# Topics in HIV Medicine™

## A publication of the International AIDS Society–USA

## Perspectives

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## **About This Issue**

This issue of *Topics in* HIV *Medicine* includes 3 summaries of talks given at the International AIDS Society–USA spring continuing medical education course held in New York. In addition, this issue contains a summary from the 2001 Conference on Retroviruses and Opportunistic Infections.

The first article summarizes Dr Charles W. Flexner's review of pharmacokinetic interactions of antiretroviral drugs and the potential clinical role of therapeutic drug monitoring. The second article is based on Dr Henry Masur's overview of lactemia and bone disease in HIV infection. The third Perspectives article summarizes a talk by Dr Frederick M. Hecht and discusses how recent trends toward increased risk behavior among HIV-seropositive patients indicate the need for increased prevention efforts in the clinical setting.

Our fourth article, an edited transcript of a lecture given by Kevin M. De Cock, MD, at the opening session of the 8th Conference on Retroviruses and Opportunistic Infections, reviews global HIV/AIDS epidemiology, focusing on disease in Africa and response to the African epidemic.

The next issue of *Topics in* HIV *Medicine* will feature additional summaries from our spring course series. Topics include: drug resistance, initial antiretroviral therapy, coronary artery disease in HIV infection, and hepatitis C virus coinfection.

## Topics in HIV Medicine<sup>™</sup>

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#### Correspondence

*Topics in* HIV *Medicine* welcomes editorial correspondence. Address letters to:

Editor, *Topics in* HIV *Medicine* International AIDS Society–USA Presidio of San Francisco 1001 B O'Reilly Avenue, PO Box 29916 San Francisco, CA 94129-0916

Phone: (415) 561-6720

Fax: (415) 561-6740

Web site: http://www.iasusa.org E-mail: topics@iasusa.org

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## Perspectives Update on HIV Pharmacology and Therapeutic Drug Monitoring

Pharmacokinetic interactions of antiretroviral drugs and the potential clinical role of therapeutic drug monitoring were discussed by Charles W. Flexner, MD, at the International AIDS Society–USA New York course in March.

The long-term success of an antiretroviral regimen depends on maintaining inhibitory concentrations of active drug at the site of HIV replication sufficient to suppress viral load and prevent viral mutation and resistance. Although HIV inhibitory concentrations can be identified for antiretroviral drugs, there are persistent issues surrounding the use of drug blood concentrations to guide treatment. In general, the higher the trough concentration, the better the inhibition of HIV. However, precise therapeutic concentration ranges have not been identified for any antiretroviral drug. Further, therapeutic drug monitoring may not be necessary if drug pharmacokinetic profiles can be optimized in other ways-eg, by exploiting beneficial pharmacokinetic interactions such as those used to maintain increased blood levels of protease inhibitors. Finally, drug concentrations alone are not the ultimate determinant of treatment outcome; other important factors include tolerability, safety, adherence, treatment history, and resistance profile.

## **Beneficial Drug Interactions**

Protease inhibitor combinations based on the ability of drugs like ritonavir to increase concentrations of the paired drug through pharmacokinetic interactions are increasingly used in treatment. Combinations that exhibit such a beneficial interaction include ritonavir/

Dr Flexner is Associate Professor of Medicine, Pharmacology, and International Health at the Johns Hopkins University in Baltimore, Maryland. saquinavir, ritonavir/indinavir, delavirdine/saquinavir, ritonavir/nelfinavir, nelfinavir/saquinavir, ritonavir/amprenavir, and lopinavir/ritonavir.

The inhibitory quotient has emerged as a way of assessing the relative clinical potency of these combinations, and a high inhibitory quotient has become an important target for newer anti-HIV drugs. The use of the inhibitory quotient is motivated by the predictive value for virologic response of protease inhibitor trough concentrations in some studies. The inhibitory quotient usually is expressed as the drug minimum blood concentration ( $C_{min}$ )

The pharmacokinetic profiles of some dual protease inhibitor regimens support further investigation of once-daily dosing

divided by the HIV 50% inhibitory concentration  $(IC_{50})$  of the drug. The  $IC_{50}$  is often adjusted for protein binding, since drugs that are highly protein bound will have an artifactually low IC<sub>50</sub> in the presence of low concentrations of protein. Caution currently is warranted in the use of publicized inhibitory quotients, since the C<sub>min</sub> and inhibitory concentration values used to derive them vary according to data set used (frequently, according to which drug combination is being touted as superior to another). For reliable inhibitory quotients, comparative data for the different protease inhibitor combinations and other drugs need to be generated under identical experimental conditions.

There is considerable interest in developing protease inhibitor combinations with pharmacokinetic profiles that will permit once-daily dosing. Combinations being considered in this regard include ritonavir/amprenavir, lopinavir/ritonavir, ritonavir/indinavir, and ritonavir/saquinavir. For example, use of amprenavir 1200 mg once daily plus ritonavir 200 mg once daily has been shown to produce trough drug concentrations comparable to those produced by amprenavir 600 mg twice a day plus ritonavir 100 mg twice a day (Wood et al, 5th Cong Drug Ther HIV Infect, 2000). This combination can also be administered with a once-daily dose of the nonnucleoside reverse transcriptase inhibitor (NNRTI) efavirenz, without adverse effect on amprenavir blood levels (Figure 1).

Recent findings, however, indicate that the combination of dual protease inhibitors with NNRTIs may require a ritonavir dose of more than 100 mg twice daily. For example, efavirenz decreased indinavir area under the concentrationtime curve (AUC) by 30% when added to indinavir 800 mg plus ritonavir 100 mg twice daily, and decreased the lopinavir AUC by 19% and  $C_{\mbox{\scriptsize min}}$  by 33% when added to standard-dose lopinavir/ritonavir (400/ 100 mg bid). Therefore it is now recommended that the ritonavir dose be increased to 200 mg twice a day in dual protease inhibitor combinations with efavirenz or nevirapine. The dose of lopinavir should be increased to 4 capsules twice daily (533/133 mg bid) when combined with efavirenz or nevirapine.

The potential advantages to once-daily dosing of antiretroviral regimens include increased convenience, the potential for better overall adherence (in terms of taking a higher proportion of total prescribed doses), and the ability to administer a once-daily regimen as directly observed therapy. There are also potential disadvantages. Once-daily dosing generally produces lower trough drug concentrations than does twice-daily dosing of the same drug at the same daily dose. In addition, the virologic consequences of missing a dose or of late dosing may be worse with a once-daily regimen than with a twice-daily regimen due to lower trough drug levels. The risk of treatment failure or emergence of resistance may be correspondingly increased.

## Drug Concentrations and Toxicity

Focus on the potential advantages of maintaining a potent antiretroviral effect by ensuring high levels of protease inhibitors should not obscure potential toxicity risks. In one recent study, higher indinavir AUC and blood maximum concentration  $(C_{max})$  values were associated with greater risk of nephrotoxicity (eg, kidney stones or flank pain) in patients taking indinavir 800 mg 3 times a day (Burger et al, 8th CROI, 2001). The indinavir  $C_{min}$  values were not associated with nephrotoxicity in this study. In another study, increasing indinavir  $C_{\scriptscriptstyle max}$  and  $C_{\scriptscriptstyle min}$  values were associated with increased incidence of nephrolithiasis, with nephrolithiasis occurring in 0%, 2%, 6%, and 10% of patients receiving indinavir/ritonavir 400/100 mg, 400/400 mg, 600/100 mg, and 800/100 mg twice daily, respectively (Lamotte et al, 8th CROI, 2001). Unpublished data from Miles and colleagues at the University of California Los Angeles have also indicated an association of higher indinavir trough concentrations (>1 µg/mL) with hyper-retinoid syndrome (characterized by acute dry lips, ingrown toenails, and loss of hair on the extremities; S. A. Miles, MD, personal communication). Such findings indicate potential for increased toxicity with higher indinavir concentrations produced by combined administration with ritonavir, and may indicate the need for reducing the dosage of one of the agents in some cases.

## Potential Role for Therapeutic Drug Monitoring

For therapeutic drug monitoring to have a role in antiretroviral therapy, active drug levels must be quantifiable, there must be a quantitative relationship between drug level and outcome of interest (eg, anti-HIV effect or toxicity, for example), and the information should translate into ability to modulate therapy to the patient's benefit. Nucleoside and nucleotide reverse transcriptase inhibitors (nRTIs and ntRTIs) require intracellular phosphorylation to their active form. Although the intracellu-



Figure **1.** Effect of efavirenz administration on amprenavir concentrations with amprenavir plus ritonavir treatment in the National Institutes of Health IRT-023 study. Courtesy of Judith Falloon.

lar half-life for many of these agents is known, and is known to be greater than the plasma half-life of the drug in most cases, the intracellular levels of the active forms currently are very difficult to measure. It is thus generally considered impractical to undertake large-scale studies to evaluate the potential benefit of therapeutic drug monitoring by measuring intracellular drug levels or to monitor serum or plasma levels of nRTIs and ntRTIs.

NNRTIS do not require intracellular activation. Plasma levels of efavirenz, for example, have been shown to correlate with drug activity. Efavirenz has a reasonably wide therapeutic index (ratio of toxic to active drug levels), a long half-life, and a good inhibitory quotient; thus, patients would probably not benefit from having drug levels monitored, since concentrations in nearly all are likely to fall within a range associated with high antiretroviral activity and no substantially increased risk of toxicity.

Therapeutic drug monitoring appears more reasonable for protease inhibitors. These agents are metabolized via the cytochrome P450 system, mainly the 3A4 enzyme, with some agents in the class being cytochrome P450 inducers and some inhibitors. Many other drugs are metabolized via the 3A4 system and thus can affect protease inhibitor metabolism. Among NNRTIs, for example, nevirapine and efavirenz are 3A4 inducers and delavirdine is a 3A4 inhibitor. Further, there is substantial interpatient variation in

metabolism of individual protease inhibitors. Figure 2 shows the relationship of peak viral load reduction to 24-hour AUC for different saquinavir dosages. Higher saquinavir dosages are associated with greater AUC values, and there is a general correlation of low AUC values with lower peak viral load reduction and of higher AUC values with greater peak reduction. However, there is significant spread in the data, such that (1) there is overlap in the range of AUC values between dosages and (2) some patients exhibit low peak viral load reductions at high AUC values and high peak reductions at low AUC values. With such variability, it is unclear whether increasing dosage will result in increased antiretroviral effect or even whether, given variations in metabolism, doubling the dose will double the AUC value in an individual. Intraindividual variability of pharmacokinetics has not been sufficiently defined for most antiretroviral drugs.

For therapeutic drug monitoring to be clinically useful, a number of criteria should be satisfied. Clinical studies should document the therapeutic range or the therapeutic trough concentration of the drug. Plasma concentration should reflect the concentration at the site of drug action. It should also be known that a lack of drug effect is detrimental to the patient. These criteria are only partially satisfied by only some of the available antiretroviral agents. From a laboratory viewpoint, the drug assay for monitoring should (1) be



Figure **2.** Peak viral load reductions and area under the concentration-time curve (AUC) values according to saquinavir soft-gel capsule (SGC) dosage in NV15107 study. Courtesy of Steven A. Miles, MD.

accurate, precise, and specific, (2) require a small sample volume, (3) yield results quickly, and (4) be relatively inexpensive. Although accurate and relatively inexpensive test methods are available, assays cannot be performed with small sample volumes for all antiretroviral drugs. The greatest problem with regard to utility of monitoring from the laboratory perspective is the extended turn-around time for test results, often 2 or 3 weeks or longer.

Clinical study data on the effects of optimizing drug concentrations have begun to accumulate. Figure 3 shows proportions of patients with reduction of viral load to less than 200 HIV-1 RNA copies/mL at 6 months in the VIRADAPT study, according to whether protease inhibitor concentrations were optimal at baseline ( $\geq$ 2 times the  $IC_{95}$ ) and whether viral genotype analysis was available for treatment decisions (Durant et al, AIDS, 2000). The best outcomes were in those patients with both optimal drug concentrations and genotype data. It is difficult, however, to generalize these findings to clinical practice; the low proportions of patients achieving viral suppression overall and the poor outcome in the standard of care group suggest that this patient population was particularly difficult to treat. This was not a therapeutic drug monitoring study; drug doses were not adjusted to produce optimal concentrations.

Additional information on pharmacokinetically-based treatment comes from the PHARMADAPT study, in which 256 treatment-experienced patients were randomized to genotypic analysis or genotypic analysis plus therapeutic drug monitoring. Pharmacokinetic analysis and genotypic analysis were performed at week 4, with modification of treatment being permitted at week 8 on the basis of available information. At 12 weeks, the proportion of patients with plasma HIV-1 RNA level below the limit of detection was not significantly greater in the therapeutic drug monitoring group (43%) compared with the genotype-only group (50%), and no difference was seen between the 2 groups in this regard at week 24 (Clevenbergh et al, 8th CROI, 2001).

The usefulness of these data are in question. The target drug concentrations in the therapeutic drug monitoring group were based on protein-adjusted  $IC_{50}$  val-

ues, which may be too low for defining an adequate target level. Approximately 60% of patients in both arms were receiving ritonavir; since such patients were already receiving pharmacokinetically enhanced regimens, they may have stood little chance to benefit from therapeutic drug monitoring. Finally, there was a delay of 8 weeks from the start of treatment until a change in dosing or treatment based on therapeutic drug monitoring. Exposure of virus to suboptimal drug concentrations over this period could have resulted in emergence of resistance by the time treatment changes were made, preventing a beneficial effect on the longer-term virologic outcome. Additional data on the efficacy and benefits of therapeutic drug monitoring are needed.

In conclusion, the potential clinical role of therapeutic drug monitoring is under investigation, but remains a controversial issue. There are at present a number of settings in which therapeutic drug monitoring might be considered in patients receiving antiretroviral drugs, including:

- Confirmation of adequate drug concentrations in children
- Confirmation of adequate concentrations in patients with renal or hepatic dysfunction
- Evaluation of the effects of drug interactions and herbal remedies (eg, St. John's wort) on drug concentrations
- Evaluation of unexplained treatment failure
- Evaluation of exaggerated toxicity





Reasons for not performing therapeutic drug monitoring include the fact that the determination of optimal drug levels remains complicated, with even experts not being able to agree on correct target values. Further, there is considerable variability in intraindividual and interindividual pharmacokinetics of many antiretroviral drugs, as well as variability and lack of standardization of laboratory findings regarding both pharmacokinetics and drug inhibitory concentrations. In the clinical setting, reasons to not perform therapeutic drug monitoring include the suspicion that drug failure is more likely to be associated with nonadherence; if nonadherence is suspected, it may be the cause of reduced antiretroviral efficacy. Finally, there is little reason to monitor drug levels in patients doing well on their current regimen.

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## Perspectives Metabolic Complications in HIV Disease: Lactemia and Bone Disease

Henry Masur, MD, discussed recent information on lactemia, osteopenia, and avascular necrosis in patients with HIV disease at the International AIDS Society–USA course in New York in March.

## **Case History 1**

A 54-year-old obese HIV-infected man presented with a 2-week history of nausea and fatigue. At presentation, he had been receiving stavudine/lamivudine/indinavir for 18 months and had a CD4+ cell count of 650/µL and viral load below detection limits. The patient had reported right hip pain for 3 months. Physical exam showed modest hepatomegaly and no range of motion abnormalities of the right hip. Laboratory tests showed mildly elevated liver function tests and a serum lactate level of 3 mmol/L, and the patient's plasma hepatitis C virus RNA assay was positive. Chest x-ray and hip x-ray were normal. Should work-up for this patient include a bone scan, magnetic resonance imaging (MRI) of the painful hip, or a computed tomographic (CT) scan of the abdomen? Should antiretroviral treatment be immediately discontinued? Should the patient's serum lactate levels be monitored?

## Lactemia

Lactemia, or lactic acidemia, is defined as a venous lactate level of more than 2.5 mmol/L (>2.0-3.0 mmol/L) in the absence of abnormal arterial pH. Lactic acidosis is defined as arterial pH of less than 7.35 mmol/L with a venous lactate level of more than 2.0 mmol/L and up to 2.5 mmol/L. Most authorities classify severity of lactemia as mild for lactate levels of 2.0 to 5.0 mmol/L, moderate for levels of 5.0 to 10.0 mmol/L, and severe for levels above 10.0 mmol/L. Acidosis is rare but symptoms of lactemia are common in moderate

Dr Masur is Chief of the Critical Care Medicine Department at the National Institutes of Health in Bethesda, Maryland. lactemia and both acidosis and symptoms are frequent in severe cases, in which mortality rate can reach 80%.

Data from a number of sources indicate that the incidence of lactemia of any severity is about 1.5 to 2.1 cases per 100

> The incidence of lactemia is approximately 1.5 to 2.1 cases per 100 patient-years of nRTI exposure

patient-years of exposure to nucleoside reverse transcriptase inhibitors (nRTIs), including an incidence of 2.3 to 2.6 per 100 patient-years of exposure to stavudine. The incidence of moderate to severe lactemia is estimated at 0.13 to 0.8 cases per 100 patient-years of exposure to antiretroviral therapy, including an incidence of 1.2 per 100 patient-years of exposure to stavudine (Fortgang et al, Am J *Gastro*, 1995; Gerard et al, AIDS, 2000; John et al, AIDS, 2001).

Data on the prevalence of lactemia are available from 4 cohorts. Prevalence rates of any lactemia were 21% among patients receiving nRTI therapy versus 3% in those receiving no antiretroviral therapy in a Sydney cohort of 218 patients. Rates were 8% with nRTI treatment and 1% with no therapy in a Swiss cohort of 880 patients, and 21% with nRTI therapy and 8% with no therapy in a Dutch cohort of 223 patients. Symptomatic lactemia occurred in 2.4% of patients receiving nRTIs and 0% of those receiving no therapy in the Sydney cohort, 1.3% of those receiving nRTIs and 0% of those receiving no therapy in a Perth cohort of 349 patients, and in none of the patients receiving no therapy in the Swiss cohort.

Associations of lactemia and lactic acidosis with nRTI use are established, with risk appearing to be greater with use of didanosine and stavudine, particularly the latter. Factors potentially associated with lactemia and lactic acidosis include female sex, older age, lower CD4+ cell count, underlying liver disease, duration of antiretroviral therapy, and pregnancy. With regard to pregnancy, 3 deaths due to this lactic acidosis syndrome have been reported in pregnant women receiving stavudine. Warnings have subsequently been issued by the US Food and Drug Administration (FDA) regarding use of didanosine or stavudine in pregnant patients.

The incidence of lactemia in patients receiving nRTIs increases within the first few months of treatment. Moreover, the long-term population average lactate concentrations rise over the initial 12 months of treatment (Figure 1). These findings suggest that lactate levels should be monitored with particular care over the initial 4 to 6 months of potent nRTI-containing therapy in patients who have any of the risk factors for lactic acidosis listed above, but better delineation is needed as to which patients truly benefit from regular screening, and how this screening (eg, frequency and duration) should be done.

## **Case History 2**

A 63-year-old woman presented with a 1month history of nausea, vomiting, and abdominal pain. She had severe acidosis (pH, 7.12; lactate level of 13.6 mmol/L), elevated liver function tests, elevated amylase and lipase levels indicative of chemical pancreatitis, and a CD4+ cell count of 192/µL. CT scan showed a fatty liver and liver biopsy showed severe microvesicular and macrovesicular steatosis. The patient had been receiving stavudine and lamivudine for 6 months; both drugs were stopped. The patient survived but required prolonged hospitalization; antiretroviral therapy was reinstituted with nelfinavir/saquinavir/nevirapine.



Figure **1.** Time to onset of lactemia from start of potent antiretroviral therapy including stavudine or zidovudine. Adapted from John et al, *AIDS*, 2001.

## **Severe Lactic Acidosis**

The clinical syndromes potentially associated with lactemia and lactic acidosis include acute hepatitis (as exhibited by the patients in both case reports), fatty liver with steatosis, acidosis with shock, osteopenia, poor outcome in pregnancy, lipodystrophy, and peripheral neuropathy. Onset of acute hepatitis may occur weeks to months after starting nRTI therapy; symptoms include fatigue, dyspnea, nausea, vomiting, abdominal pain, and edema. In addition to hepatomegaly, encephalopathy and arrhythmia may be present. Laboratory findings include characteristic elevated liver function tests, and biopsy shows steatosis, necrosis, and inflammation. In one study, time to fat wasting was markedly accelerated in patients with lactemia compared with patients with normal lactate levels (White et al, Antivir Ther, 2000).

Management of severe lactemia includes withdrawal of nRTIs, with the time to return to normal lactate levels being on the order of 3 to 12 months. It is unclear whether nRTIs can or should be used in future treatment, although many practitioners would avoid stavudine or didanosine use. Patients with mild to moderate lactemia are at risk for developing acidosis and hepatitis, as well as chronic liver disease, lipodystrophy, and neuropathy, but it cannot be predicted in which patients these disorders may ultimately occur. It currently is recommended that serum lactate not be monitored routinely in every patient receiving nRTI therapy. However, monitoring should be performed in those patients with such symptoms as fatigue, nausea, and vomiting and in those with hepatitis, lipoatrophy, osteopenia, or history of lactic acidosis, those exhibiting anion gap or low HCO<sub>3</sub>

It is recommended that nRTI administration be stopped immediately in cases of severe lactemia or moderate lactemia with symptoms

levels, and pregnant patients. In addition to stopping nRTI administration in those with severe lactemia, it is recommended that nRTIs be stopped in those with lactate levels of 5.0 to 10.0 mmol/L if symptoms or signs are present, and that other potential causes of lactemia be investigated in those with levels of 5.0 to 10.0 mmol/L without symptoms and in patients with levels of 2.0 to 5.0 mmol/L with or without symptoms while therapy is continued.

## **Bone Disease**

Potential explanations for the hip pain in the patient in case history 1 include pathologic fracture due to osteopenia and avascular necrosis. The prevalence of osteopenia in HIV disease currently is unknown, although the disorder is being documented with increasing frequency. In one multivariate analysis, osteopenia was associated with both lactemia (odds ratio, 2.39; 95% confidence interval, 1.39-4.11) and lipoatrophy (odds ratio, 1.73; 95% confidence interval, 0.72-4.07). Thus far, pathologic fractures have not been reported with increased frequency among patients with HIV disease; however, there is concern that such reports will eventually begin to accumulate given the increasing recognition of osteopenia and osteoporosis in these patients. Currently, routine screening for osteopenia is not recommended. Potentially remediable causes of osteopenia should be sought, including cigarette smoking, inactivity, and hypogonadism. Management includes calcium supplementation and weight-bearing exercise. Neither growth hormone treatment nor oxandrolone treatment has been shown to be effective in improving bone density over 24 weeks of treatment.

More than 100 cases of HIV diseaseassociated avascular necrosis have been reported in small patient series in the literature. The hip is the most commonly affected site, although disease of the ankle, shoulder, and elbow also have been reported. The cause of avascular necrosis remains unknown. After diagnosing avascular necrosis in a group of HIV-infected patients referred for unexplained bone pain and noting a high number of hip replacement procedures among patients from practices of referring physicians, investigators at the National Institutes of Health performed a prospective study of the prevalence of avascular necrosis in HIV-infected subjects.

A total of 339 HIV-infected patients who reported no bone pain symptoms and 118 HIV-seronegative controls underwent MRI evaluation. Avascular necrosis of the hip was found in 15 HIV-infected individuals (4.4%) compared with none of the control subjects (P = .015). Analysis of potential risk factors among the HIV-infected patients showed significant associations of avascular necrosis with testosterone use (relative risk [RR], 3.9; P = .01), corticosteroid use (RR, 3.8; P = .02), body building or long-distance running (RR, 3.3; P = .03), and use of lipid-lowering agents (RR, 4.7; P = .004). Disease shown on MRI typically consisted of large lesions, with bilateral disease in many patients. The hip was the site of disease in the vast majority of cases, although necrosis of the knee, ankle, clavicle, and other bones was also observed. It remains unclear whether the factors associated with avascular necrosis in this study are causal factors. To date, no

Asymptomatic avascular necrosis of the hip was found in 4.4% of HIVinfected patients in one prospective study

case of avascular necrosis has been observed in an HIV-infected patient who was not receiving antiretroviral therapy.

The patient discussed in case history 1 had no resolution of hip pain and was found to have avascular necrosis on MRI evaluation, with the lesion becoming evident on plain x-ray film 1 month later. Within 1 year, the patient underwent total hip replacement.

The finding of a high prevalence of asymptomatic avascular necrosis in HIVinfected patients is disturbing. The potential for an association of osteonecrosis with increased survival duration, increased duration of exposure to antiretroviral drugs, or increased exposure to other drugs used by HIV-infected patients is suggested by the increasing frequency of reports of such disease in the literature and by findings indicating an increasing frequency of diagnosis of disease. The frequency of osteonecrosis in HIV-infected individuals in the Johns Hopkins HIV Clinic Cohort has increased substantially from 1995 to 2000 (Keruly et al, 8th CROI, 2001). from 0 to 4.8 per 1000 person-years.

It currently is uncertain what steps might be taken for prevention of the disorder. The natural history of asymptomatic lesions is unclear, although it is evident that patients do not necessarily become symptomatic within months of diagnosis. With regard to the risk factors identified in the prospective study, there is reluctance to suggest that patients with small asymptomatic lesions should discontinue testosterone therapy or weight-bearing exercise, since a causal relationship with the disorder has not been established and since both testosterone and exercise may be associated with other quality of life benefits. Similarly, it is unclear what recommendations should be made with regard to altering antiretroviral treatment. Currently, therapeutic options are limited to analgesia and assisted walking. Joint decompression frequently is performed; however, current experience does not convincingly show that this measure has a beneficial effect on the natural history of hip avascular necrosis or delays the time until joint replacement is necessary.

## Summary

More information on the causes of and optimal management for lactemia and lactic acidosis and bone diseases in patients with HIV disease is desperately needed. Currently, it is known that lactemia is more common than lactic acidosis in HIV-infected patients, but the progression from the former to the latter is unpredictable. Monitoring of lactate levels to permit timely withdrawal of potentially offending nRTI drugs is recommended for patients with elevated lactate levels and symptoms or conditions that appear to indicate increased risk of acidosis, hepatitis, and other lactemia-associated clinical svndromes. The association of lactemia with bone disease suggests a common underlying role of mitochondrial dysfunction. However, the causes of osteopenia and avascular necrosis, both of which appear to be increasing in frequency among HIVinfected individuals, remain unclear. Improvements in prevention or management await a better understanding of the etiology of these disorders.

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## New Cholesterol and Triglyceride Evaluation and Treatment Guidelines Issued by the National Cholesterol Education Program

The Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) contains major updates for clinical practice guidelines on the prevention and management of high cholesterol in adults, and may be of interest to practitioners currently caring for HIV-infected patients with lipid, insulin, or other metabolic abnormalities. Developed over 20 months by 27 panel members and consultants, the report updates earlier guidelines issued in 1988 and 1993. The new guidelines are expected to substantially expand the number of Americans being treated for high cholesterol, including raising the number on dietary treatment from about 52 million to about 65 million, and increasing the number prescribed a cholesterol-lowering drug from about 13 million to about 36 million. Key changes include:

- Better identification of those at high risk for a heart attack and more aggressive cholesterol-lowering treatment
- Use of lipoprotein profile as the first test for evaluation of a high cholesterol level

- A new threshold at which low levels of high-density lipoprotein becomes a major risk factor for heart disease
- A new set of "therapeutic lifestyle changes," which includes intensified use of nutrition, physical activity, and weight control to improve cholesterol levels
- Risk assessment: identifying a "metabolic syndrome" of risk factors linked to insulin resistance, which often occur together and dramatically increase the risk for coronary events
- More aggressive treatment for elevated triglycerides
- Advising against the use of hormone replacement therapy as an alternative to cholesterol-lowering drugs

A complete copy of the new guidelines is available online on the National Heart, Lung, and Blood Institute Web site at www.nhlbi.nih.gov.

This announcement is adapted from JAMA, 2001;285(19): 2486-2497.

## **Perspectives Approaches to HIV Prevention Among Seropositive Patients in the Clinical Care Setting**

As discussed by Frederick M. Hecht, MD, at the International AIDS Society–USA course in New York in March, recent trends toward increased risk behavior among HIVseropositive patients indicate the need for increased prevention efforts in the clinical setting.

A growing body of data indicates that HIV risk behaviors are increasing among men who have sex with men (MSM) and other risk groups in a number of locations in the United States. Since 1994, the proportion of MSM in San Francisco who report using condoms during all sexual encounters has decreased from 70% to just over 50%. Over the same period, both the rate of rectal gonorrhea in men and the proportion of these men who report having multiple partners and unprotected anal sex have increased from approximately 20% to more than 40% (Figure 1).

In apparent association with these disturbing trends, the estimated number of new HIV infections per year in San Francisco has increased from just over 500 in 1997 to approximately 800 in 2000. Outbreaks of syphilis have been reported elsewhere on the West Coast. In Los Angeles, the number of new cases of syphilis in homosexual men increased from 26 during the first 6 months of 1999 to 66 in the first 6 months of 2000. Of these 66 cases, 57 persons (86%) knew their HIV serostatus and 34 (60%) were HIV-seropositive. Similar reports have come from other parts of the industrialized world; in Amsterdam, for example, the number of annual new cases of rectal gonorrhea in homosexual men nearly tripled between 1994 and 1999.

Ongoing sexual risk behaviors are also being reported among HIV-infected heterosexuals. In a cohort of 256 HIV-infected patients in Bronx, New York, 50% of women reported having unprotected sex, including 65% of those who trade sex for money. Unprotected sex was reported by 29% of heterosexual men, and overall, 29% of patients reported having a new sexually transmitted disease (STD) since receiving diagnosis of HIV infection (McGowan et al, 8th CROI, 2001).

A number of factors are likely to be contributing to increasing risk behavior, including feelings of burn-out among target audiences in response to prevention messages and reduced motivation to avoid HIV transmission in association with advances in treatment. Indeed, there is a degree to which, in places such as San Francisco, the image of HIV infection has been routinized, a process abetted by advertisements that many feel portray the taking of antiretroviral medications to be simply part of a modern, active, robust lifestyle.

It is probably also the case that treatment advances have led to behavior disinhibition by reducing the extent to which those with HIV infection are surrounded by constant reminders of the disease in the form of friends and acquaintances who are obviously ill or who are dying with AIDS. The effectiveness of antiretroviral therapy in prolonging life and increasing the number of people living with HIV disease has been attended by the additional problem of transmission of drug-resistant virus. Proportions of cases of transmission involving drug-resistant virus in San Francisco increased sharply in 2000; nearly one third of cases involved infection with virus having at least 1 primary resistance mutation for an antiretroviral drug.

In the context of what medical care can do to prevent HIV transmission, it needs to be recognized that although decreased viral load is associated with decreased risk of transmission, and it is tempting to believe that effective antiretroviral therapy can eliminate or reduce risk of transmission on the model of treatment for bacterial STDs, there are limitations to medical treatment as a preventive measure. Unlike bacterial infection, HIV infection is not cured by treatment. Potentially infectious cell-associated virus persists in patients with viremia below detection limits, and patients do not immediately know when they are experiencing viral breakthrough, which is likely to coincide with emergence of drug-resistant virus. Further, it has been



Figure **1.** Increase in HIV risk behaviors among men who have sex with men in San Francisco, 1994 to 1999. Adapted from the San Francisco Department of Public Health.

Dr Hecht is Associate Professor of Medicine at the University of California San Francisco and Co-Director, UCSF Center for AIDS Research Behavioral Science Core.

estimated that even a 10% increase in risk behavior on the part of infected people can counteract the preventive effect of current treatment strategies on the community level (Blower et al, *Science*, 2000).

For many years, prevention efforts have been focused on keeping HIV-seronegative people free from infection. There is a pressing need now to renew efforts to address risk behaviors in the HIV-infected population. There is clear potential for instituting prevention efforts in clinical care, since it provides a setting for contact with many HIV-infected individuals and since there is evidence that interventions in this setting can be successful.

## **Rationale for Preventive** Intervention in the Clinic

Clinicians may sometimes despair of being able to effect behavioral change in their patients. Yet there is considerable evidence from the literature that risk behaviors of different types can be reduced with even brief interventions.

In one 1992 study in Los Angeles, a single small group session in an STD waiting room reduced STD reinfection rates (Cohen et al. Public Health Rep. 1992). In the Project Respect study, performed by the Centers for Disease Control and Prevention (CDC), 2-session, pre- and post-HIV test counseling reduced the rate of new STDs by 30% (Kamb et al, JAMA, 1998). In another study, a 2-session intervention in homosexual men reduced rates of unprotected insertive anal sex (Valdiserri et al, AIDS, 1989). Brief counseling sessions by physicians have been shown to increase guit rates in smokers by 5% to 10% (Ockene, Prev Med, 1987; Richmond, Addiction, 1994), reduce alcohol consumption by 25% to 35%, and reduce the proportion of excessive drinkers by 45% (Richmond, Addiction, 1994). More comprehensive interventions involving clinicians have been shown to result in smoking quit rates of 10% to 35% (Wilson, JAMA, 1988) and reduce the proportion of excessive alcohol drinkers by 60% to 70% (Richmond, Addiction, 1994).

## Achieving Behavior Change in the Clinic

Given the ordinary demands on clinicians in many settings, behavioral interventions in the clinic need to be brief. It would be ideal for clinicians to be recognized for the time spent on intervention, and the Institute of Medicine has recommended that such counseling be considered a billable service. Although such a measure will probably be a key to incorporating counseling intervention in clinical practice, prevention efforts should not await formalization of such an incentive. In practice, expectations for changing behavior need to be realistic. Most medical interventions are not 100% effective; even a 10% or 20% reduction in risk behavior could have an important impact on HIV transmission in the community.

The stages of change model and motivational interviewing, elements of behavior counseling drawn from substance abuse intervention models, may be useful in prevention counseling in the clinic. Stages in the behavioral change process can be considered to consist of precontemplation (not thinking about change), contemplation (unsure about change), preparation (ready for change), action (engaged in change), and maintenance (maintaining change in behavior). People at different stages in this process are likely to benefit from a different focus in intervention.

Components of motivational interviewing interact with the stages of behavioral change. This technique is client-centered, addressing the patient in the context of his or her readiness for change and supporting the idea that the patient is expert in what he or she feels and believes will be useful in daily life. The counselor provides information, feedback, and skill

## Table 1. Elements of Motivational Interviewing

Element	Description
1. Express empathy	Build rapport with the patient in a nonjudgmen- tal manner
2. Develop discrepancy	Identify what is discrepant between the patient's stated goals and behavior and provide feedback on the discrepancy to the patient in a manner that allows the patient to interpret the discrep- ancy in his or her own terms
3. Avoid argument	Avoid direct confrontation of the patient regard- ing negative aspects of behavior
4. Roll with resistance	Move a patient toward insight and decisions using his or her own words (resistance can be a sign of damaged rapport that needs to be repaired)
5. Support self-efficacy	Build the patient's skill and confidence in accom- plishing and maintaining behavior change

building to guide the patient in the process of change, with lecturing being avoided to avoid resistance to change. Motivational interviewing consists of 5 elements, which are summarized in Table 1.

## **Issues in HIV Counseling**

Development of rapport with the patient regarding prevention of HIV transmission is an essential first step in intervention. For new patients, the subject of prevention can be initially addressed by asking if they are sexually active, acknowledging that practicing safe sex is hard to do all the time, and asking if they have difficulty in this regard at times. The clinician's concern regarding increases in HIV transmission and drugresistant virus transmission can be shared with the patient in this discussion. Another way to broach the topic of risk behavior is to incorporate similar questions into screening for other STDs. Responses in these initial interactions should provide some idea of a patient's readiness for change.

Other initial steps that must be taken include identification of barriers to behavior change. Drug or alcohol use should be identified and appropriate counseling or referral provided. Social context should be considered for each patient with the aim of identifying and addressing triggers for risk behavior. An important aspect of current culture in San Francisco is that concordant HIV serostatus is frequently assumed among individuals practicing unsafe sex. Clinicians should emphasize that this assumption frequently is wrong. One approach to encourage discussion of serostatus between partners is to promote the idea that by not discussing it, the patient is giving away the power to influence transmission. Discussion of this topic with the patient enables the clinician to identify and highlight discrepancies between behavior and goals. Motivation for change or support for decreased risk behavior can be in part provided by appealing to the self-interest of the patient in reducing risk for other STDs, by supporting the feeling of discomfort that most patients have with putting other people at risk and the benefit of retaining the power to decide whether others will be at risk, by strengthening the patient's knowledge of current increases in HIV and other STD transmission, and by providing feedback on risks of transmission associated with the patient's current practices.

Many patients engaging in risk behaviors are not going to eliminate all such behavior. Behaviors that carry greatest risk (ie, unprotected insertive anal sex with a discordant partner and vaginal sex with a discordant partner) should be identified. Strategies for risk reduction may be identified for patients who are unwilling to practice protected sex on all occasions, including having partners who have disclosed their own HIV-infected status (with acknowledgment that there is still risk for other STDs), having only 1 such partner with whom sex is unprotected, and ensuring that sex is protected with partners of unknown or negative HIV serostatus.

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## Heterogeneity and Public Health in the Global HIV/AIDS Epidemic

At the opening session of the 2001 Conference on Retroviruses and Opportunistic Infections in February, Kevin M. De Cock, MD, reviewed global HIV/AIDS epidemiology, focusing on disease in Africa and response to the African epidemic from a public health perspective.

It is estimated that 36.1 million people were living with HIV/AIDS and that 21.8 million people had died with HIV disease by the end of 2000. In 2000, there were an estimated 5.3 million new HIV infections and 3 million AIDS deaths. The most important events in the second decade of the epidemic have been the introduction of new antiretroviral regimens, the advent of effective interventions to prevent mother-to-child transmission of HIV, and prolongation of healthy life in infected people in industrialized countries.

## **Trends in the United States**

In the United States, abrupt declines in AIDS incidence and mortality began in 1996, with the introduction of potent antiretroviral regimens. However, incidence and mortality rates have stabilized since 1998. The range of AIDS rates per 100.000 population by state is wide, the rate in New York in 2000 being approximately 66 times that in North Dakota. Current major trends in disease include an increasing proportion of AIDS cases in women, now accounting for 24% of cases; a decreasing proportion of cases attributable to men having sex with men, now accounting for 40% of cases; and an increasing proportion attributable to heterosexual contact, now accounting for 25% of cases. Non-Hispanic blacks accounted for 48% of AIDS cases reported in 1999. and 54% of recently reported cases of HIV infection.

Potential causes of the stabilization of AIDS rates include reaching the limits to which therapy can extend survival, drug

Dr De Cock is Director of CDC Kenya, the collective title for the public health activities and research in Kenya.

resistance, treatment adherence failure, late HIV testing, lack of access to care, and increased HIV infection incidence. The Centers for Disease Control and Prevention estimates that up to one third of the approximately 900,000 people living with HIV infection in the United States do not know of their infection status. Data from several sources indicate that the national incidence of HIV infection has remained stable at approximately 40,000 new infections per year since the early

Science should determine public health policy. The scientific and philosophic underpinnings of public health are epidemiology and social justice; and surveillance is both the witness and judge in any epidemic. The Institute of Medicine defines public health as what we, as a society, do collectively to assure the conditions for people to be healthy. Social justice can be taken to mean the fair distribution to people of society's benefits and burdens and their consequences.—From Dr De Cock's prefatory remarks.

1990s. Approximately 70% of incident infections are in men, and more than half of all new infections are in African Americans. Men who have sex with men have the highest incidence rates, with most studies indicating a rate of approximately 2 per 100 person-years. Compounding the failure to reduce the national incidence of HIV infection are increasing reports of unsafe behavior among men who have sex with men, including increased incidence of rectal gonorrhea, increased anal intercourse, and decreased condom use in San Francisco; and syphilis outbreaks in King County, Washington and elsewhere. Reports of increased risk behavior among men who have sex with men have also come from Canada, London, and Amsterdam.

## **Trends Elsewhere**

In Latin America, HIV transmission among men who have sex with men and from injection drug use account for most AIDS cases, but heterosexual transmission of HIV is increasing, with a corresponding increase in proportions of infections in women. HIV epidemiology in the Caribbean is reminiscent of that in Africa, although currently the highest HIV-seroprevalence rate in the region, in Haiti, is considerably less than 10%.

The highest AIDS incidence in western Europe in 1999 was in Portugal, with the rate of 10 per 100,000 population being approximately 40% of that in the United States (Figure 1). In this region, the proportion of cases acquired heterosexually is now 31%, approaching the proportion



Figure **1.** AIDS cases per million population in selected countries in western Europe, 1984 to 1999. Data are those reported by June 30, 2000, and are adjusted for reporting delays.

attributed to injection drug use. Cases of perinatal infection have declined in most countries. Available data suggest that HIV incidence has stabilized in western Europe since the early 1990s, as in the United States. Large proportions of heterosexually acquired HIV infections in western European countries are in persons born in other countries where heterosexual transmission predominates, primarily African countries (Figure 2).

Rates of HIV infection have remained relatively low in much of central Europe. Rates have declined in Romania since the widespread infection of children with infected blood products in the early 1990s. HIV has spread explosively in many areas of eastern Europe since the mid-1990s. Reports of HIV infection in the Russian Federation increased by 410% between 1998 and 1999, and increases have also occurred in Latvia and Ukraine. Currently, most infections in this region are associated with injection drug use, ongoing epidemic syphilis, and increased commercial sex activity. Erosion of health infrastructure makes future trends in HIV infection unpredictable in this region of the world.

The spread of HIV/AIDS in Southeast Asia has been greatest in Cambodia, Thailand, and Myanmar (Figure 3), with the epidemic being driven by injection drug use and commercial sex. Infection rates remain relatively low in such countries as Japan, Indonesia, and the Philippines. An estimated 4 million people in India are HIV-infected, with a seroprevalence of 2% to 4% among pregnant women in Mumbai and Pune in the west contrasting with a seroprevalence of less than 1% in Calcutta and Delhi. Injection drug use drives the epidemic in the northeastern states near Myanmar, where seroprevalence among drug users is more than 70%. Seroprevalence rates among injection drug users in Yunan Province in China increased to 70% or greater in the early 1990s, with the first appearance of HIV infection in sex workers in China occurring in this region. Yunan Province likely accounts for half of the estimated 500,000 to 1 million individuals with HIV infection in China.

## **Trends in Africa**

Sub-Saharan Africa, with a population of approximately 600 million and 10% of the global population, accounted for 72% (3.8 million) of incident HIV infections and 80% (2.4 million) of AIDS deaths in 2000, and accounts for 70% (25.3 million) of the estimated total of HIV-infected people worldwide. Seroprevalence rates in pregnant women now exceed 40% in some areas of Zimbabwe and Botswana. Reductions in seroprevalence rates in pregnant women have been observed in some settings in Uganda and Zambia, possibly due to behavior changes, but trends in these areas are uncertain. In eastern and southern Africa, crude death rates are now 50% to 500% higher than expected, with increased mortality most evident in young adults and children under 5 years of age. Currently, 30% to 50% of Africans dving with AIDS have tuberculosis, with rates of this disease having doubled or tripled in many countries. The lifetime risk of dving with HIV disease now exceeds 60% for adolescents in southern African countries. Life expectancy will decrease by more than 30 years in some areas. By the end of 1999, more than 12 million African children had





lost their mother or both parents to AIDS, and there are now at least twice as many AIDS orphans in Africa as there are refugees and displaced persons (Table 1); perhaps no other aspect of HIV/AIDS has greater implications for social stability and security in Africa, yet there has been no organized international response to this crisis to date.

## **Epidemiologic Patterns**

Current epidemiology indicates that, although vigilance regarding the spread of HIV is required everywhere, Africa is a world apart concerning HIV/AIDS. Only Africa is marked by high-prevalence, generalized population epidemics with equal or more women affected than men. With the exception of the lower-prevalence epidemic in the Caribbean, epidemics in other regions of the world are concentrated around specific risk groups, consisting of injection drug users, providers and consumers of commercial sex, and men who have sex with men.

## Epidemiologic Heterogeneity: Why is Africa So Disproportionately Affected?

The global diversity of the HIV epidemic must be explicable through one of two models. Qualitatively, the epidemiology of any infectious disease reflects interactions among the agent, host, and environment. Numerically, epidemic growth depends on the basic reproductive rate, the number of secondary infections generated on average by 1 primary case. For a sexually transmitted infection, the basic reproductive rate depends on the rate of partner change, the transmissibility of the agent, and the duration of infectiousness. The effects of these parameters on transmission, however, are not linear and people with frequent partner change have a disproportionate impact on the spread of HIV.

With regard to the agent, HIV-2 illustrates the impact of inherently lower transmissibility compared with that of HIV-1, which probably explains why we face a pandemic of HIV-1 but not HIV-2 infection. HIV-1 is classified into 3 major subgroups, M, N, and O, with M being the pandemic form. In addition to 9 basic subtypes, other sub-subtypes and recombinant forms have been identified. The dominant global subtypes are: A, mainly in Africa; C, found in southern Africa and parts of India; and B, in Europe and the Americas; as well as the recombinants A/E found in Asia and A/G found largely in West Africa. Indicative of the ancestry of HIV-1, all subtypes are found in Africa, with an astonishing diversity of subtypes in Central Africa, especially the Democratic Republic of the Congo. Biologic attributes of subtype C have been postulated to confer increased efficiency of transmission and replication, but epidemiologic proof of such effects is lacking. In summary, there is no firm evidence of biologic or virologic reasons for Africa's severe HIV/AIDS epidemic.

With regard to host factors, the presence of other sexually transmitted diseases and increased viral load in genital fluids and blood are associated with increased transmission; other data indicate that male circumcision is associated with a protective effect in acquisition of infection. One multicenter study compared low- and high-prevalence cities in east and west Africa, and concluded that prevalence differences are associated with transmission efficiency rather than behavior; key risk factors were lack of male circumcision and the presence of genital herpes. However, such conclusions need to be tempered by the awareness that it is difficult for epidemiology to capture certain factors relevant to disease transmission, including qualitative differences between groups. Types of sexual partners may be more important than absolute number of partners and mixing patterns (assortative vs nonassortative) may be important determinants of the spread of disease, with nonassortative mixing resulting in more efficient spread. There is also difficulty in assessing the effects of low-potency risk factors that are widely distributed



Figure **3.** Spread of HIV over time in Asia, 1984 to 1999. Adapted from UNAIDS, June 2000. Available at: http://www.unaids.org/epidemic\_update/report/index.html.

and thus may have important public health impact, and how risk factors can interact in a multiplicative rather than additive fashion, enhancing each others' impact.

Finally, effects of population level characteristics and norms are also difficult to assess. Although effects of individual risk

Table 1. Estimated Cumulative Number	of	Children	Orphaned	by	AIDS	at A	ge '	14
or Younger, End of 1999				-			-	

Region	Estimated Cumulative Number
Sub-Saharan Africa	12,100,000
South and Southeast Asia	850,000
Latin America	110,000
Caribbean	85,000
North America	70,000
North Africa and Middle East	15,000
Western Europe	9000
East Asia and Pacific	5600
East Europe and Central Asia	500
Australia and New Zealand	<500

Adapted from UNAIDS, June 2000. Available at: http://www.unaids.org/publications/graph-ics/index.html.

factors can be quantified, it is more difficult to determine population-attributable risks-for example, the proportion of people in a given population with levels of viral load likely to result in transmission. Early in an epidemic, many infected persons may have elevated viral loads in association with seroconversion; this could result in a wave of a new subtype washing over a population, falsely suggesting virusspecific enhanced transmissibility. It is possible (though unproven) that in a mature epidemic, enhancement of viral replication by intercurrent illnesses, such as malaria or tuberculosis, could result in a population with an increased prevalence of higher viral loads, thus creating an environment conducive to increased transmission efficiency. If added to this scenario are social risk factors such as poverty, conflict, and migration, which predispose to partner change and sexual disease transmission, then a high-risk environment can be envisaged in which a single act of unprotected sex carries risk of transmission substantially higher than that elsewhere, without implying major differences in the biology of the agent or in the behavior of most individuals.

## **Response to the Epidemic**

Efforts to strengthen human rights in Africa and to combat stigma and discrimination against people with HIV infection need to be supported, but for successful efforts against the epidemic, the philosophic stance that pits human rights against public health needs to be abandoned. The response to the HIV epidemic in Africa is inadequate in character and intensity. The epidemic is unfolding imbedded in and inseparable from the context of collapsing public health and other social infrastructures; many of the public health issues surrounding the epidemic would need to be confronted even if an effective vaccine were available today.

Epidemiology is unforgiving, even in industrialized countries. In the United States, resurgence of unsafe behaviors, the absence of a reduction in HIV infection incidence, and the flattening of the decline in AIDS cases emphasize the need for improved surveillance to understand trends in the epidemic. The current uncertainty regarding HIV trends in high-transmission areas in the United States is unnecessary. Yet, support for HIV surveillance, including financial support, is weak.

The CDC recommended in 1999 that HIV reporting be conducted by name, allowing integrated tracking of HIV diagnoses, AIDS, and AIDS deaths across the population, and permitting linkage of infected mothers and their exposed infants for evaluation of programs that could eliminate mother-child transmission. In addition, studies on behavior and disease morbidity, seroprevalence and seroincidence surveys in particular groups, and drug resistance and toxicity monitoring are needed.

Focusing efforts to prevent sexual and drug injection-associated transmission on HIV-infected persons is made easier in industrialized countries by the availability of effective antiretroviral therapy. Overall, greatly increasing voluntary testing to diagnose all infected persons, treating all infected persons medically according to guidelines, focusing prevention efforts on and around those with HIV infection, and implementing effective surveillance may constitute the most effective approach to HIV/AIDS prevention in industrialized countries today. Such an approach would also address the unacceptably large proportion of persons unaware of their serostatus, who may transmit HIV unknowingly and who are not benefiting from care; for more than 40% of persons with AIDS in the United States, preventable illness was the first indication of HIV infection.

AIDS exceptionalism, the practice of confronting the HIV/AIDS epidemic in ways different from how other lethal or sexually transmitted infections are confronted, contributes to suboptimal response to the epidemic in this country and internationally. The fundamental question regarding HIV/AIDS in Africa is whether the epidemic will simply run its course or public health and biomedical interventions are capable of interrupting transmission and alleviating disease. If the answer is to be the latter, public health, social justice,

Many of the public health issues surrounding the epidemic in Africa would need to be confronted even if an effective vaccine were available today

and medical ethics offer a better preventive framework than does AIDS exceptionalism. As stated by New York State's Commissioner of Health, Herman Biggs, in 1913: "Public health is purchasable. . . . A community can determine its own death rate. . . . No duty of society . . . is paramount to this obligation to attack the removable causes of disease."

In much of Africa, the public health infrastructure has eroded and what is taken for granted elsewhere, such as blood supply safety, cannot be assumed. In the mid-1990s, a survey of donations in 6 hospitals in 1 country showed that, with seroprevalence among donors ranging from 2% to 20%, only 72% of seropositive units were correctly identified, with 17% being misdiagnosed and 10% not being recorded; 2% of apparently screened transfusions may have transmitted HIV.

In rural western Kenya, deaths in children under 5 years of age have increased 2to 3-fold since the 1980s, with 1 in 4 children now dying before age 5. With the adult HIV prevalence of approximately 25%, it is likely that at least one third of the pediatric mortality is HIV-related, but these appalling mortality rates also reflect high-level, stable malaria and its ineffective treatment due to chloroquine resistance; an overall decline in vaccination rates to only 50%; diarrheal diseases and malnutrition; and an eroding health care system. In such a context, measurable benefit from perinatal HIV prevention may not be achieved unless we simultaneously address traditional health problems that aggressively compete for mortality.

Public health measures that must be put into place in Africa include HIV testing. There is an unmet demand for voluntary counseling and testing for people who are well, as a prevention service and to help people facing life decisions. When services are convenient and inspire confidence. demand and uptake are greater than usually anticipated. Voluntary testing and counseling aims to keep those who are HIV-seronegative uninfected and to link those who are infected with prevention, care, and support services. The availability of rapid tests using whole blood should increase access to and uptake of testing. Seronegative persons in HIV-discordant relationships, who have been shown to have an infection incidence of 12 per 100 person-years in one study in Uganda, may constitute the largest vulnerable group on the continent. Keeping such persons uninfected is a priority for prevention of orphanhood.

In the setting of medical care, routine, universal, confidential testing offers the best chance for rational medicine, whatever the resources available for treatment. Due to emphasis on pretest counseling and anonymity as well as lack of organized and systemic AIDS care in health care settings, untested HIV-infected patients fill hospital wards and tuberculosis clinics without their underlying condition being formally diagnosed or communicated to them. Some HIV-seronegative patients are misdiagnosed with AIDS on clinical grounds and abandoned.

A maternity hospital in Nairobi, the largest in Africa, performs almost 25,000 deliveries per year, approximately 4000 involving HIV-infected women. The women receive antenatal care in clinics outside the hospital that do not test for HIV; even if they did, tracking and transmittal of laboratory results would not be feasible. The pragmatic solution in this case would be routine, universal, rapid testing in labor, with provision of nevirapine to HIVseropositive mothers and their infants. However, such a practice is controversial, and currently no services are provided; the result is that approximately 1000 perinatal infections occur annually in this single hospital, a number several times greater than the annual number of perinatal infections in the entire United States.

In an ambitious perinatal program in Botswana, fewer than 10% of HIV-infected mothers receive zidovudine because of low voluntary test uptake. Short-term zidovudine treatment has an efficacy rate considerably less than 50%, and such programs will have little or no impact on pediatric HIV infection without universal testing of pregnant women.

More widespread testing is needed to allow such relatively inexpensive therapies as prophylaxis with isoniazid and cotrimoxazole to be provided, with the spectrum of disease in Africa being such that considerable benefit would be derived from their use. As it stands, few people in the health care setting are tested, target populations are difficult to identify, and service delivery is challenging. The same constraints would apply to use of antiretroviral drugs even if they were provided free of charge, quite apart from the challenges inherent in managing longterm therapy (adherence, toxicity, drug resistance) and countering the potential weakening of prevention practices that attends availability of treatment.

On the other hand, antiretroviral drugs are sold in every major city in Africa, and

pilot programs in Uganda and Côte d'Ivoire have shown that they can be used safely. It is inevitable that as benefits of treatment in rich, low-prevalence northern areas become ever more evident, the loud-

From Dr De Cock's closing remarks: In closing, I ask myself what we as a society would do to assure conditions for people to be healthy if the United States faced African HIV prevalence. Have underfunding, AIDS exceptionalism, and the 'individual rights' approach to the US epidemic unwittingly reinforced a deep cultural reluctance in Africa to deal with the taboos of sex and death, and promoted, rather than prevented, silence, stigma, and HIV transmission? Are we accepting this African holocaust in a way we never would if it were here? If so, then at some time, epidemiology will be heard and we will have to account for public health passivity in what is unquestionably Africa's greatest catastrophe since slavery. . . . For those to whom Africa may seem far away and who may legitimately wonder 'am I my brother's keeper?' I think we should acknowledge debts to the continent for all it has taught us about HIV/AIDS, and remember the African proverb: 'I am because of what I see of me in your face; I am because you are.'

er will be the call for access to antiretrovirals in the poor, high-prevalence south. International donors and technical agencies will face critical questions regarding drug implementation and the structures

needed to support it: will they be willing to initiate necessary programs and to build and maintain necessary infrastructure? Operational research questions abound with the inevitability of drug access and demand for treatment: When to start? What to start with? When to switch and what to switch to? What is minimum safe monitoring? What populations should be targeted? How can adherence be promoted? What opportunistic infection prophylaxis is to be used? Outside of the private practice setting, treatment approaches will have to be standardized, simple, generalizable, confidential, but not anonymous, and treatment will probably have to be delivered by dedicated clinics. If the international experience with programs for tuberculosis is to serve as a historical analogy, it is clear that the road ahead is a difficult one.

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<sup>&</sup>lt;sup>1</sup>International Committee of Medical Journal Editors. Uniform requirements for manuscripts submitted to biomedical journals. *N Engl J Med.* 1997;336:309-315.

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