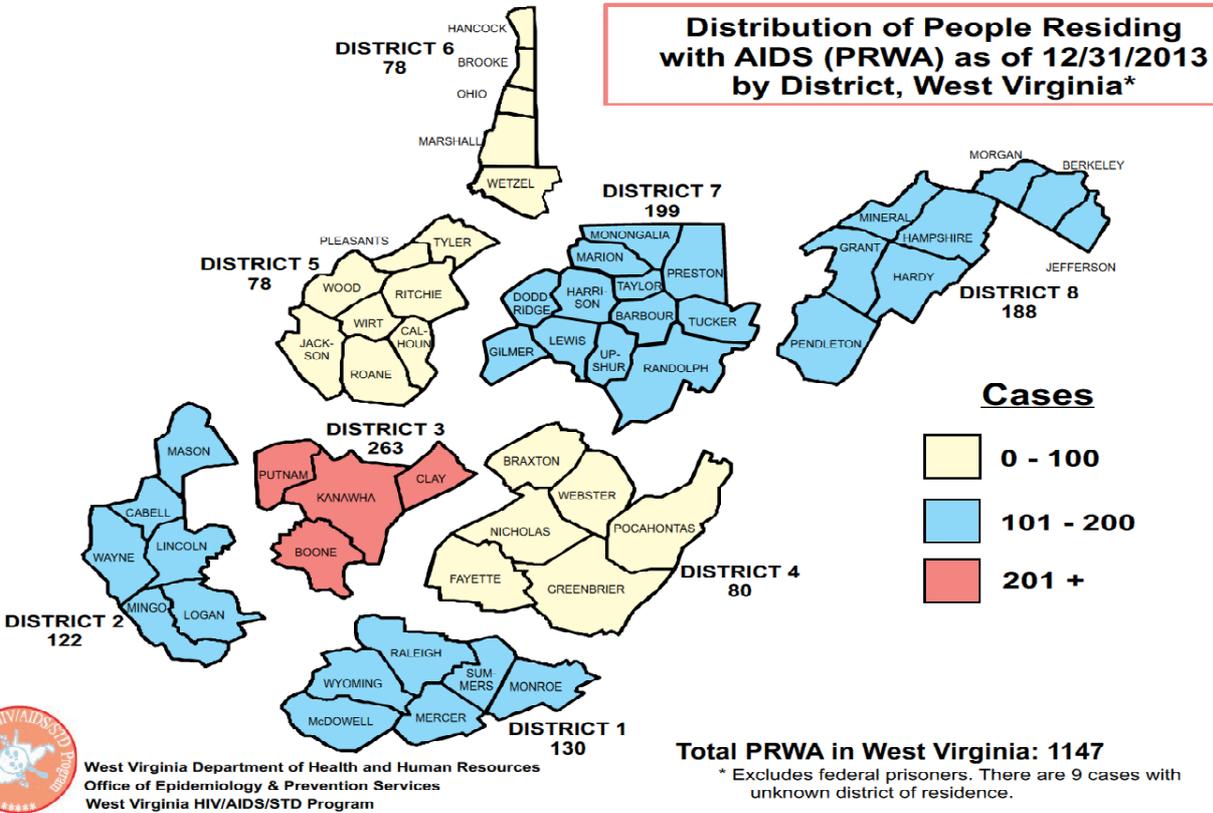
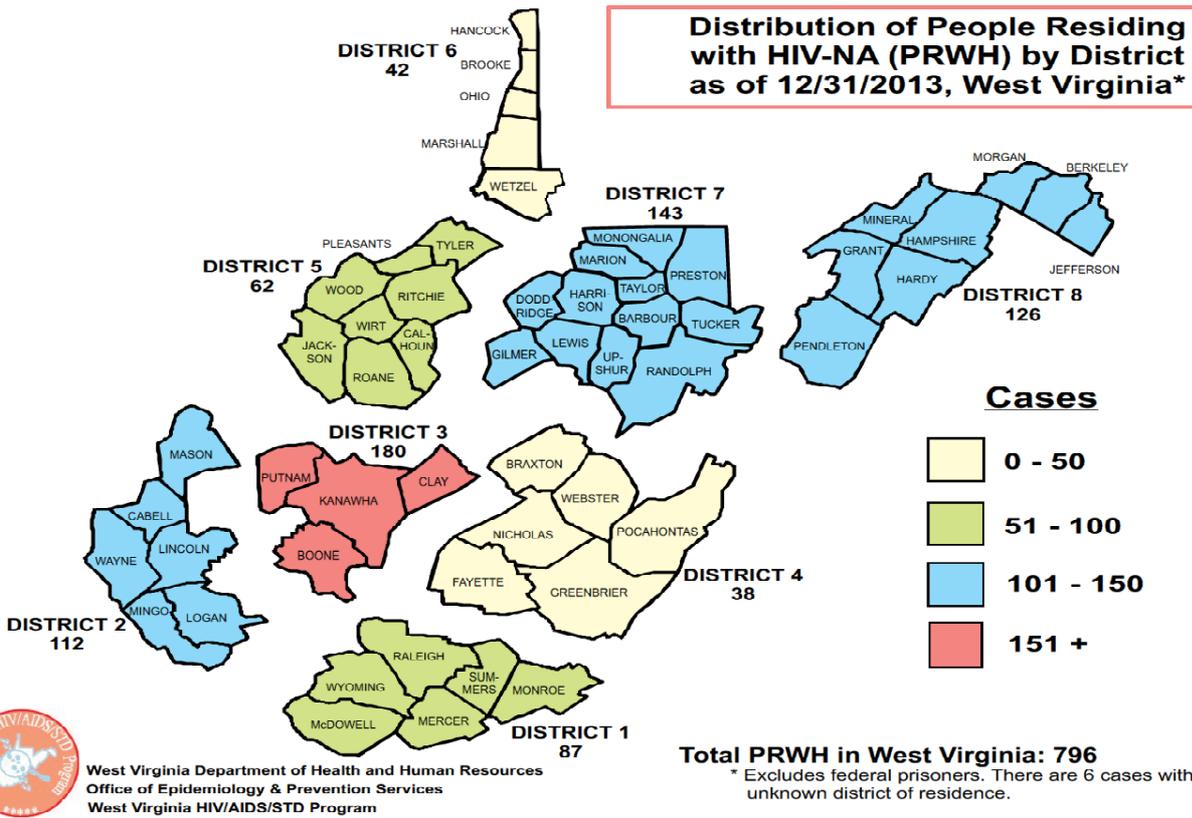
Current federal prisoners are excluded. Percentages may not add to 100% due to rounding.

† HIV/AIDS provides information on the person's earliest diagnosis of HIV or AIDS in WV. HIV-NA provides information on individuals diagnosed with HIV but not AIDS in WV. These individuals may have been diagnosed with AIDS in another state. Individuals with AIDS may or may not have been diagnosed with HIV in WV.

**"Other" race categories include Hispanic, Asian, Native Hawaiian, Pacific Islander, American Indian, Alaskan Native, Multiple Races, and Unknown race.

***"Other" risk categories include hemophilia, blood transfusion, and risk not reported or not identified.

§ Excludes two persons with invalid diagnosis dates.



(HIV Care, continued from page 1)

by the US Food and Drug Administration (FDA), and its use is recommended by the Centers for Disease Control and Prevention for screening patients because it can detect HIV during the early acute retroviral syndrome stage at Fiebig stage 2 — unlike the WB results, which require waiting for 2-3 months after viral transmission at Fiebig stage 5.

Advantages of this early detection include the possibility of functional cure (discussed below), treatment at the time of maximum risk for transmission, and the opportunity for direct entry into HIV care versus the long delay required for obtaining a positive WB result. This delay also promotes the problem that 20%-25% of patients with a positive WB never actually receive these results so their care may be delayed indefinitely.

(2) Point-of-Care HIV Viral Load Testing: Point-of-care (POC) HIV testing has been extremely successful as a screening tool to detect HIV. Now, there is a POC CD4 count test that permits staging HIV at the site of care, and it is anticipated that a POC viral load test will also be available, although the timeline for this development is unclear.

The advent of the POC viral load test permits patients to test their own viral load to facilitate HIV management in an outpatient setting, often without the need for frequent medical evaluation except to test for drug toxicity, comorbidities, and HIV-related complications. The long-term goal would be self-care akin to standard diabetes management.

Preventing, Treating, and Curing Disease

(3) Early HIV Therapy to Achieve “Functional Cure”: There is now good evidence to show that the HIV reservoir with chronic HIV infection is substantial and is probably an important factor in immune activation and our inability to achieve cure, despite viral suppression with traditional monitoring.

Note that “cure” is now described in 2 categories: a “sterilizing cure,” in which the virus is eliminated, and a “functional cure,” in which the virus continues to be present but does not require antiretroviral therapy (ART) for viremic control.

The “Berlin patient” who underwent stem cell transplantation is regarded as the only person to have achieved sterilizing cure. The “Mississippi baby” is considered a functional cure because she has had virologic

control off therapy for longer than 1 year after being treated at birth and briefly after birth, but it is not clear that the virus is eliminated.

Possibly the best example of the impact of early therapy is the VISCONTI cohort. This is a group of patients in France treated early in the course of HIV infection who have remained off ART for months or years, without treatment or detectable virus.

The presumed explanation is that treatment early in the course of acute infection limits substantial infection of the reservoir. Thus, recognition of acute disease with rapid implementation of ART now becomes an important priority in the context of HIV management.

(4) Preventing HIV Infection: The rate of new cases of HIV infection in the United States has held steady at around 50,000–55,000 cases per year since 1996, even though many effective methods for preventing HIV transmission are available. There does not seem to be any strategy that consistently reduces annual rates of new infections despite 17 years of trying.

We have a particularly important development in the HPTN 052 trial, which showed that “treatment is prevention” — presumably because HIV infection, like virtually all infections, obeys the rule that probability of transmission is directly correlated with inoculum size. This tactic makes biologic sense and has now been proven in a well-controlled clinical trial.

This is a game-changer in the sense that universal ART coverage is now a commonly accepted strategy in the United States and will be recommended by the World Health Organization when resources are available. The dual goal is to improve both individual health and public health based on mathematical modeling showing that treatment is an effective prevention strategy.

Preexposure prophylaxis (PrEP) is a newer option and seems to work in clinical trials, but the challenge of adherence may make it more difficult to implement in practice. Interestingly, concerns raised 55 years ago with the introduction of the first birth control pill, Enovid, are now being raised with PrEP, including cost, side effects, and impact on sexual behavior.

(5) Eliminating the Hepatitis C Coinfection Cohort: It is estimated that 30%-35% of persons with HIV infection also have hepatitis C infection. In the United States, hepatitis C infection is the major cause of liver failure, liver transplant,

(See HIV Care, page 7)

(HIV Care, continued from page 6)

and liver death, with an annual mortality that now exceeds that of HIV.

The sudden and dramatic change in hepatitis C management is now virtually guaranteed, with an extraordinary array of new drugs expected to cure the majority of hepatitis C-infected patients.

(6) P4P4P to Address the Gardner HIV Cascade Challenge: The Gardner cascade is well known to the HIV care community, but it represents a humbling pox on our HIV care system because it shows the very disappointing reality of HIV outcome. Despite the availability of powerful drugs for virtually all patients, only about 28% of the estimated 1.1 million Americans with HIV infection have achieved the goal of no detectable virus. The major issues accounting for this disappointing outcome are lapses in care at each step of the cascade — testing, enrollment in care, retention in care, and adherence to ART. Many articles have been written about this cascade and have described possible methods to address each step, but none have clearly achieved a major advance.

The potential breakthrough in this stalemate is P4P4P, or “pay for performance for patients,” which provides financial or other reward for patients to get tested, engage care, stay in care, and achieve viral suppression. It is now being studied in a controlled trial in Washington, DC, and Bronx, New York.

The reason for optimism is that P4P4P seems to have worked well in virtually all areas of chronic care that are dependent on patient adherence, including hypertension, diabetes, smoking, obesity, and measurement of INR. This approach to medical management of chronic disease is controversial, so it is not included in HIV guidelines or polite discussions, even though it is low-cost and virtually always works. Instead, we spend long hours and great resources to achieve this goal by other methods.

It is anticipated that the well-controlled National Institutes of Health-sponsored trial of P4P4P will impart validity and acceptability to this rarely discussed topic.

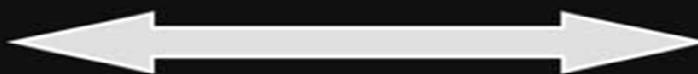
(7) New Approaches in HIV Therapeutics on the Horizon: There will always be a need for new antiretroviral agents owing to resistance and toxicity, but the small number of new drugs in the pipeline possibly reflects the adequacy of the current supply of 28 FDA-approved agents as well as the anticipated rush to generics (discussed below).

However, there is increasing enthusiasm about the use of nanotechnology to achieve novel antiretroviral drug formulations to facilitate viral control, such as long-acting rilpivirine (rilpivirine LA) and the new integrase inhibitor GSK744. These drugs are given parenterally and maintain therapeutic levels for 1-3 months. Both are currently in clinical trials to treat persons at risk for HIV infection (ie, as PrEP) and patients with established HIV infection.

(See HIV Care, page 8)

Continuum Engagement in Care

**Not in
Care**



**Fully
Engaged**

Unaware of
HIV status
(not tested or
never
received
results)

Aware of HIV
status
(not referred
to care; didn't
keep referral)

May be
receiving
other medical
care but not
HIV care

Entered HIV
primary
medical care
but dropped
out
(lost to
follow-up)

In and out of
HIV care or
infrequent
user

Fully
engaged in
HIV primary
medical care

(HIV Care, continued from page 7)

It is anticipated that this will bring a new method of HIV management that is completely different from what we are currently doing, and it is especially appealing for populations in whom daily pill taking is a great challenge.

The other anticipated departure from contemporary practice is the abandonment of “2 nukes and a third drug” — the 3-drug combination containing 2 nucleoside reverse transcriptase inhibitors and a “third drug” — the basic combination that has been standard since 1996.

A New Paradigm for HIV Care Delivery

(8) Redefining the HIV Provider: It seems clear that healthcare reform will have a major impact on medical care in general, and certainly on HIV care as well. One of the key issues is defining who will be the HIV care provider. Will it be done primarily by an HIV specialist, will HIV be enveloped within primary care, or will there be some sort of mix, as with diabetes?

Arguments for the shift to primary care include the fact that HIV care is now much easier with the current menu of drugs and more than 50% of the patients with HIV are now older than 50 years, so diseases of aging must also be addressed. However, the HIV Medicine Association and the Infectious Diseases Society of America defines an HIV care provider as a provider with a panel size of at least 25 HIV-infected patients, even though there are no data to support superior outcomes by this definition in studies conducted over the past 20 years.

The impression of payers is that most patients will be able to keep their current provider, but we should expect great variations by state and payer in the coming years.

(9) Evolving Ethical Issues in HIV Care: The ethics of HIV care under healthcare reform is a good example of an evolving controversy that is likely to have an important impact on HIV drug selection in the future. It is very

reminiscent of the highly quoted 1993 editorial by Marcia Angell, former editor of the *New England Journal of Medicine*, which stated that the doctor had become a “double agent,” considering our sometimes conflicted obligation to both the patient and the payer.

This will be an individual provider/patient issue with unpredictable outcomes, but it is likely to introduce a new and very uncomfortable decision process. Although we are reminded that our oath is to be the advocate of the individual patient, we also recognize that we work in a society that is screaming for lower healthcare costs.

(10) Generic Drugs for HIV: HIV care is expensive, with annual costs averaging \$25,000-\$30,000, of which 67%-70% is spent on antiretroviral drugs. In the United States, healthcare reform is coming just as first-line HIV drugs are starting to go off patent. The anticipated result is great pressure for the use of generic drugs for HIV treatment, as for all medical conditions.

A cost analysis using generic efavirenz plus generic lamivudine with trade-branded tenofovir shows a potential savings compared with Atripla® of \$6000 per patient per year, or about \$940 million per year on the basis of current US sales. The switch would require the patient to take 3 pills once daily instead of 1 pill once daily. This would be a difficult transition for some patients, but the convenience factor may be a hard sell to payers given relative costs.

It seems likely that some payers will require the change and that the issue will become increasingly important as more drugs become generic, guidelines change, and payers become more savvy. Additional factors that could affect its acceptance are the future of the AIDS Drug Assistance Plan (ADAP) and an interesting recent proposal that patient expense for drugs should be routinely included in the description of side effects, as well as the recommendation from the American College of Physicians that we be “parsimonious” in our delivery of care. These possible changes in ADAP, the introduction of generics, and the attention to cost in HIV care delivery could have a marked impact on HIV patient management. ❖

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